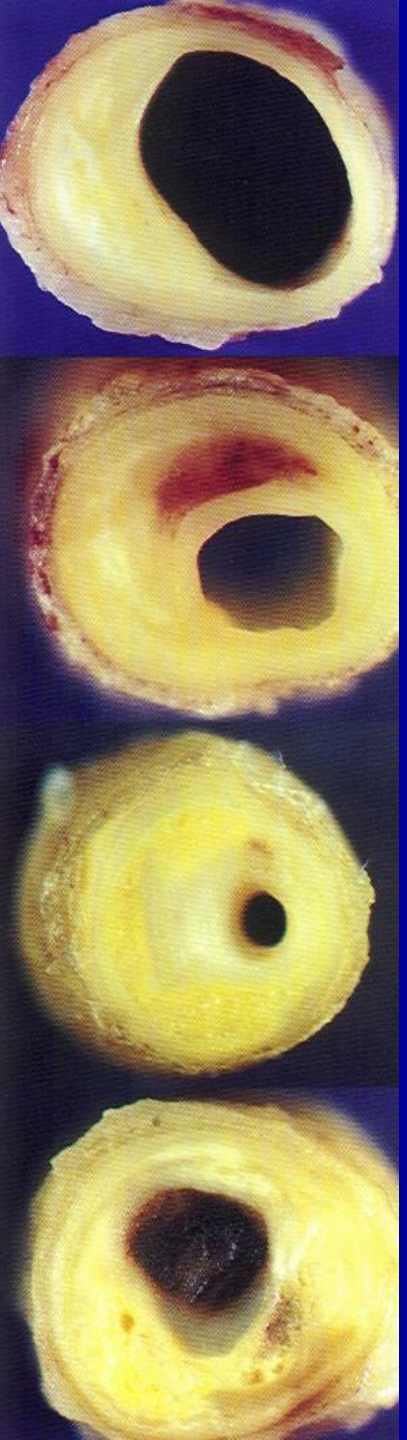
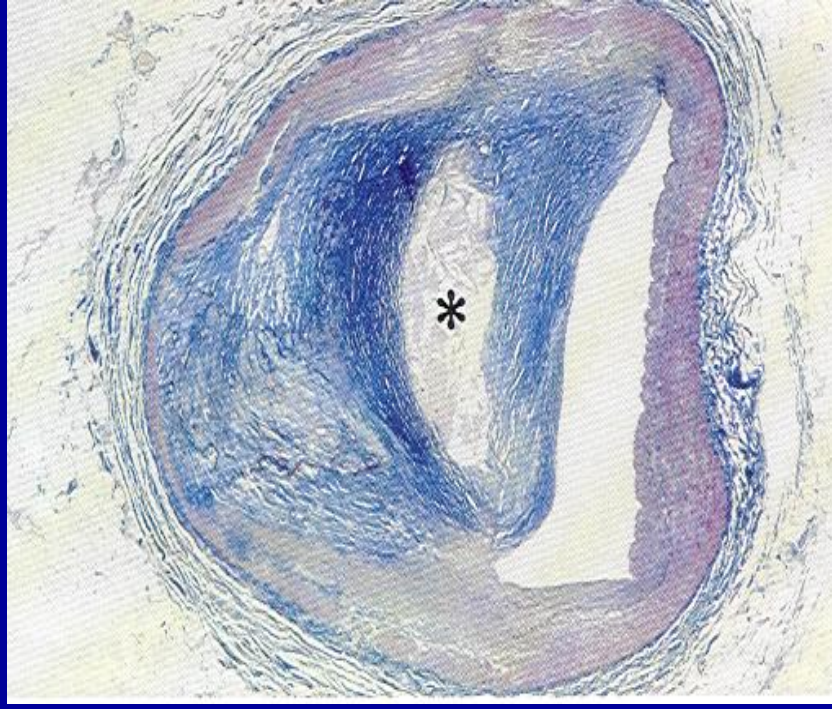


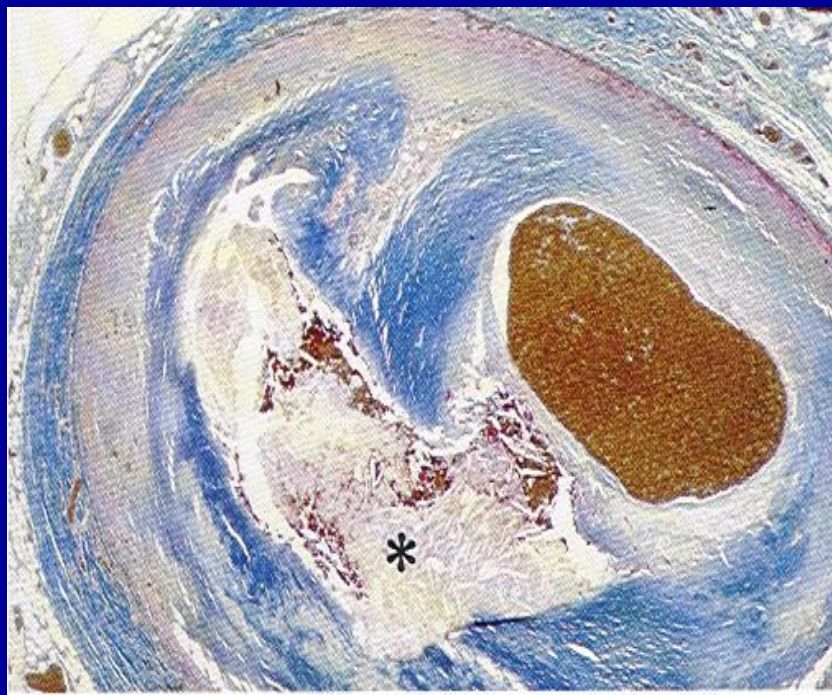
ISCHAEMIC HEART DISEASE (IHD) TREATMENT

RISK FACTORS

- **a) risk factors atherogenezis**
- **(ED, lipidic nucleus, proliferation)**

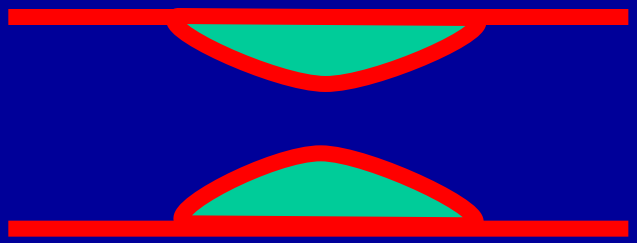
- **b) risk factors thrombotic arterial occlusion**
- **(plaque destabilization, thrombotická occluson, fibrinolysis)**





