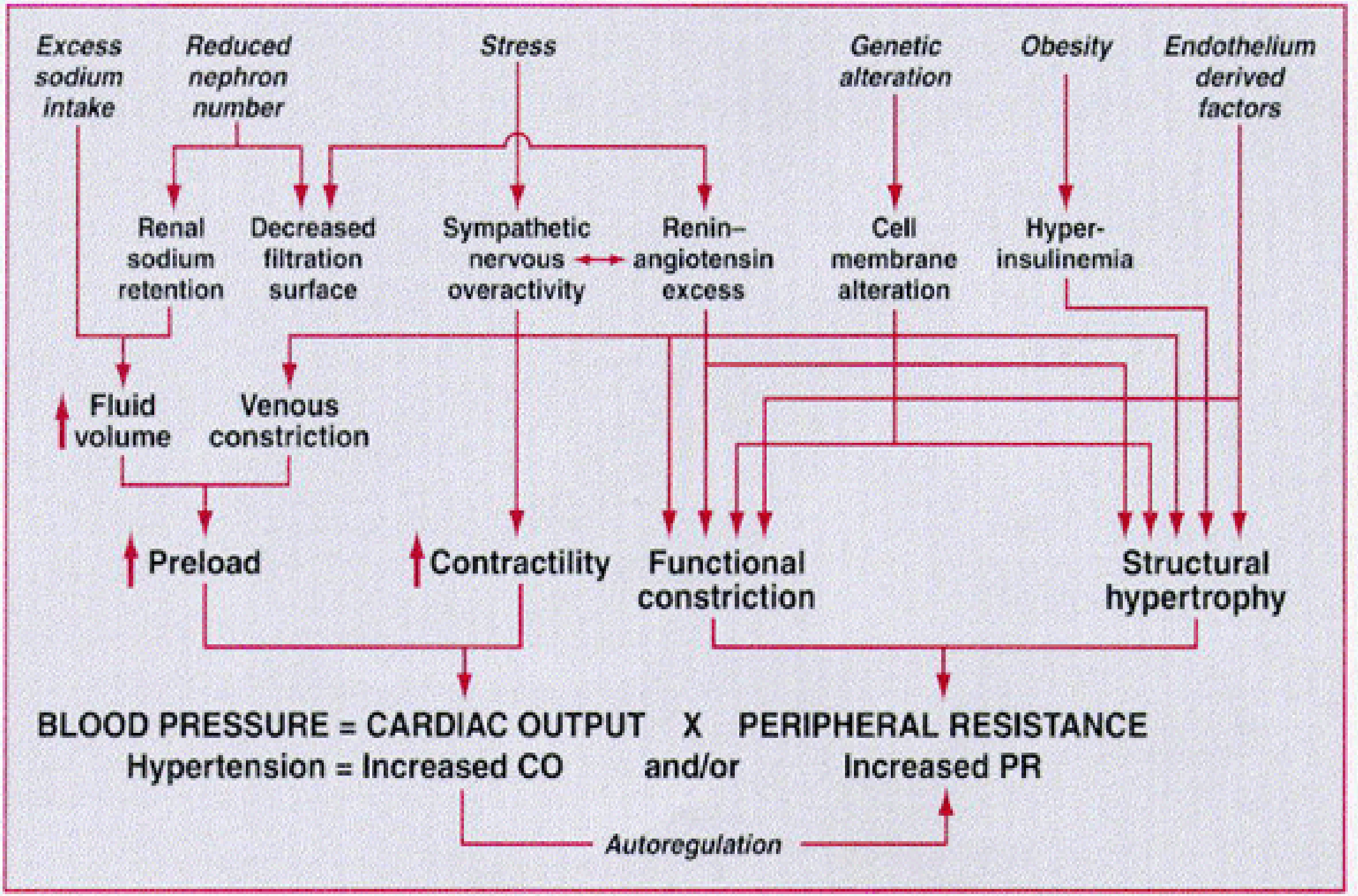
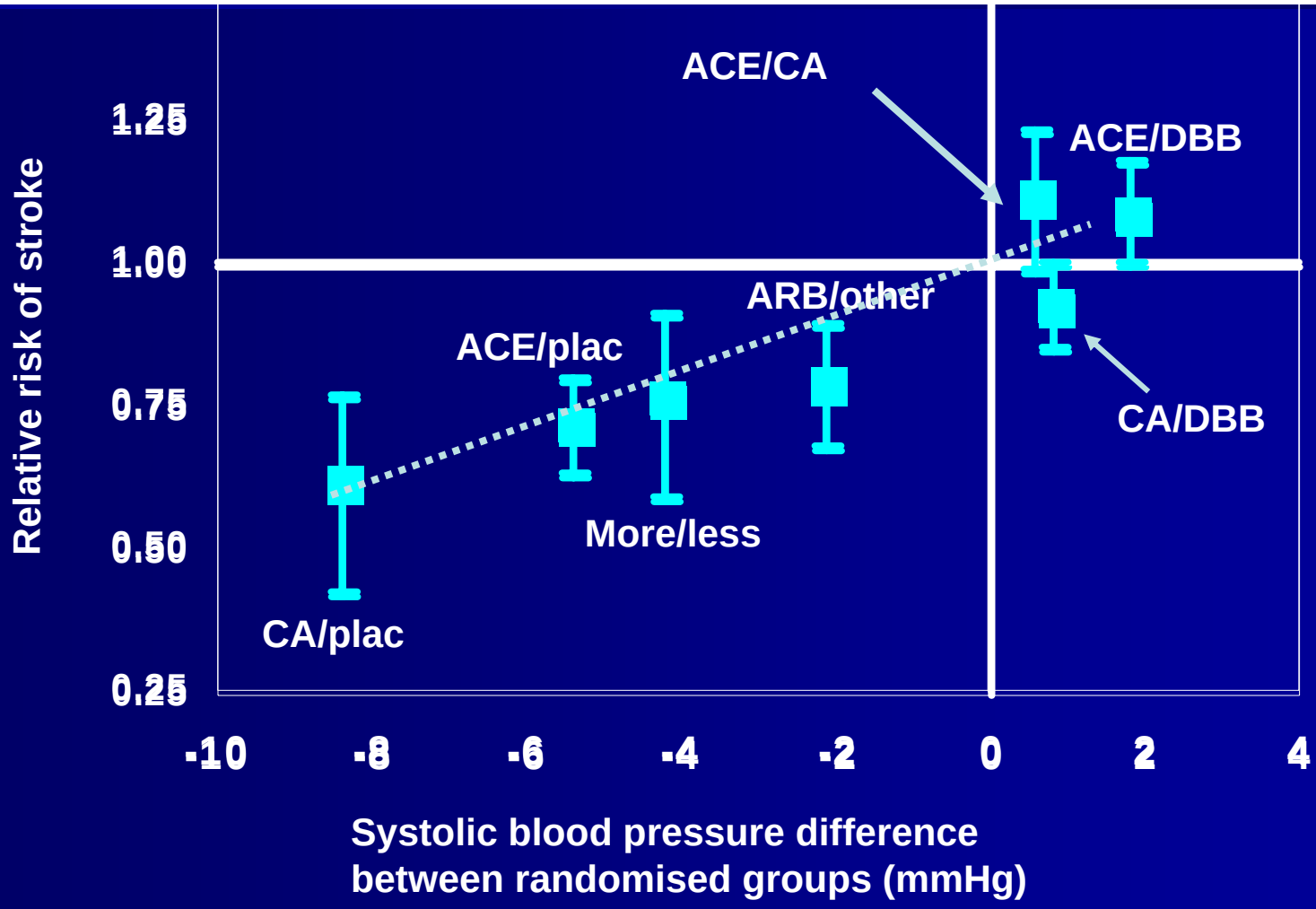
Calcium Channel Blocker beyond BP lowering Effect

계명의대
김기식

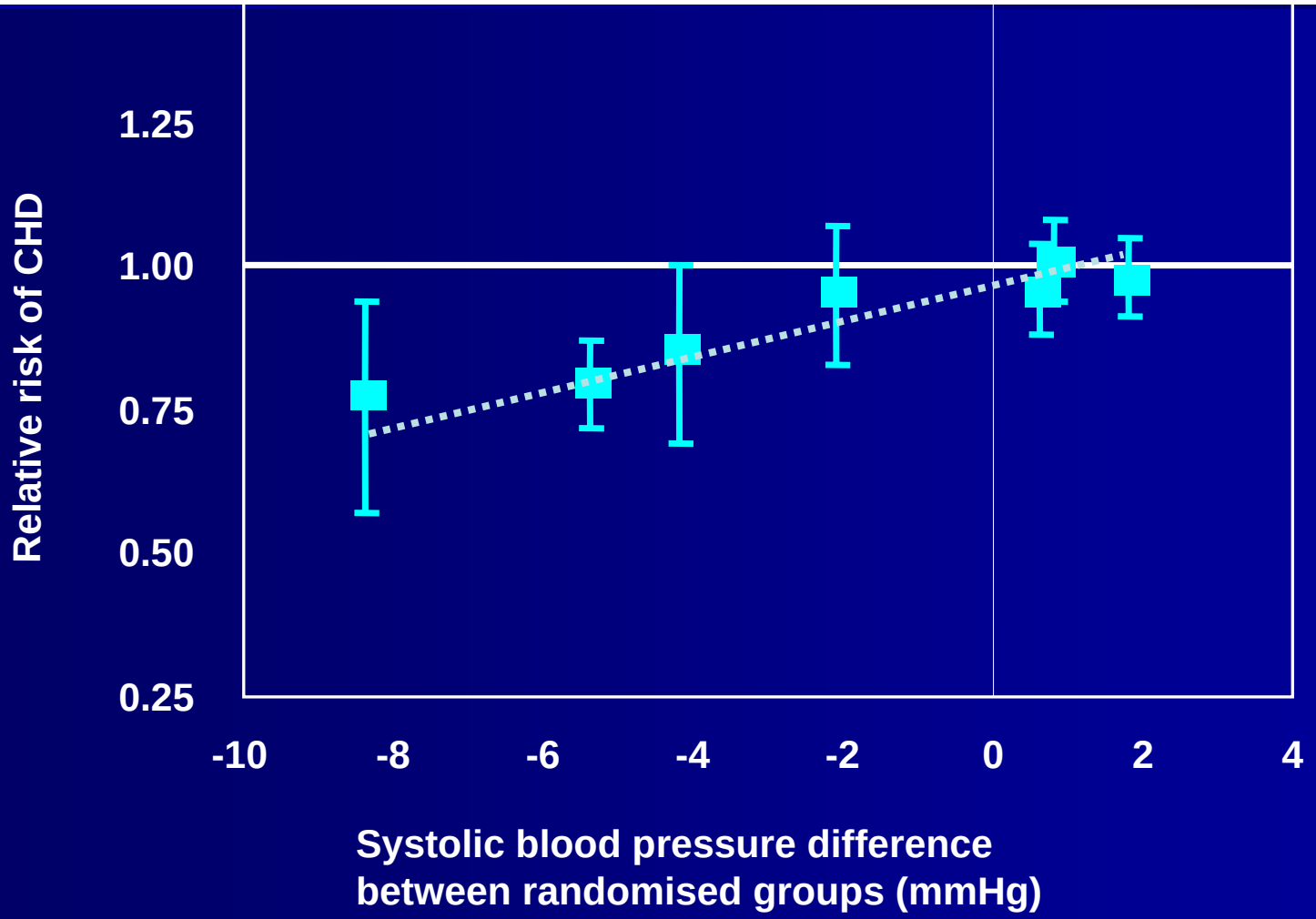

Excess sodium intake
Reduced nephron number
Stress
Genetic alteration
Obesity
Endothelium derived factors
Renal sodium retention
Decreased filtration surface
Sympathetic nervous overactivity
Renin–angiotensin excess
Cell membrane alteration
Hyper-insulinemia
Fluid volume
Venous constriction
Preload
Contractility
Functional constriction
Structural hypertrophy
BLOOD PRESSURE = CARDIAC OUTPUT X PERIPHERAL RESISTANCE
Hypertension = Increased CO and/or Increased PR
Autoregulation

Role of BP reduction

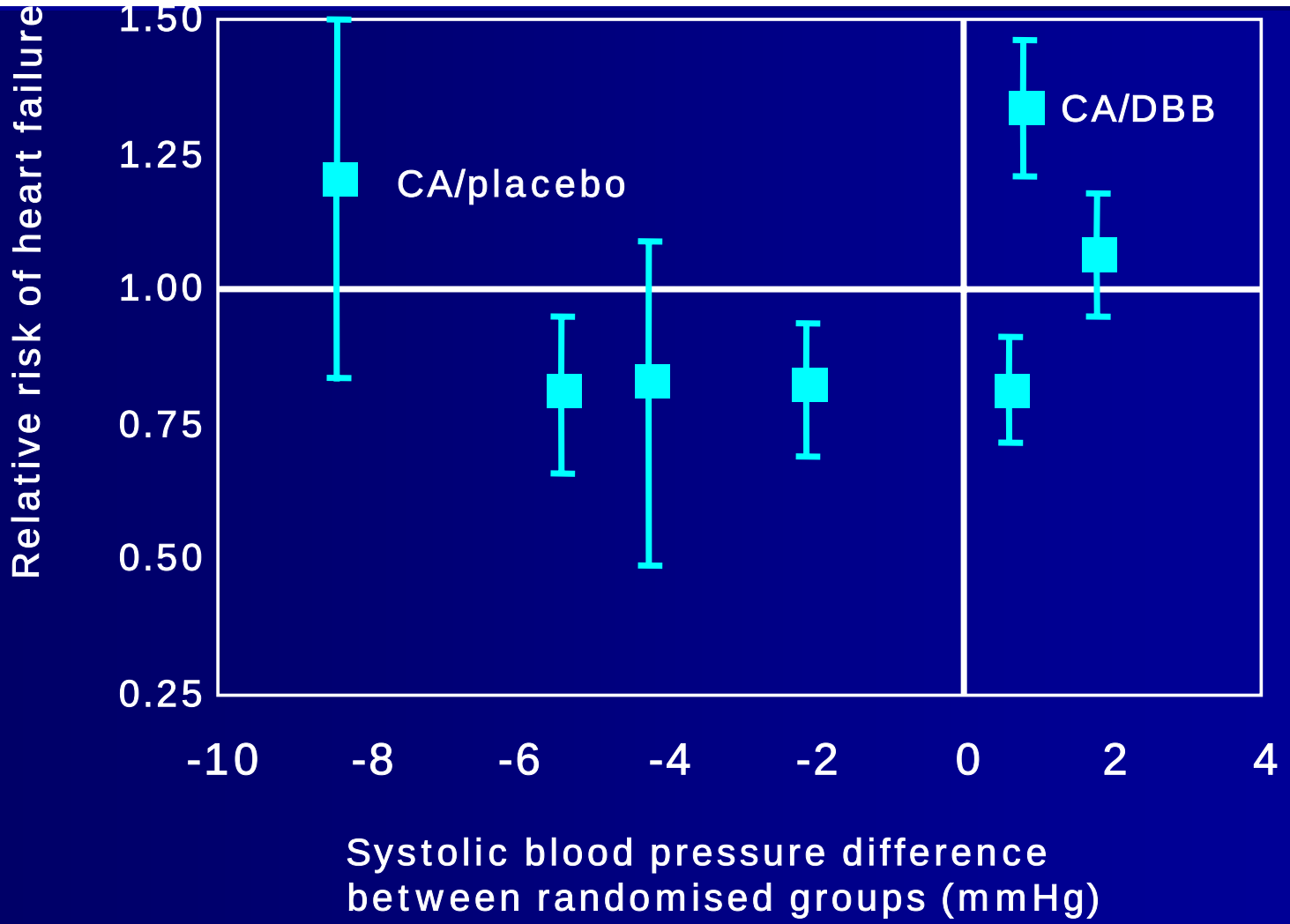
Stroke


ACE/CA
ACE/DBB
ARB/other
ACE/plac
More/less
CA/DBB
CA/plac
Relative risk of stroke
1.25
1.00
0.75
0.50
0.25
-10
-8
-6
-4
-2
0
2
4
Systolic blood pressure difference
between randomised groups (mmHg)

