2007년 춘계 대한순환기학회

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New Concept of Calcium Channel Blocker In The Improvement of Cardiovascular Function

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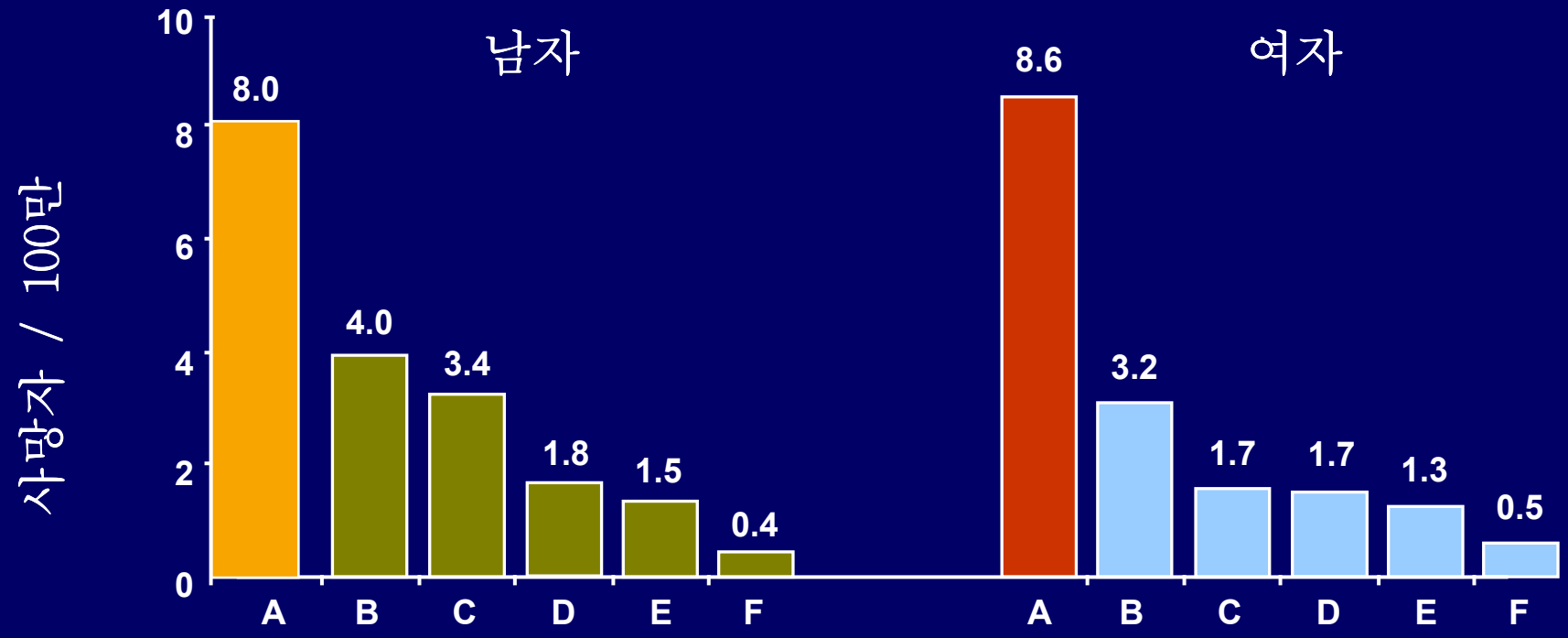
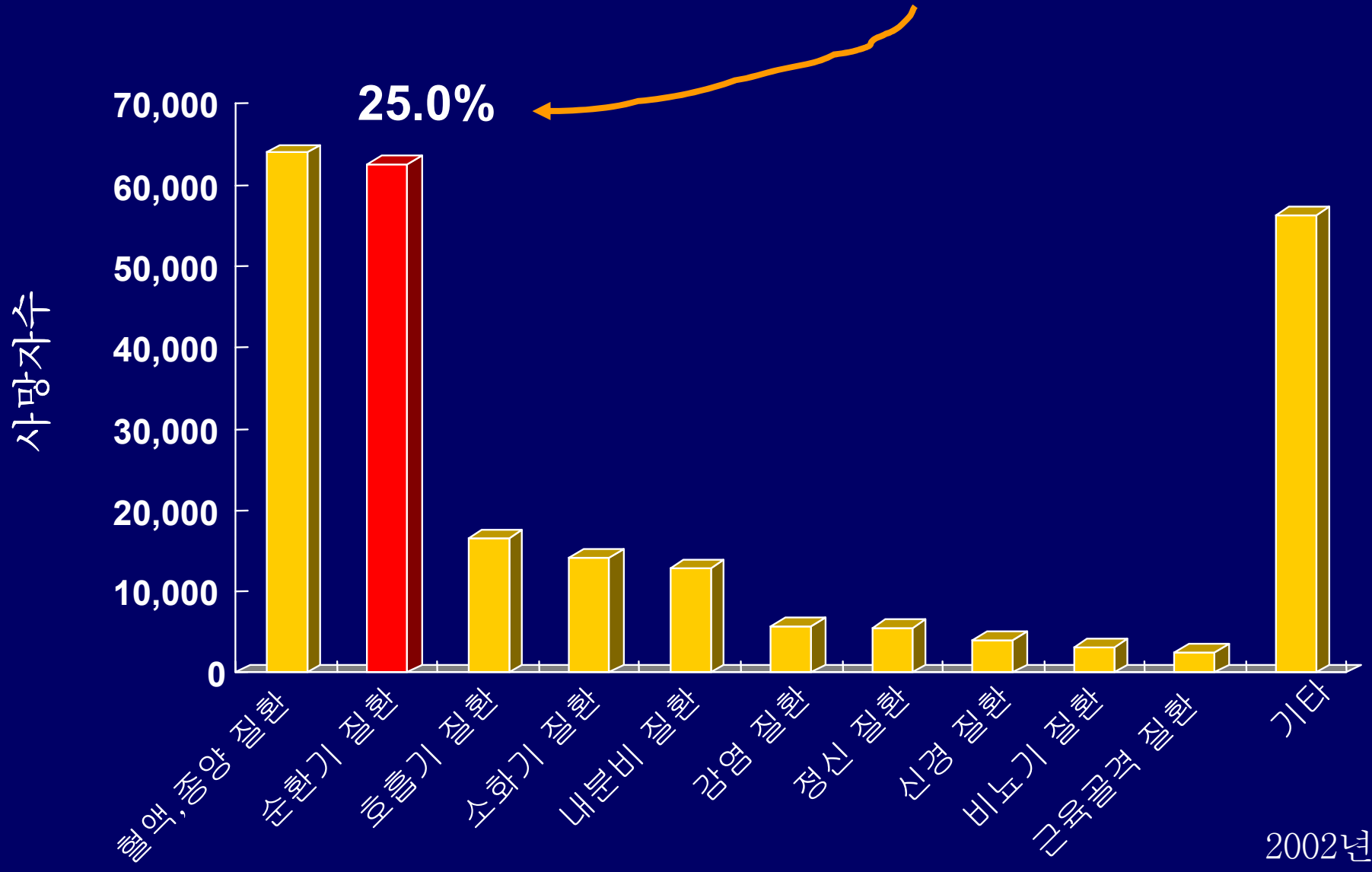
심혈관질환은 전세계 사망원인 1위



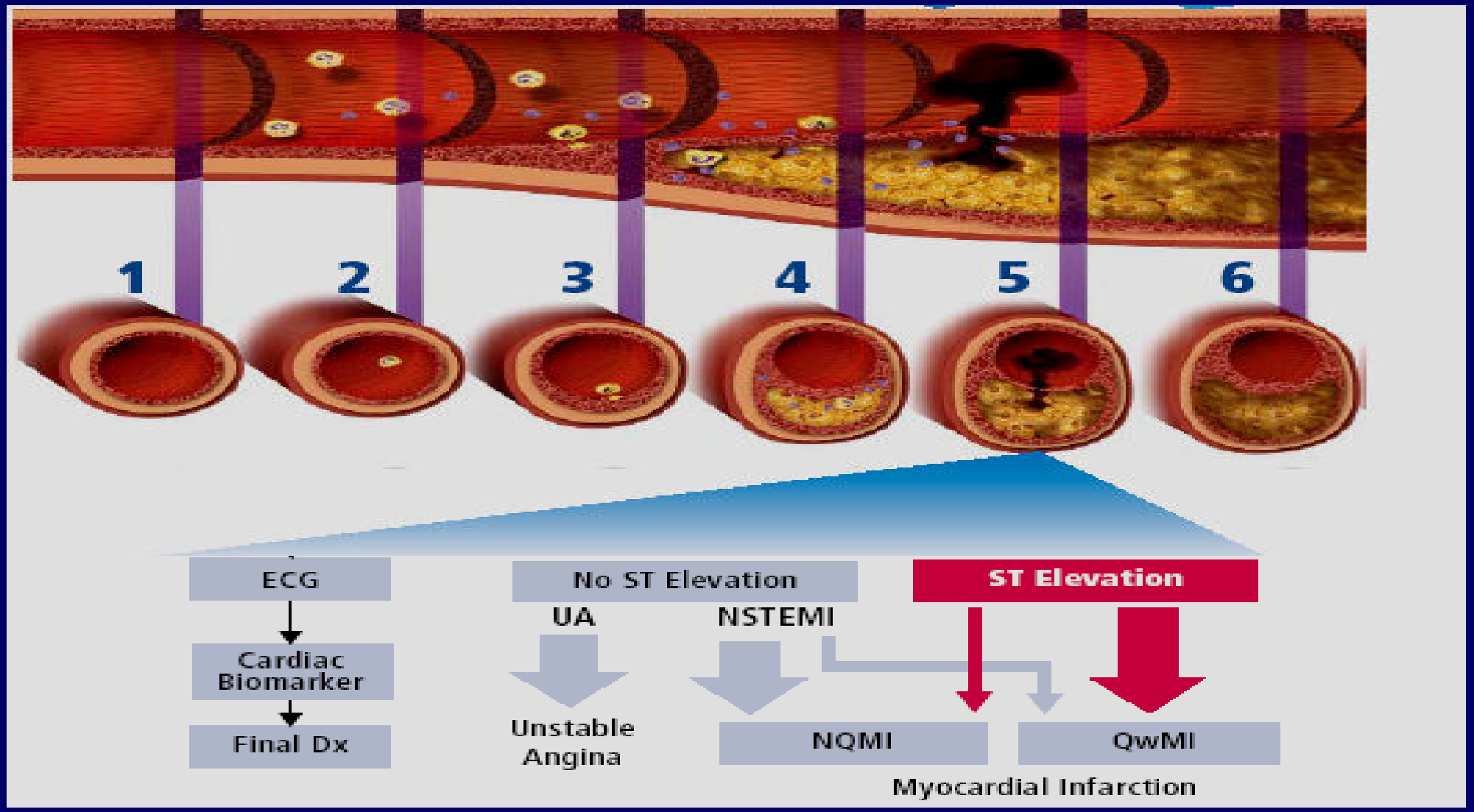
(2001년 WHO)