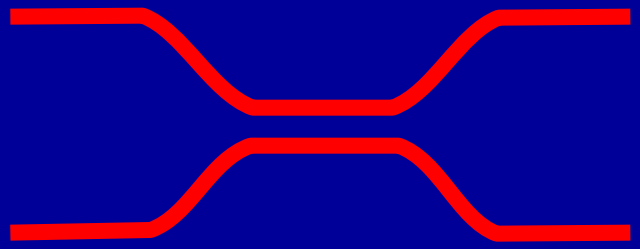
•organic stenosis

•- stabile AP



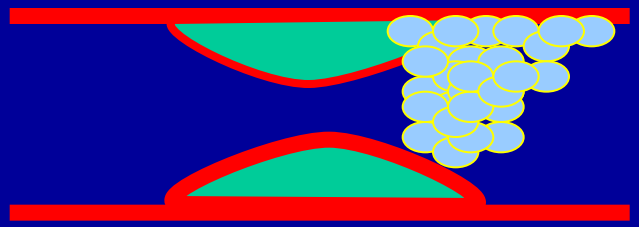
•vasospastic stenosis

•vasospastic AP

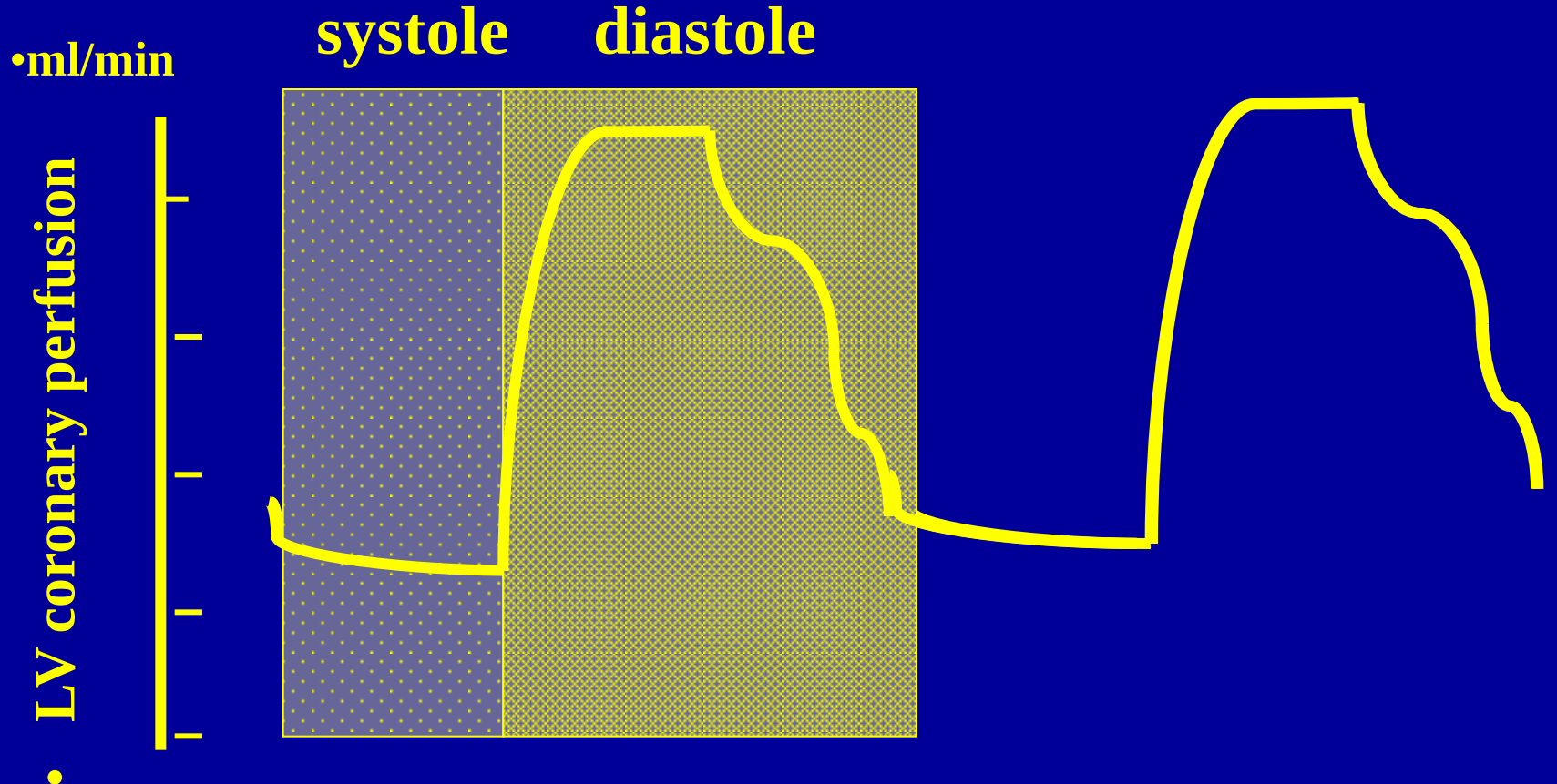


•Stenosis and thrombus

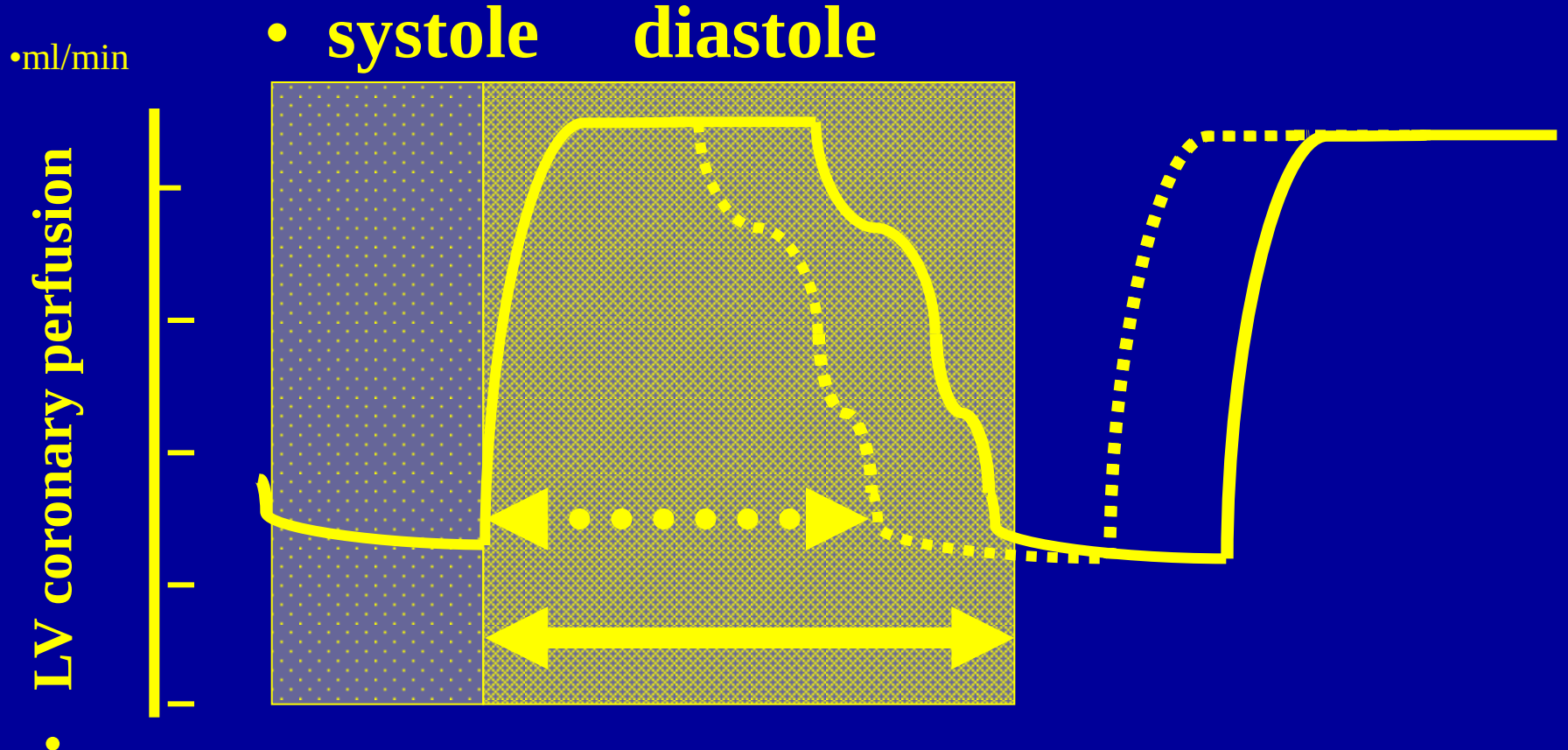
•nonstable AP, MI



For LV coronary perfusion is diastolic interval decisive



Increased coronary perfusion during decreased heart frequency



COMPLEX TREATMENT IHD:

- **a) stop atherogenic progresion – plaque stabilization – elimination of endotelial dysfunction**
- **b) avoid arterial thrombotic occlusion (or rapid restoration of perfusion)**
- **c) decrease of myocardial ischemia**
  - **improvement of flow through ischemic myocardium**
  - **decrease myocardial metabolic requirements**
  - **optimalization of metabolic energy utilization**
- **d) prevention of arrythmia**