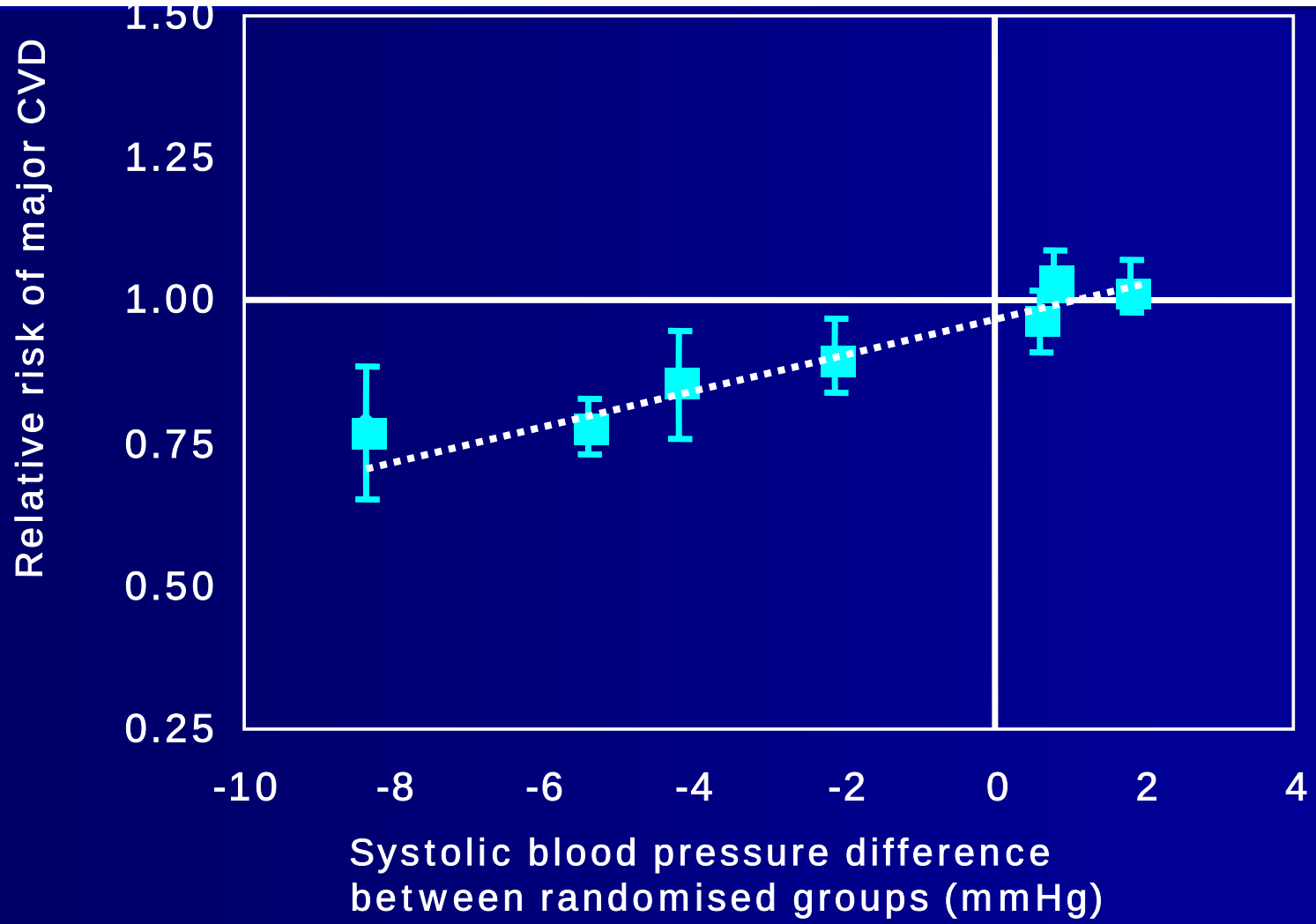
Coronary heart disease



Heart failure



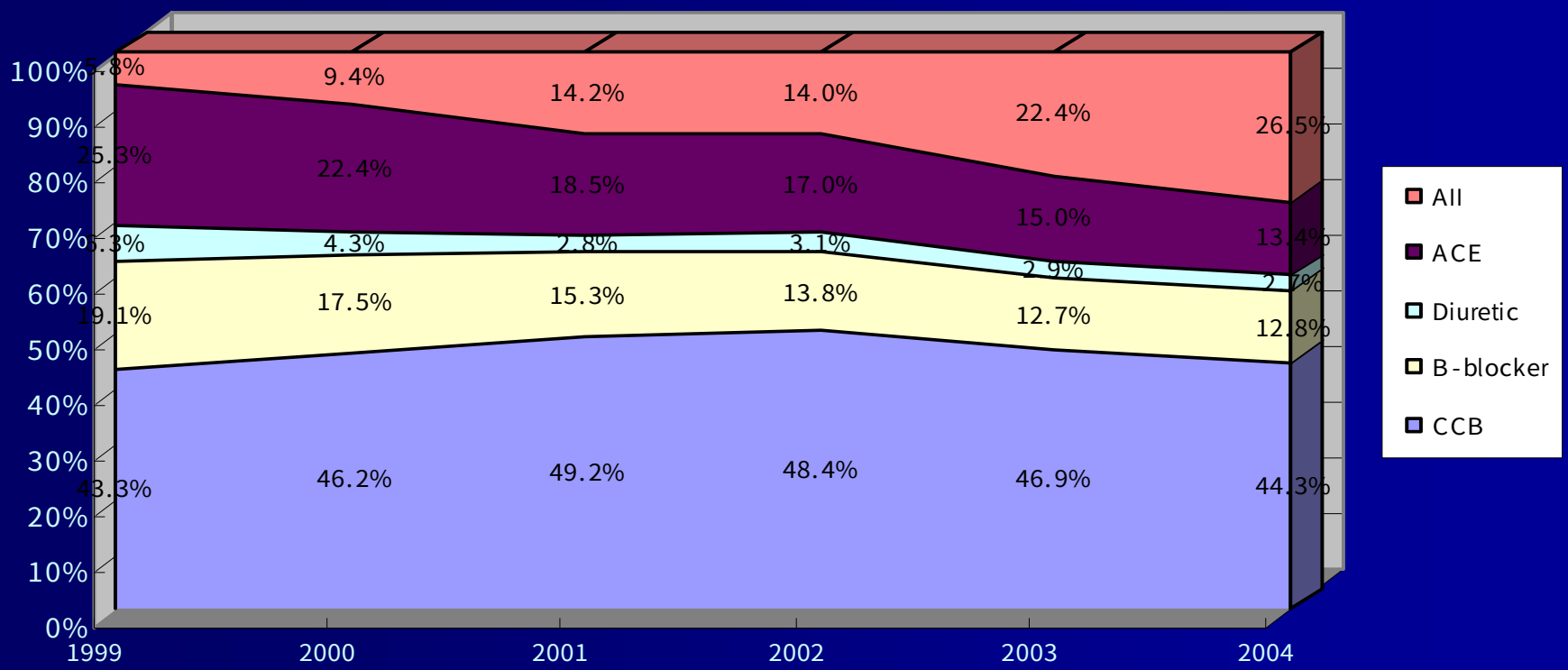
Major cardiovascular events



Antihypertensives Market

- Annual Market Share -

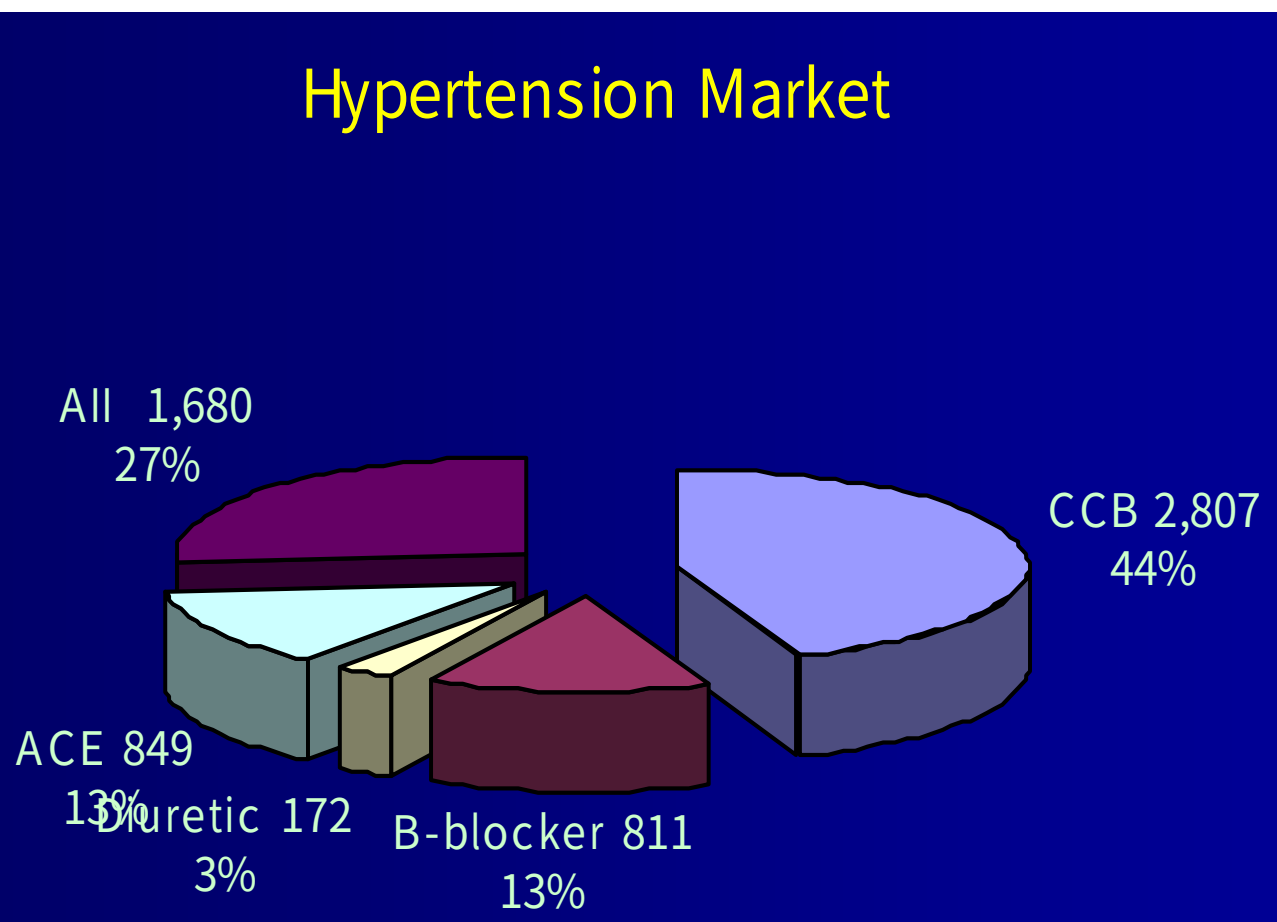
치료군별 점유율



Source) IMS 2/4Q data

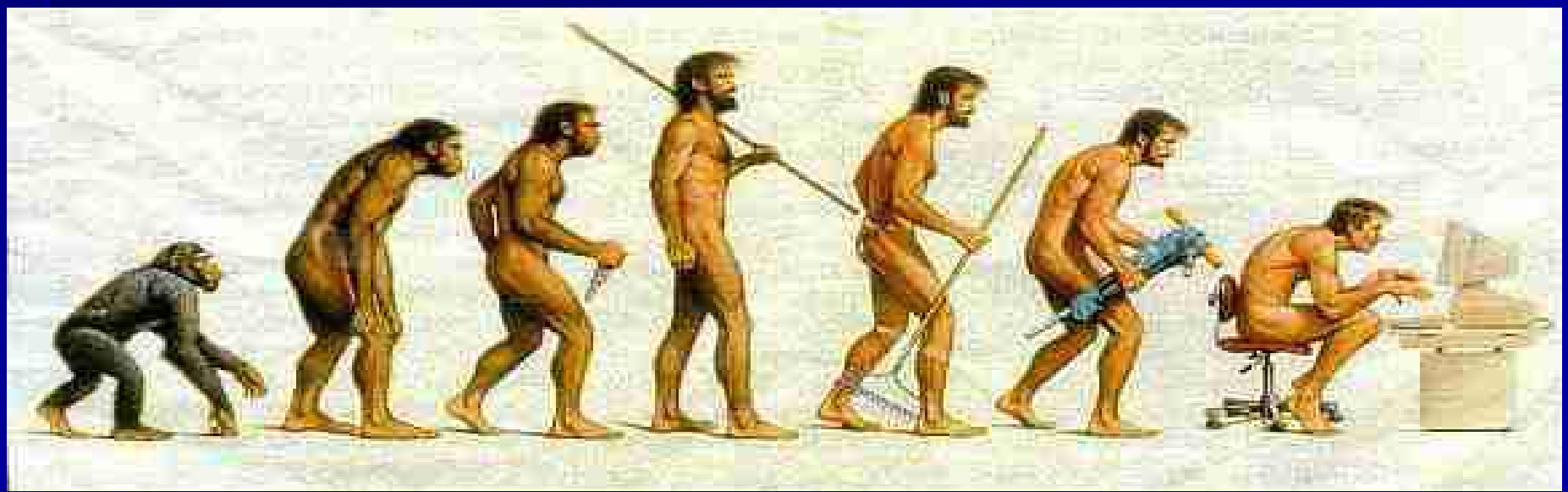
Antihypertensives Market

- Market Share in 2004 -



History of Calcium Channel Antagonists

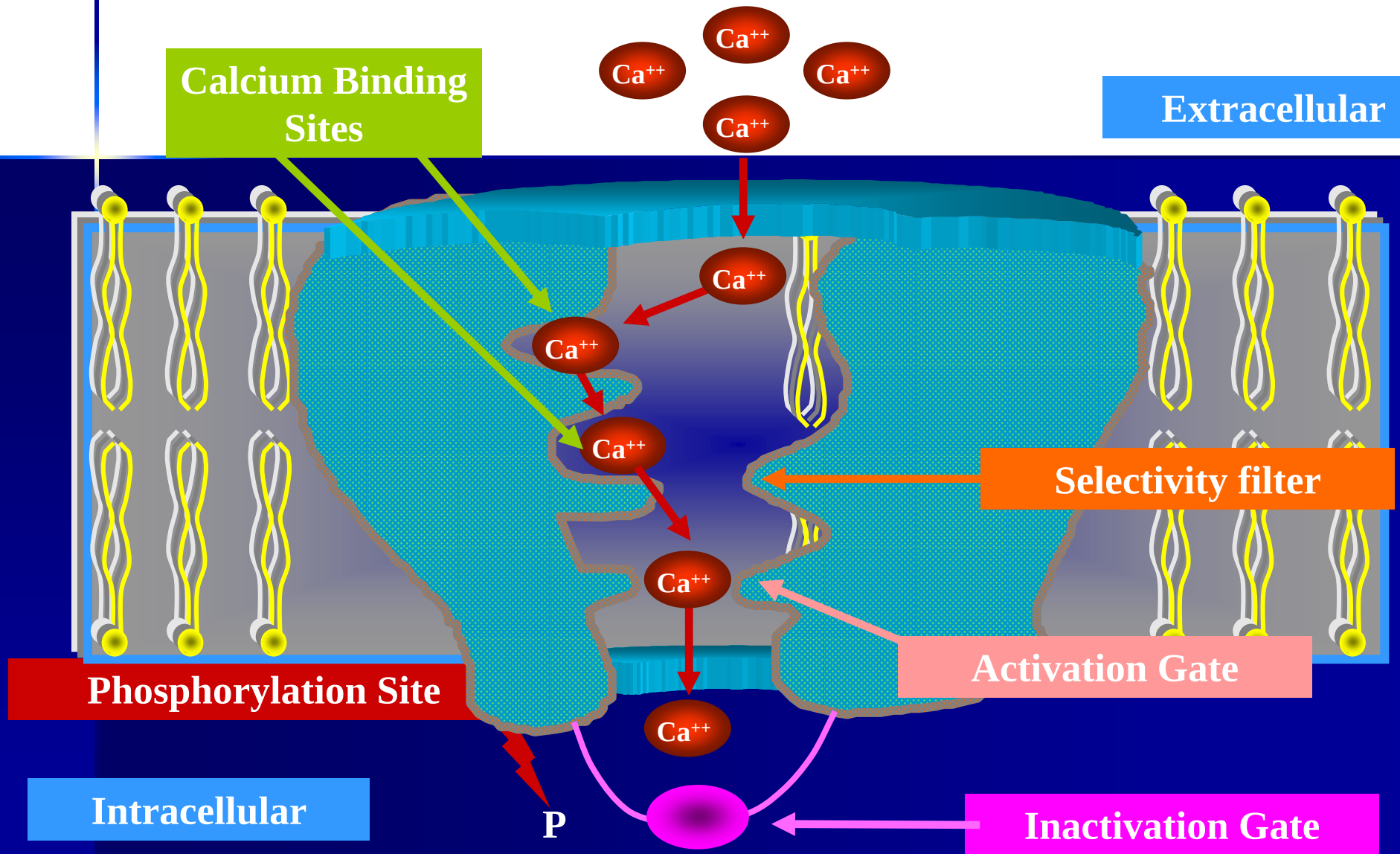
- First introduced for clinical use in late 1970's
- First generation prototypical CCAs problematic with hemodynamic fluctuations
- Evolution to longer acting agents and third generation formulations



Current Recommended Uses of CCAs

- Hypertensive Therapy
- Symptomatic relief of stable angina
- “Stabilized” UA/NSTEMI
- Symptomatic relief of diastolic heart failure
- Rate control of persistent afib

Voltage-Gated Ca^{++} Channels



Characteristics of Ca^{++} Channel Carried Currents

L-Type

L-type currents require strong depolarization (high activation threshold), are long lasting (slow inactivation rate) and are blocked by organic calcium antagonists of dihydropyridine, phenylalkylamines and benzothiazepine chemical classes. They are the main currents recorded in muscle and endocrine cells initiating contraction and secretion.

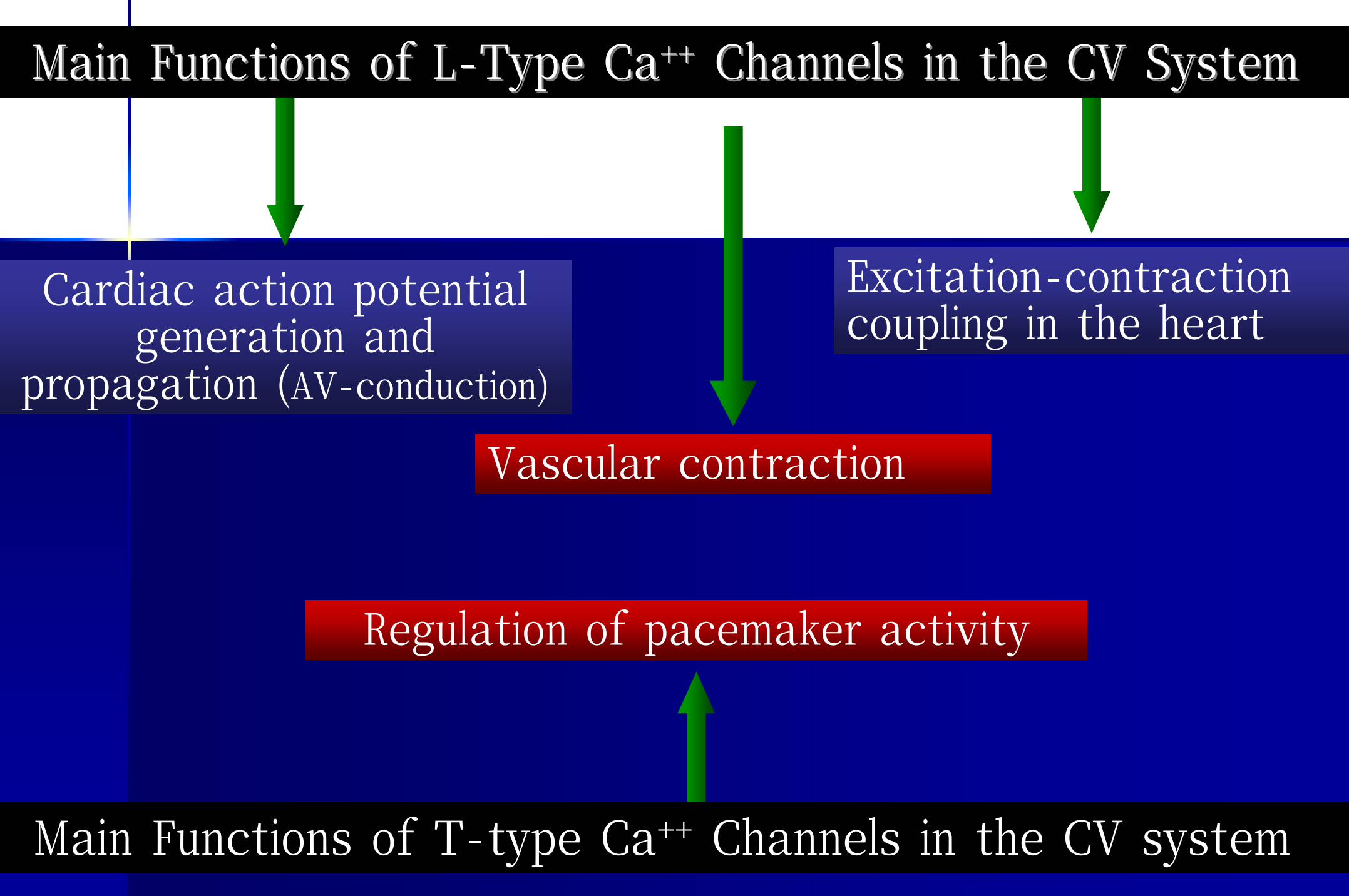
T-Type

T-type currents are activated at weak depolarization potentials, are transient (fast inactivation) and resist to L-type and N- and P/Q-type blockers. They are involved in the shaping of the action potentials and controlling patterns of repetitive firing in a wide variety of cell types.

