Will New CCBs surpass amlodiine ?

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- DM cardiology (1979) from Kanpur.
- Commonwealth Fellowship in Cardiology, Leeds, UK (1981-82).
- Professor of Cardiology and subsequently **Emeritus Professor of Cardiology** at Jhansi UP**.**
- Past National President, Indian College of Cardiology and Indian Society of Electrocardiology
- Past President, UP CSI and National Vice President, CSI.
- National Convener, Hypertension sub speciality council of CSI (2018-19).
- Organized UPCSI (2000), Mid term UPCSI (2004), ICC Khajuraho (2006), 1st CSI- Cardiac Prevent 2014 -Agra (2014).

HYPERTENSION

World Health Organization

A SILENT KILLER

World Health Organization

Hypertension is a silent, invisible killer that rarely causes symptoms. Increasing public awareness is key, as is access to early detection. Raised blood pressure is a serious warning sign that significant lifestyle changes are urgently needed. People need to know why raised blood pressure is dangerous, and how to take steps to control it.

Dr Margaret Chan

World Health Organization

HOW HYPERTENSION IS DEFINED ?

- **Hypertension isdefined as a systolic blood pressure equal to or above 140 mm Hg and/or diastolic blood pressure equal to or above 90 mm Hg**

WHO/ISH CLASSIFICATION OF BLOOD PRESSURE

CATEGORY	SYSTOLIC (mmHg)	DIASTOLIC (mmHG)
Optimal	<120	<80
Normal	<130	<85
Grade 1	140- 159	> 90-99
Grade 2 Hypertension	160- 179	>100- 109
Grade 3 Hypertension ("severe")	>180	>110
Isolated Systolic Hypertension	>140	<90

CLASSIFICATION*

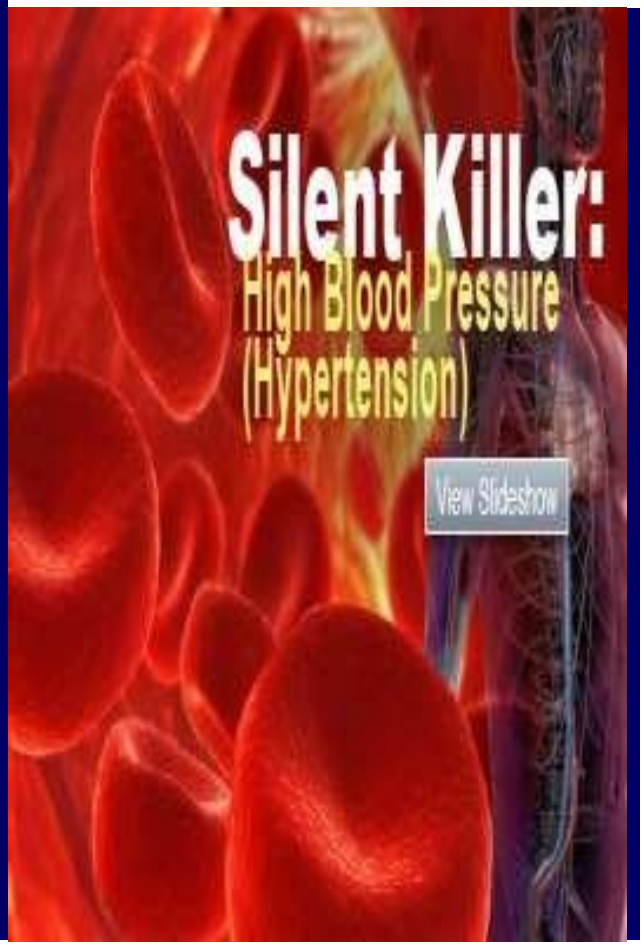
BP Classification	SBP mmHg		DBP mmHg
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Stage 1 Hypertension	140–159	or	90–99
Stage 2 Hypertension	≥160	or	≥100
Isolated systolic hypertension	≥140	–	<90

-JNC-7

WHY HYPERTENSION IS A MAJOR PUBLIC HEALTH ISSUE?

- Globally cardiovascular disease accounts for approximately 17 million deaths a year, nearly one third of the total deaths. Of these, complications of hypertension account for 9.4 million deaths worldwide every year .
- Hypertension is responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke .

World Health Organization



Recent reports indicate that nearly 1 billion adults (more than a quarter of the world's population) had hypertension in 2000, and this is predicted to increase to 1.56 billion by 2025.

Today, mean blood pressure remains very high in many African and some European countries. The prevalence of raised blood pressure in 2008 was highest in the WHO African Region at 36.8%