우리나라에서는 사망률 2위
성인 사망률 1위는 순환기질환



2002년 통계청

Atherosclerosis: A Progressive Disease



Coronary Thrombosis

Myocardial Infarction

Arrhythmia & Loss of muscle

Sudden Death

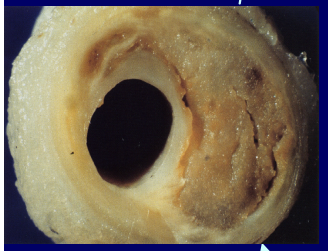
Myocardial Ischemia

- Silent
- Angina
- Hibernation

Remodeling

Ventricular dilatation

Congestive Heart Failure

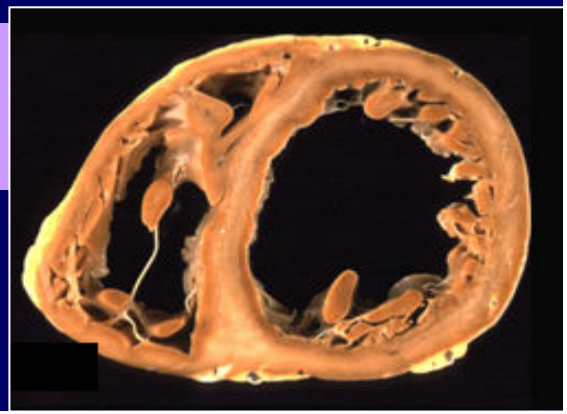


CAD

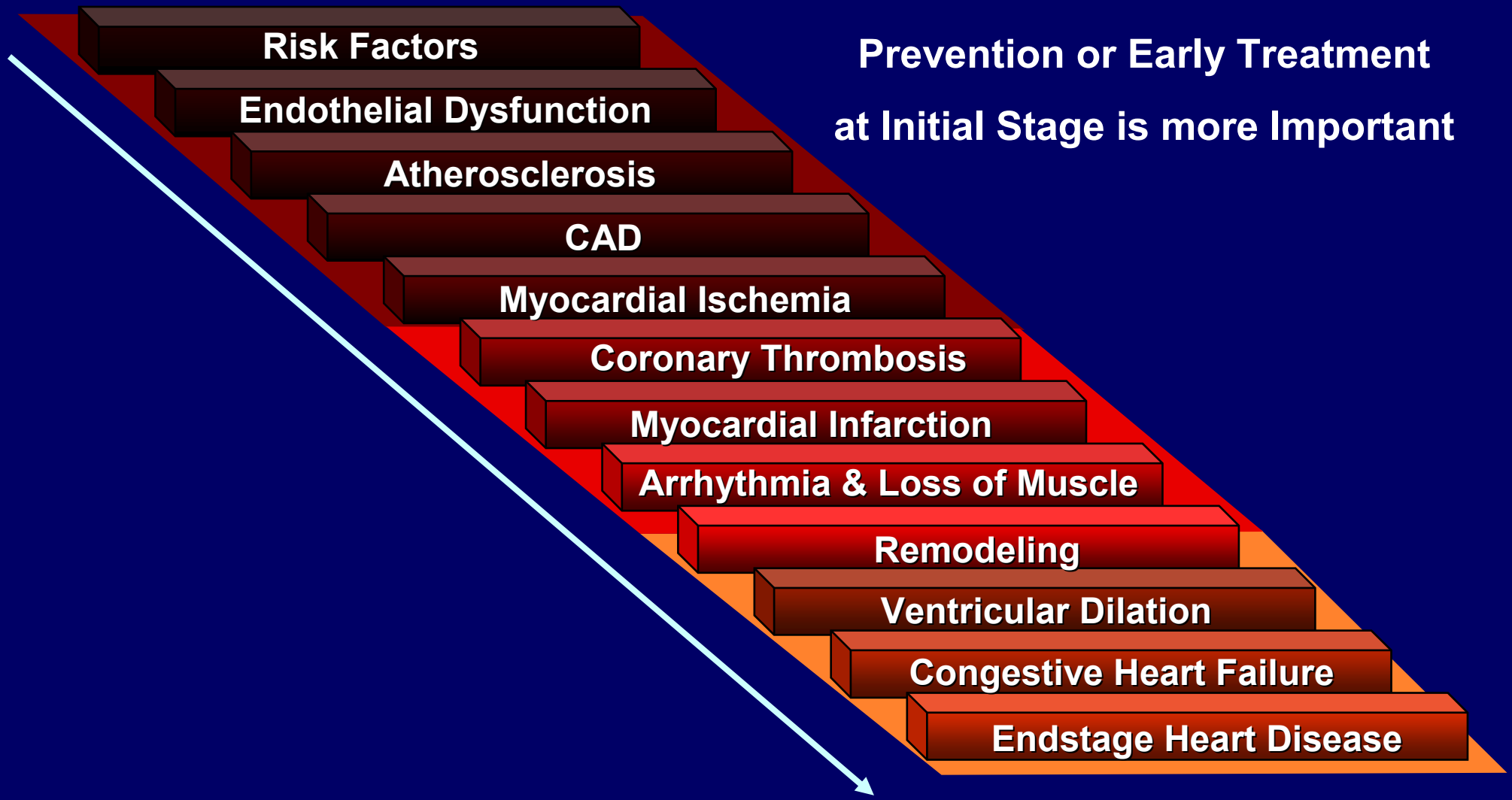
Atherosclerosis, LV Hypertrophy

Risk Factors (smoking, HL, HT, DM, insulin resistance, arterial stiffness…)

End Stage Heart Disease



Progressive Development of Cardiovascular Disease



Prevention or Early Treatment at Initial Stage is more Important

Hypertension and Cardiovascular Disease

- For persons over age 50, SBP is a more important than DBP as CVD risk factor
- Starting at 115/75 mmHg, CVD risk doubles with each increment of 20/10 mmHg throughout the BP range
- Persons who are normotensive at age 55 have a 90% lifetime risk for developing HTN
- Those with SBP 120–139 or DBP 80–89 mmHg should be considered prehypertensive who require health-promoting lifestyle modifications to prevent CVD

JNC VII report. JAMA 2003;289:2573-2575

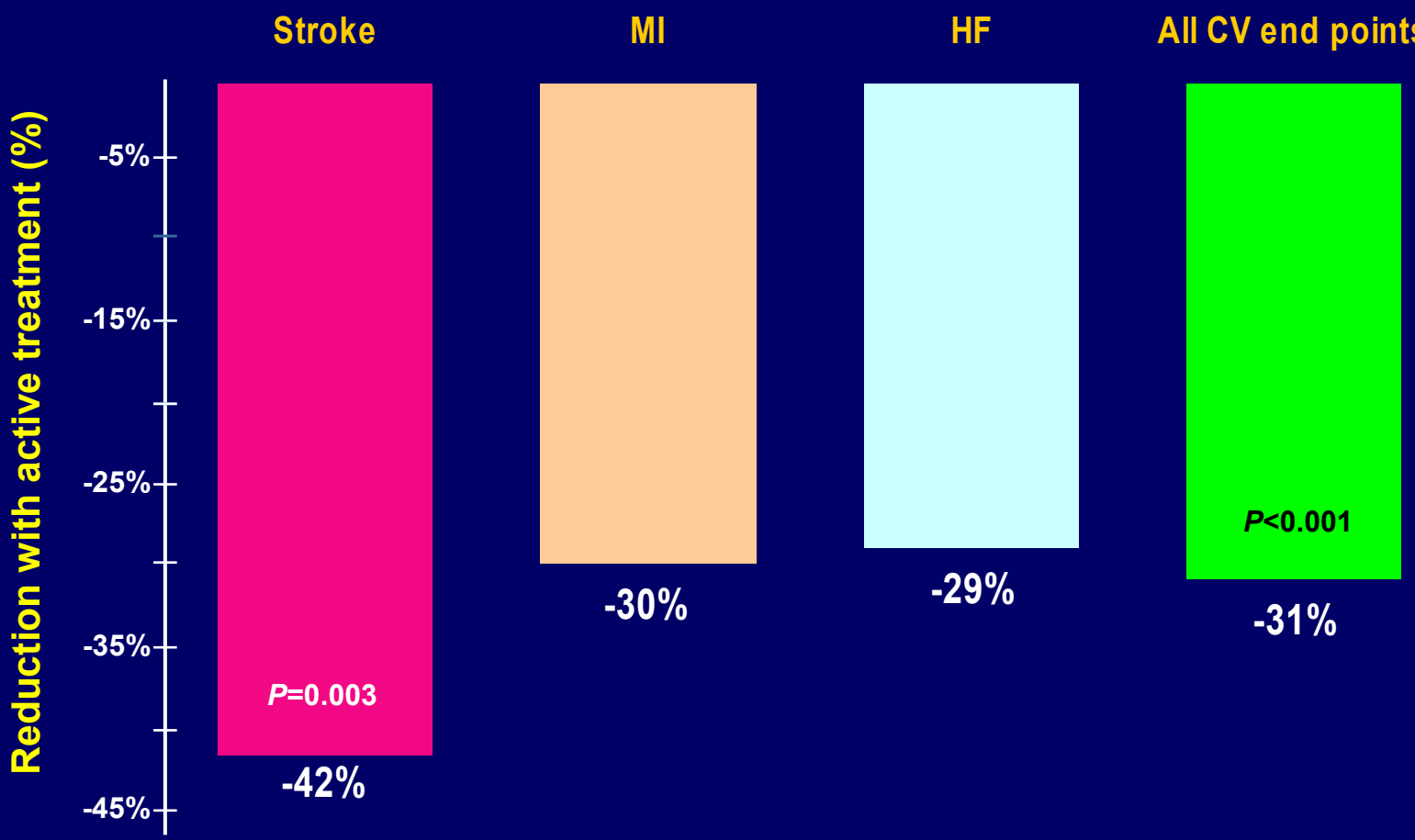
Hypertension and Cardiovascular Disease

- **Benefits from BP control**

	Average Percent Reduction
Stroke incidence	35–40%
Myocardial infarction	20–25%
Heart failure	50%

JNC VII report. JAMA 2003;289:2573-2575

Hypertension and Cardiovascular Disease



Subjects are elderly persons with ISH

Syst-Eur Trial. Staessen et al. Lancet 1997

Korea Acute Myocardial Infarction Registry (KAMIR) STUDY – 위험 인자

		STEMI (n=4149)	NSTEMI (n=2724)
고혈압			
	Yes (%)	1829(44.1)	1432(52.6)
	No (%)	2032(55.9)	1292(47.4)
당뇨병			
	Yes (%)	1012(24.4)	830(30.5)
	No (%)	3137(75.6)	1894(69.5)
고지혈증			
	Yes (%)	261(6.3)	275(10.1)
	No (%)	3888(93.7)	2449(89.9)
흡연			
	Yes(%)	1904(45.9)	980(36.0)
	No(%)	2245(54.1)	1744(64.0)

2006년 10월 대한순환기학회 7,164 명 분석 결과

Hypertension and CAD: Beyond BP Lowering

- **BP is strongly linked to the risk for CAD and CVA**
  : caused by atherosclerosis associated with ***endothelial dysfunction and stiffening of artery***

- **Incidence of CAD**
  : higher in treated hypertensive patients than in matched controls, despite similar BP levels
  : cardiovascular function may be more important than BP reduction

Furberg et al. Ann Intern Med 2001

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)

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

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)