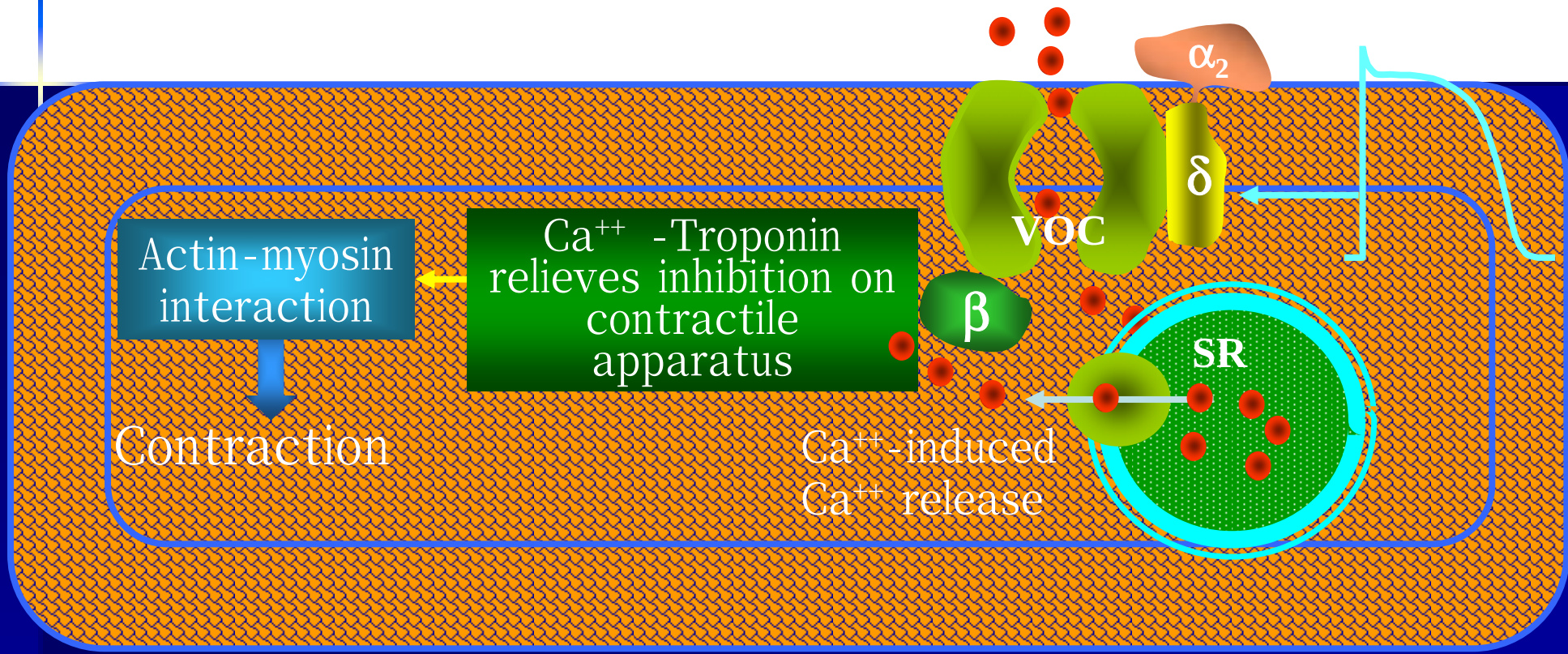
N-Type
P-Type
Q-Type
R-Type

These currents also require strong depolarization stimuli for activation, but are resistant to L-type blockers. They are blocked by specific polypeptide toxins isolated from cone snail and funnel web spider venoms. These currents are found primarily in neurons where they initiate neurotransmission at the most fast synapses and contribute to Ca^{++} transient in cell bodies and dendrites.

L=long lasting; N=neither L nor T currents, neuronal; P=Purkinje fibers; Q=?; R=remaining, toxin resistant; T=transiently activated.


Main Functions of L-Type Ca++ Channels in the CV System
Cardiac action potential generation and propagation (AV-conduction)
Vascular contraction
Excitation-contraction coupling in the heart
Regulation of pacemaker activity
Main Functions of T-type Ca++ Channels in the CV system

Ca^{++} Entry into the Cardiac Myocyte Induces Ca^{++} Release from the Sarcoplasmic Reticulum Necessary for Contraction



- L-type cardiac Ca^{++} channels open at a level of depolarization of ~-60 mV. The entry of small amount of Ca^{++} triggers Ca^{++} release from SR. Thus, blockade of this channel produces negative inotropic effects.

Classes of CCB

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
Benzothiazepines	Vascular = Myocardium	Diltiazem	Diltiazem SR	
Phenylalkylamines	Vascular < Myocardium	Verapamil	Verapamil SR Gallopamil	

Cardiovascular Effects of CCB

Intended:

- Vascular smooth muscle cell relaxation
- Negative inotropic effects
- Negative chronotropic effects

Unintended:

- Reflex activation of sympathetic system
- Reflex activation of renin-angiotensin-aldosterone system

Calcium channel blocker in Hypertension

Clinical Trials With 1st Generation CCAs

- **Short acting nifedipine**

Nifedipine may paradoxically exacerbate the frequency of angina pectoris!!!
Am Heart J 1983;106(4 pt1):644-52

Short acting nifedipine (when given in doses > 60 mg/day)
increases mortality in patients with CAD!-
Circ 1995;92(5)1326-31

Diltiazem treatment associated with 63% increase in
rate of MI in hypertensive patients!!!
J Am Geriatr Soc 1995;274(8):620-5

Diltiazem increases risk of decompensated CHF and death in pts
With post-MI LV dysfunction!!!
Circ 1991;83(1):52-60

What Happened?

- Rapid onset and short duration of short-acting formulations lead to neurohormonal activation, which can be detrimental in CAD and CHF
- Because arterioles are more affected by CCA than larger epicardial arteries, “coronary steal” (to non-ischemic myocardium) via collaterals may worsen angina
- Other RCTs demonstrated that verapamil had no adverse cardiac effects, and even mortality reduction in some cases
  - Verapamil is metabolized to long-acting norverapamil

2nd and 3rd Generation CCAs

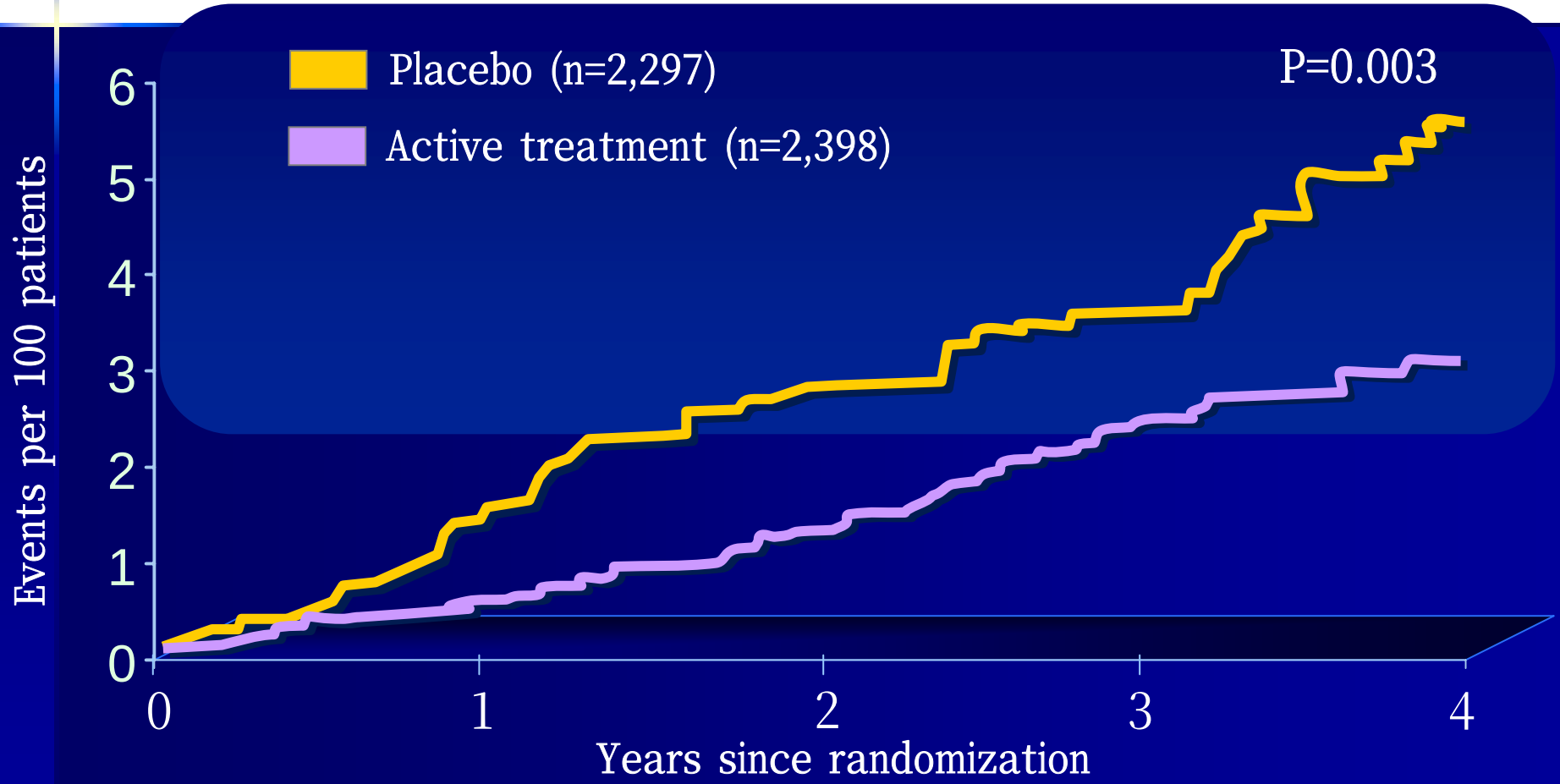
- Meta-analysis of placebo controlled trials with longer-acting CCA suggest mortality *benefit* in treated patients (HTN, post-MI, CHF, CAD)[1]
- RCTs with amlodipine[2] and felodipine[3] in pts with LV dysfunction revealed equivalent (if not improved) mortality rates

[1]Opie LH. JACC 2000;36(6):1967-71
[2]Packer et al. NEJM 1996;335(15):1107-14
[3]Cohn et al. Circ 1997;96(3):856-63

Anti-hypertensive trials with CCB's

- Placebo controlled
  - STONE
  - Sys-Eur
  - Sys-China
- Comparative trials with other anti-HT drugs
  - NORDIL
  - STOP-Hypertension-2
  - INSIGHT
  - ALLHAT

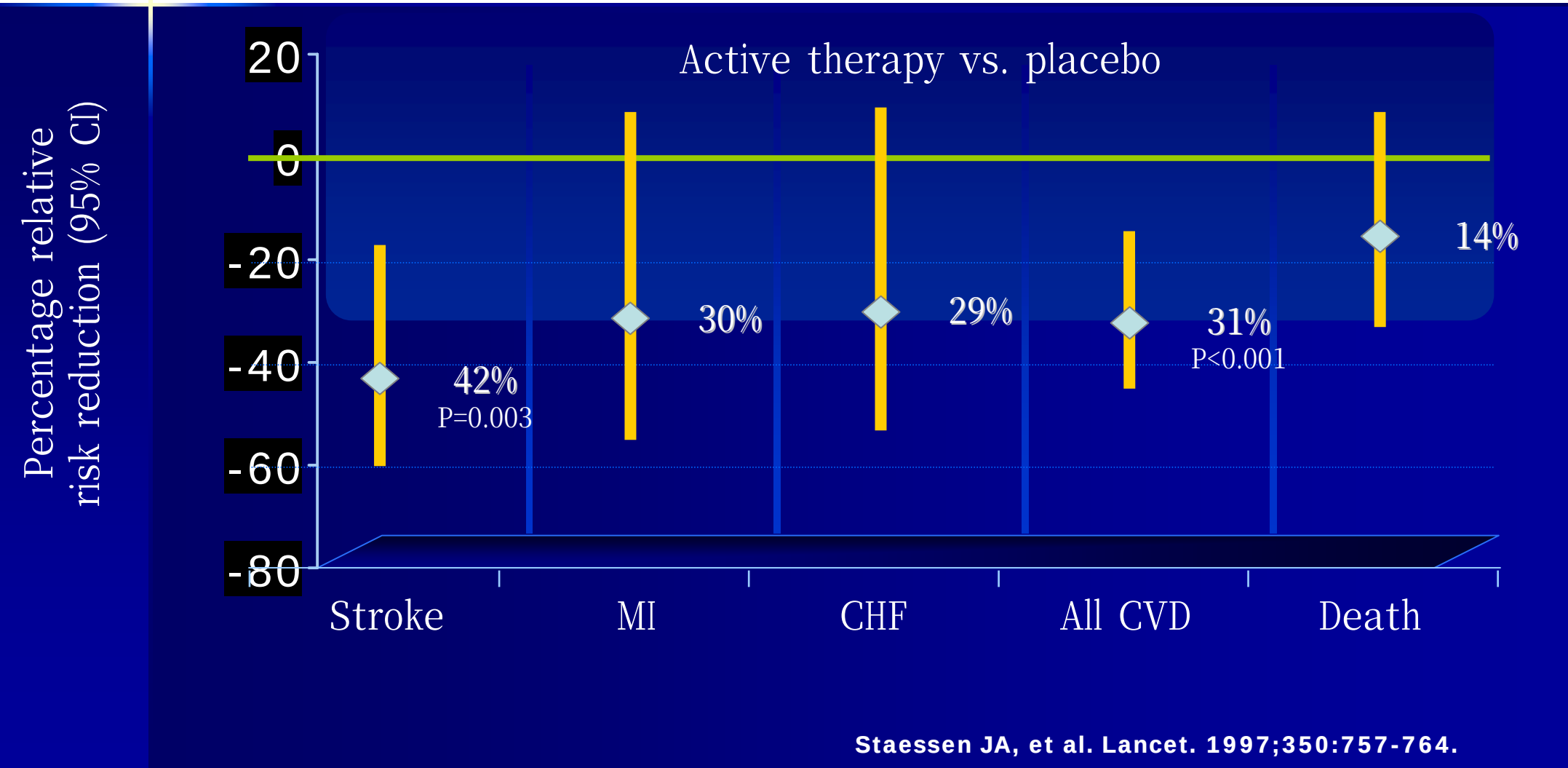
Syst-Eur Primary Endpoint
Fatal and Nonfatal Stroke



Syst-Eur=Systolic Hypertension in Europe Trial

Staessen JA, et al. Lancet. 1997;350:757-764.

Syst-Eur
Cardiovascular Disease Endpoints



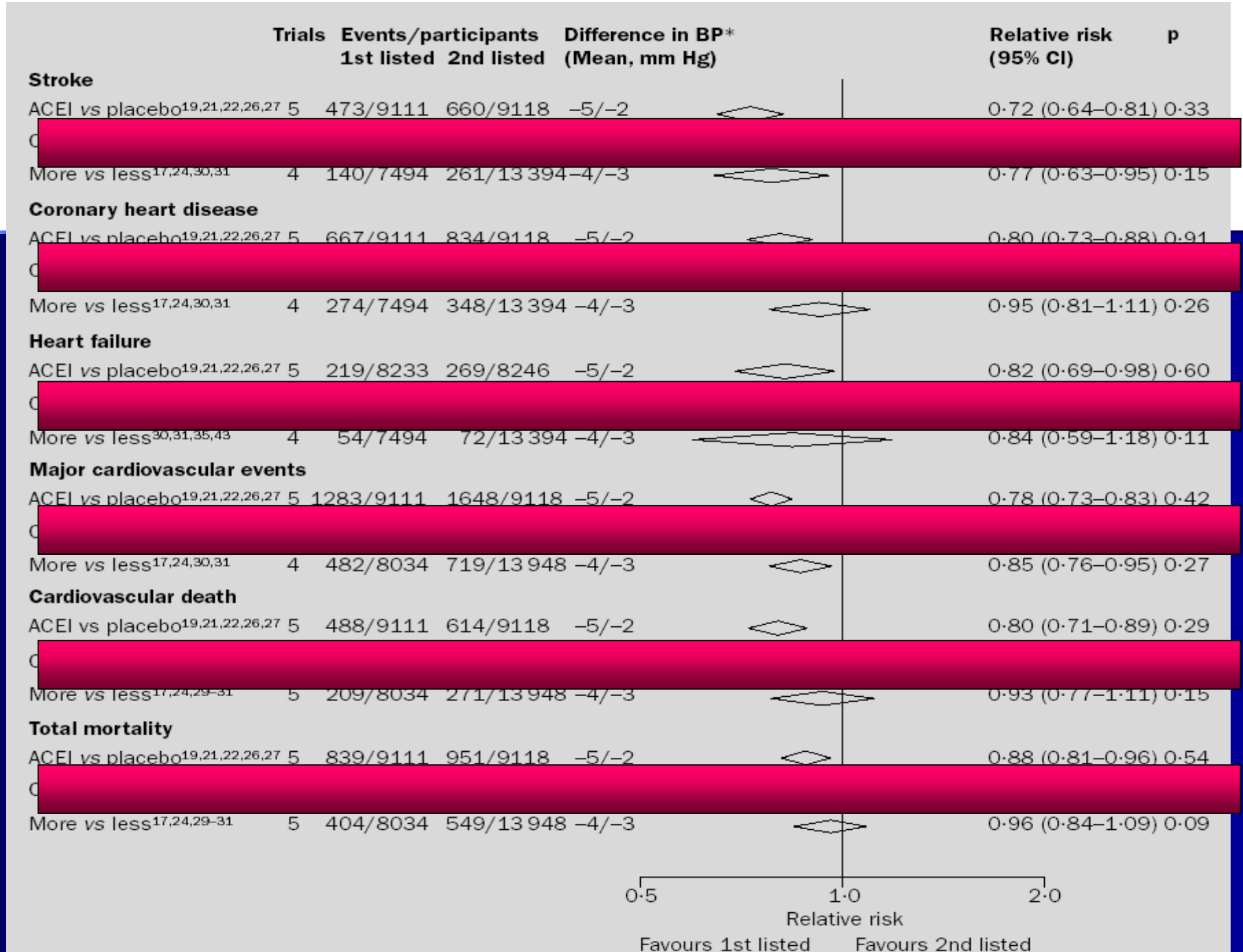
Staessen JA, et al. Lancet. 1997;350:757-764.