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INDIAN SCENARIO*

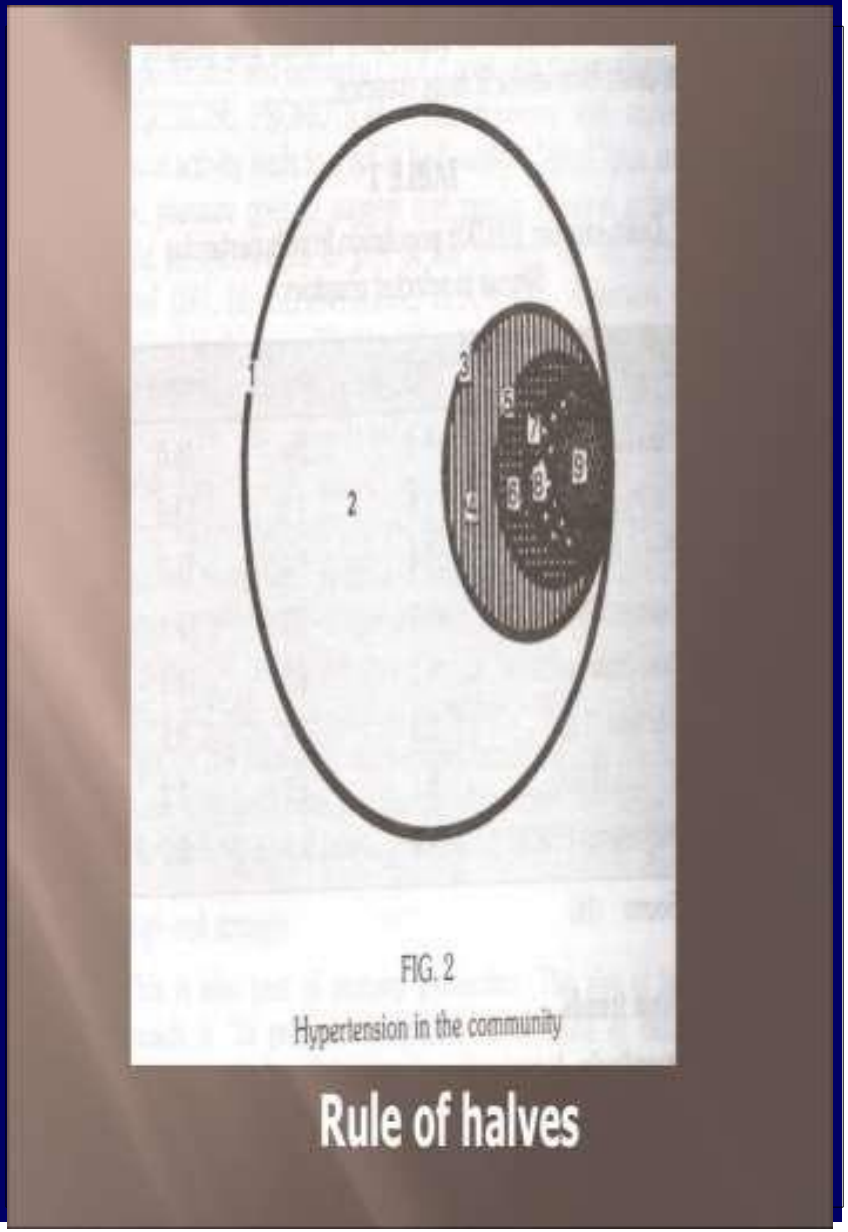
- **Recent studies from India have shown the** prevalence of HTN to be 25% in urban and 10% in rural people in India .
- According to the WHO estimates , the prevalence of raised BP in Indians is 32.5% (33.2% in men and 31.7% in women) .
- Andhra Pradesh (13.3%), Odisha (9%), Chhattisgarh (8.4%) and Gujarat (6.7%) have highest prevalence while Assam and Rajasthan (1.4%), Kerala (2.4%), Bihar (2.7%), Madhya Pradesh (2.8%) and Uttar Pradesh (3.6%) are low prevalence states.

Journal of Hypertension: June 2014 - Volume 32 - Issue 6 - p 1170–1177

RULE OF HALVES

Despite the high prevalence; prevention, detection, treatment, and control of hypertension is still suboptimal in developing countries like india

Rule o f halves' states that ‘half of hypertensive patients remain undiagnosed, half of known do not receive treatment and half of treated, do not achieve adequate control



Guideline Comparisons of Goal BP and Initial Drug Therapy for Adults With Hypertension

Guideline	Population	Goal BP, mm Hg	Initial Drug Treatment Options
JNC 8 2014 Hypertension guideline	General ≥60 y	<150/90	**Nonblack:** thiazide-type diuretic, ACEI, ARB, or CCB
	General <60 y	<140/90	**Black:** thiazide-type diuretic or CCB
	Diabetes	<140/90	Thiazide-type diuretic, ACEI, ARB, or CCB
	CKD	<140/90	ACEI or ARB
NICE 2011	General <80 y	<140/90	**<55 y**: ACEI or ARB
	General ≥80 y	<150/90	≥55 y or black: CCB
KDIGO 2012	CKD no proteinuria	≤140/90	ACEI or ARB
	CKD + proteinuria	≤130/80	

JAMA. 2013;():. doi:10.1001/jama.2013.284427

Calcium Channel and Cardiovascular System

- Various types calcium channels are present in human body
- BP regulation and calcium channel

: About 6 types of calcium channels are involved

: L-type
: T-type
: N-type

} Main target of pharmacologic treatment (CCB)

Characteristics of Ca^{++} Channel

L-type

- Require strong depolarization (high activation threshold)
- Long Lasting (slow activation rate)
- Main currents recorded in muscle and endocrine cells
- Blocked by organic CCB (DHP, Phenylalkylamines, benzothiazepines)

T-type

- Activated at weak depolarization potential
- Transient (fast inactivation)
- Resist to L-type and N- and P/Q-type blockers

N-type

- Require strong depolarization for activation
- Resistant to L-type blockers
- Found primarily in neurons: initiate neurotransmission
- Blocked by specific polypeptide toxins

CCBs

Calcium channel blocking agents (CCBs) inhibit the movement of calcium ions across the cell membrane by blocking the L-type (slow) calcium ion channel. This blockade reduces contraction of both smooth and cardiac muscle, and cells within the sinoatrial (SA) and atrioventricular (AV) nodes. The main actions of the CCBs include dilatation of coronary and peripheral arterial vasculature, a negative inotropic action, reduction of heart rate, and slowing of AV conduction

CCB and Cardiovascular Diseases

- Developed as vasodilators
- Widely used in various cardiovascular diseases
  - : Hypertension
  - : Symptomatic relief of stable angina
  - : Stabilized UA/NSTEMI
  - : Symptomatic relief of diastolic heart failure
  - : Rate control of persistent atrial fibrillation

Classes of Calcium channel blocker

Chemical Group	Tissue Selectivity	1st Generation	2nd Generation	3rd Generation
Dihydropyridines	Vascular > Myocardium	Nifedipine Nicardipine	Nifedipine SR/GITS Nicardipine SR Felodipine Isradipine Nimodipine Nisoldipine Nitrendipine	Amlodipine Lacidipine Cilnidipine Lercarnidipine
Benzothiazepines	Vascular = Myocardium	Diltiazem	Diltiazem SR	
Phenylalkylamines	Vascular < Myocardium	Verapamil	Verapamil SR Gallopamil	

First Generation CCBs

- Inhibit voltage-dependent L-type calcium channel
  - : Vascular smooth muscle relaxation (vasodilator)
  - : Negative chronotropic and inotropic effects in the heart
- Vasodilation-triggered, baroreceptor-mediated reflex increase in sympathetic tone
  - : Indirect cardiostimulation
  - : Associated with adverse events

Clinical Trials with 1st generation CCBs

Nifedipine may paradoxically exacerbate the frequency of angina pectoris!!!