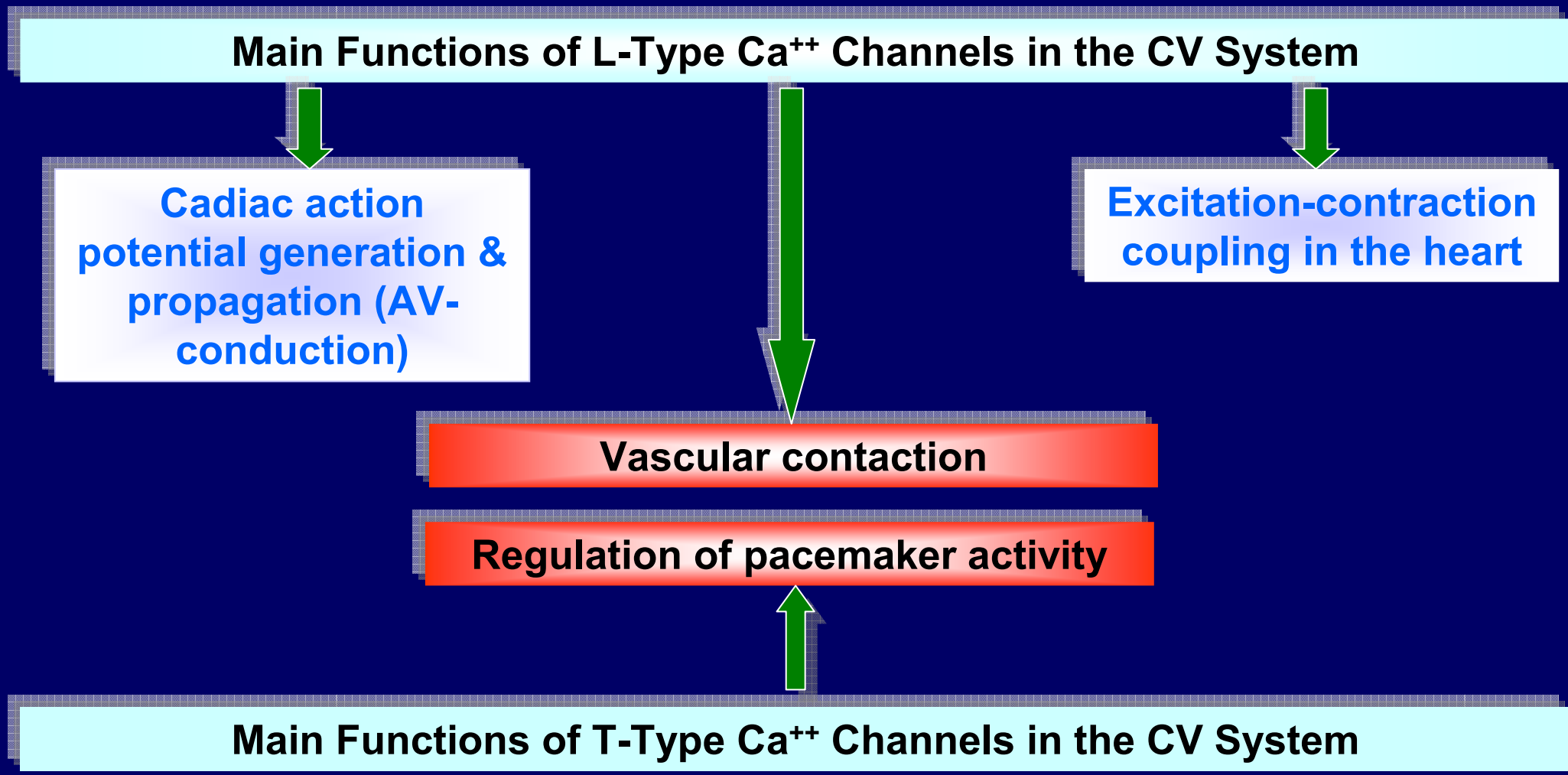
T-type

- 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

Main Functions of Ca^{++} Channel



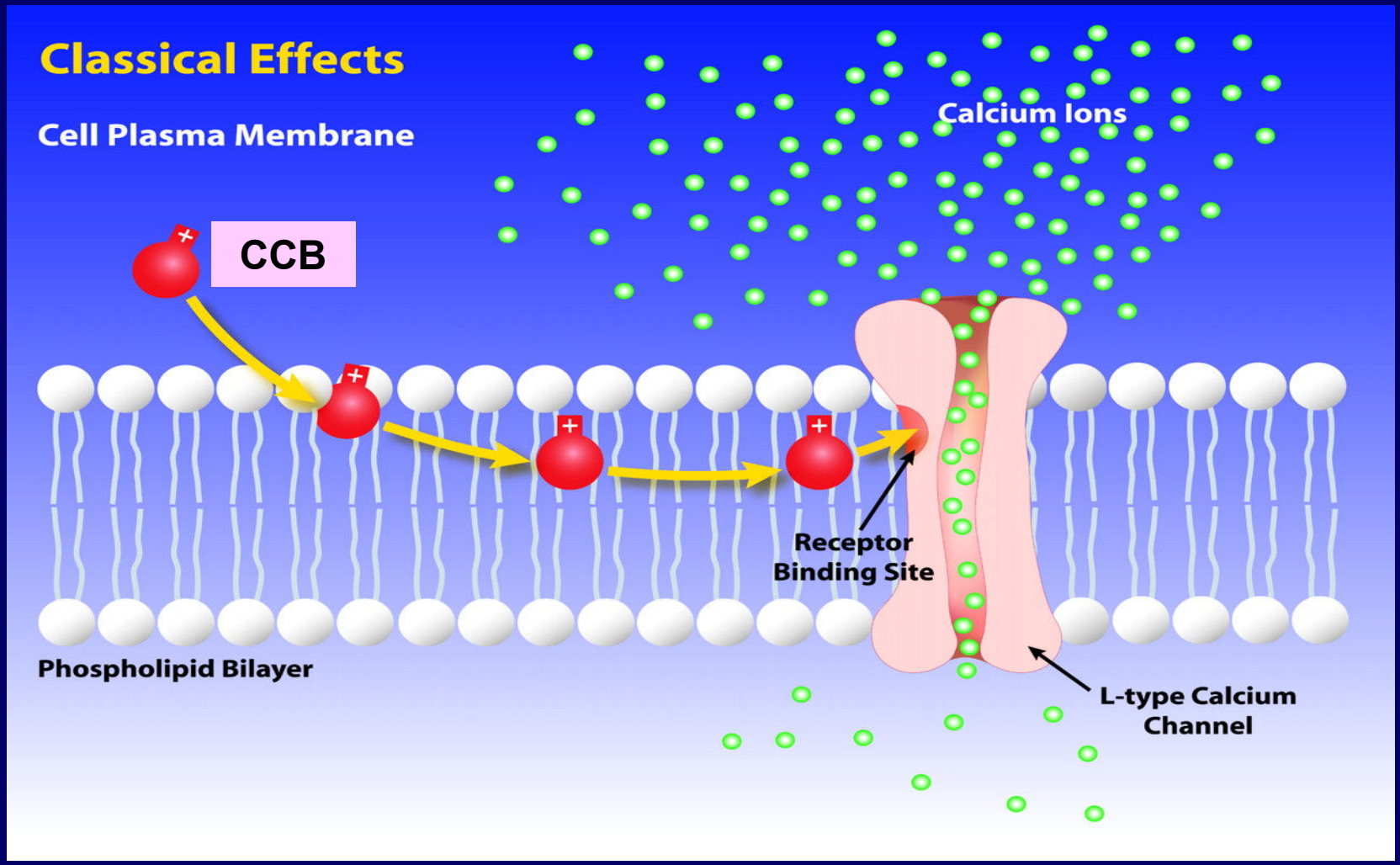
Classes of Calcium channel blocker

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

Classical Effects of First Generation CCBs



Mason RP & Hintze TS. ATVB 2003;23:2155-63

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)

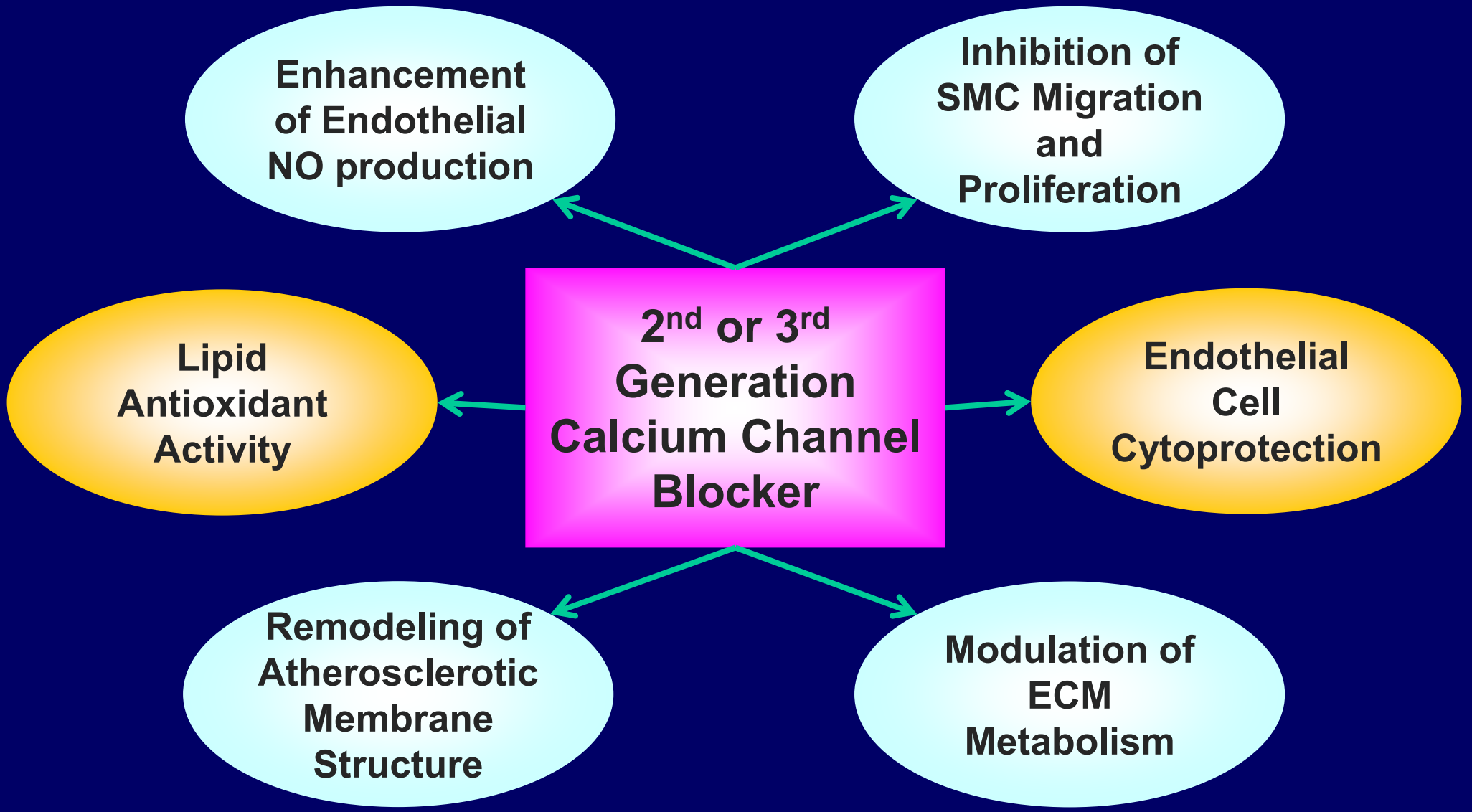
Opie LH. JACC 2000

- 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



Endothelial Function and CCB

- Lacidipine restores endothelium dependent FMD of brachial artery in patients with HT