	Treatment comparison	n	Trial design	Entry criteria*	Follow-up (years)
Active treatment vs placebo					
ACE inhibitor vs placebo					
HOPE[26]	Ramipril vs placebo	9297	DB	CHD, CVD, or DM+RF	4·5
PART2[29]	Ramipril vs placebo	617	DB	CHD or CVD	4·7
PROGRESS[21]	Perindopril (+/- indapamide) vs placebo(s)	6105	DB	Cerebrovascular disease	3·9
QUIET[27]	Quinapril vs placebo	1750	DB	CHD	2·3
SCAT[28]	Enalapril vs placebo	460	DB	CHD	4·0
More intensive vs less intensive regimens					
AASK[29]	MAP ≤92 vs 102–107 mm Hg	1094	Open	HBP+nephropathy, Afr	3·8
ABCD (H)[30]	DBP ≤75 vs ≤90 mm Hg	470	Open	HBP+DM	5·3
ABCD (N)[30]	DBP 10 below baseline vs 80–89 mm Hg	480	Open	DM	5·3
HOT‡[31]	DBP ≤80 vs ≤85 or ≤90 mm Hg	18790	Open†	HBP	3·8
UKPDS-HDS[24]	DBP <85 vs <105 mm Hg	1148	Open	HBP+DM	8·4
ARBs vs control regimens					
IDNT[13]	Irbesartan vs placebo§	1148	DB	HBP+DM +nephropathy	2·6
RENAAL[14]	Losartan vs placebo§	1513	DB	DM +nephropathy	3·4
SCOPE[12]	Candesartan vs placebo§	4937	DB	HBP, 70–89 years	4·5
LIFE[15]	Losartan vs atenolol	9193	DB	HBP +CVD RF	4·8
Different drug classes					
ACE inhibitor vs diuretic or β blocker[29]					
AASK[29]	Ramipril vs metoprolol	877	DB	HBP+nephropathy, Afr	4·1
ALLHAT[32]	Lisinopril vs chlorthalidone	24328	DB	HBP + RF	4·9
ANBP2[33]	Enalapril vs hydrochlorothiazide	6083	Open†	HBP, 65–84 years	4·1
CAPPP[34]	Captopril vs β blocker or diuretic	10985	Open†	HBP	6·1
STOP-2[35]	Enalapril or lisinopril vs atenolol or metoprolol or pindolol or hydrochlorothiazide+amiloride	4418	Open†	HBP, 70–84 years	5·0
UKPDS-HDS[24]	Captopril vs atenolol	758	DB	HBP+DM	8·4

Blood Pressure Lowering Treatment Trialists' Collaboration: A Meta-Analysis Of Clinical Outcomes

Lancet 2003.Vol 362;1527-35

Lancet 2003. Vol 362;1527-35



Benefits Beyond Better Blood Pressure???

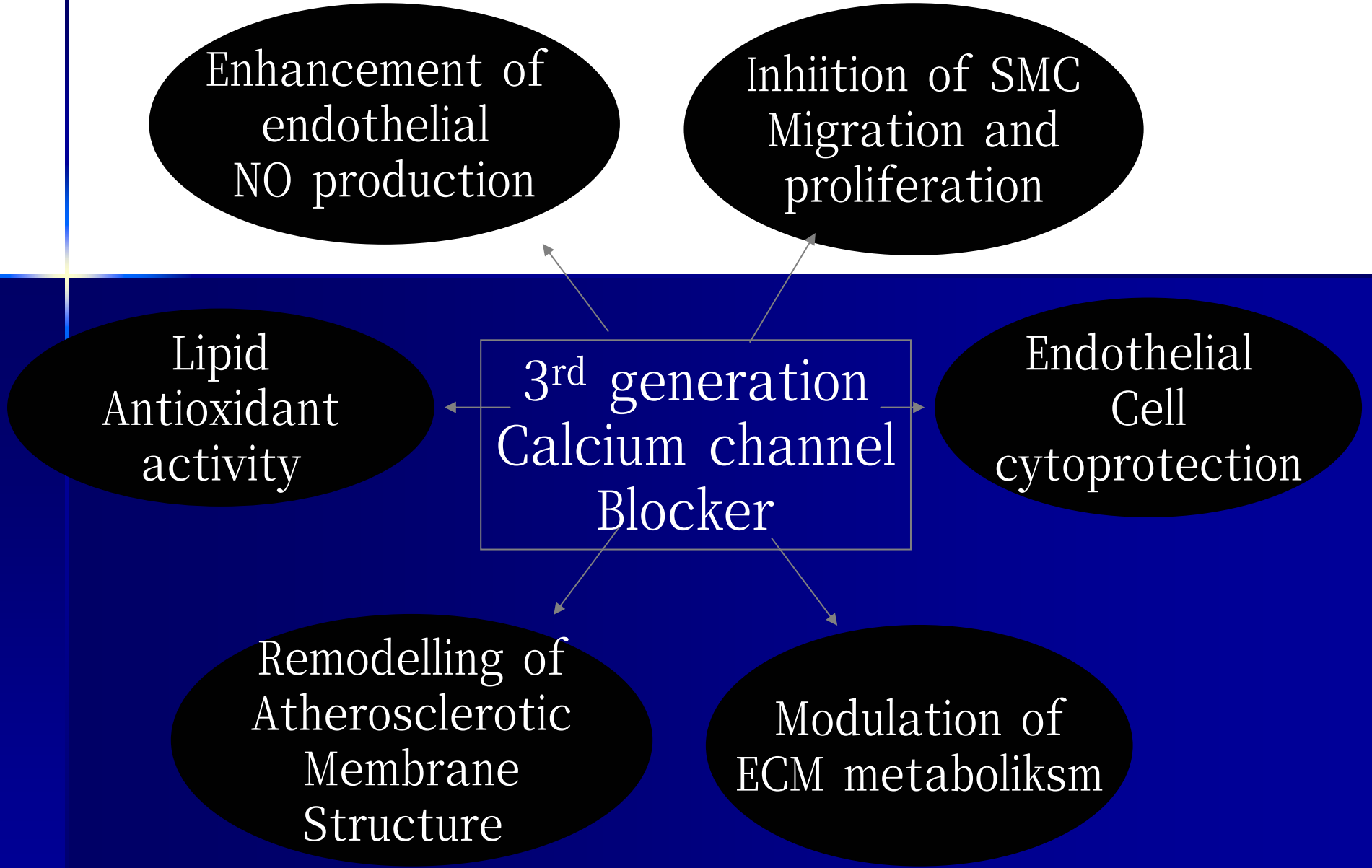
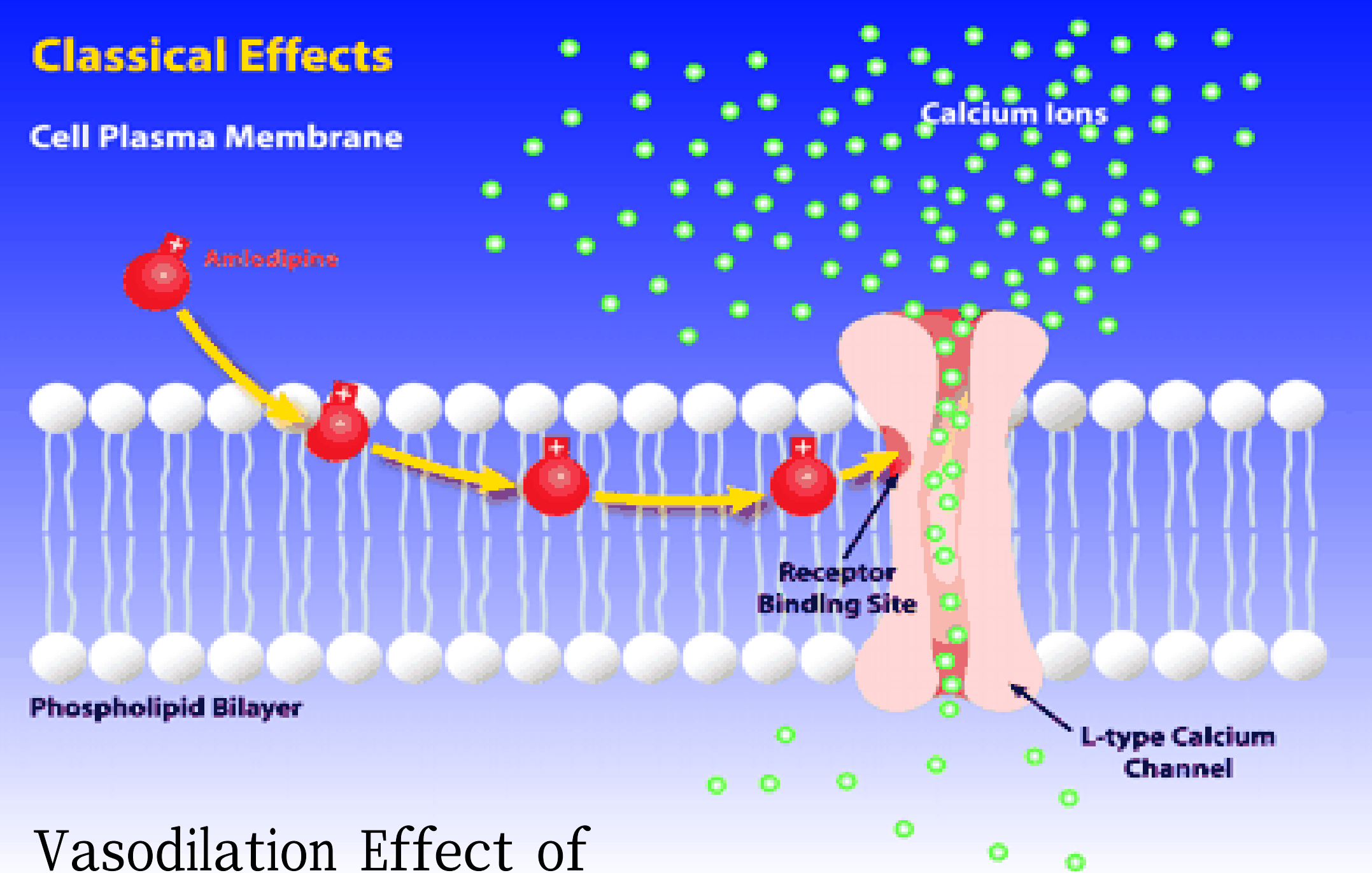


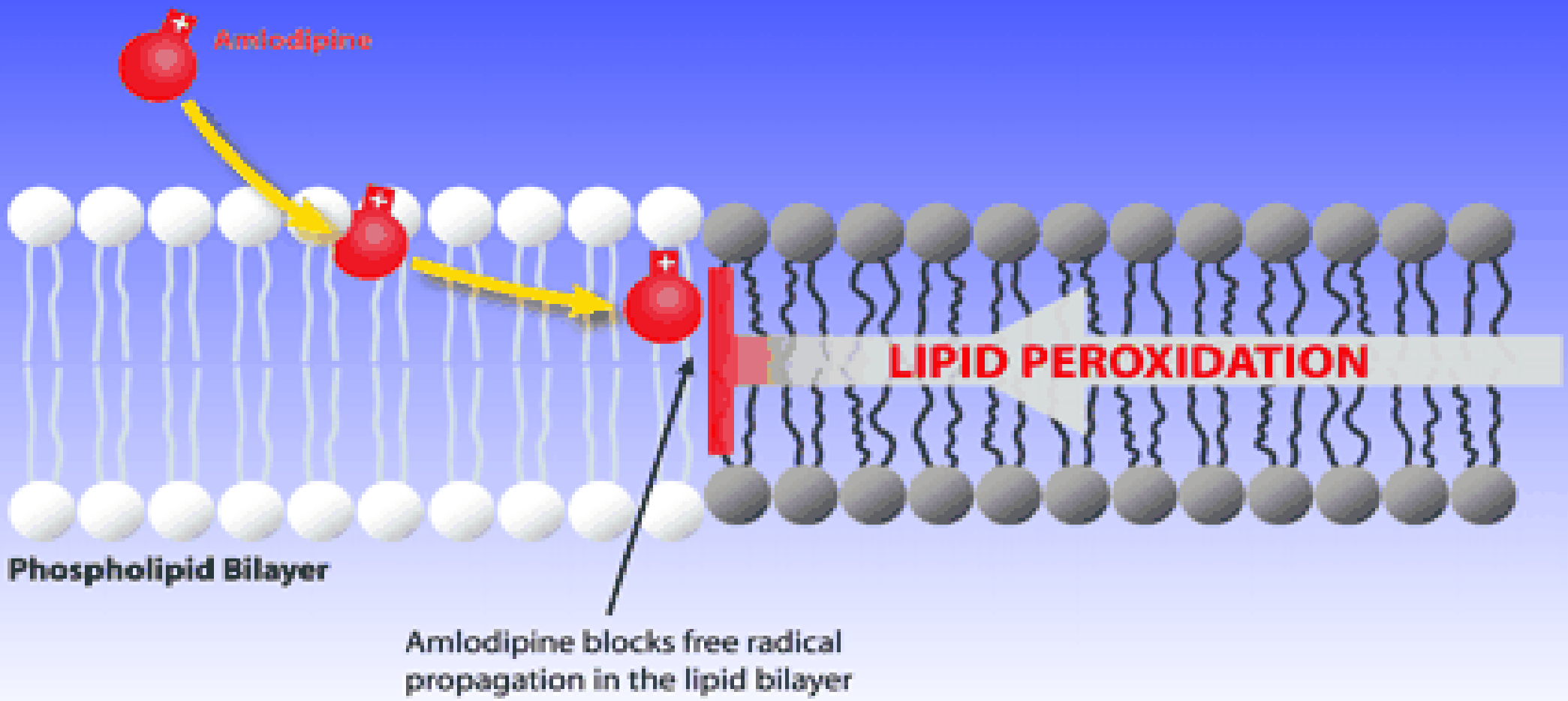
그림 potential anti-atherosclerotic mechanism of action for Calicum channel blocker