Am Heart J 1983;1066(4 pt 1):644-52

Short acting nifedipine increases mortality in patients with CAD!!!

Circ 1995;92:1326-31

Diltiazem associated with 63% increase in rate of MI in hypertensive pts!!!

J Am Geriatr Soc 1995;274:620-5

Diltiazem increases the risk of ADHF and death in pts with post-MI

Circ 1991;83:52-60

Clinical Problems of First Generation CCBs

- Rapid onset and short duration of short-acting formulations
  - : Lead to neurohormonal activation
  - : Can be detrimental in CAD and CHF
- Reflex-mediated increase in sympathetic tone
  - : Reflex tachycardia
  - : Worsening angina, CHF or increased risk of mortality
- Coronary steal to non-ischemic myocardium via collaterals
  - : Arterioles are more affected by CCB than larger epicardial coronary arteries

Second and Third Generation CCBs

- Slower onset and longer duration of action
- Less pronounced increase in sympathetic tone
  : Reduced reflex tachycardia
- Reduced likelihood of negative inotropic effects
- Beneficial cardiovascular effects beyond BP lowering
  : So called “pleiotropic effects” of CCB

2nd & 3rd Generation CCBs

- Meta-analysis of placebo controlled trials with longer-acting CCB suggest mortality benefit in treated patients (HTN, post-MI, CHF, CAD)

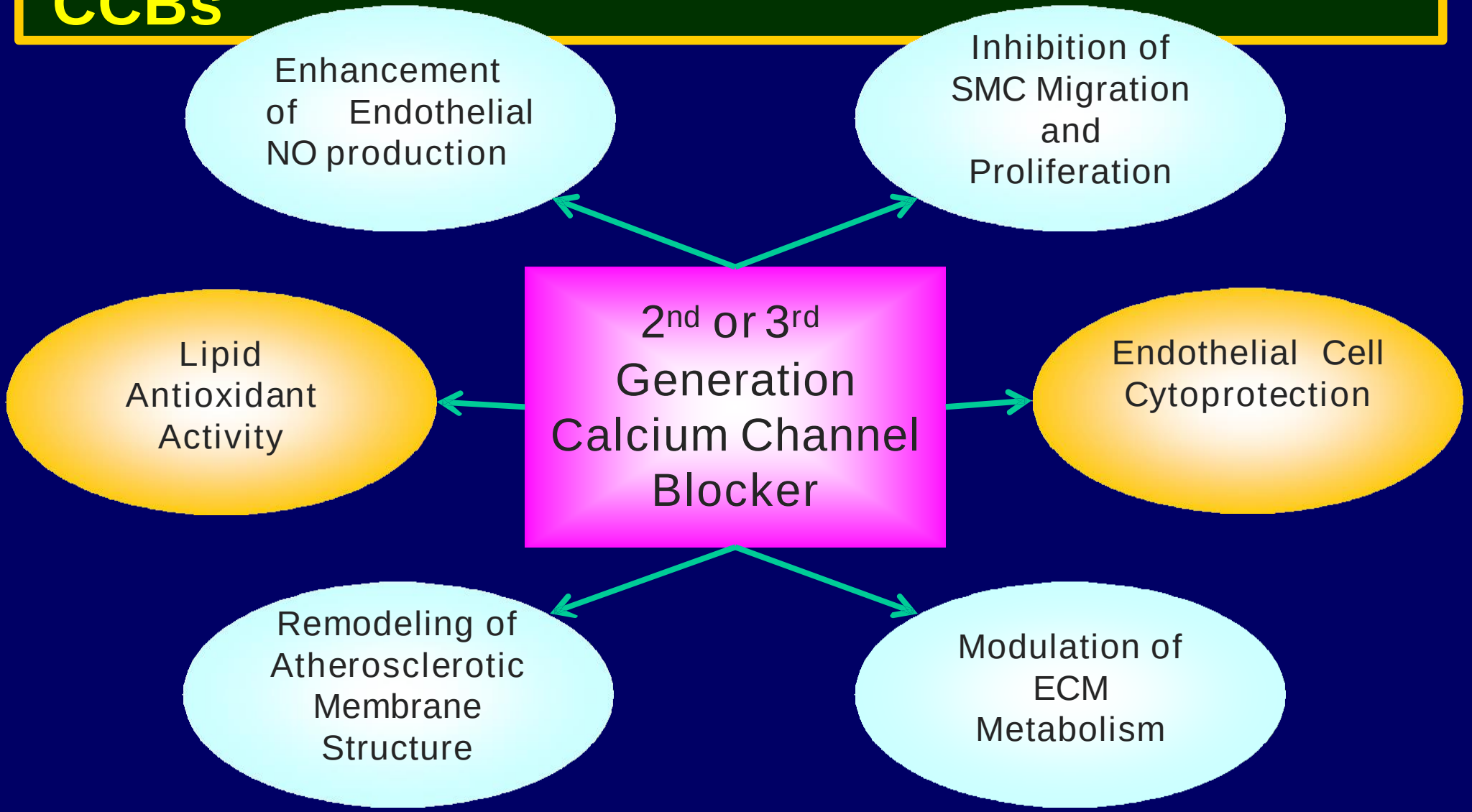
Opie LH. JACC 2000

- RCTs with amlodipine & felodipine in patients with LV dysfunction revealed equivalent (if not improved) mortality rates