Taddel et al. Hypertension 1997

- Combination of nifedipine and cerivastatin improves coronary endothelial function measured by QCA change of coronary diameter after intracoronary infusion of acetylcholine

ENCORE Investigators. Circulation 2003

Endothelial Function and CCB

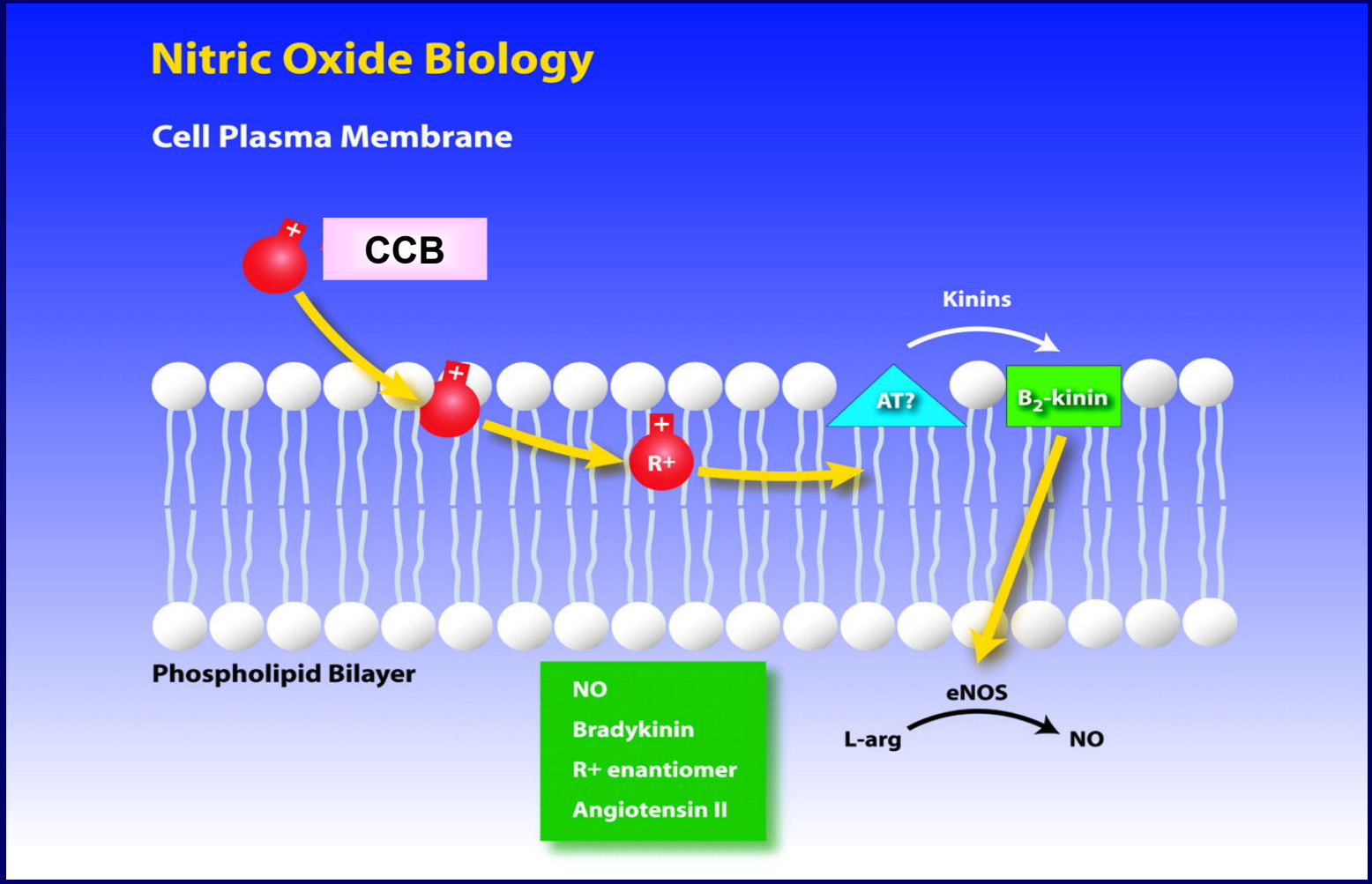
- Benidifine improves endothelium dependent FMD of brachial artery in patients with HT

Mikino et al. Blood Press 2005

- Calcium channel blocker not only protect the endothelium through their blood pressure lowering action but also improve endothelial function through the stimulation of NO production

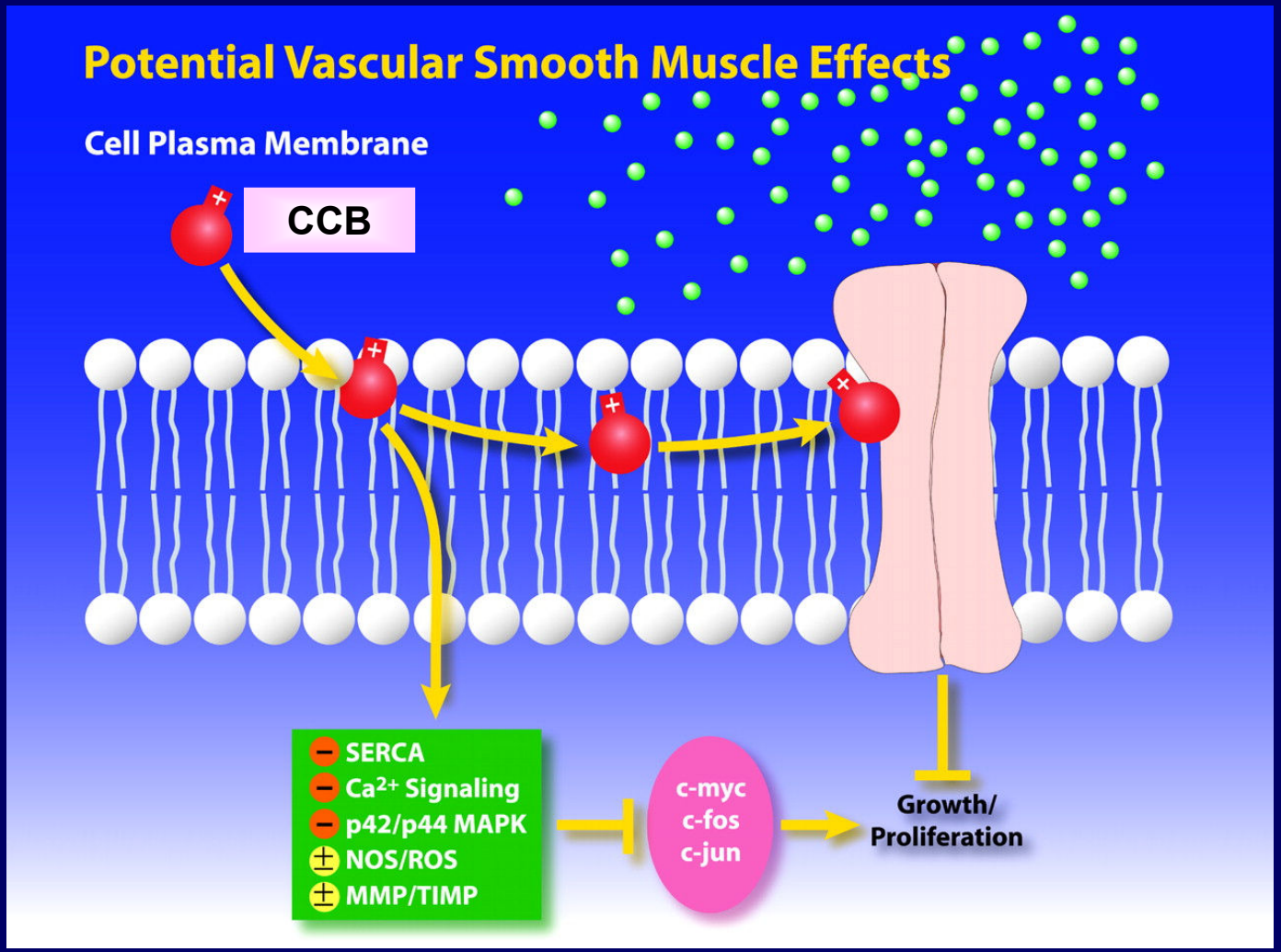
Yasuda et al. Clin Calcium 2005

Endothelial Function and CCB: NO Biology



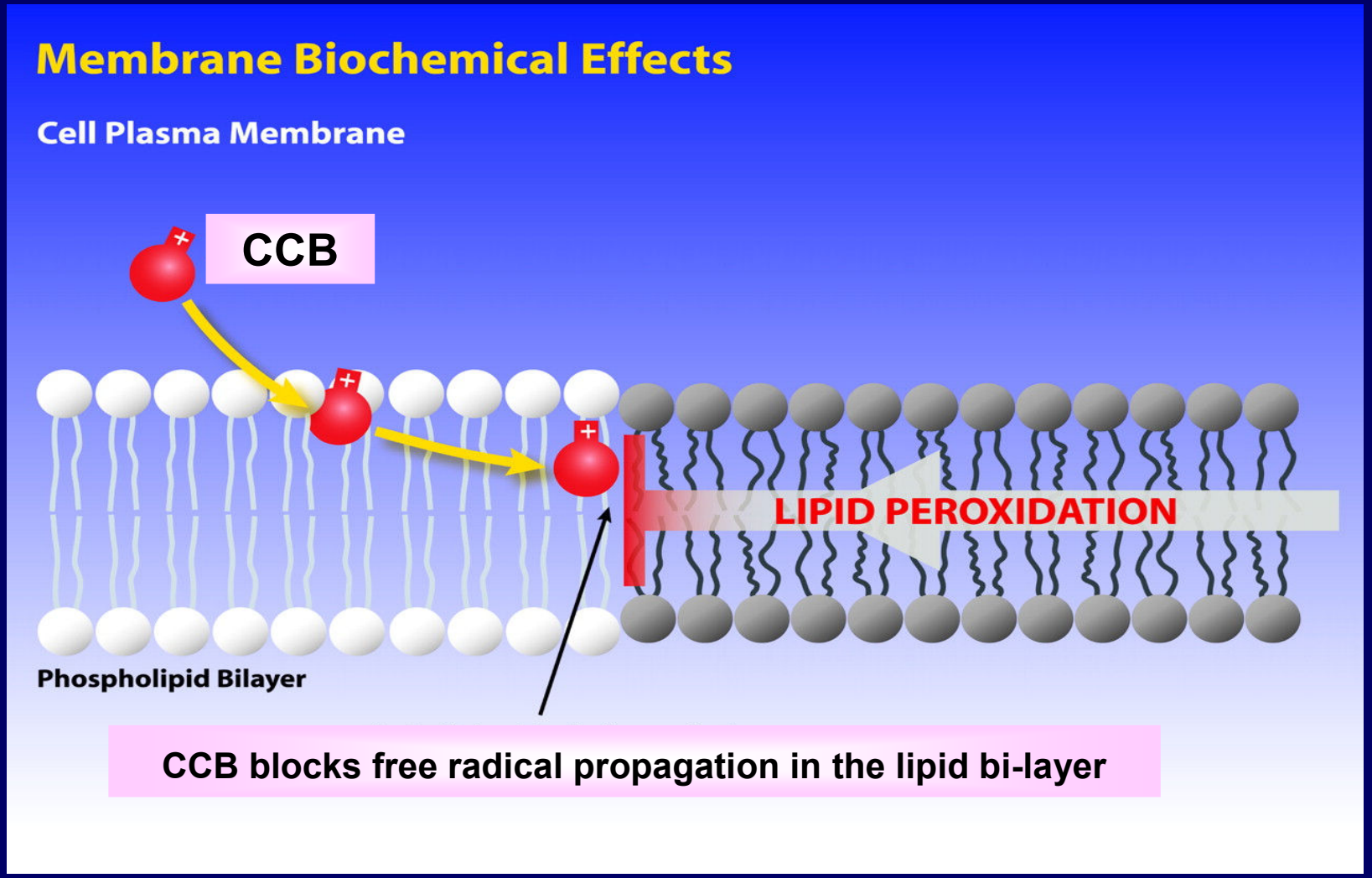
Mason RP & Hintze TS. ATVB 2003;23:2155-63