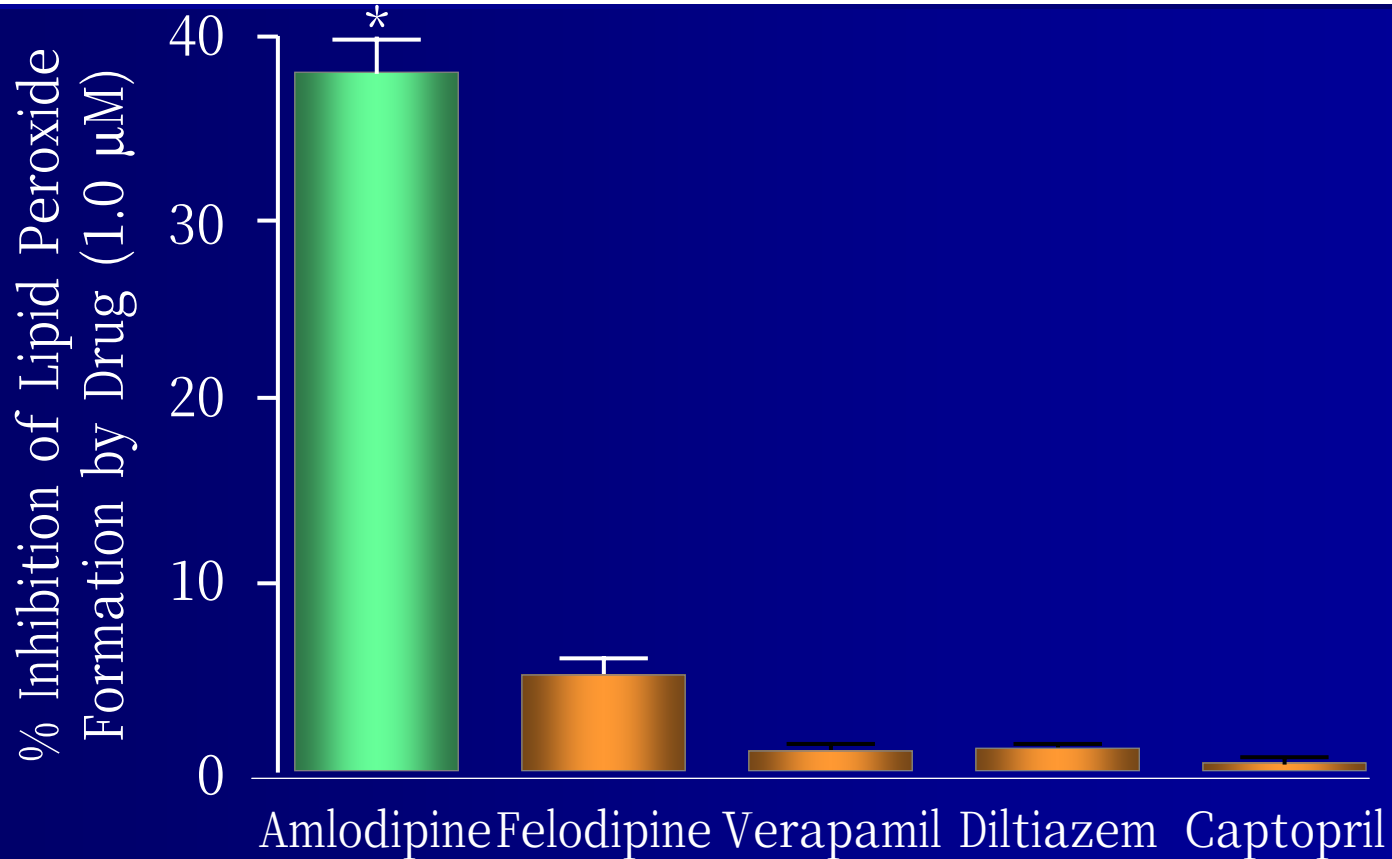
Vasodilation Effect of

Membrane Biochemical Effects

Cell Plasma Membrane



Amlodipine Inhibits Membrane Lipid Peroxidation as compared to Other CCBs



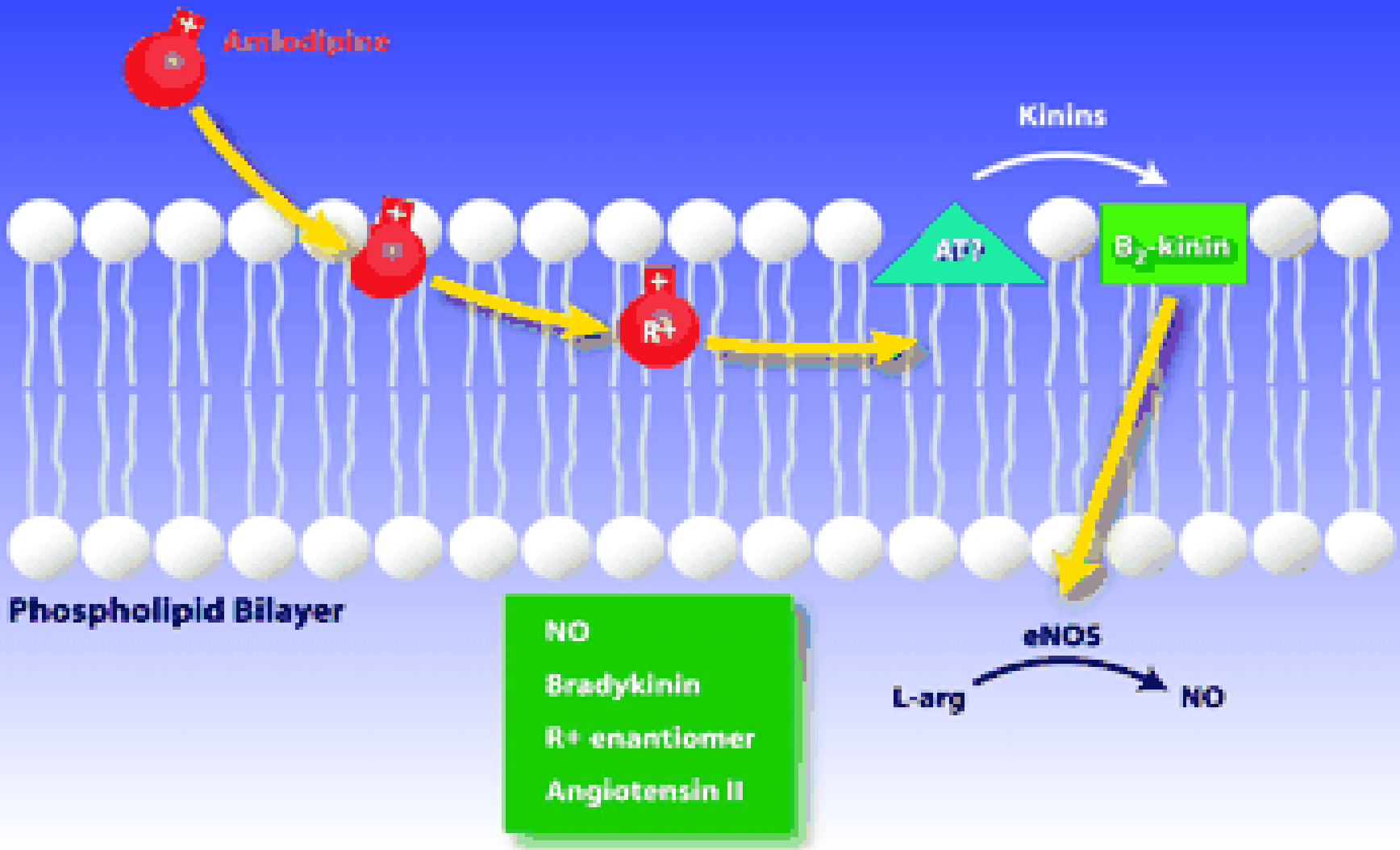
Mean ± SD.

*P<.001 vs control.

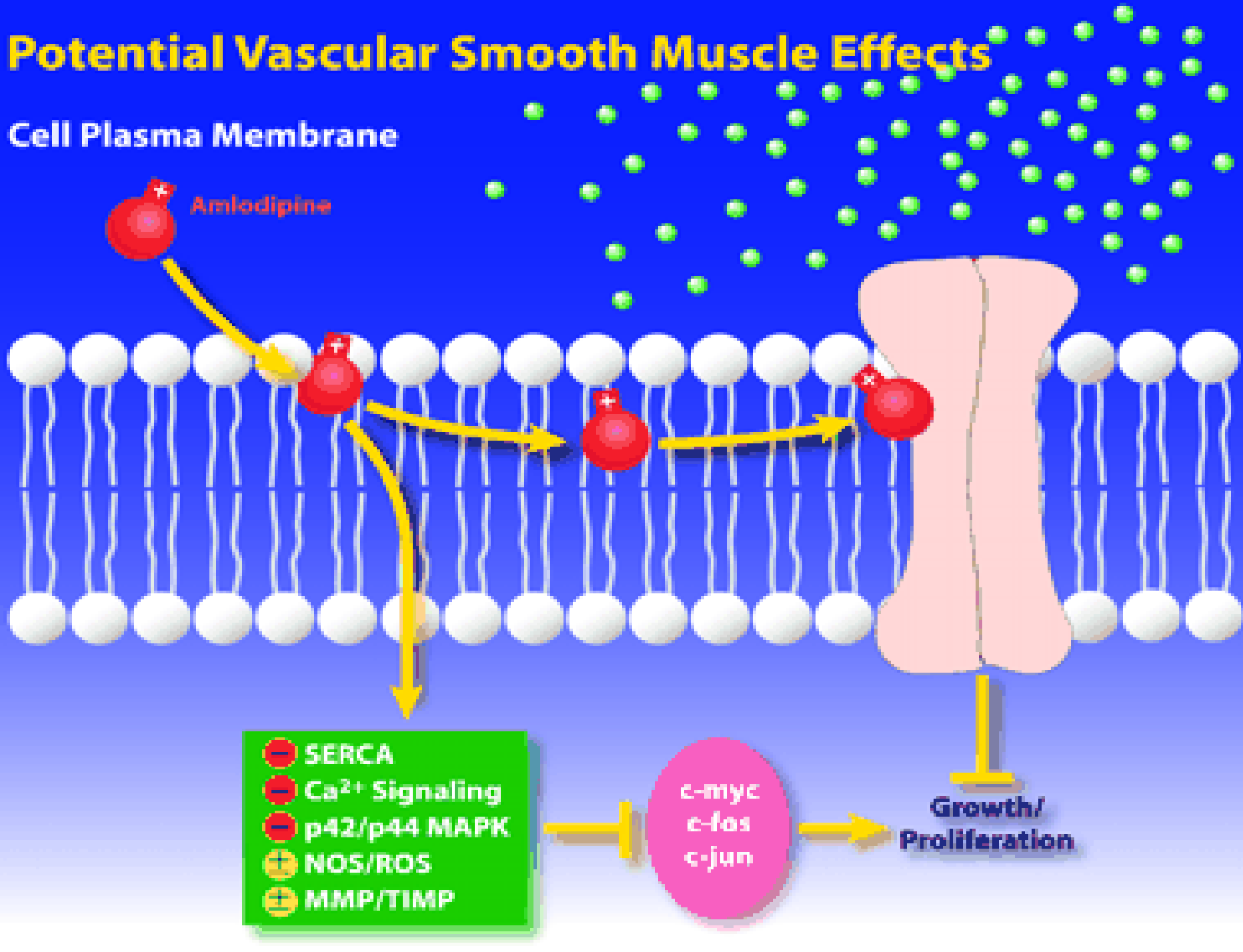
Mason et al. *J Mol Cell Cardiol.* 1999;31:275-281.

Nitric Oxide Biology

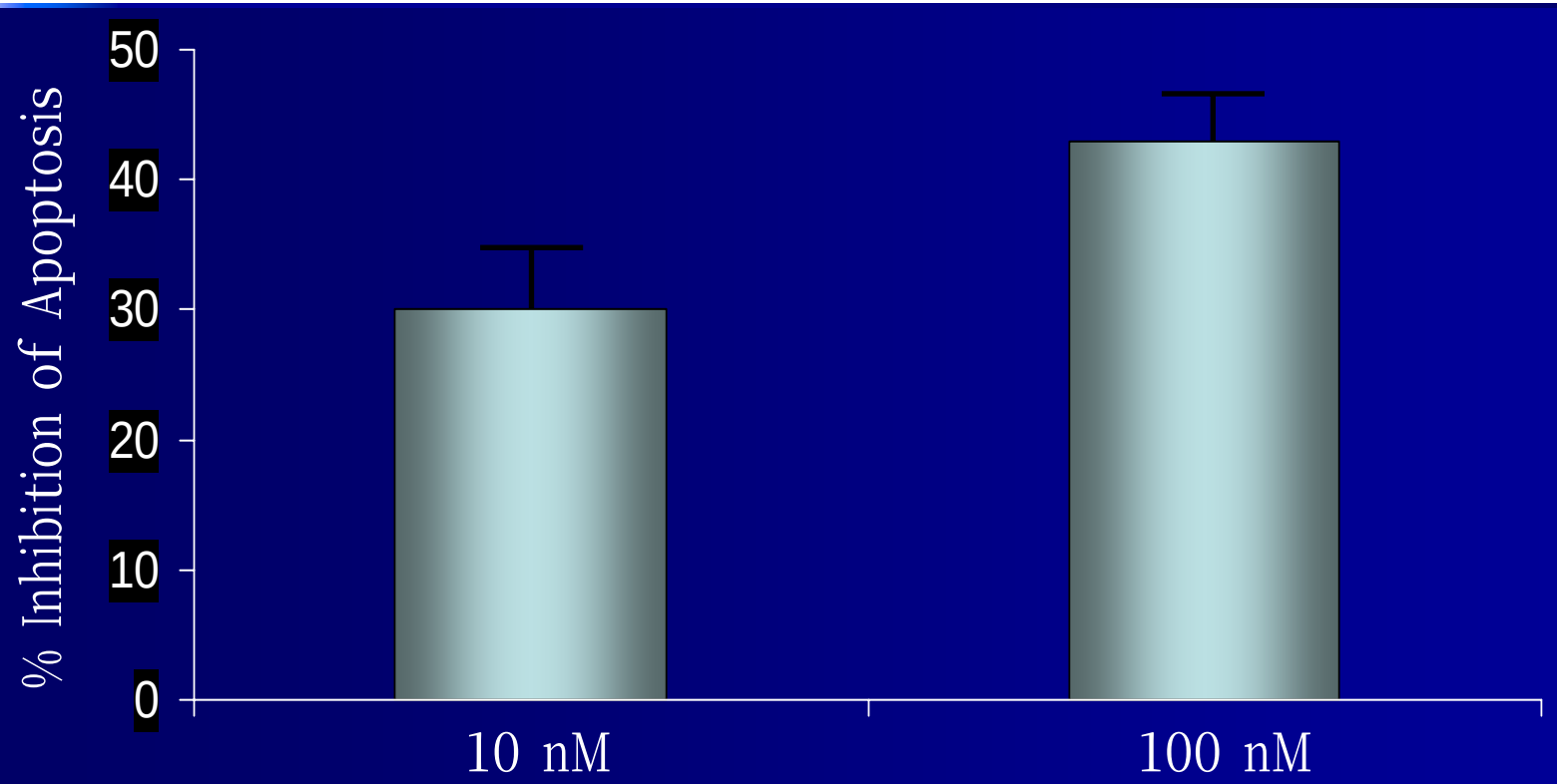
Cell Plasma Membrane



Potential Vascular Smooth Muscle Effects



Amlodipine Protects Against TNF-α–Induced Endothelial Cell Apoptosis



Apoptosis determined by Hoechst 33258 assay
20 ng/mL TNF-α 24-h incubation.

Data on file. Pfizer Inc.
Mason. *Am J Hypertens.* 1998;11:254A. Abstract.

Amlodipine: Additional Mechanisms Under Investigation May Impact on Atherosclerosis

- Membrane-stabilizing effects
- Inhibition of smooth muscle cell migration/proliferation
- Increased nitric oxide production

Mason et al. *J Mol Cell Cardiol*. 1999;31:275-281.
Tulenko et al. *J Cardiovasc Pharmacol*. 1995;26(suppl A):S11-S17.
Zhang and Hintze. *Circulation*. 1998;97:576-580.

CCB and Atherosclerosis

- CCB may have some antioxidant properties
- Small animal studies suggest that some CCBs:
  - Reduce influx of LDL into arterial wall
  - Suppress progression of atherosclerosis in aorta
  - Decrease thromboxane A2 production
- Human studies limited, less compelling
  - Some evidence suggests decrease in new plaque formation
  - Enhanced effect when given with pravastatin?
  - Stronger evidence for carotid plaque regression

Hernandez. Am J of Therap 2003;10:409-14

Carotid IMT Regression – Clinical trials with Calcium Antagonists

Study name	No patients	duration	Comparative	Results drugs
ELSA (*Zanchetti et al, 1998*)	2259	4 years	Lacidipine vs atenolol	Significantly **less carotid IMT progression** in lacidipine group
MIDAS (*Borhani,et al 1996*)	883	3 years	Isradipine vs hydrochlorothiazide	No difference in rate of carotid IMT progression between treatment groups
VHAS (*Zanchetti et al, 1998*)	498	4 years	Verapamil vs chlorthalidone	**Regression** of larger lesions significantly greater in verapamil group
PREVENT (*Pitt et al, 2000*)	825	3 years	Amlodipine vs placebo	**Less carotid IMT progression** in amlodipine group

Effect of Long-acting Nifedipine on Mortality and Cardiovascular Morbidity in Patients With Stable Angina Requiring Treatment (ACTION)

- Goal: to determine effects of long-acting CCA on pts with SAP
- Patients: 7665 pts with treated SAP
- Design:
  - Double-blind, randomized, placebo-controlled trial
  - Nifedipine GITS 60 mg PO QD vs Placebo
- End-point:
  - Combination of death, acute MI, refractory angina, new onset CHF, debilitating stroke, peripheral revascularization

Poole-Wilson et al. Lancet. Vol 364 Sept 4, 2004; 849-857

ACTION: Baseline Treatment Regimens

	Nifedipine (n=3825)	Placebo (n=3840)
Antianginal drug		
β blocker	3032 (79%)	3066 (80%)
Organic nitrate, as needed	2157 (56%)	2175 (57%)
Organic nitrate, daily maintenance	1455 (38%)	1417 (37%)
Other vasodilator	158 (4%)	148 (4%)
Any of the above	3775 (99%)	3784 (99%)
Any two of the above	1888 (49%)	1960 (51%)
Any three or four of the above	563 (15%)	520 (14%)
Lipid-lowering		
Statin	2409 (63%)	2389 (62%)
Fibrate	242 (6%)	246 (6%)
Other	45 (1%)	68 (2%)
Any of the above	2607 (68%)	2591 (67%)
Blood-pressure lowering		
ACE inhibitor	771 (20%)	792 (21%)
Angiotensin-II antagonist	90 (2%)	93 (2%)
Diuretic	432 (11%)	447 (12%)
Other	113 (3%)	81 (2%)
Any of the above	1165 (30%)	1166 (30%)
Other cardiovascular		
Acetylsalicylic acid	3293 (86%)	3304 (86%)
Vitamin K antagonist	156 (4%)	149 (4%)
Cardiac glycoside	30 (1%)	50 (1%)
Amiodarone, sotalol, or other antiarrhythmic	138 (4%)	157 (4%)

Data are number of patients (%).

Poole-Wilson et al. Lancet. Vol 364 Sept 4, 2004; 849-857

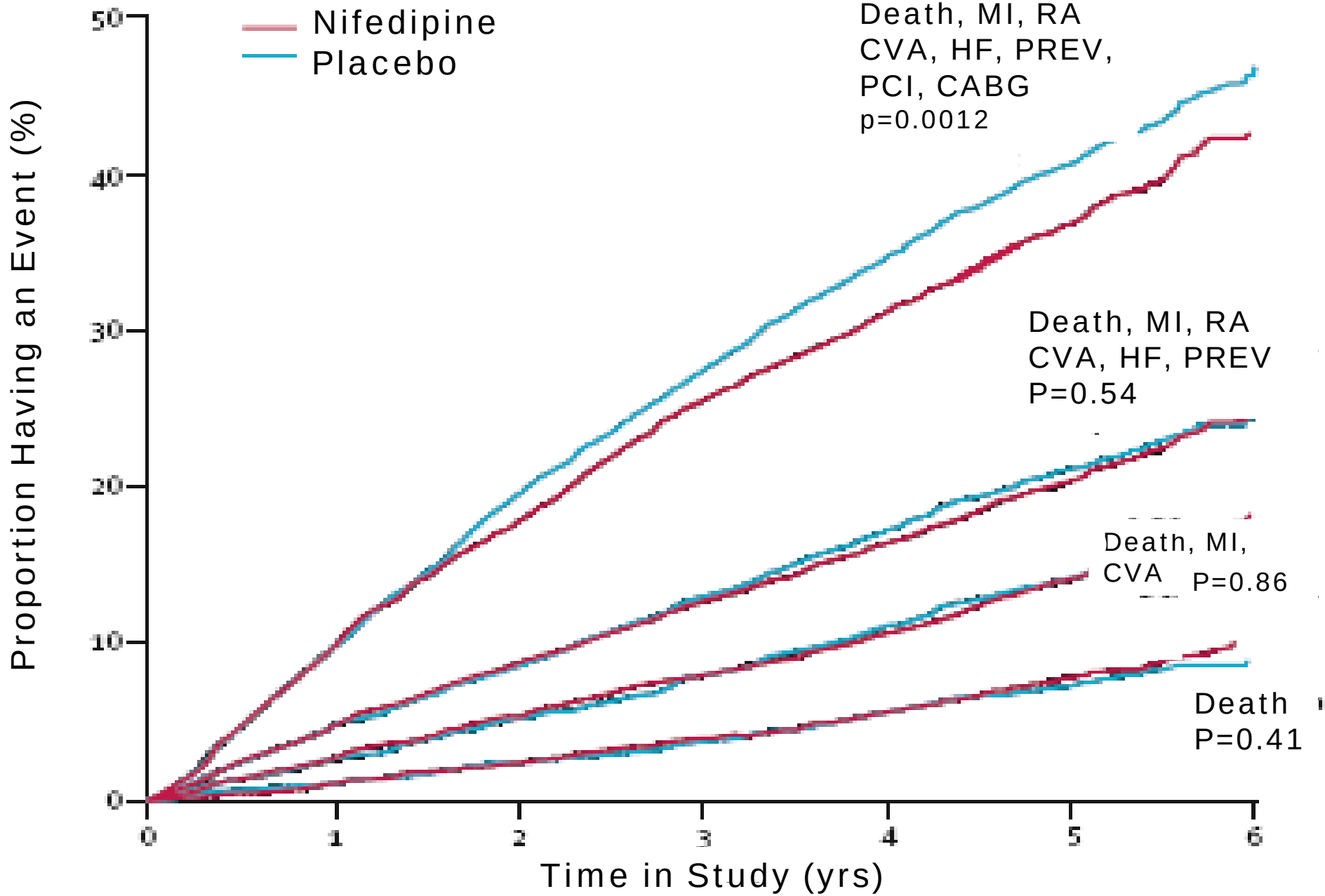
ACTION: Incidence of Clinical Events

	Nifedipine (n=3825)		Placebo (n=3840)		Hazard ratio* (95% CI)	p
	Total number of events	Number of patients with event (incidence per 100 patient-years at risk)	Total number of events	Number of patients with event (incidence per 100 patient-years at risk)		
All-cause mortality	310	310 (1·64)	291	291 (1·53)	1·07 (0·91–1·25)	0·41
Non-cardiovascular	132	132 (0·70)	114	114 (0·60)	1·16 (0·90–1·49)	0·24
Cardiovascular or unknown†	178	178 (0·94)	177	177 (0·93)	1·01 (0·82–1·24)	0·93
Myocardial infarction	320	267 (1·46)	296	257 (1·39)	1·04 (0·88–1·24)	0·62
Refractory angina	171	150 (0·81)	190	174 (0·94)	0·86 (0·69–1·07)	0·18
New overt heart failure	117	86 (0·46)	158	121 (0·65)	0·71 (0·54–0·94)	0·015
Debilitating stroke	82	77 (0·41)	108	99 (0·53)	0·78 (0·58–1·05)	0·10
Peripheral revascularisation	187	146 (0·79)	144	118 (0·63)	1·25 (0·98–1·59)	0·073
Coronary angiography	1200	895 (5·46)	1357	1068 (6·69)	0·82 (0·75–0·90)	<0·0001
Percutaneous coronary intervention	512	385 (2·15)	548	417 (2·34)	0·92 (0·80–1·06)	0·25
Coronary bypass surgery	299	294 (1·62)	373	371 (2·06)	0·79 (0·68–0·92)	0·0021

*Comparison of nifedipine with placebo. †Includes cause unknown (24 nifedipine, 28 placebo).