Packer et al. NEJM 1996

Cohn et al. Circ 1997

Pleiotropic Effect of 2nd & 3rd Generation CCBs

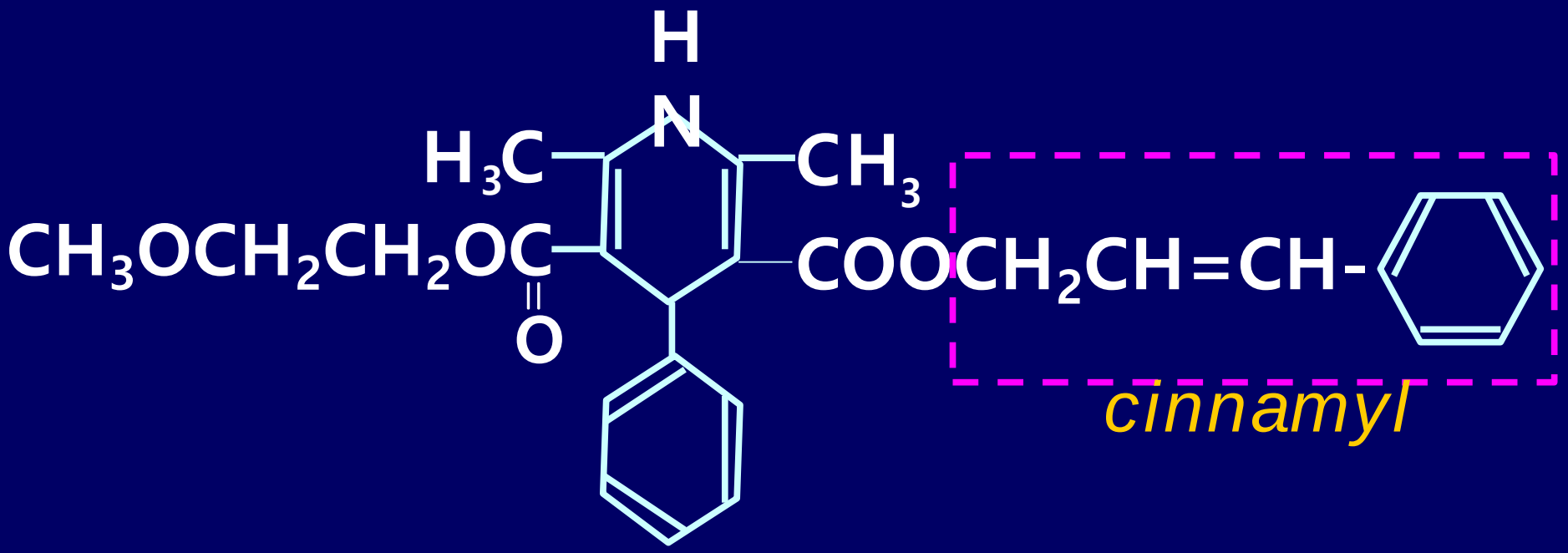


Anti-atherogenic Properties of CCB

- Anti-oxidant properties
- Small animal studies suggest that some CCBs
  - : Reduce influx of LDL into arterial wall
  - : Suppress progression of atherosclerosis in aorta
  - : Decrease thromboxane A_2 production
- Human studies (limited, less compelling)
  - : Some evidence suggests decrease in new plaque formation
  - : Enhanced effect when given with statins
  - : Stronger evidence for carotid plaque regression