- **e) prevention of myocardial remodelation and development of heart failure**

Atherosclerotic plaque stabilization

- **a) endothelial dysfunction adjustment**
  - **(hypolipidemics, ACEI, estrogens, prostanoids, argininem suplementation, calcium chanels blockers)**
- **b) atherosclerotic plaque stabilization**
  - **soft nucleus (diet, hypolipidemics - statins)**

Effect of antioxidants on plaque

- **Clinical studies**
  - **Secondary prevention > 20 000 pacients**
  - **vit. C, vit. E, β-karoten, 5 year tratment**
- **No any effect on cardiovascular mortality and morbidity**

- **Study HOPE (vitamine E)**
  - **Secundary prevention 9 500 patients, 4-5 year**
  - **No any effect on cardiovascular mortality and morbidity**
- **Scavangeres have no effect**

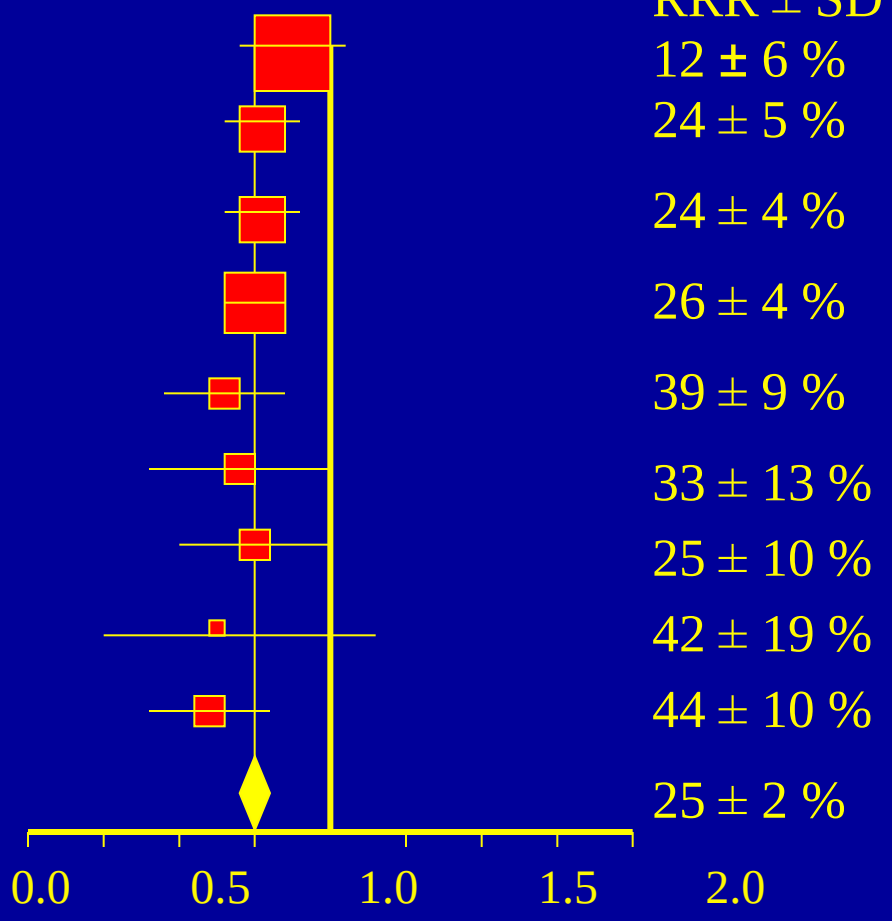
COMPLEX TREATMENT IHD:

- a) stop atherogenic progresion – plaque stabilization – elimination of endotelial dysfunktion
- b) avoid arterial thrombotic occlusion (ev. rapid restoration of perfuson)
- c) decrease of myocardial ischemia
  - improvement of flow through ischemic myocard
  - decrease myocardial metabolic requirements
  - optimalization of metabolic energy utilization
- d) prevention of arythmiaa
- e) prevention of myocardial remodelation and development of heart failure

ANTIPLATELET TRIALIST COLLABORATION

CV-mortality, MI, strake

studies	příhody	populace	RRR ± SD
primární	1176	27210	12 ± 6 %
prev. cerebrální	1916	9530	24 ± 5 %
po IM	2270	15529	24 ± 4 %
AIM	2783	18126	26 ± 4 %
AP	398	3450	39 ± 9 %
CABG/PTCA	245	3057	33 ± 13 %
ICHDK	444	3864	25 ± 10 %
po DVT	67	4771	42 ± 19 %
ostatní	283	3948	44 ± 10 %
celkem	9789	90297	25 ± 2 %



Br Med J 1994

DECREASE OF MYOCARDIAL ISCHEMIA

NITRATES
and
NO DONORS

NITRATES

- **Mechanism of action**
- - metabolized in vessel wall (enzymes or nitrosothiol) to NO (identical with EDRF), stimulation cGMP
- - smooth muscle dillatation (arteries, veins, but arterioles very small)
- **Clinical effectivity**
- - dilatation of eccentric stenosis in epicardial arteries
- - prophylaxis and treatment of coronary spasm
- **(increased tolerance, decreased number of angina, no evidence for better prognosis)**
- - veins dilatation (only short term effect)
- - high doses arteriolodilatation (hypotension)

NITRATES

Generick names	Admin.	dose	onset	duration
• Nitroglycerin (NTG, GTN)	• subling. • transderm. • p.o.	• 0,3 – 0,6 mg • - • 2,5 – 19,5 mg	• 30 s • 1 h • 1 h	• 15 – 20 min • 6 – 14 h • 2 – 4 h
• Isosorbitdinitrate (ISDN)	• subling. • p.o.	• 2,5 – 10 mg • 20 – 120 mg	• 5 min • 30 min	• 1 – 2 h • 4 – 6 h
• Isosorbit 5 mono- nitrate (ISMN)	• p.o.	• 20 – 100 mg	• 30 min	• 8 – 12 h

NITRATES

treatment of myocardial ischemia –

equivalent to calcium channel blockers

Usually underdosed – not properly used high dose galenic forms ISDN a ISMN

ISMN or ISDN – first line

GTN (nitroglycerine) – only exceptionally

NITRATES

Adverse reactions:

- - headache (frequently limits use)
- - hypotension (rarely)
- - suspision for increased oxidation stress in vessel wall

- **Nitrates tolerance:**
- - decreased vasodilatation after long lasting treatment
- - SH group depletion, decreased cGMP, activation of contra-regulation
- - intermitent treatment (nitrate-free interval)

MOLSIDOMINE

- Syndonimine group – NO donors
- Same mechanism as nitrates – NO release
- Prodrug
- No need for SH-group, without tolerance
- onset 20 – 40 min
- lasting 4 – 6 h
  8 – 12 h retard form
- dilatation smooth muscle in stenotic region
- Fibrinolysis activation (not clear effect)
- Indication: prophylaxis AP
  combination with nitrates

CALCIUM CHANNELS BLOCKERS
CCB

Calcium channel blockers

- **-** effective for myocardial ischemia (better quality of live)
- **-** short acting (**nifedipine**) **worsening patients prognosis**
- **-** long lasting – slow down atherogenesis and probably better prognosis

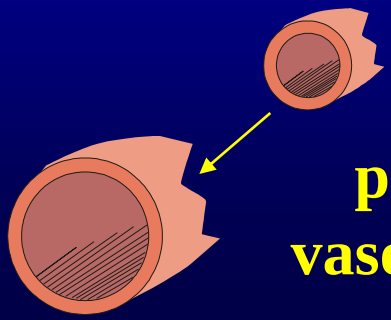
- **- antihypertensive effect** and **antiarythmic effect**

CCB groups

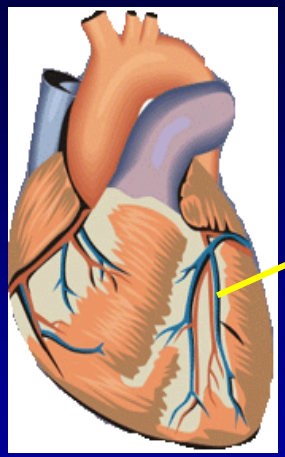
- **I. generation: low vascular selectivity**
  short time effect
- **(*nifedipine, verapamile, diltiazem*)**
- **II. generation: high vascular selectivity**
- **long lasting effect**
  (*felo-, isra-, niso-, nitre-, nilva-, nimodipin*)
- **III. generation:**
  high affinity to cell membranes
  slow onset, long lasting effect
  antiatherogenic effect
  (*amlo-, barni-, laci-, lercainidipin*)

Pharmacodynamic effect of CCB

dihydropyridines
Selective vasodilatation

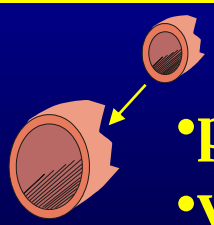


peripheral vasodilatation



coronary vasodilatation

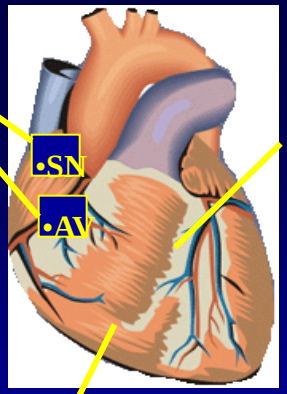
non - dihydropyridines
Myocardial depresiom