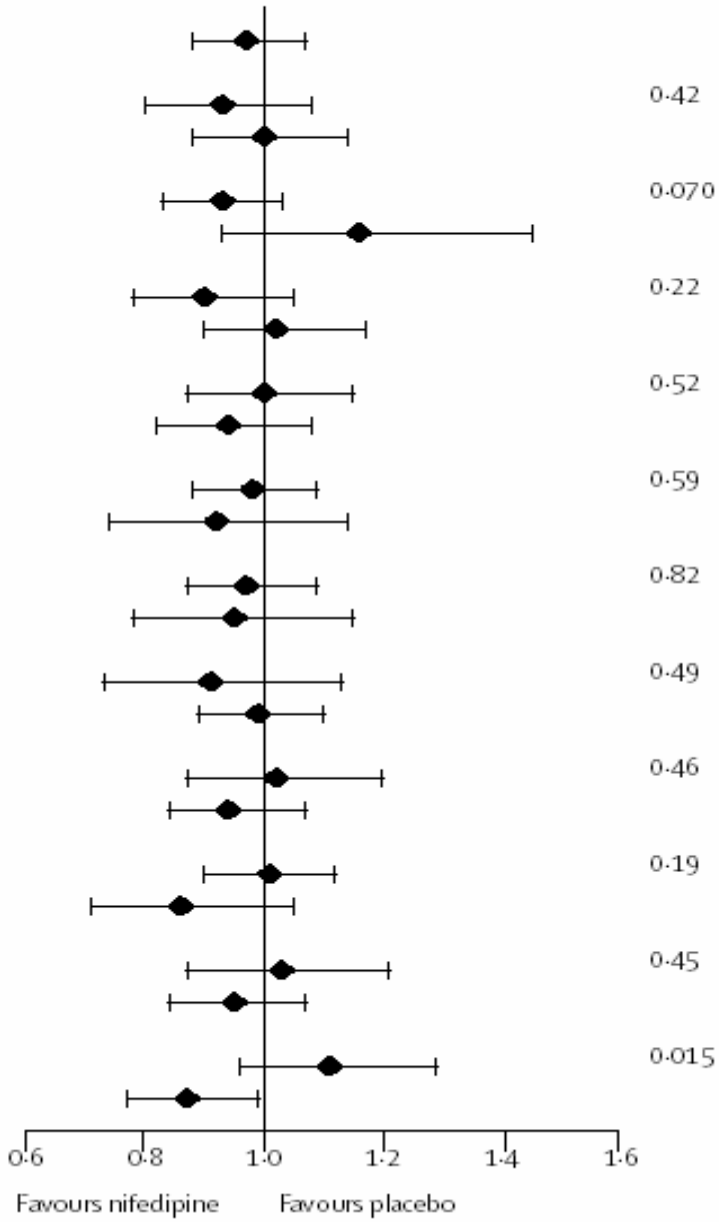
Poole-Wilson et al. Lancet. Vol 364 Sept 4, 2004; 849-857

Time to First Clinical Event



Poole-Wilson et al. Lancet. Vol 364 Sept 4, 2004; 849-857

	Number of patients Nifedipine/placebo	Number of patients with event (rate*) Nifedipine/placebo	p†
All	3825/3840	804 (4·60)/828 (4·75)	
Age (years)			
<65	2053/2064	337 (3·52)/362 (3·79)	0·42
≥65	1772/1776	467 (5·93)/466 (5·90)	
Sex			
Men	3041/3043	638 (4·59)/681 (4·95)	0·070
Women	784/797	166 (4·66)/147 (4·00)	
History of myocardial infarction			
No	1851/1916	345 (4·01)/388 (4·43)	0·22
Yes	1974/1924	459 (5·18)/440 (5·06)	
History of coronary revascularisation			
No	2115/2121	418 (4·32)/420 (4·32)	0·52
Yes	1710/1719	386 (4·96)/408 (5·29)	
Diabetes			
No	3260/3295	640 (4·25)/658 (4·34)	0·59
Yes	565/545	164 (6·81)/170 (7·42)	
Past use of calcium channel blockers			
No	2971/3017	596 (4·39)/620 (4·51)	0·82
Yes	854/823	208 (5·34)/208 (5·63)	
On β blockade at entry			
No	793/774	154 (4·28)/166 (4·72)	0·49
Yes	3032/3066	650 (4·69)/662 (4·75)	
On lipid-lowering drugs at entry			
No	1218/1249	296 (5·50)/297 (5·39)	0·46
Yes	2607/2591	508 (4·21)/531 (4·45)	
On ACE inhibitor or angiotensin-II antagonist at entry			
No	2966/2960	620 (4·56)/615 (4·53)	0·19
Yes	859/880	184 (4·76)/213 (5·50)	
Ejection fraction (%)			
<45	1056/1074	284 (6·02)/281 (5·86)	0·45
≥45	2749/ 2744	517 (4·08)/541 (4·31)	
SBP ≥140 mmHg or DBP ≥90 mmHg			
No	1847/1837	364 (4·28)/328 (3·84)	0·015
Yes	1975/2002	439 (4·90)/500 (5·61)	



Poole-Wilson et al. Lancet. Vol 364 Sept 4, 2004; 849-857

ACTION: Conclusions

In pts with SAP on adequate medical therapy, nifedipine GITS:

- Lowered BP
- Raised HR
- Decreased incidence of:
  - New overt heart failure
  - Coronary angiography
  - Coronary artery bypass surgery
- Did NOT effect:
  - Cardiovascular or all-cause mortality
  - Incidence of myocardial infarction

CAD trials

- INTACT (International Nifedipine Trial on AtherosClerotic Therapy)
  - Fewer new lesions with CCBs
- MHINT (Montreal Heart Institute Nicardipine Trial)
  - Less progression of minimal lesions with CCBs
- CAPARES (The Coronary AngioPlasty Amlodipine REstenosis Study)
  - Reduce need for PTCA & combined endpoint of major adverse clinical events
- PREVENT (The Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial)

Effect of Amlodipine on the Progression of Atherosclerosis and the Occurrence of Clinical Events (PREVENT)

- Goal: to determine the effects of amlodipine on atheroslcerotic progression and cardiovascular clinical events
- Patients: 825 pts with angiographic CAD
- Design:
  - Prospective, multicenter, randomized, placebo-controlled, double-masked clinical trial
  - Treatment with amlodipine vs placebo
  - 3 yr follow-up
- Outcomes measured:
  - Angiographically evaluated (non-intervened) coronary atherosclerosis
  - Carotid artery atherosclerosis (ultrasound)
  - All-cause mortality, cardiovascular events

Pitt et al. Circ 2000;103(13):1503-1510

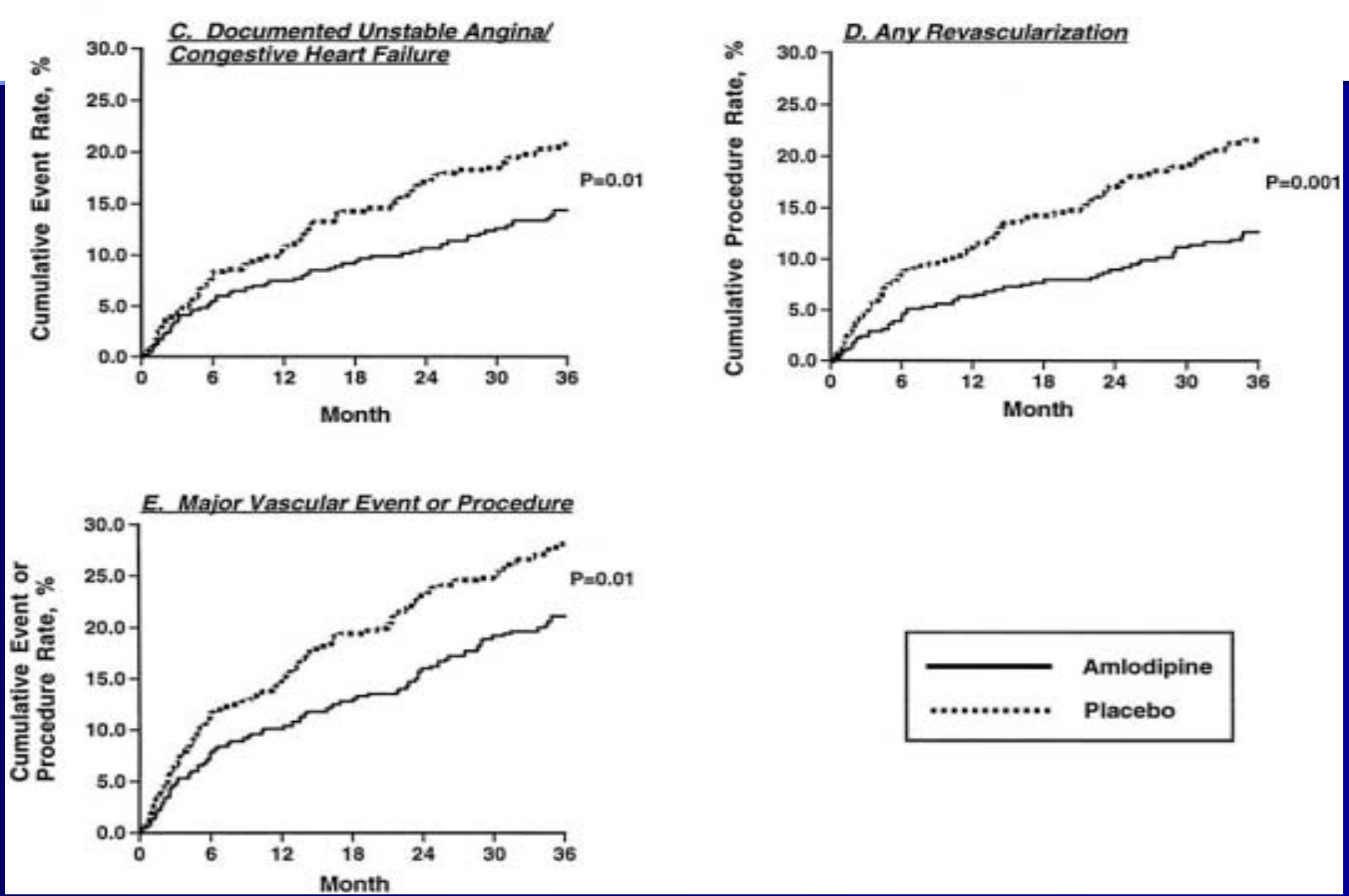
PREVENT: Clinical Events/Procedures

Event	Amlodipine Group (n=417) No. of Participants With Event	Amlodipine Group (n=417) Annualized Rate per 100	Placebo Group (n=408) No. of Participants With Event	Placebo Group (n=408) Annualized Rate per 100	HR (Amlodipine/ Placebo)	95% CI for HR*	Life-Table P*
All-cause mortality	6	0.5	8	0.7	0.74	0.26–2.12	0.57‡
Major vascular events							
Fatal/nonfatal MI	19	1.5	20	1.6	0.94	0.50–1.76	
Fatal/nonfatal stroke	5	0.4	5	0.4	0.99	0.29–3.41	
Other fatal vascular events	0	0.0	4	0.3	...	...	
Any major vascular event	23	1.8	28	2.3	0.82	0.47–1.42	0.47‡
Other documented nonfatal vascular events							
Major vascular procedures							
CABG	17	1.4	29	2.4	0.57	0.31–1.03	
Other major procedure†	40	3.2	67	5.5	0.56	0.38–0.83	

*From proportional hazards models (*P* values presented only for prespecified composite event outcomes).
†Includes angioplasty, stenting, and arthrectomy.
‡Prespecified event of interest.