Hernandez et al. Am J of Therap 2003

Cilnidipine: Cinalong ®



- Newer 3rd generation long-acting CCB
- Dual mechanism of action

  : Block both L-type and N-type calcium channel

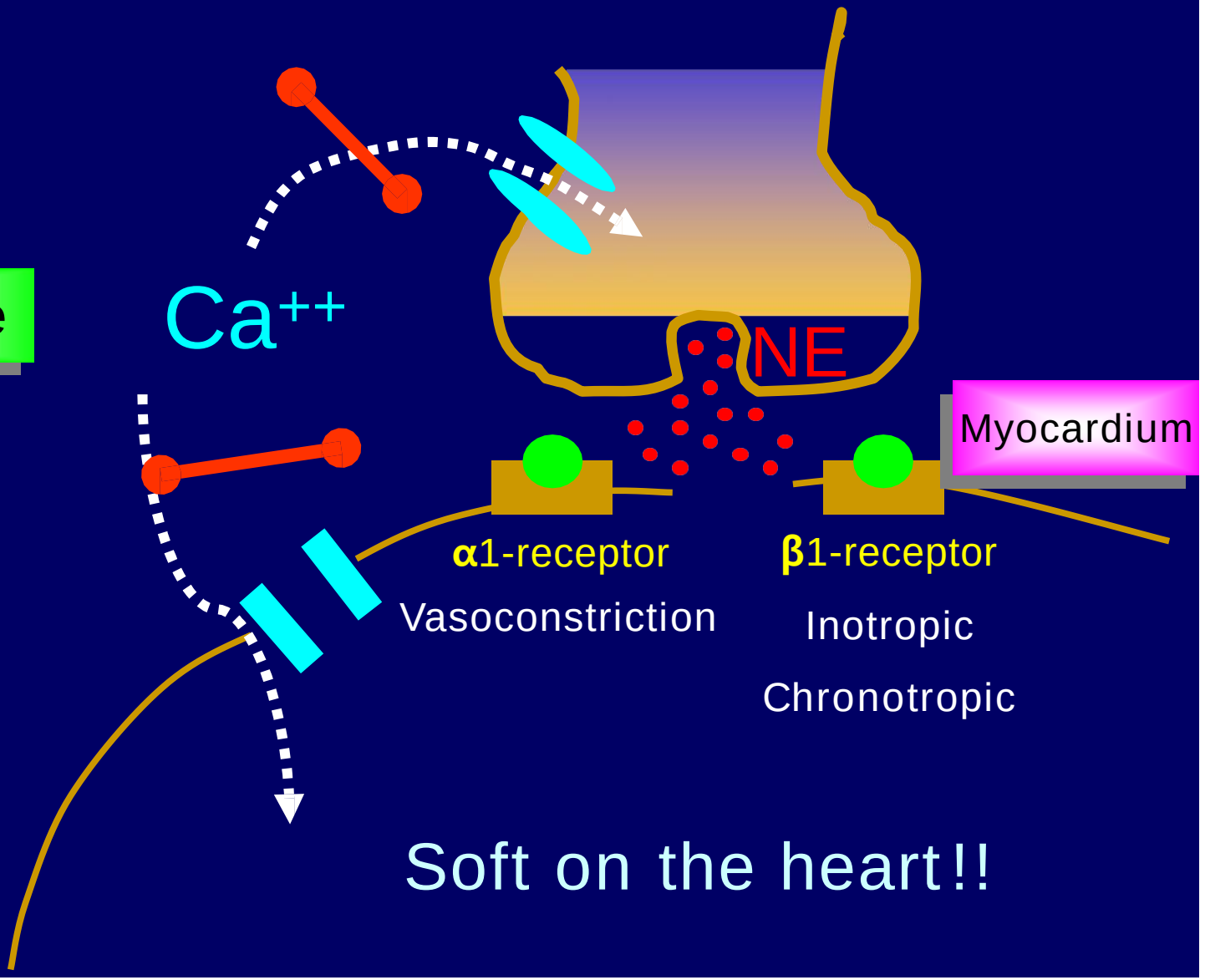
Cilnidipine: Mechanism of Dual Action

N-type Ca channel

Sympathetic Nerve

L-type Ca channel

VSMC

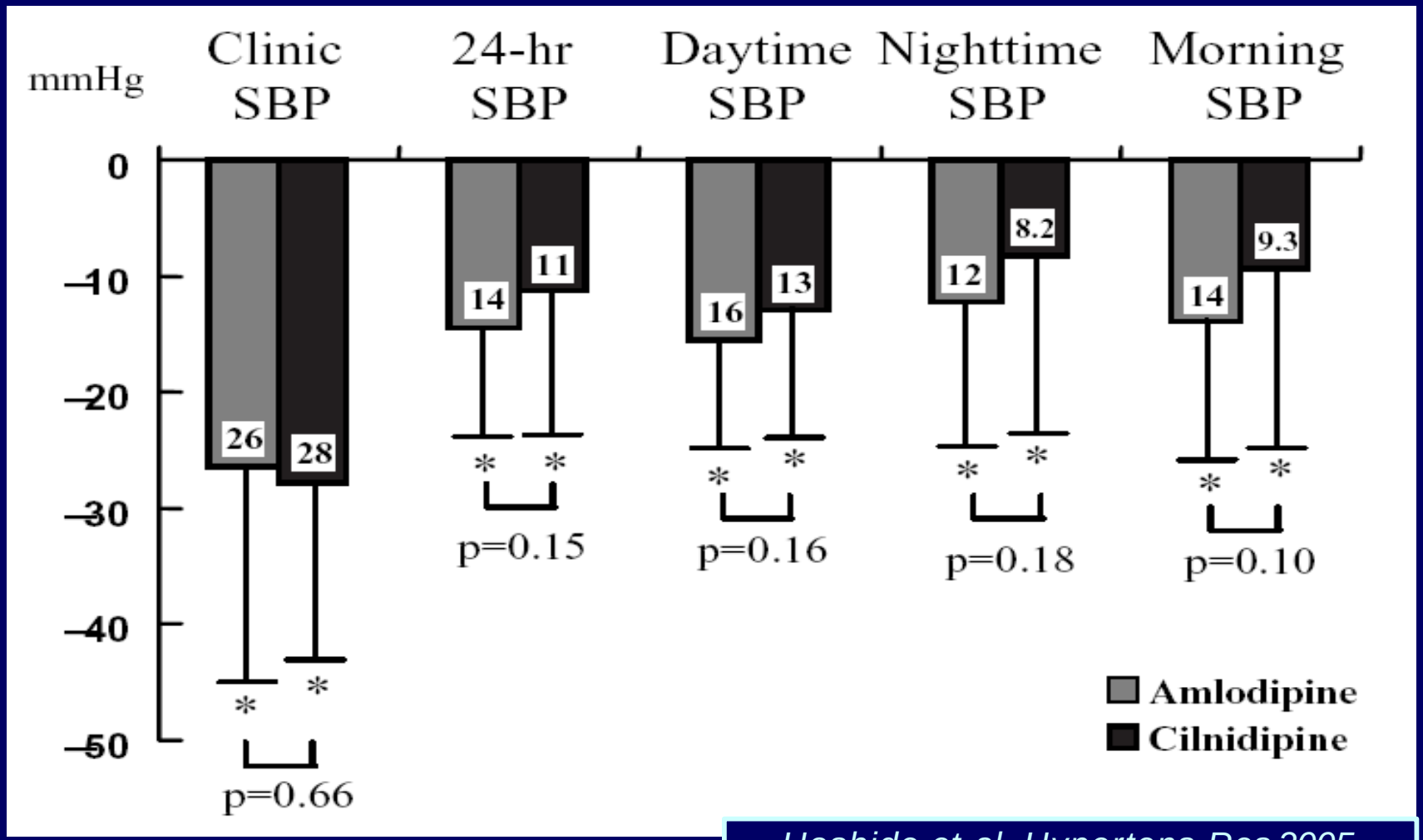


Soft on the heart!!