VSMC Growth/Proliferation and CCBs



Mason RP & Hintze TS. ATVB 2003;23:2155-63

Ant-oxidant Effect of CCBs



Mason RP & Hintze TS. ATVB 2003;23:2155-63

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

Carotid IMT Regression: Clinical trials with CCB

Study name	No Pts	Duration	Comparative	Results drugs
ELSA (1998)	2259	4 yrs	Lacidipine vs. atenolol	Significantly less carotid progression in lacidipine group
MIDAS (1996)	883	3 yrs	Isradipine vs. hydrochlorothiazide	No difference in rate of carotid IMT progression between treatment group
VHAS (1998)	498	4 yrs	Verapamil vs. chlorthalidone	Regression of larger lesions significantly greater in verapamil group
PREVENT (2000)	825	3 yrs	Amlodipine vs. Placebo	Less carotid IMT progression in amlodipine group

CAD and CCB: CAMELOT Study

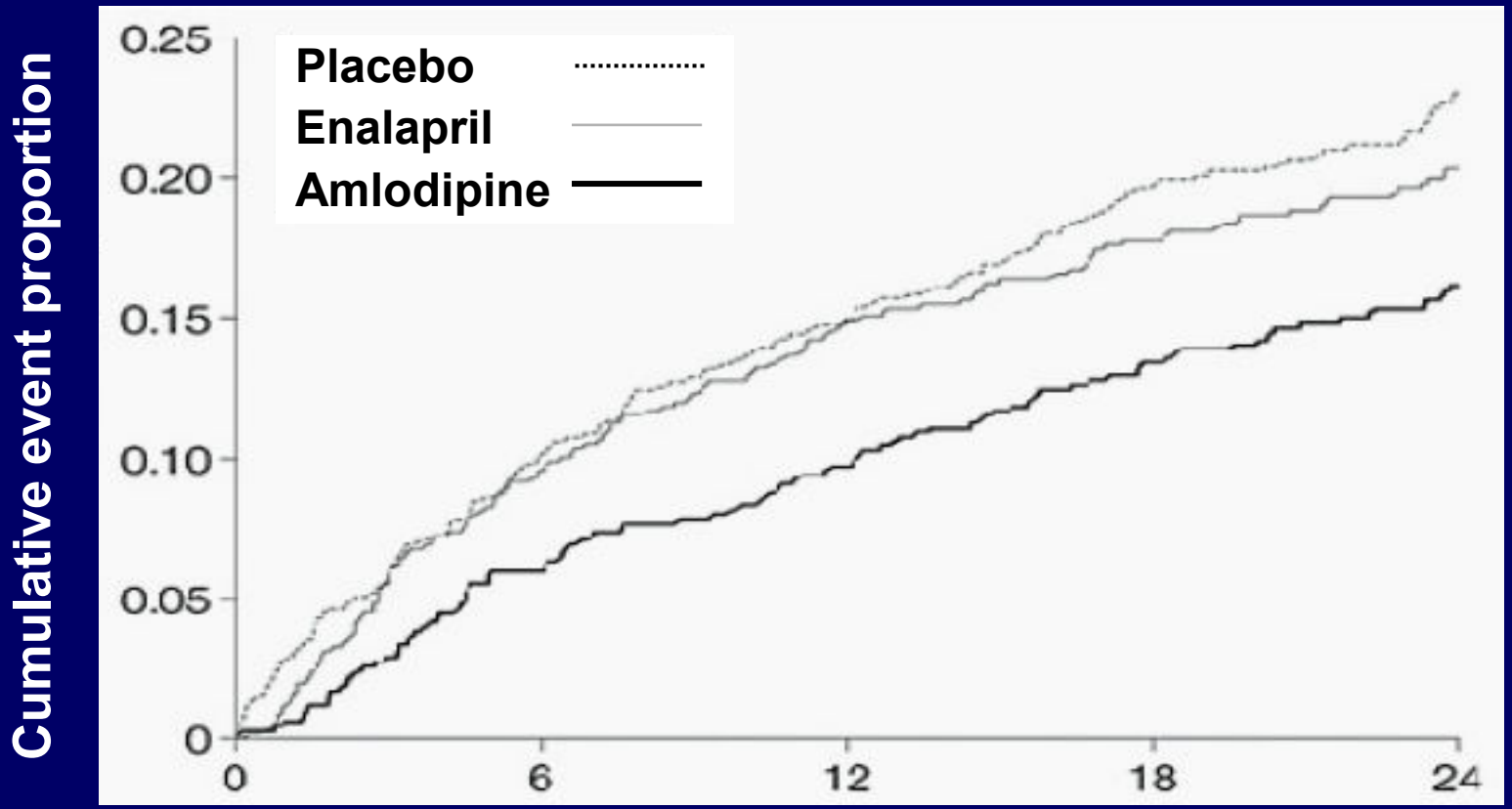
- To evaluate the effect of antihypertensive agents on CV events in patients with CAD and normal BP

  : CCB (Amlodipine) or ACEI (Enalapril) vs. Placebo

- 1991 patients with documented CAD and DBP < 100 mmHg
- Study endpoints
  - : Incidence of CV events (CV death, MI, cardiac arrest, coronary revascularization, hospitalization)
  - : Anti-atherosclerotic effects measured by IVUS