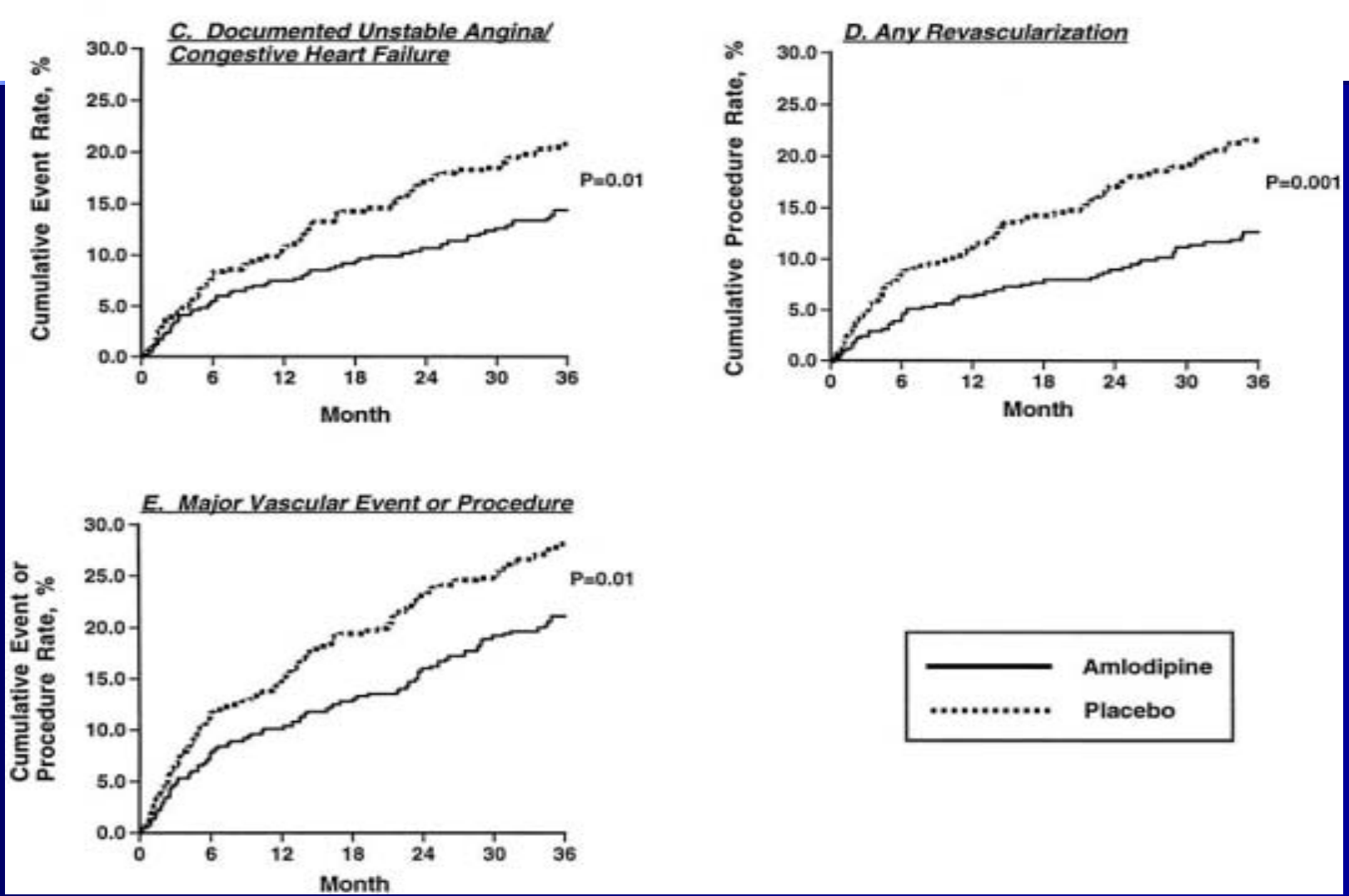
Pitt et al. Circ 2000;103(13):1503-1510

PREVENT: Other Endpoints



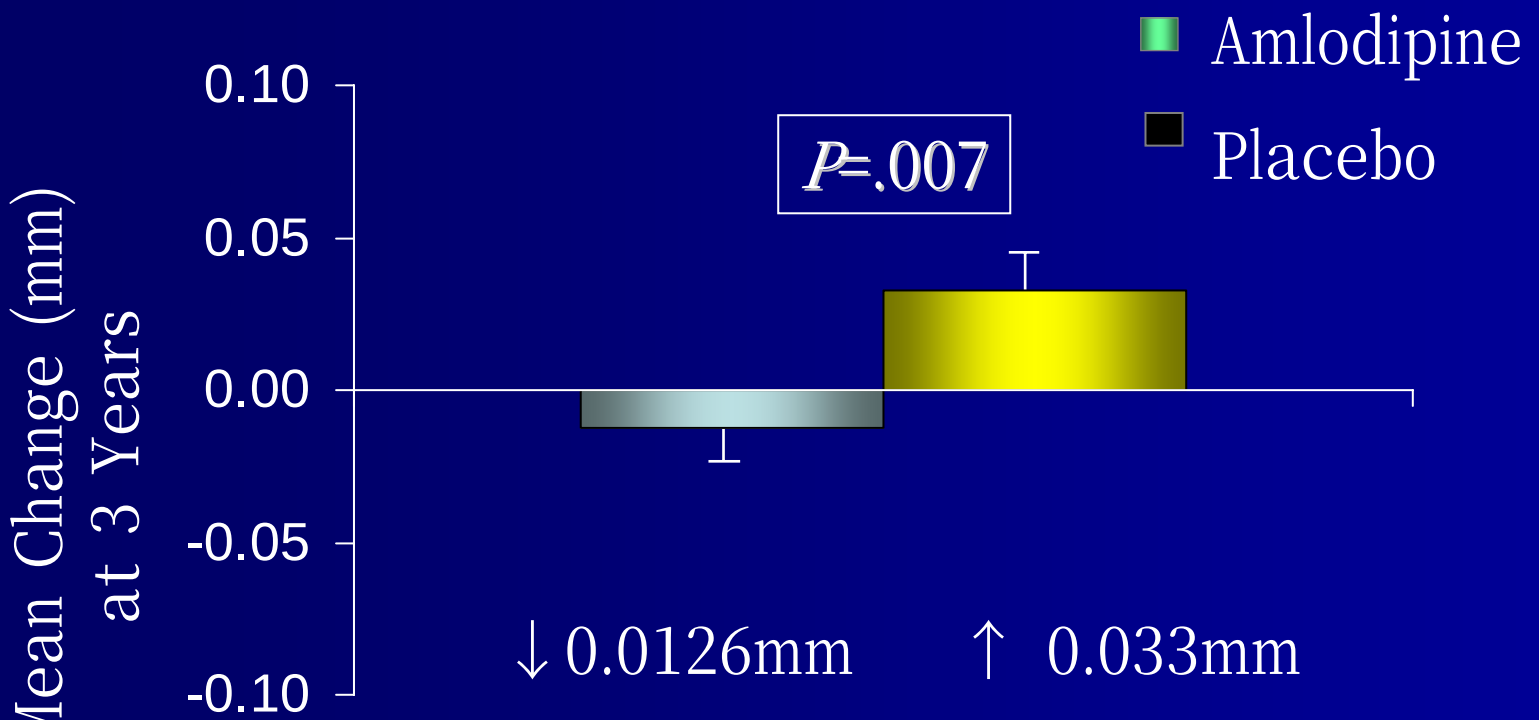
Pitt et al. Circ 2000;103(13):1503-1510

PREVENT: Other Endpoints



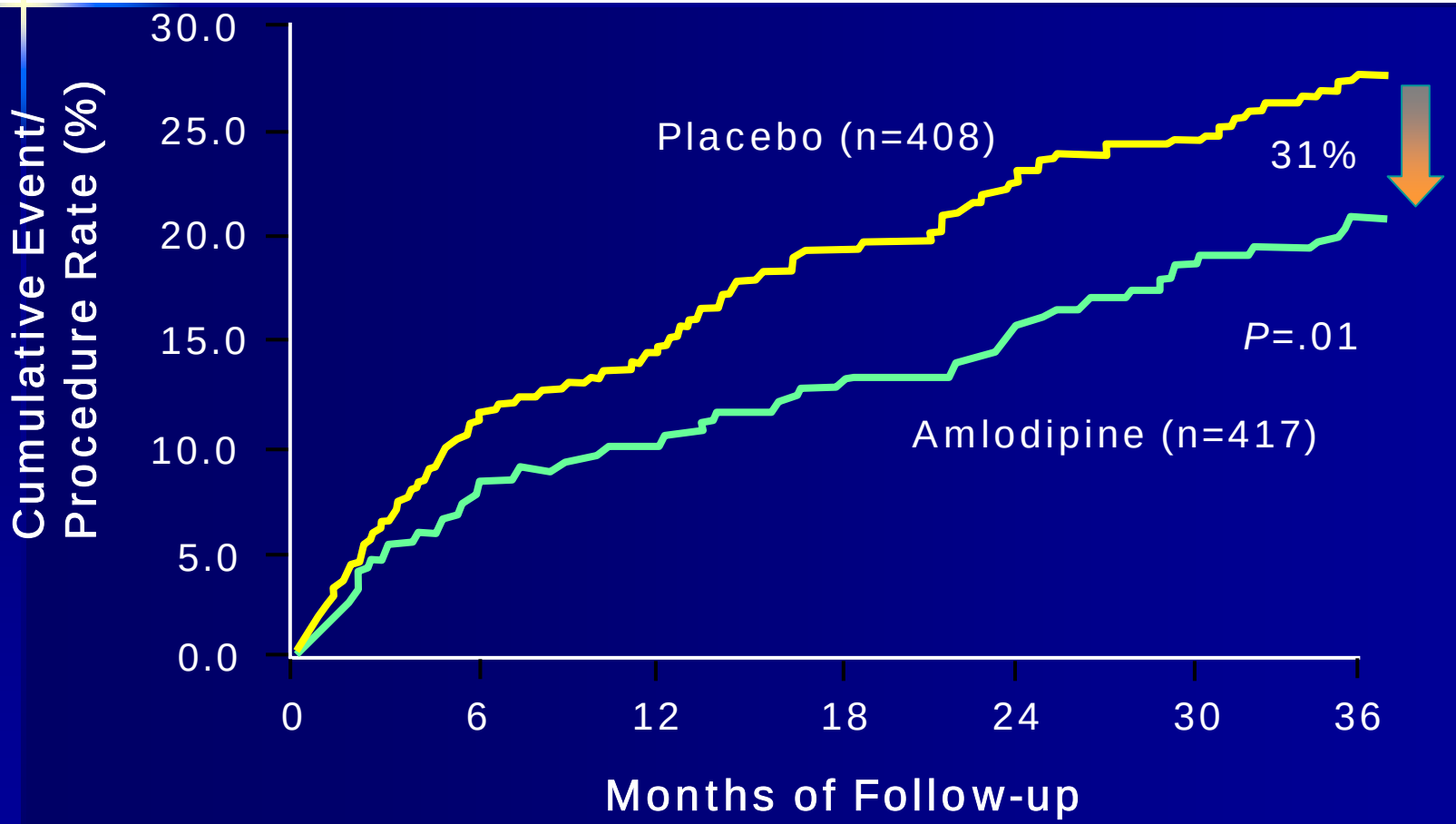
Pitt et al. Circ 2000;103(13):1503-1510

PREVENT: Effect of Amlodipine on Carotid Atherosclerosis by B-Mode Measurement of IMT



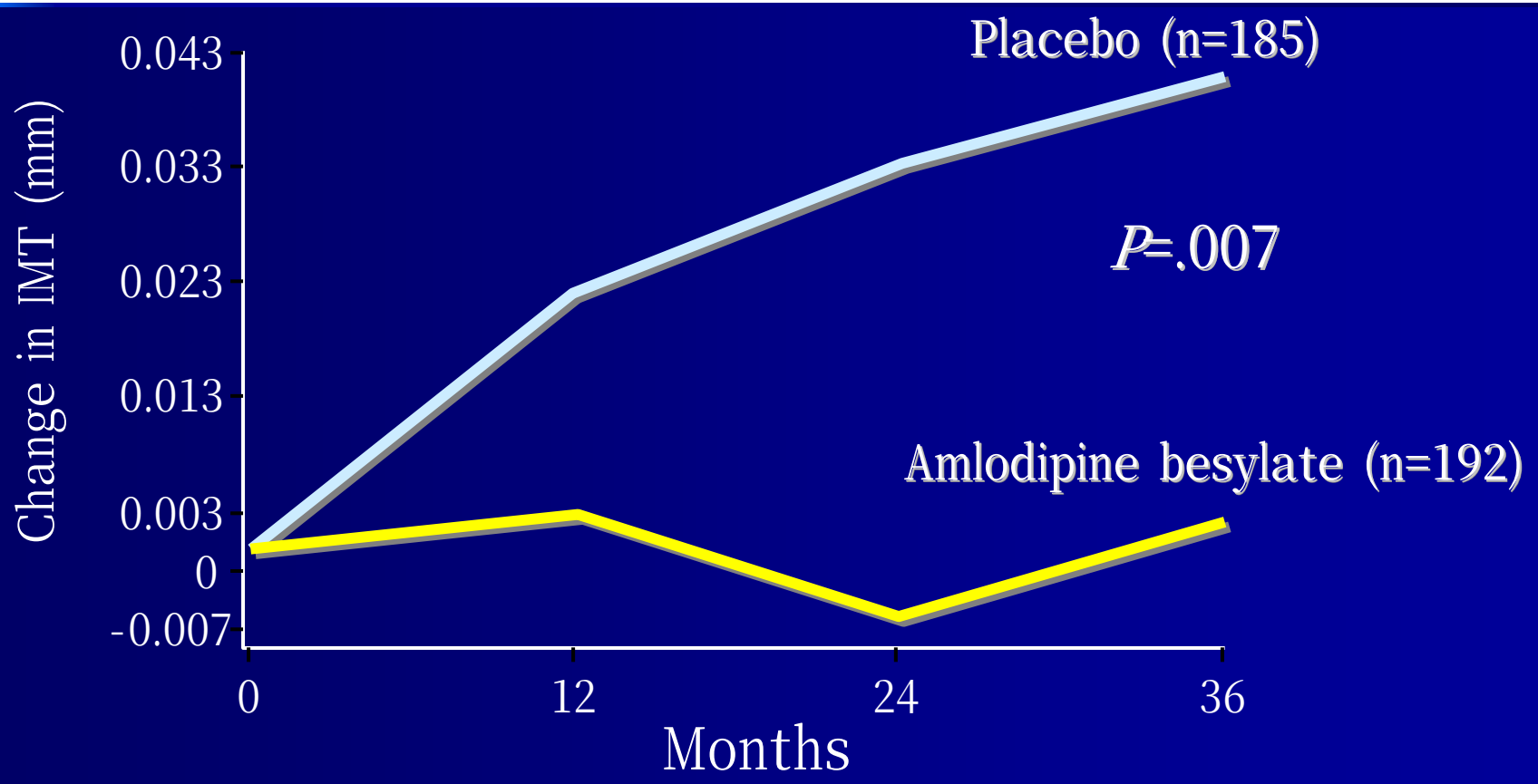
Pitt et al. *Circulation*. 2000;102:1503-1510.

PREVENT: Occurrence of Major Vascular Event or Procedure



Pitt et al. *Circulation*. 2000;102:1503-1510.

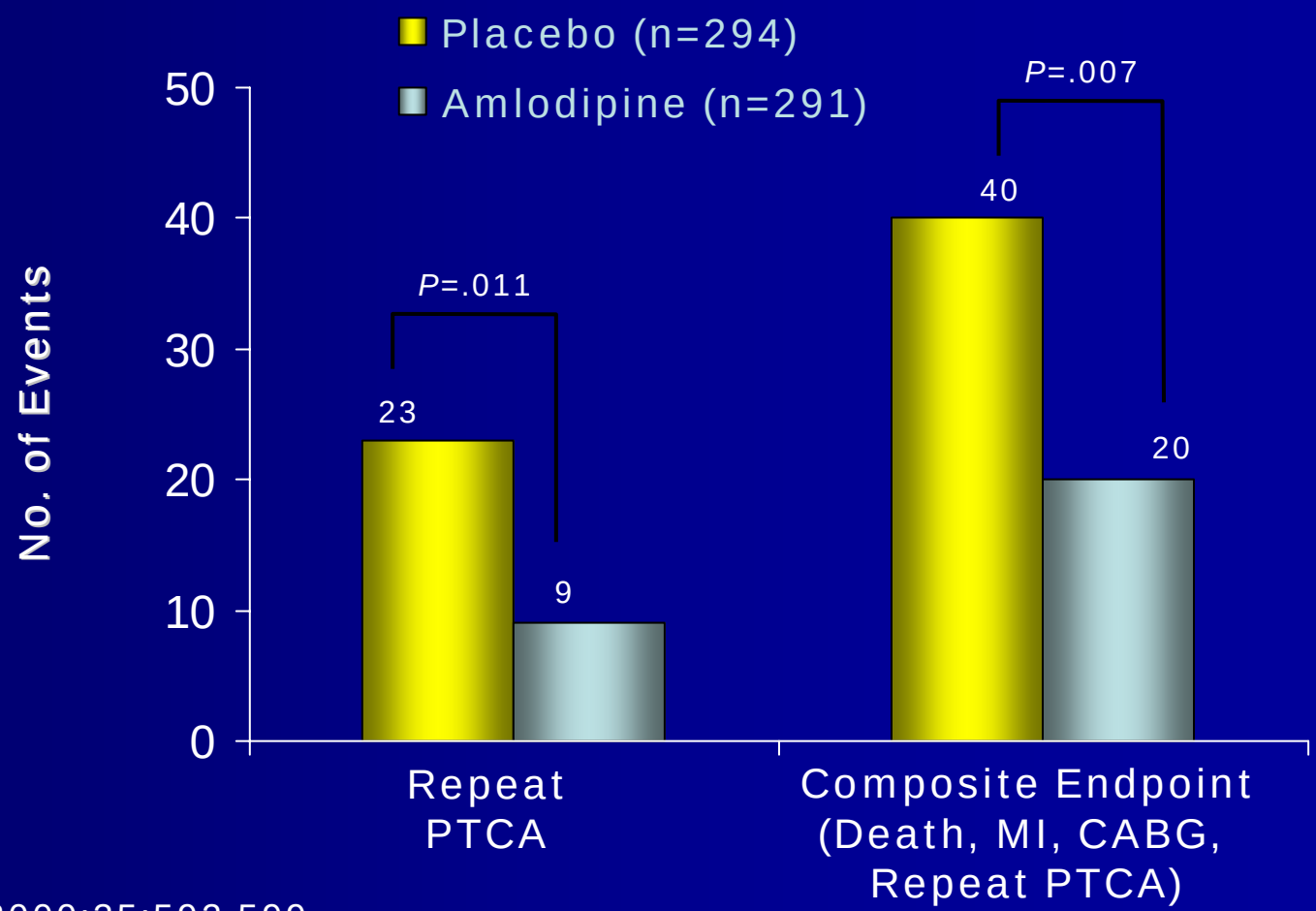
PREVENT: Effect of Amlodipine besylate on Carotid Atherosclerosis by B-Mode Ultrasound



N=27,478 observations.
Average baseline IMT=0.95 mm.

CAPARES: Amlodipine Treatment Reduced Need for Repeat PTCA

- N=635
- No change in primary endpoint: loss in minimal lumen diameter
- Significant reduction in composite clinical endpoint and repeat PTCA



Jørgensen et al. *J Am Coll Cardiol*. 2000;35:592-599.

Effect of Antihypertensive Agents on Cardiovascular Events in Patients With Coronary Disease and Normal Blood Pressure (CAMELOT)

- Goal: compare the effects of amlodipine or enalapril vs placebo in pts with CAD
- Patients: 1991 pts with angiographically documented CAD and diastolic BP <100 mmHg
- Design: Multicenter, double-blind, randomized, placebo-controlled trial
- Outcomes measured:
  - Incidence of cardiovascular events (cv death, nonfatal MI, cardiac arrest, coronary revascularization, hospitalization for angina/CHF, CVA/TIA, PVD)
  - Subgroup analysis with IVUS to determine antiatherosclerotic effects

Nissen et al. JAMA 2004;292(18):2217-26

CAMELOT: Baseline Characteristics and Treatments

Baseline Characteristics	No. (%) of Patients			
	Amlodipine (n = 663)	Placebo (n = 655)	Enalapril (n = 673)	*P* Value*
Age, mean (SD), y	57.3 (9.7)	57.2 (9.5)	58.5 (9.9)	.02
Men	506 (76.3)	478 (73.0)	484 (71.9)	.16
White race	593 (89.4)	583 (89.0)	601 (89.3)	.97
Weight, mean (SD), kg	89.7 (18.3)	88.4 (16.4)	88.5 (18.4)	.31
Body mass index, mean (SD)†	29.9 (5.5)	29.7 (5.0)	29.7 (5.5)	.72
Low-density lipoprotein cholesterol, mean (SD), mg/dL	104 (32)	100 (32)	101 (31)	.04
Blood pressure, mean (SD), mm Hg				
Systolic	129.5 (15.5)	128.9 (15.6)	128.9 (16.3)	.76
Diastolic	77.7 (9.1)	77.6 (8.9)	77.2 (9.4)	.54
Medical history				
Hypertension	407 (61.4)	395 (60.3)	402 (59.7)	.82
Stroke	24 (3.6)	27 (4.1)	30 (4.5)	.74
Diabetes	115 (17.3)	130 (19.8)	118 (17.5)	.42
Class 4 angina‡	54 (8.1)	65 (9.9)	56 (8.3)	.45
Vessel disease§				
1	203 (30.6)	185 (28.2)	187 (27.8)	.47
2	217 (32.7)	223 (34.1)	243 (36.1)	.42
3	230 (34.7)	239 (36.5)	234 (34.8)	.74
Percutaneous intervention	173 (26.1)	199 (30.4)	192 (28.5)	.22
Coronary artery bypass graft surgery	54 (8.0)	54 (8.2)	46 (6.8)	.59
Myocardial infarction	248 (37.4)	247 (37.7)	271 (40.3)	.50
Current smoker	178 (27.0)	182 (27.9)	166 (24.8)	.41
Treatment received				
Titrated to full target dosage	575 (86.7)	588 (89.8)	567 (84.3)	.01
Dose received, mean (SD), mg	8.6 (2.0)	NA	17.4 (3.7)	NA
Completed trial	619 (93.4)	614 (93.7)	622 (92.4)	.62
Discontinued study medication	194 (29.3)	204 (31.1)	236 (35.1)	.07
Concomitant medications				
Statin	551 (83.1)	552 (84.3)	550 (81.7)	.46
Diuretic	213 (32.1)	219 (33.4)	180 (26.8)	.02
β-Blocker	492 (74.2)	516 (78.8)	503 (74.7)	.11
Aspirin	626 (94.4)	625 (95.4)	637 (94.7)	.69
Angiotensin-converting enzyme inhibitor	49 (7.4)	84 (12.8)	47 (7.0)	<.001
Angiotensin receptor blocker	11 (1.7)	15 (2.3)	11 (1.6)	.61
Calcium channel blocker	33 (5.0)	79 (12.1)	41 (6.1)	<.001

Abbreviation: NA, not applicable.
SI conversion factor: to convert cholesterol to mmol/L, multiply values by 0.0259.
*Calculated by analysis of variance or χ^2 test.
†Calculated as weight in kilograms divided by the square of height in meters.
‡Canadian Cardiovascular Society class 4 (angina at any level of physical exertion).
§Number of vessels with at least 1 stenosis >20% by visual estimation