Cilnidipine: Clinical Characteristics

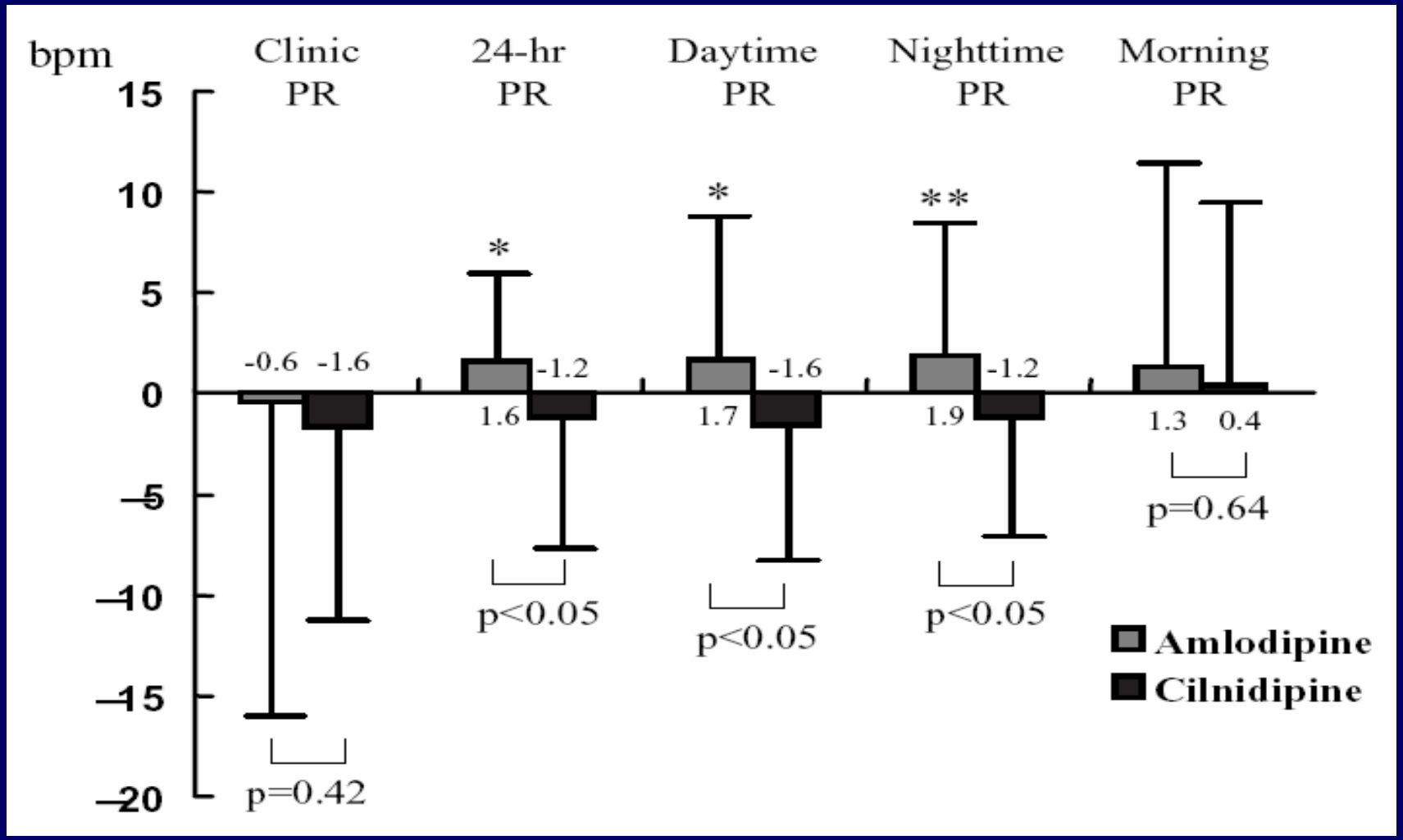
- Effective BP lowering CCB without HR change
- Long duration of action: stable and steady BP control
- Favorable effects on lipid metabolism
- Favorable effects on glucose metabolism
- Improve LVH and diastolic function