- peripheral
- vasodilatacion

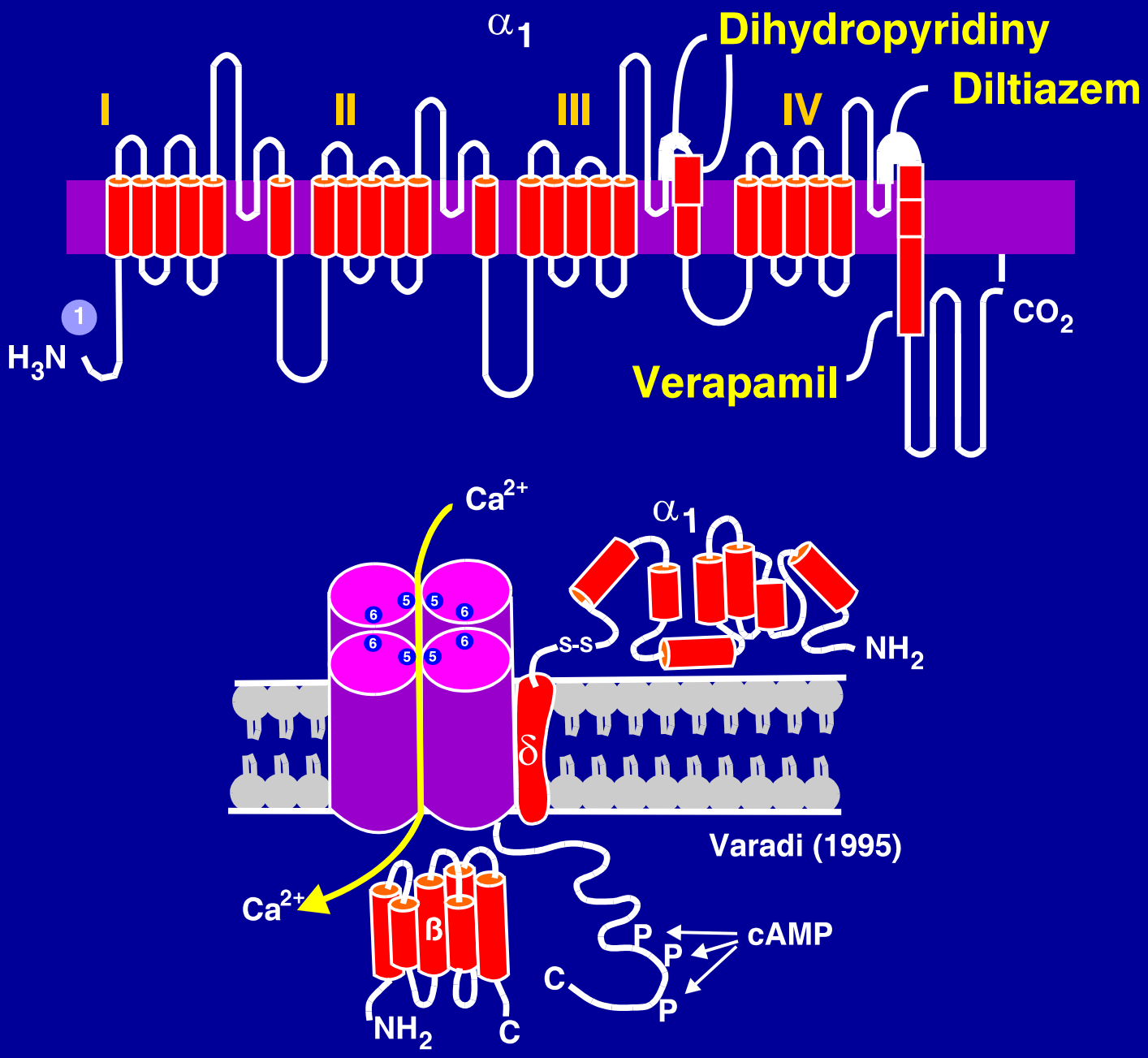
↓heart rate

↓impulse propagation

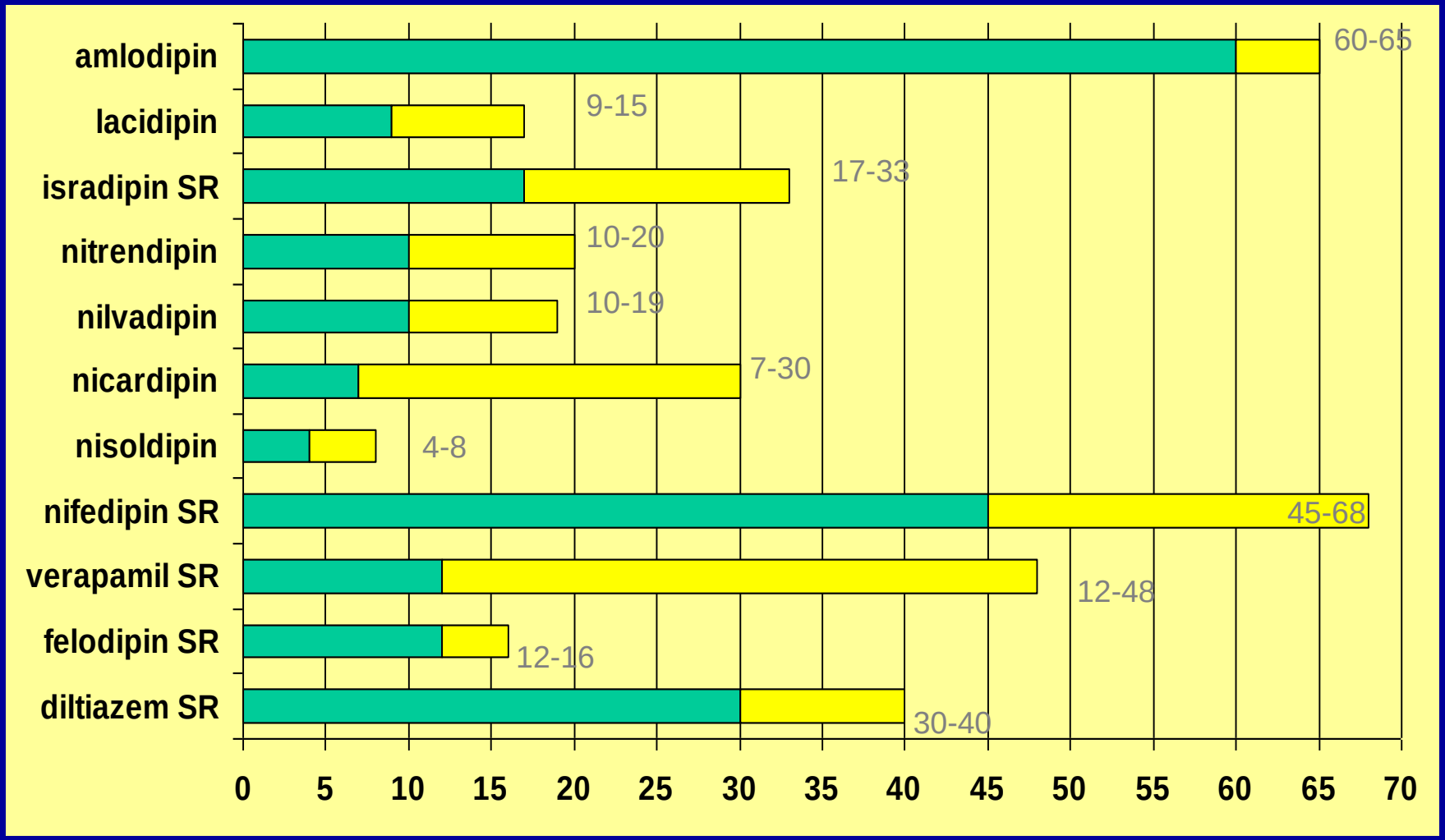


- Coronary
- dilatation