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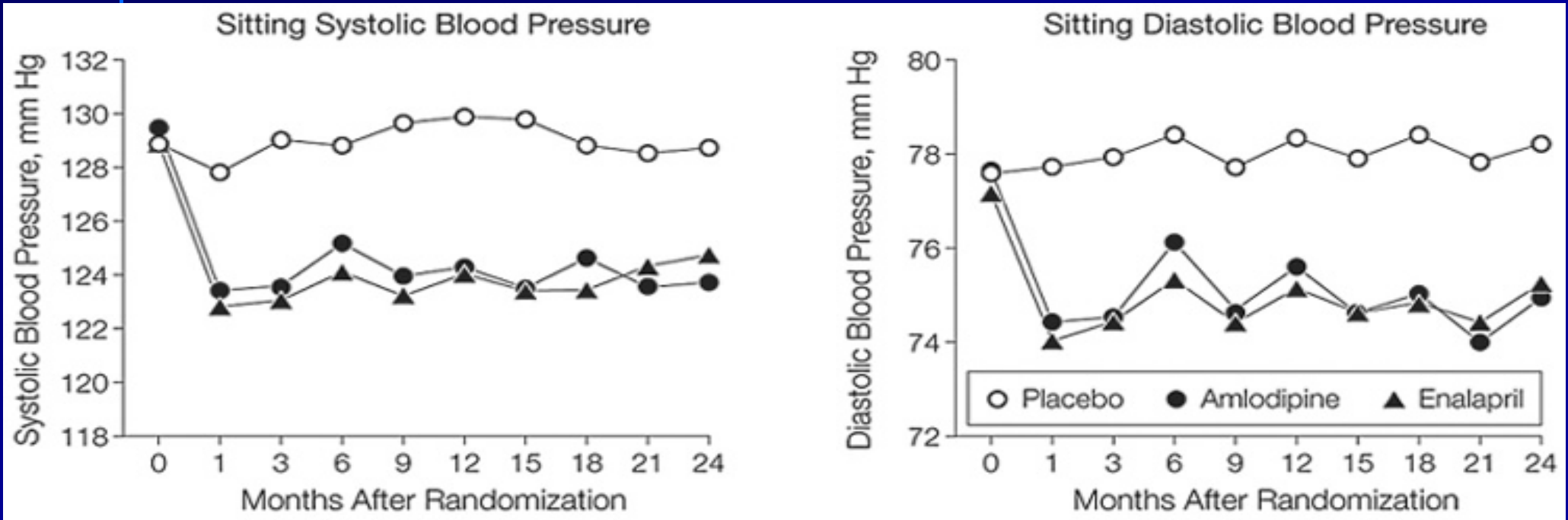
CAMELOT: Mean Blood Pressure



P<.001 for both vs placebo

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CAMELOT: Event Rates

Outcomes	Cardiovascular Event Rates, No. (%)			Amlodipine vs Placebo		Amlodipine vs Enalapril		Enalapril vs Placebo	
	Amlodipine	Placebo	Enalapril	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Individual components									
Nonfatal MI	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0.37-1.46)	.37	1.32 (0.60-2.90)	.49	0.55 (0.26-1.15)	.11
Stroke or TIA	6 (0.9)	12 (1.8)	8 (1.2)	0.50 (0.19-1.32)	.15	0.76 (0.26-2.20)	.61	0.66 (0.27-1.62)	.36
Cardiovascular death	5 (0.8)	2 (0.3)	5 (0.7)	2.46 (0.48-12.7)	.27	1.07 (0.31-3.70)	.91	2.33 (0.45-12.1)	.30
Hospitalization for CHF	3 (0.5)	5 (0.8)	4 (0.6)	0.59 (0.14-2.47)	.46	0.78 (0.17-3.47)	.74	0.78 (0.21-2.90)	.71
Resuscitated cardiac arrest	0	4 (0.6)	1 (0.1)	NA	.04	NA	.31	0.24 (0.03-2.15)	.17
New-onset peripheral vascular disease	5 (0.8)	2 (0.3)	8 (1.2)	2.6 (0.50-13.4)	.24	0.63 (0.21-1.93)	.41	3.91 (0.83-18.4)	.06
All-cause mortality	7 (1.1)	6 (0.9)	8 (1.2)	1.14 (0.38-3.40)	.82	0.92 (0.33-2.53)	.87	1.26 (0.44-3.65)	.67

Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

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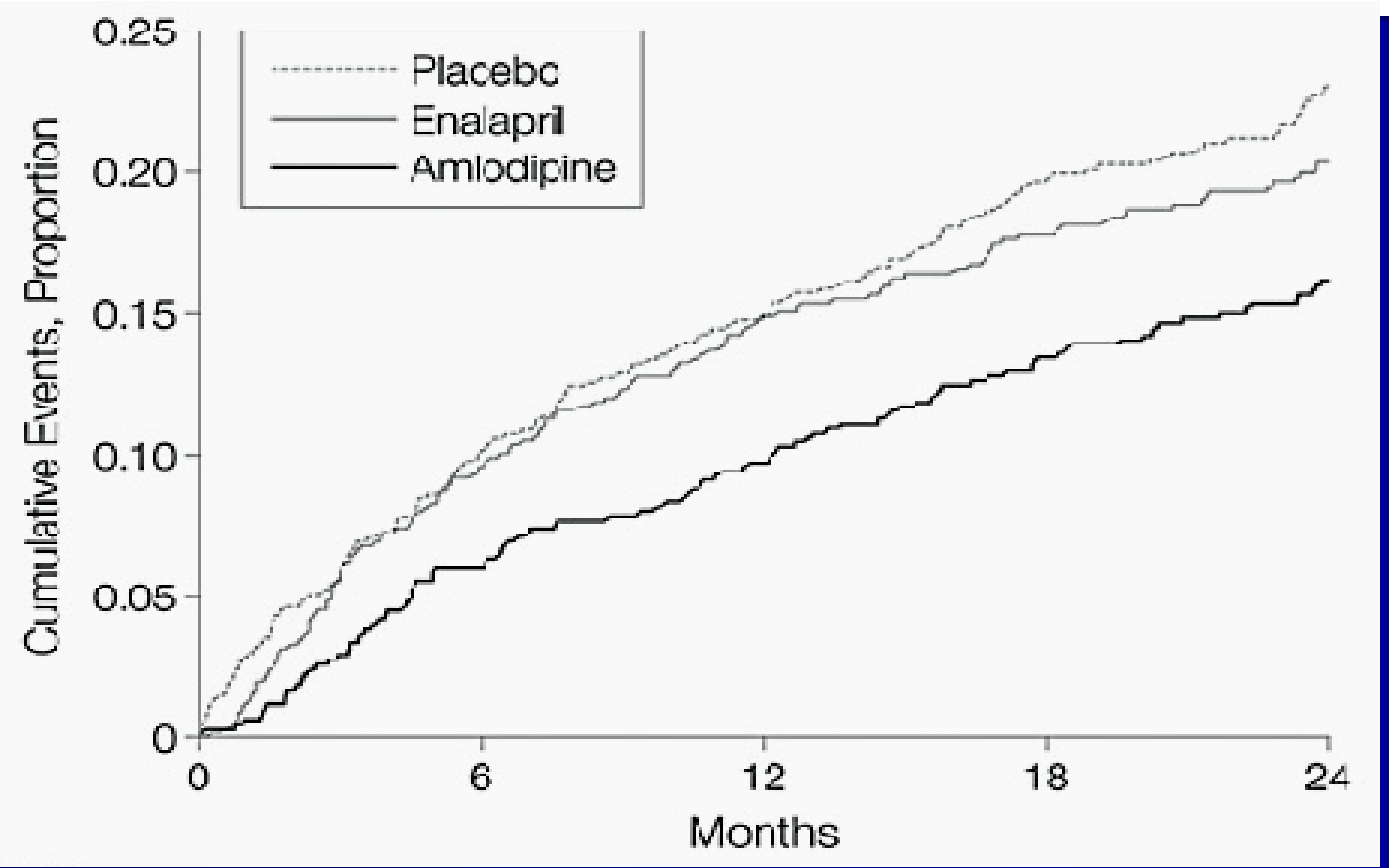
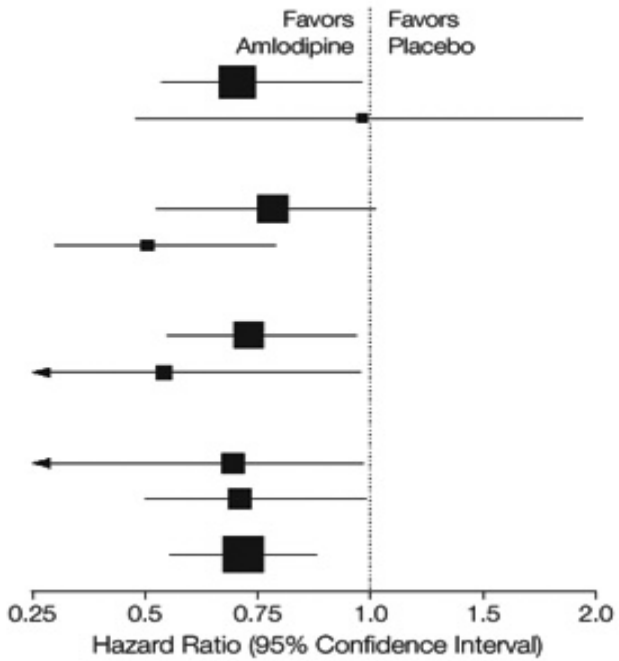
CAMELOT: Cumulative Event Rates



Nissen et al. JAMA 2004;292(18):2217-26

CAMELOT: Amlodipine vs Placebo Subgroup Analysis

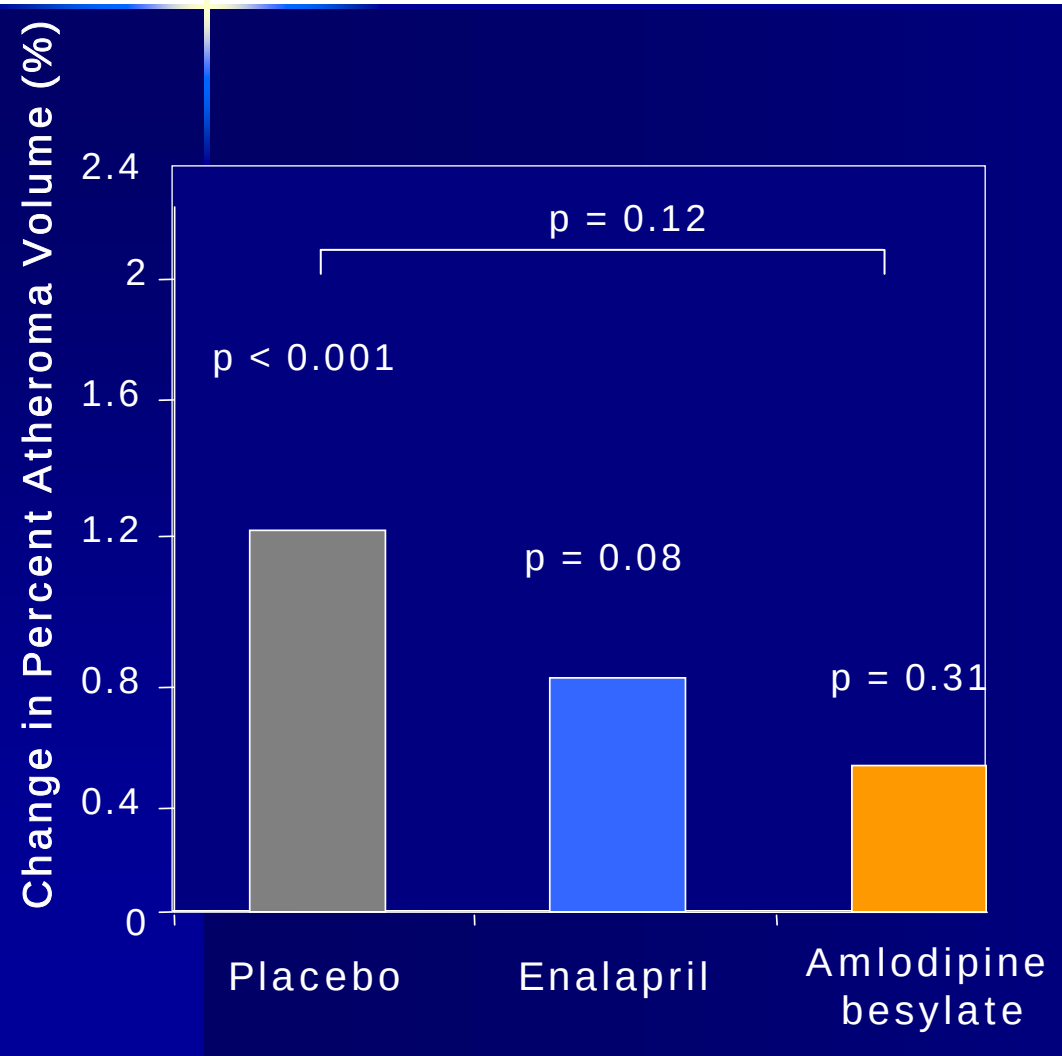
Lipid-Lowering Therapy	2-Year Event Rates, No./Total (%) Amlodipine	Placebo	*P* Value	Relative Risk Reduction, %
Treated With Statin	93/551 (16.9)	135/552 (24.5)	.002	33.9
Not Treated With Statin	17/112 (15.2)	16/103 (15.5)	.91	4.1
Age, y				
<65	84/487 (17.2)	109/498 (21.9)	.07	22.9
≥65	26/176 (14.8)	42/157 (26.8)	.006	49.3
Sex				
Male	88/506 (17.4)	110/478 (23.0)	.03	26.8
Female	22/157 (14.0)	41/177 (23.2)	.03	42.8
Sitting Systolic Blood Pressure				
≤Mean	51/340 (15.0)	77/359 (21.4)	.03	32.2
>Mean	59/323 (18.3)	73/295 (24.7)	.04	29.6
All Patients	110/663 (16.6)	151/655 (23.1)	.003	30.9



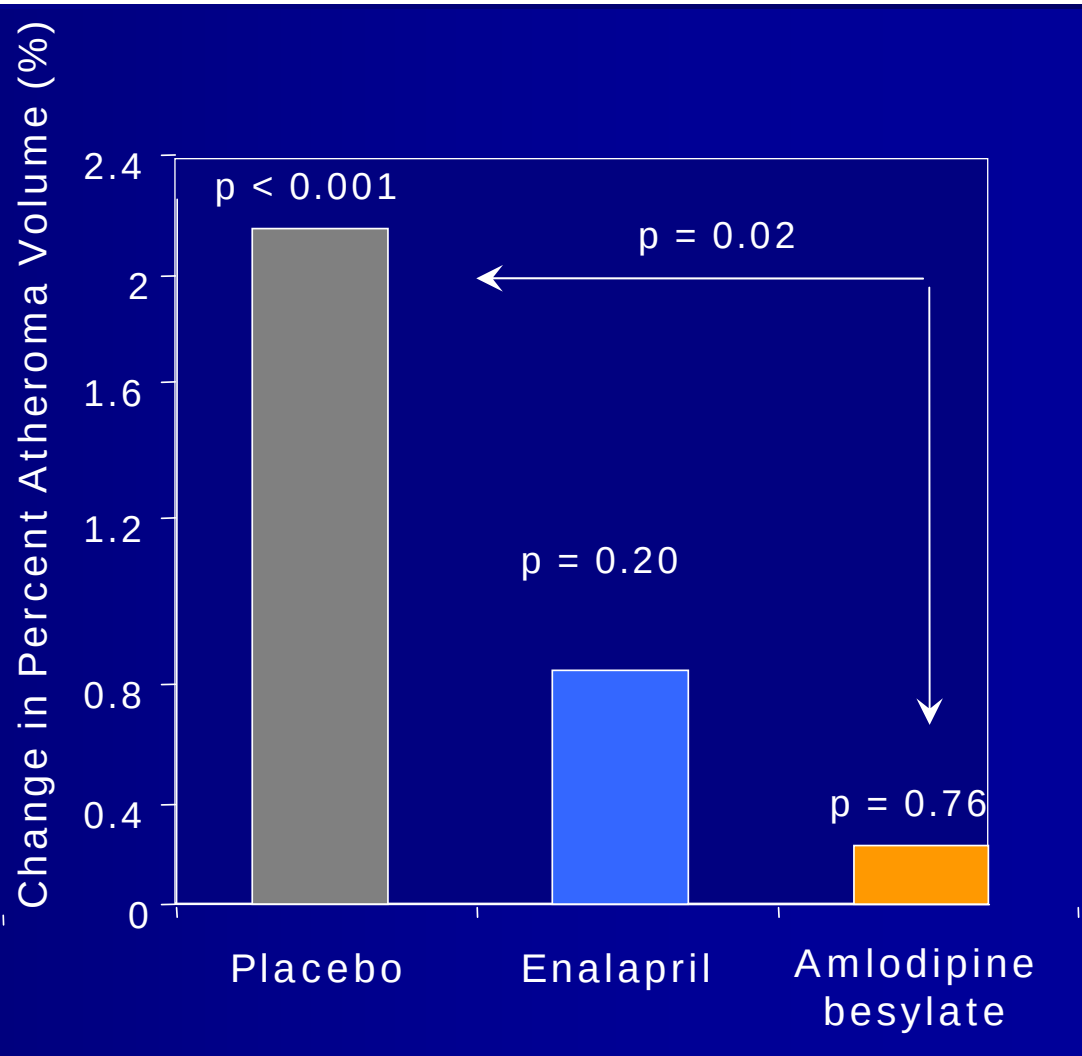
Nissen et al. JAMA 2004;292(18):2217-26

IVUS Progression: Percent Atheroma Volume

All randomized patients (n=274)



Patients with BP ≥mean (n=136)



CAMELOT: Conclusions

In normotensive pts with CAD, additional amlodipine therapy:

- Further decreases
  - Overall adverse cardiovascular events
  - Rates of coronary revascularization
  - Hospitalization for angina
  - Revascularization after MI
  - Rate of coronary atherosclerotic progression
  -
- Did not effect rates of:
  - Cardiovascular and all-cause mortality
  - Nonfatal MI or CVA
  - Hospitalization for CHF

Conclusions

- Not all CCBs are created equally
  - 1st generation, short-acting formulations may be detrimental in CAD, CHF
  - 2nd & 3rd generation, long-acting formulations are generally safer
  -
- CCBs have a well-established role in treating HTN and angina

Conclusions

In stable pts, CCBs:

- May have additional benefits of carotid plaque regression and CVA reduction
- Have equivalent mortality rates compared to diuretic, beta-blocker and ARB therapy
- Have equivalent (or more favorable) rates of MI
- Decrease anginal symptoms and need for invasive procedures
- (DHPs) do *not* increase risk of CHF

Thank you for your attention