BP Lowering Effect: Cilnidipine vs. Amlodipine



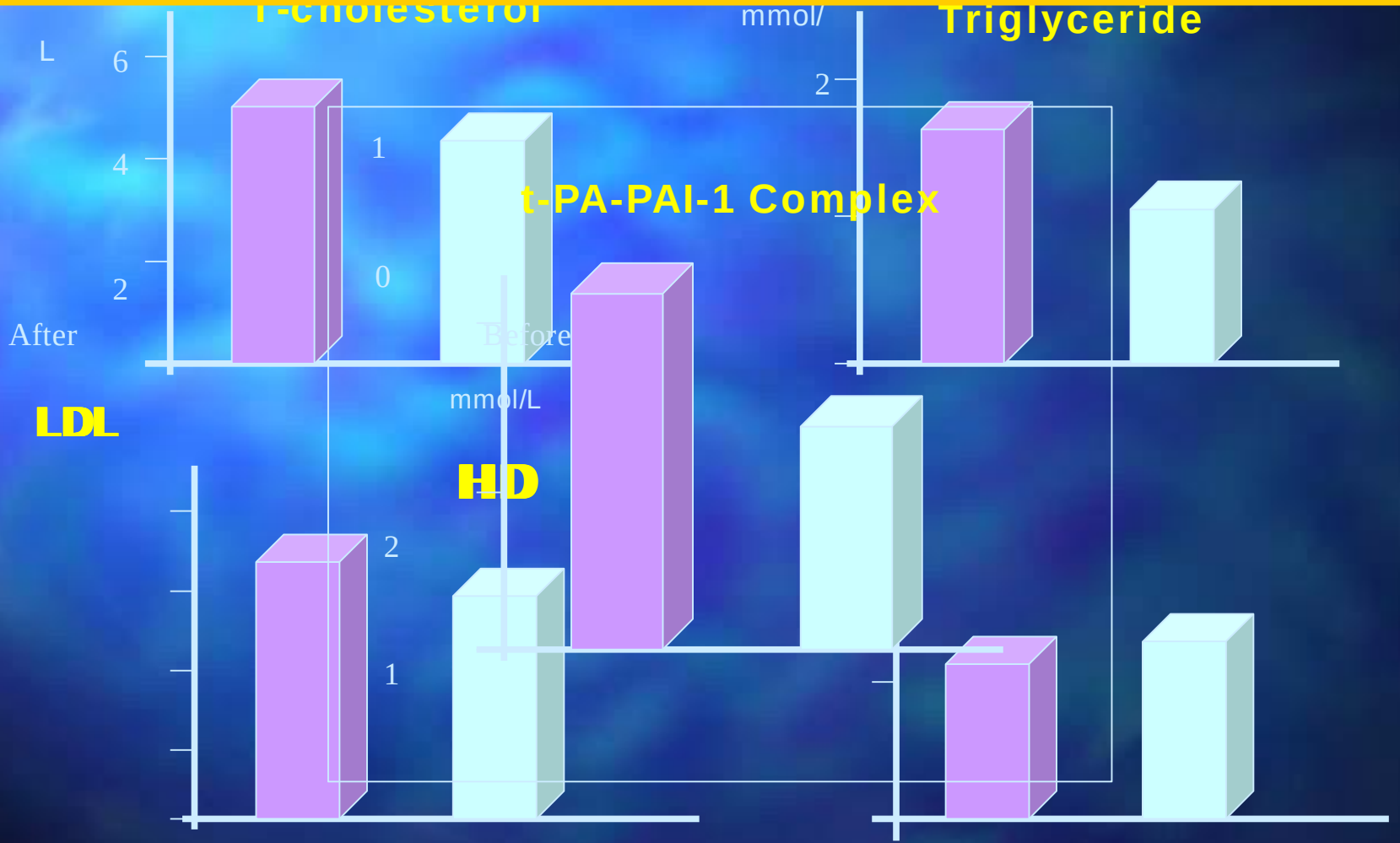
Hoshide et al. Hypertens Res 2005

Changes in HR: Cilnidipine vs Amlodipine



Hoshide et al. Hypertens Res 2005

Cilnidipine: Lipid and Fibrinolytic Parameters



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Cilnidipine: LVH and Diastolic Function

	Baseline	1Mon	3Mon	6Mon
SBP(mmHg)	174 ± 17	148 ± 10***	143 ± 9***	142 ± 11
DBP(mmHg)	96 ± 10	82 ± 16*	80 ± 6*	78 ± 8
HR(beats/min)	59 ± 7	60 ± 11	59 ± 9	60 ± 9
NE(ng/mL)	0.5 ± 0.3	0.5 ± 0.2	0.4 ± 0.1	0.4 ± 0.2
M-mode & Pulsed Doppler Echocardiographic Variables				
LVMI(g/㎡)	131 ± 22	132 ± 17	129 ± 18	126 ± 20*
E(㎝/s)	55 ± 8	65 ± 10*	63 ± 8*	69 ± 7*
A(㎝/s)	73 ± 7	74 ± 11	72 ± 8	71 ± 8
E/A	0.7 ± 0.1	0.9 ± 0.2**	0.9 ± 0.1**	1.0 ± 0.1***
Pulsed Tissue Doppler Imaging Variables				
Ew(㎝/s)	8.6 ± 1.8	8.8 ± 1.9	11.3 ± 2.1***	11.8 ± 2.1 ***
Aw(㎝/s)	9.3 ± 1.3	9.5 ± 1.5	9.7 ± 1.6	9.5 ± 1.6
Ew/Aw	0.9 ± 0.2	0.9 ± 0.4	1.2 ± 0.3**	1.3 ± 0.4**

Cilnidipine, * p<0.05, ** p<0.01, ***p<0.0001

Perspectives

- Promising anti-atherogenic effects (Pleiotropic effects)
  - : Enhancement of endothelial function and arterial stiffness
  - : Anti-oxidant activities
  - : Favorable effects on lipid and glucose metabolism
  - : Enhanced fibrinolytic activity
  - : Inhibition of VSMC growth and proliferation
  - : Slowing of the progression of atheroma volume/IMT

CCB induced pedal edema : Mechanism

Amlodipine dilates only arterioles (and not the venules)

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Increased capillary pressure and capillary permeability

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Expulsion of fluid into the surrounding tissue