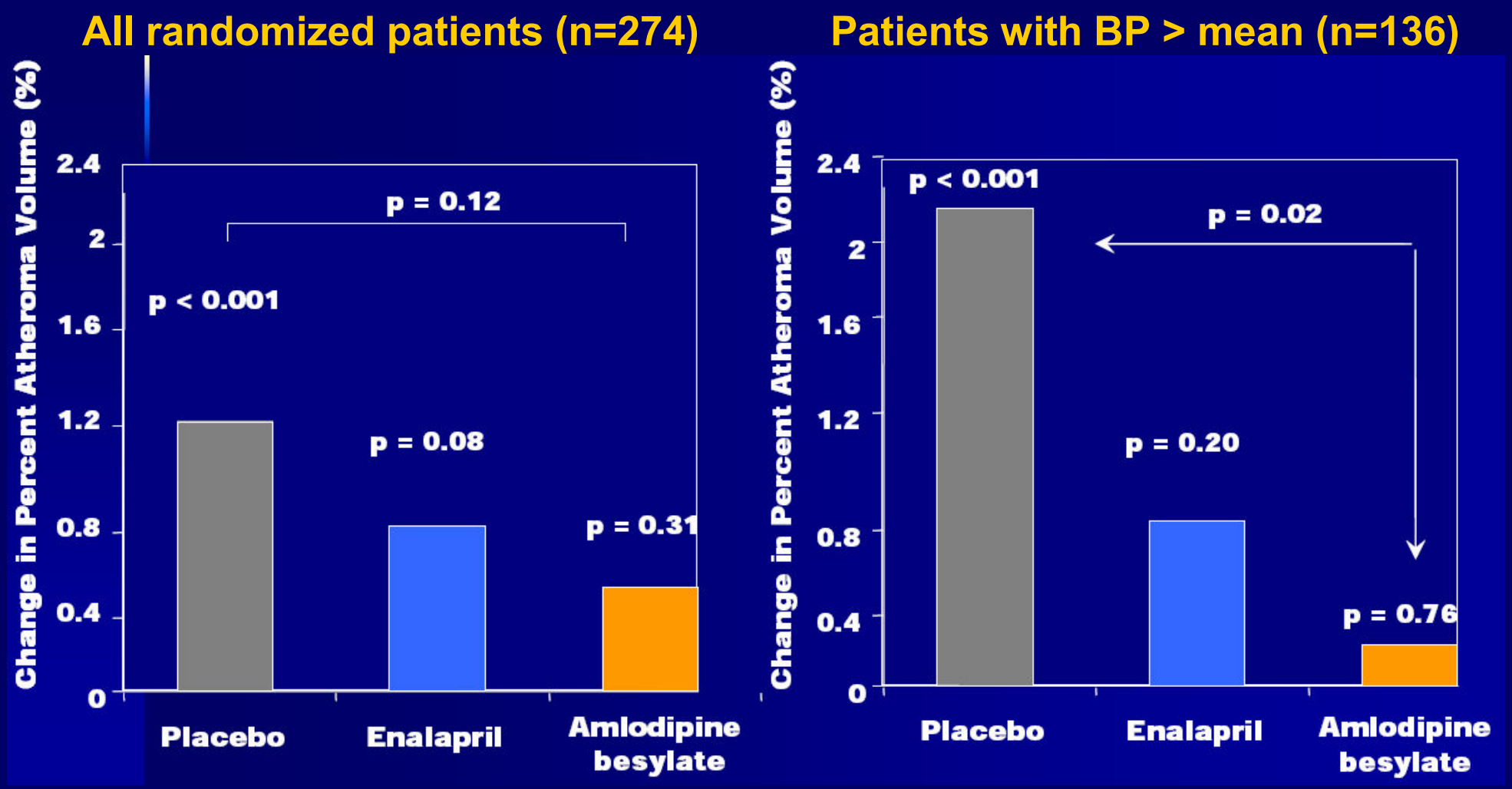
Nissen SE et al. JAMA 2004;292:2217-25

CAD and CCB: CAMELOT Study



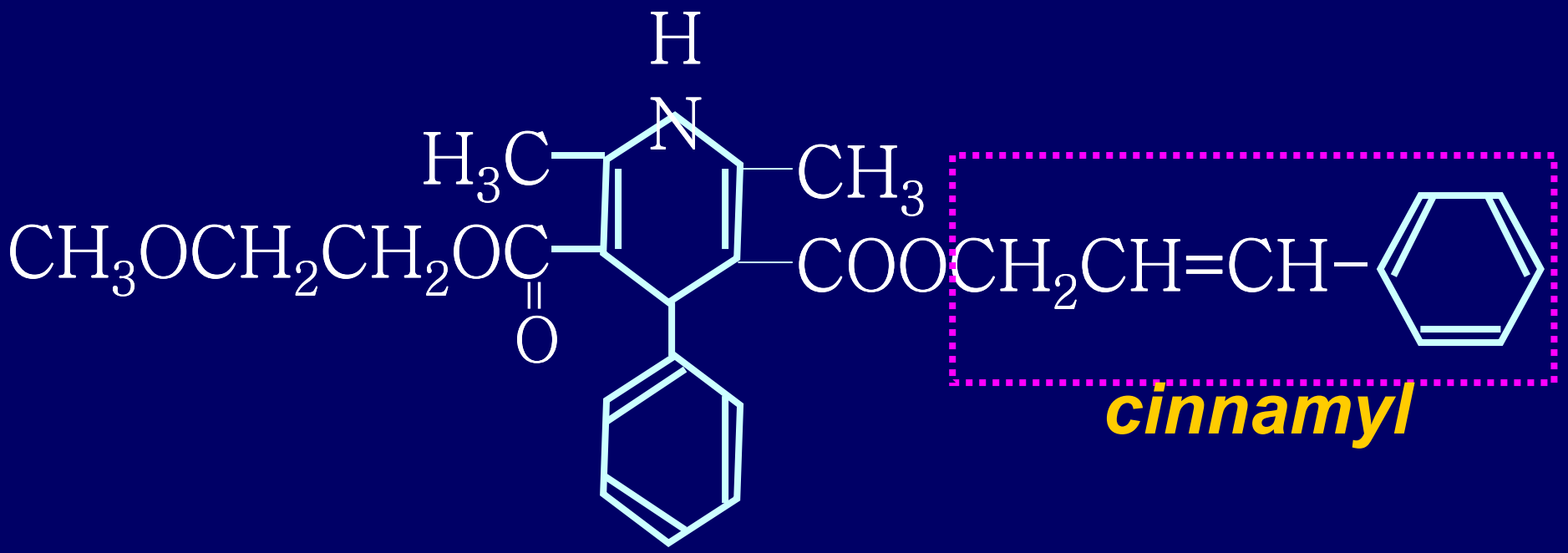
Nissen SE et al. JAMA 2004;292:2217-25

Changes of Percent Atheroma Volume: CAMELOT



Nissen SE et al. JAMA 2004;292:2217-25

Cilnidipine: Cinalong ®



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

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

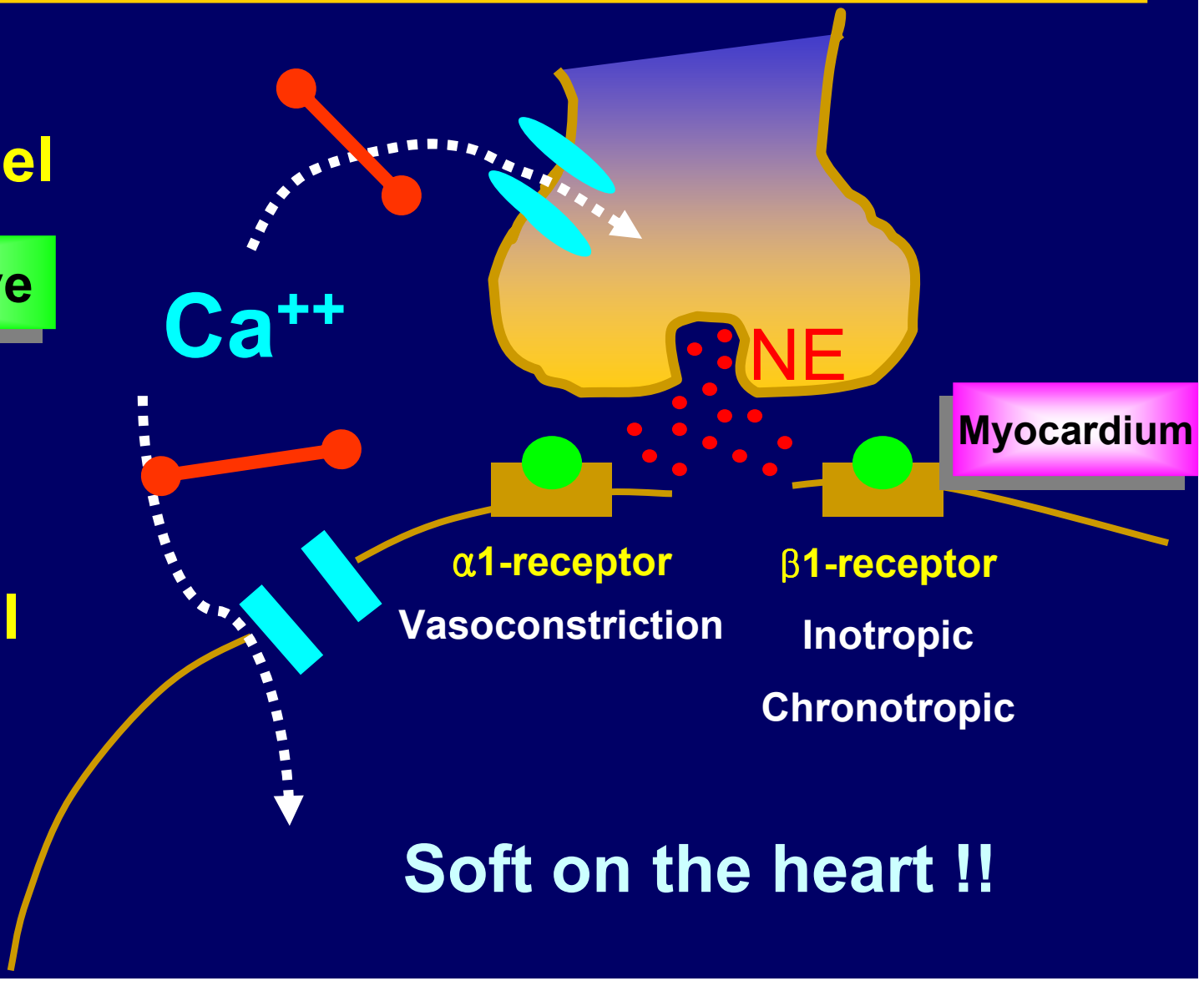
Cilnidipine: Mechanism of Dual Action

N-type Ca channel

Sympathetic Nerve

L-type Ca channel

VSMC

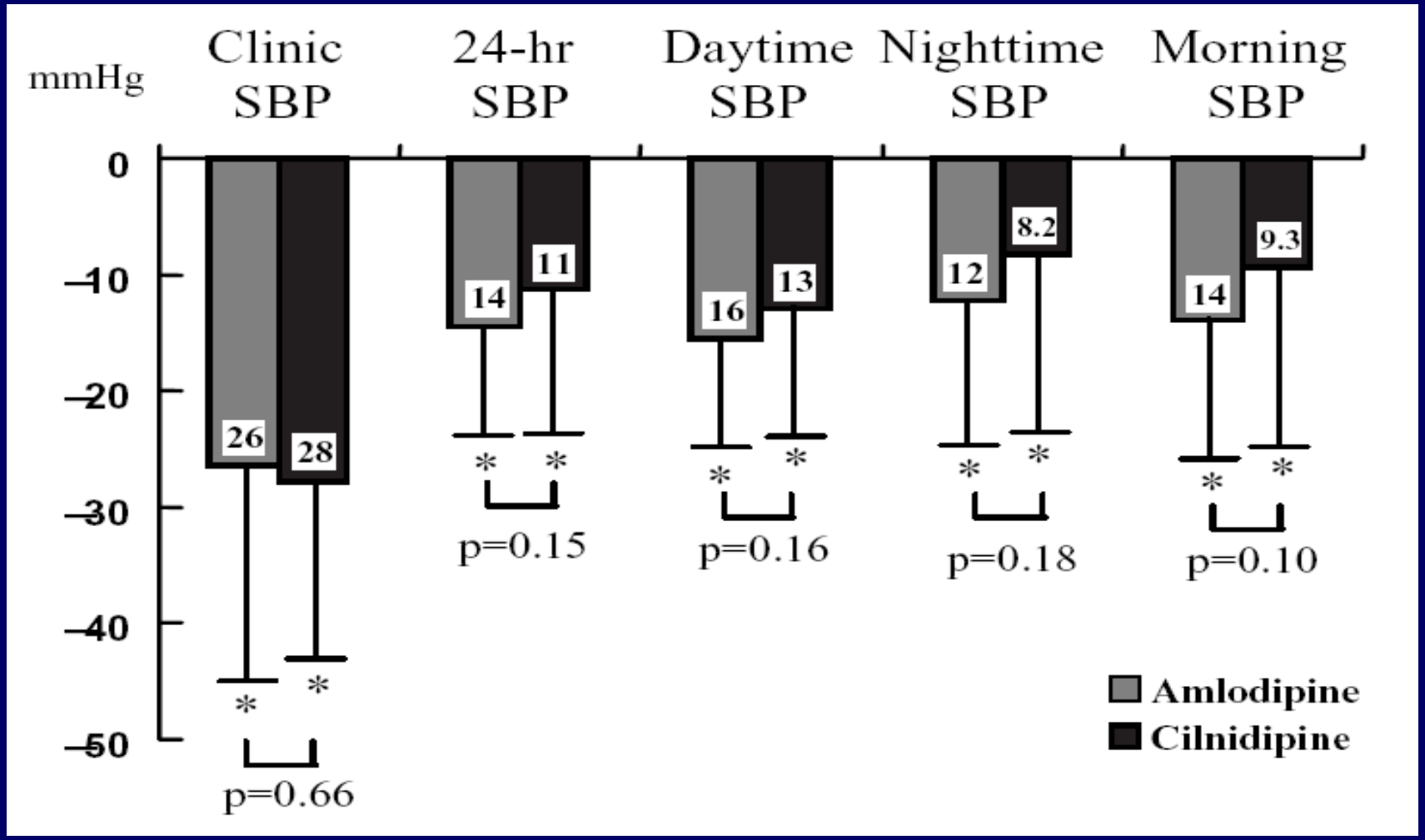


Soft on the heart !!

Cilnidipine: Clinical Characteristics

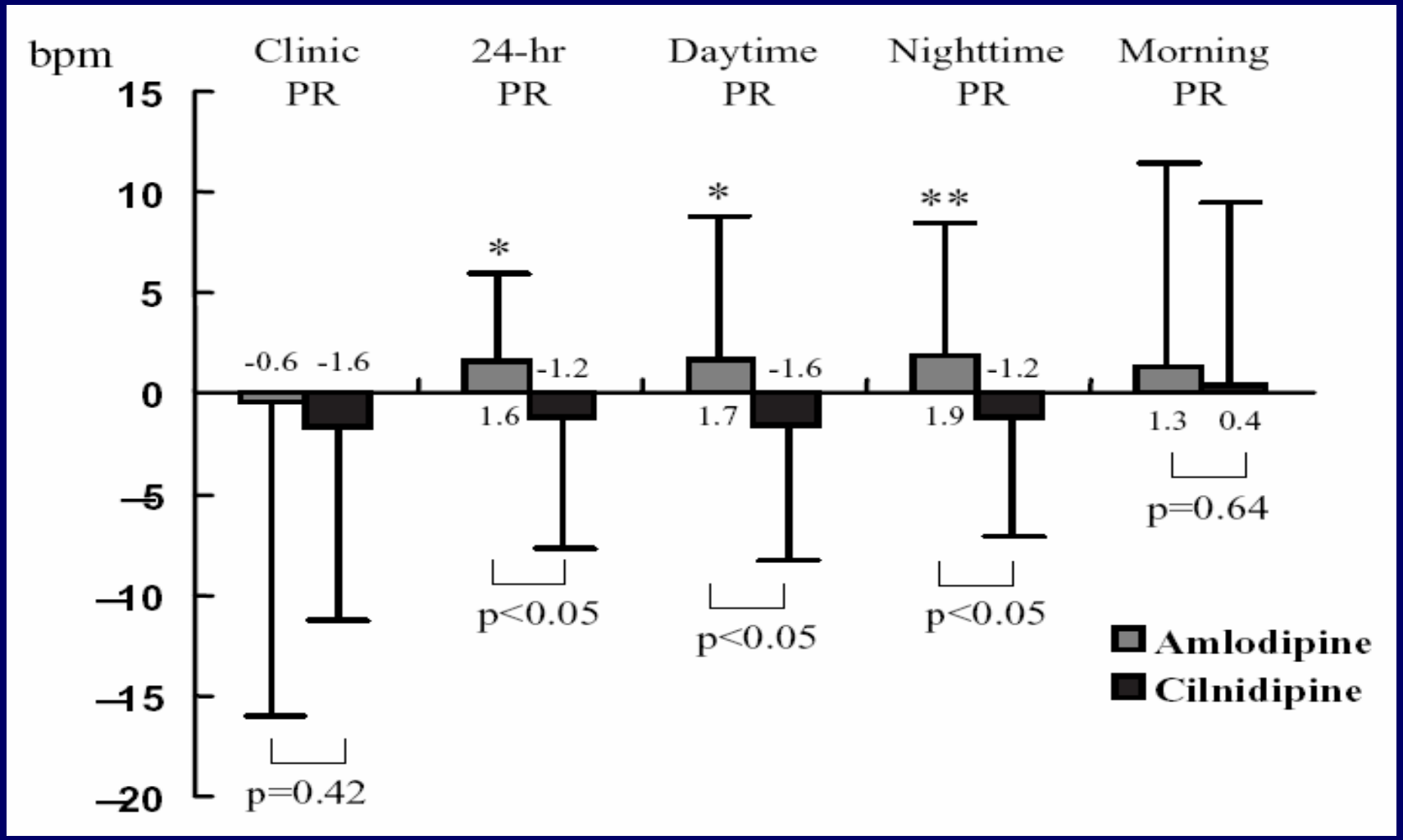
- Effective BP lowering CCB without HR change
- Long duration of action: stable and steady BP control
- Favorable effects on lipid metabolism
- Favorable effects on glucose metabolism
- Improve LVH and diastolic function