↓Myocardial contractility

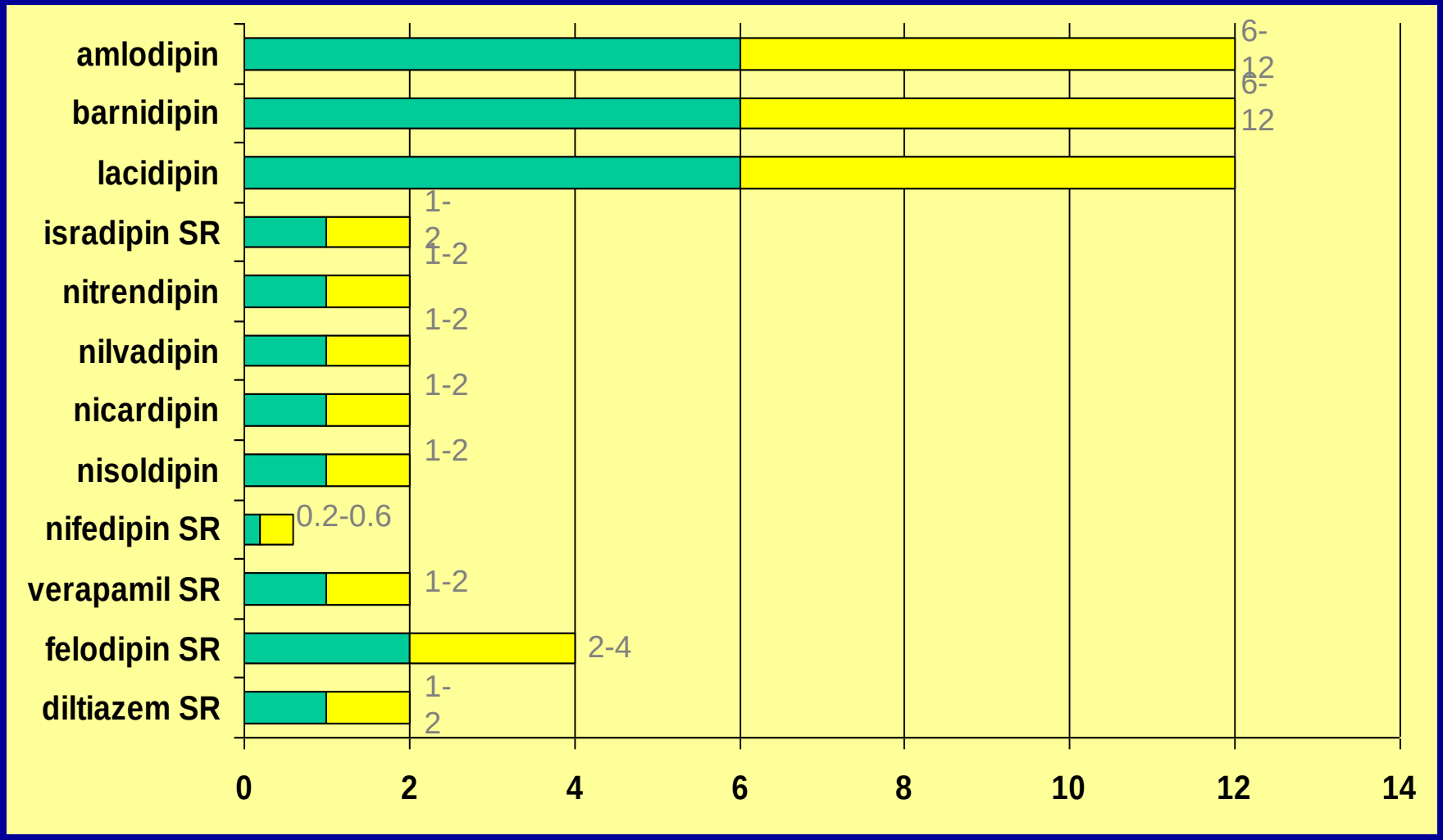

α1
Dihydropyridiny
Diltiazem
I
II
III
IV
1
H3N
CO2
Verapamil
Ca2+
α1
5
6
S-S
NH2
δ
Varadi (1995)
Ca2+
β
P
cAMP
C
NH2
C