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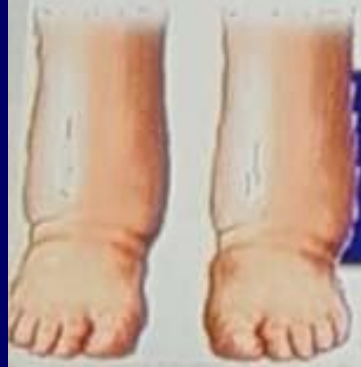
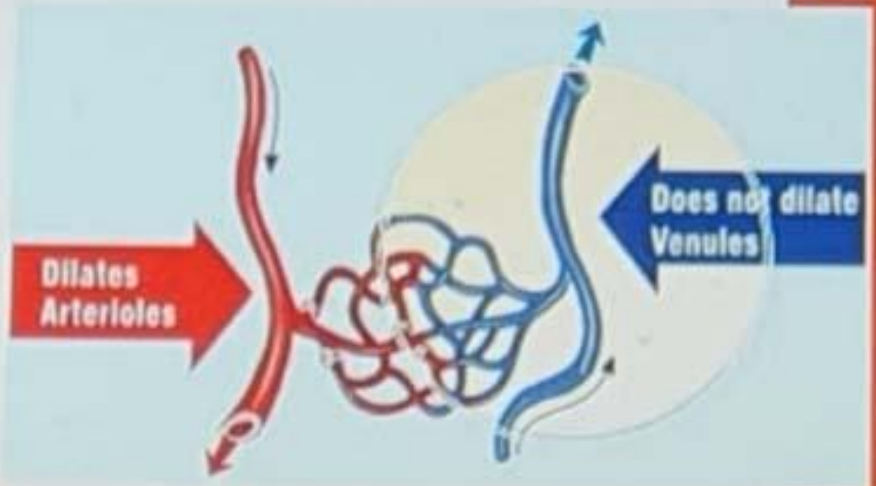
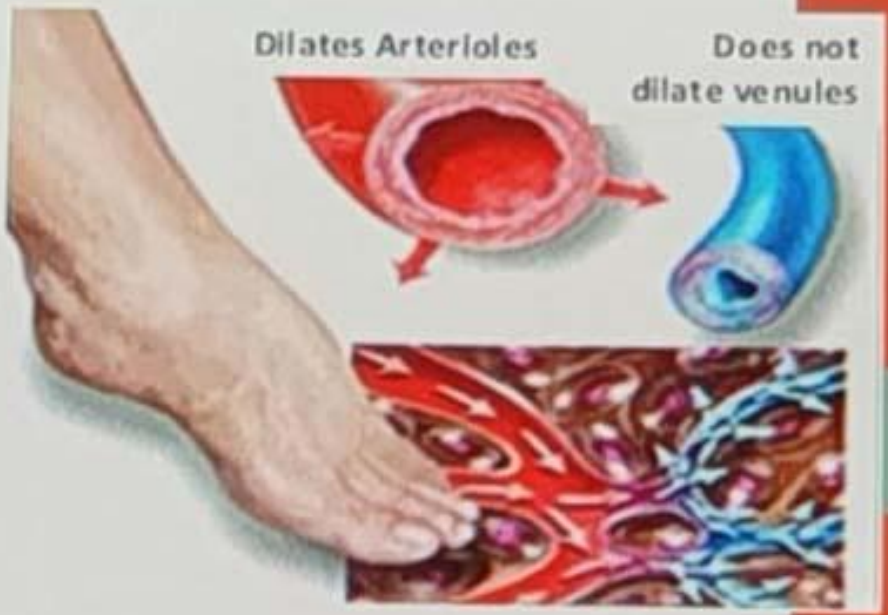
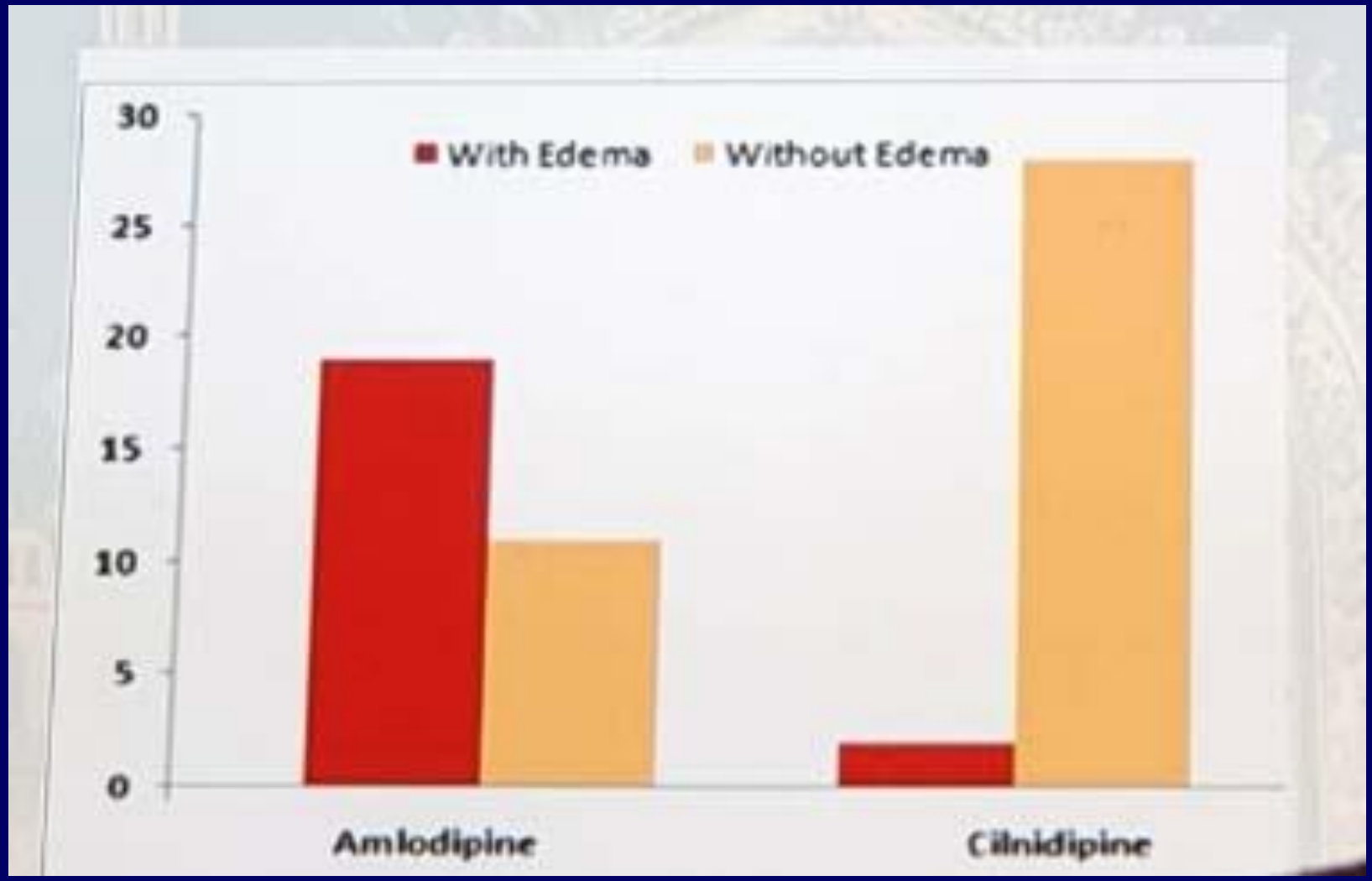
Pedal edema







Pedal elema cilnidipine vs Amlodijpine Adake et al



Conclusion

- Not all CCBs are created equally
- First generation, short-acting formulations may be detrimental in CAD, CHF
- Second and third generation, long-acting formulations are generally safer
- Well-established role in treating HTN and angina
- Additional clinical benefits with combined ACEI (esp. Cilnidipine + Capril) - improve endothelial dysfunction, arterial stiffness, vascular inflammation and renal dysfunction

Clevidipine

- Clevidipine butyrate – New/I/V CCB for Hypertensive emergencies.
- 3rd GenDihydropyridine
- Acts on L type Channel
- Half Life 02 minutes
- Infusion 2 mg/Hr increased at interval of 3 minutes to max 32 mg/


thank
YOU