BP Lowering Effect: Cilnidipine vs. Amlodipine



Hoshide et al. Hypertens Res 2005

Changes in HR: Cilnidipine vs Amlodipine



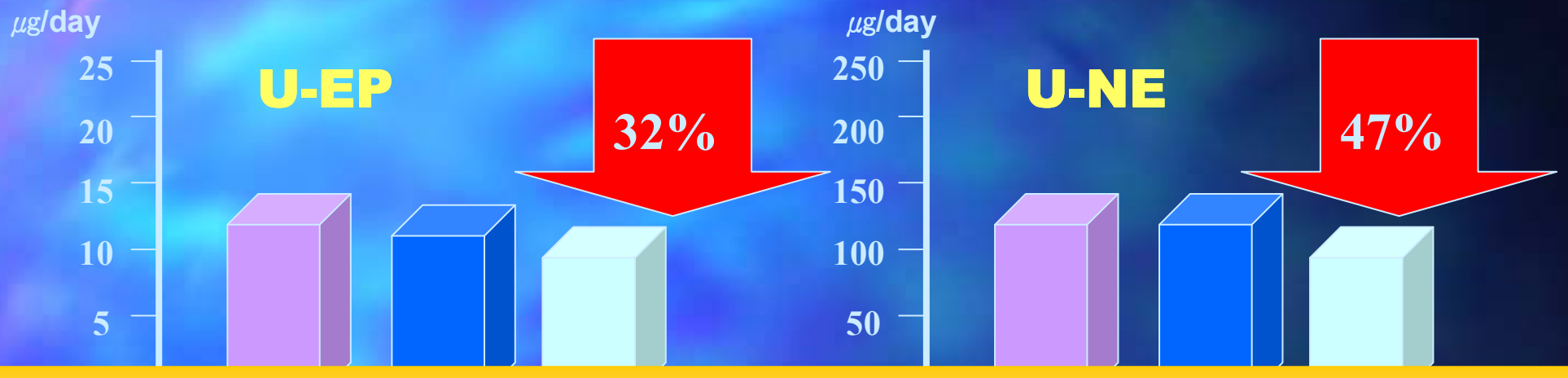
Hoshide et al. Hypertens Res 2005

Cilnidipine: Lipid and Fibrinolytic Parameters

- Trend of changes in lipid and lipoprotein levels
  : TC ↓, HDLC ↑, HDLC/TC ↑, TG ↓, LDLC ↓
- Trend of changes in fibrinolytic parameters
  : tPA ↑, tPA-PAI-1 complex ↓
- Beneficial lipid change and enhanced fibrinolysis
  : important in anti-atherogenic actions in hypertensive patients

Drugs Exptl. Clin Res 2000

CiInidipine: Catecholamine and C-peptide



- **N-type calcium channel**

  : More important in pancreatic β-cell insulin secretion than L-type

- **Improve insulin resistance**

  : By inhibition of hyper-secretion of NE, dopamine (U-DA)

- **L, N-type CCB cilnidipine**

  : More effectively reduced the urinary levels of catecholamines and C-peptide (U-CRP) than L-type CCB nilvadipine (NVP)

Diabetes Research & Clinical Practice 1999

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

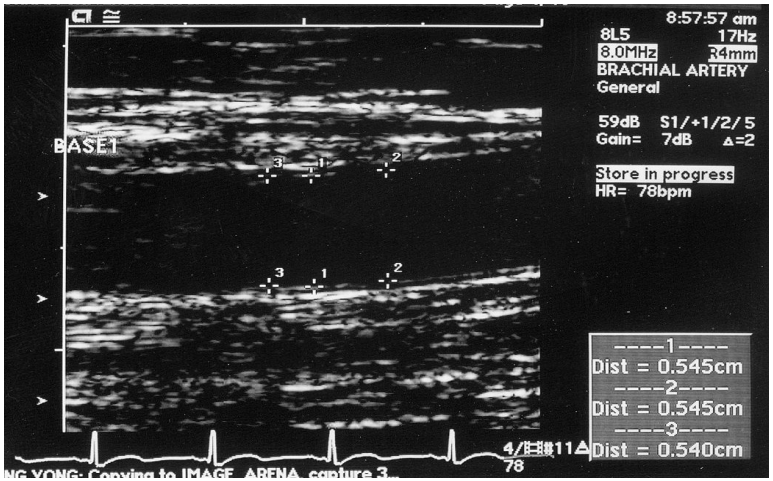
- Effective decreasing of SBP, DBP
- Without changing HR -> heart protective effects
- LVMI : significantly decreased
- LV Wall motion velocity patterns : significantly improved
- LV diastolic function : improved
- Conclusion

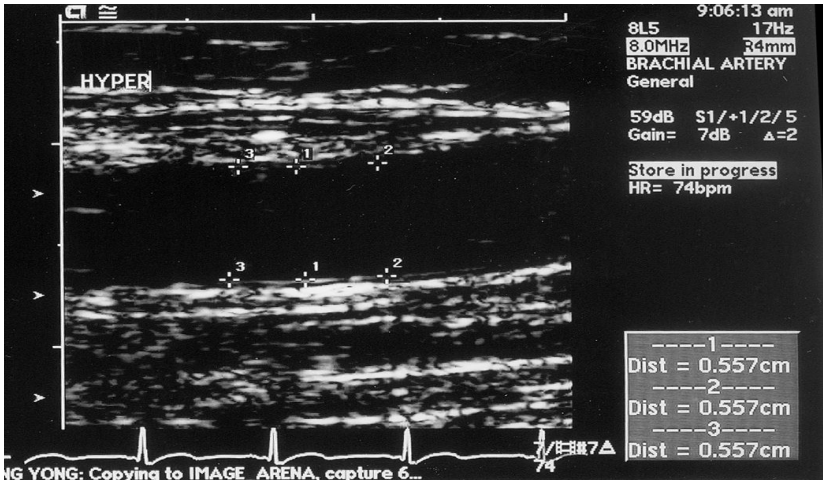
  CCB (esp. cilnidipine) has an important myocardial-protecting action in addition to its antihypertensive effect

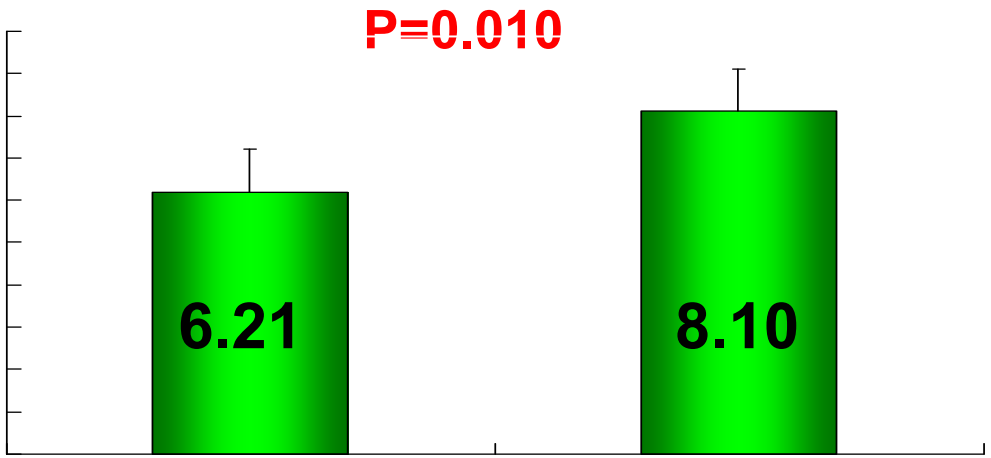
Cilnidipine, * p<0.05, ** p<0.01, ***p<0.0001

Yukiko et al. Jpn Circ J 2001.