Bioavailability CCB



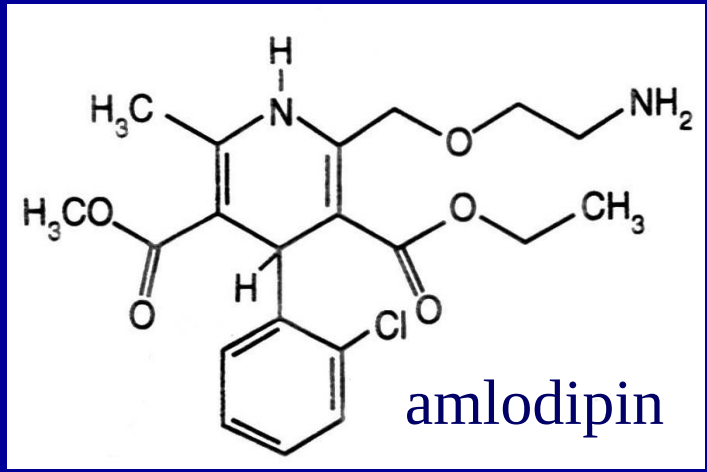
Maximal plasma levels CCB

t_{max}



Slow onset mechanism for CCB III generation

- Lipophilic compound
- Terminal aminogroup
  hydrophilic



amlodipin

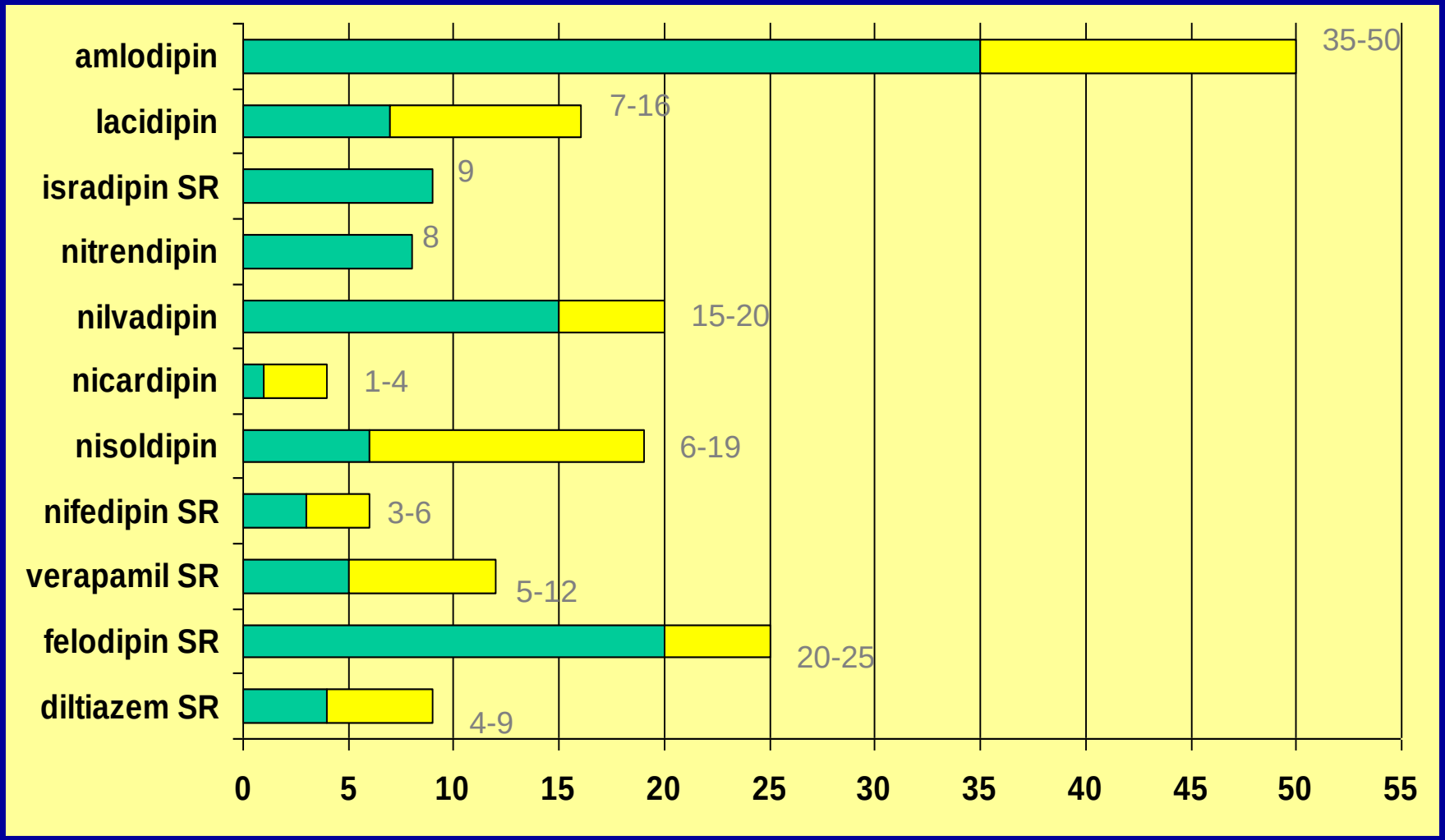
- combination hydro- and lipoph-
  terminal allowed interaction with phospholipids layer of sarcolema (binding to membranes)

Slow onset mechanism for CCB III generation

- slow and stable decrease of BP,
  no activation of contra-regulation

1) no limited antihypertensive effect
   (no vasoconstriction and fluid retention)
2) no proarythmogenic effect and tachycardia
3) no metabolic effect

Plasma halflife CCB



ADVANTAGES OF AMLODIPINE LONG HALFLIFE

- **minimal plasma level fluctuations during day**

- **T/P index – ratio between minimal and maximal blood level**

  -FDA requirements : effect "trough" 2/3 of "peak"