FMD



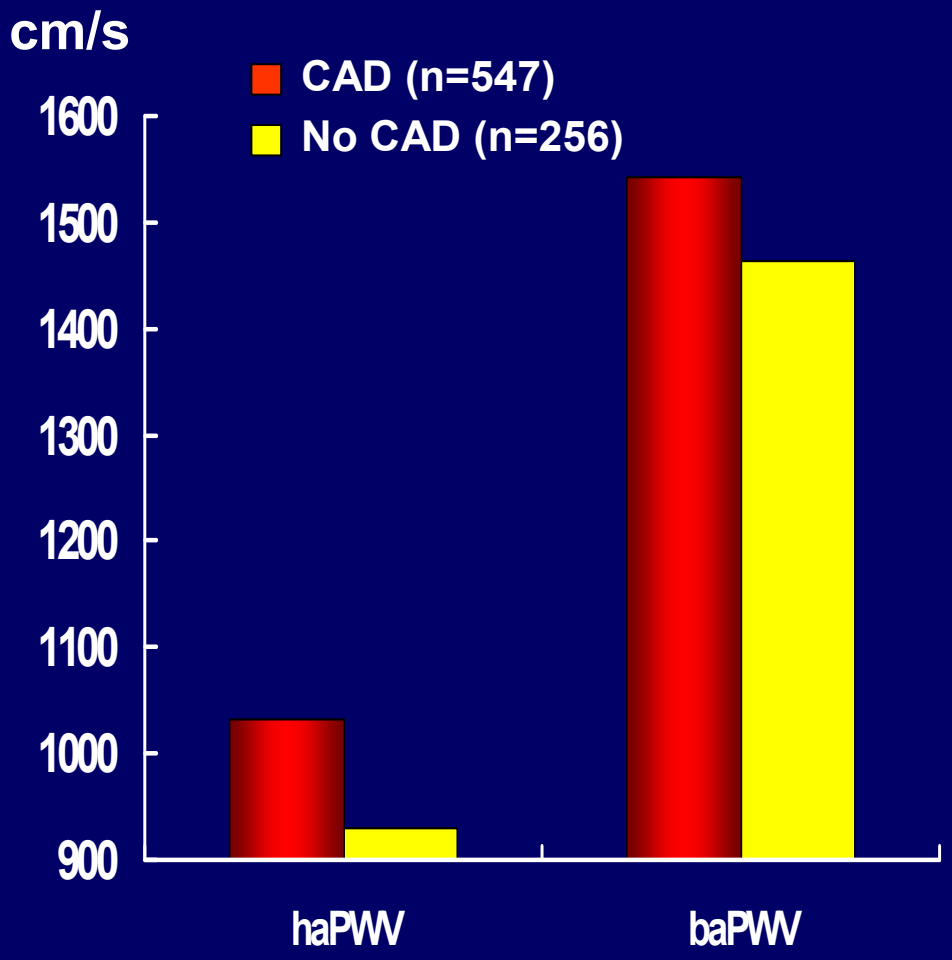




4 weeks after CCB Treatment in stage I or II HT

CNUH Data. Korean Hypertension J 2006;1:13-18

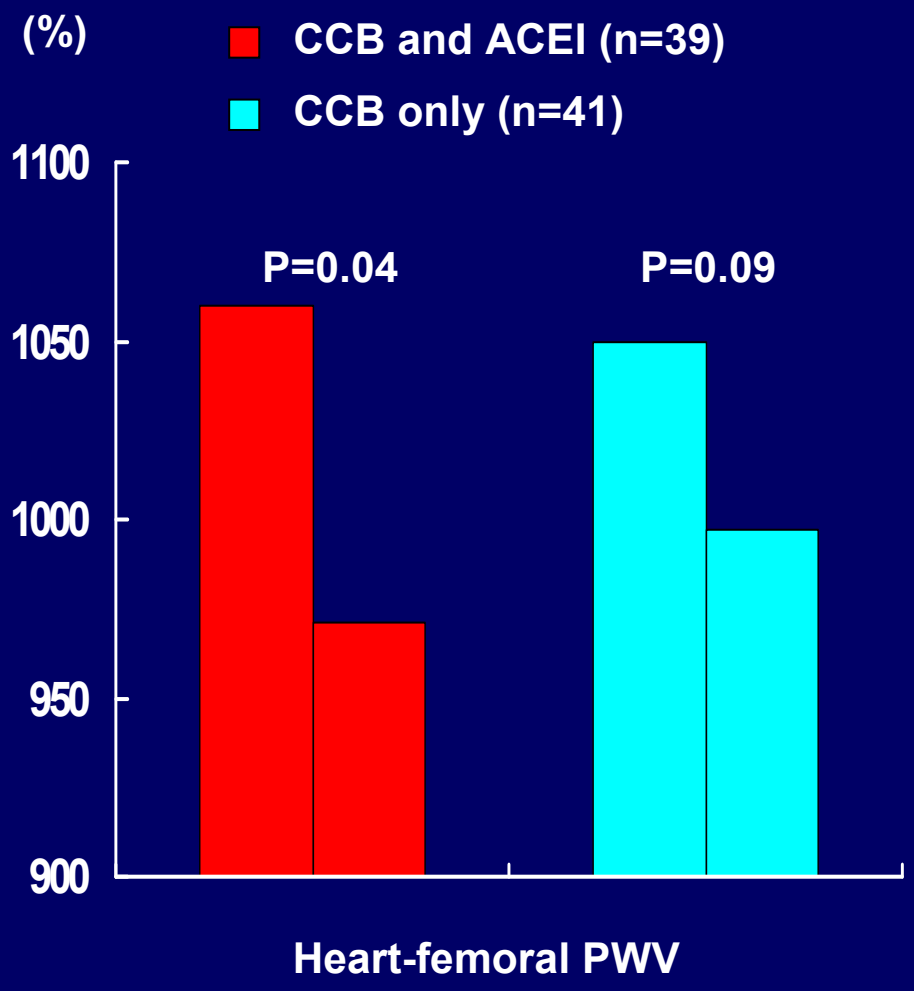
Arterial Stiffness and CAD



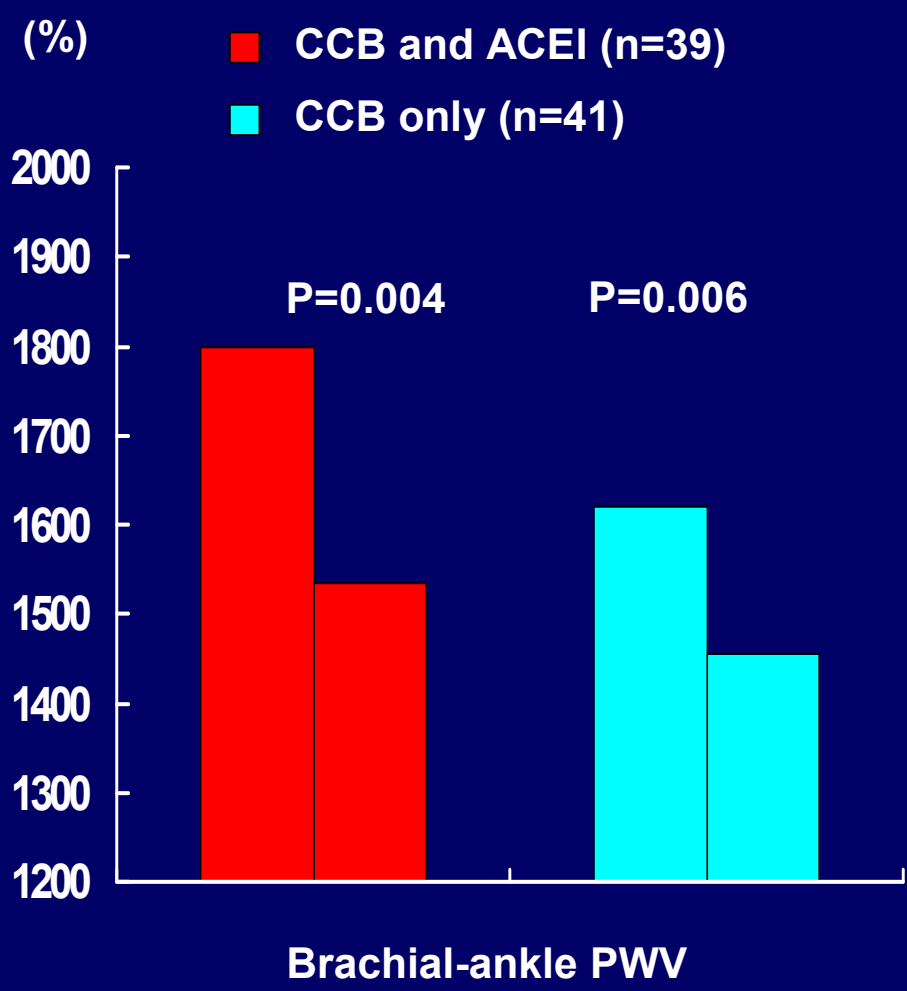
- Heart-femoral pulse wave velocity
  : significantly correlated with CAD
  : 1033.0±247.4 vs. 930.0±212.3 cm/s (p<0.001)
- Brachial-ankle PWV
  : significantly associated with CAD
  : 1542.0±340.4 vs. 1463.6±288.1 cm/s (p<0.001)

CNUH data, 2006 Korean Society of Internal Medicine, 2007 TCT-Asia

Arterial Stiffness in Angina Following Cilnidipine (Cinalong®) and Captopril (Capril®)



Heart-femoral PWV



Brachial-ankle PWV

CNUH data, 2007 ACC

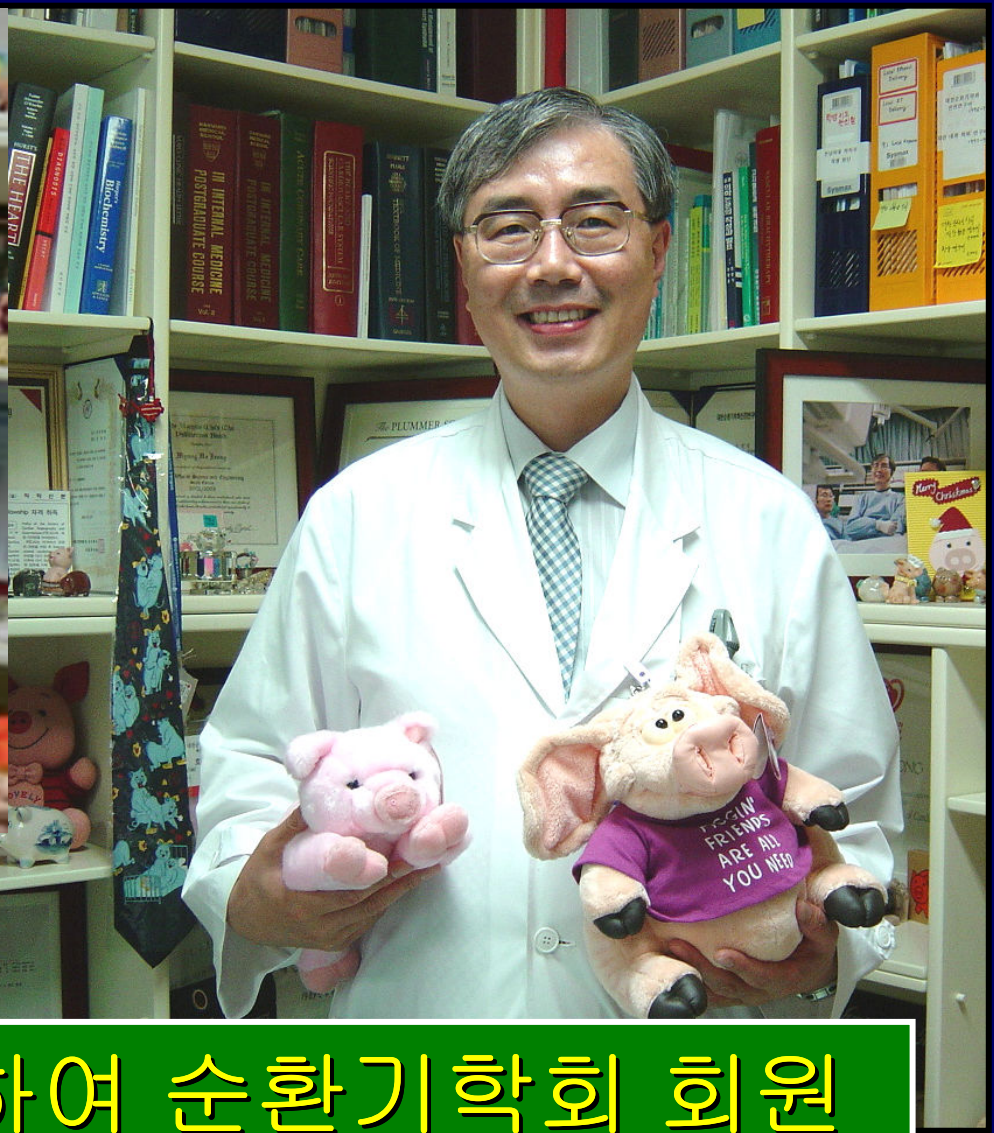

ACC.07
김계훈 홍영준 Lerman Schwartz 정명호 안영근 조장현

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. Cinalong + Capril) - improve endothelial dysfunction, arterial stiffness, vascular inflammation and renal dysfunction

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



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