  - *amlodipin* T/P index 68%,

  - *lacidipin, felodipin ER, verapamil SR and nifedipin GITS* index 37-66%

safety limits for missing dose

FARMACODYNAMIC PROPERTIES OF CCB

ANTIISCHEMIC EFFECT

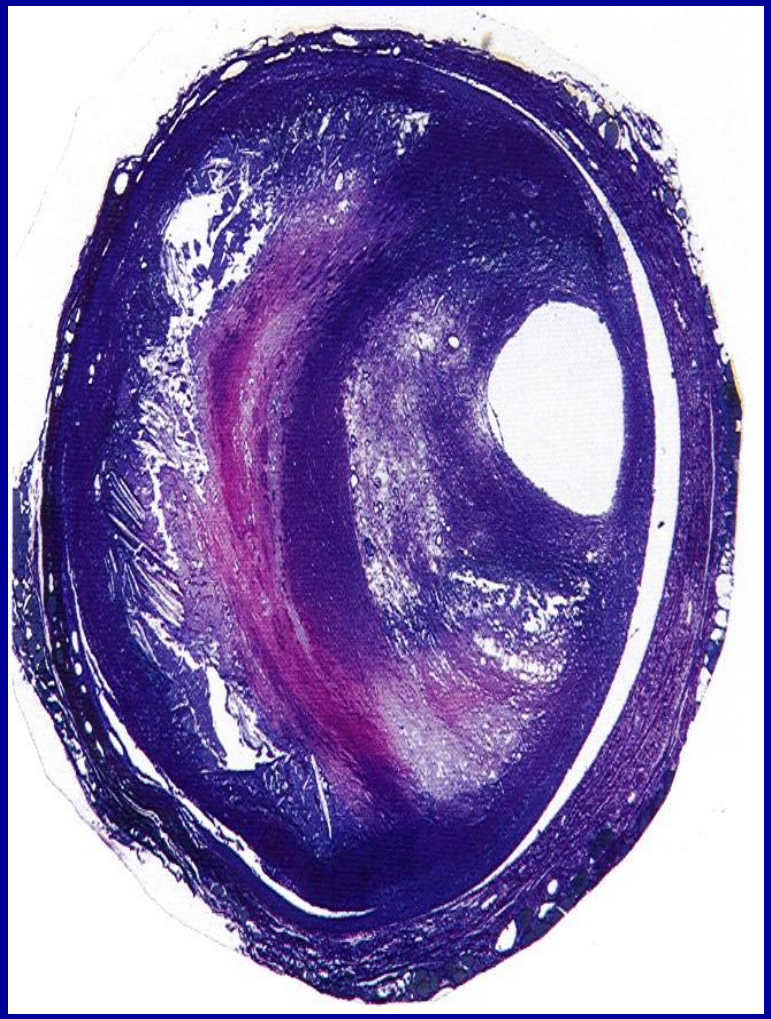
- direct vasodilatation
- endothelial function improvement

- ANTIATHEROGENIC EFFECT

Prophylactic effect of CCB

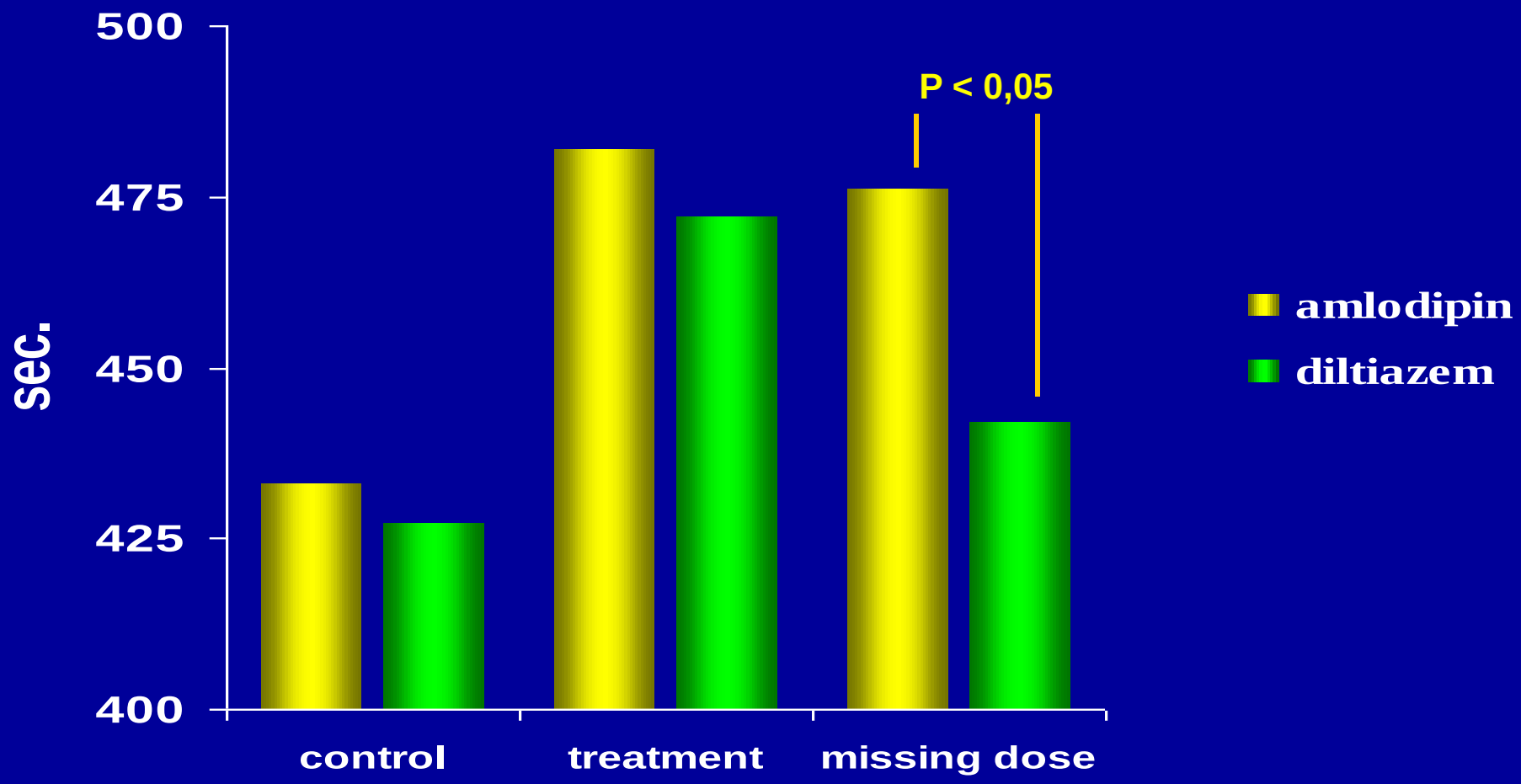
1) Vessel wall relaxation at excentric stenosis
2) Block vasoconstriction induced by exercise
3) Coronary spasm block (variant AP)
4) Decreased heart rate
   - increased perfusion
   - decreased metabolic demand

   (non-dihydropyridines)



CAPE II - MONOTERAPY

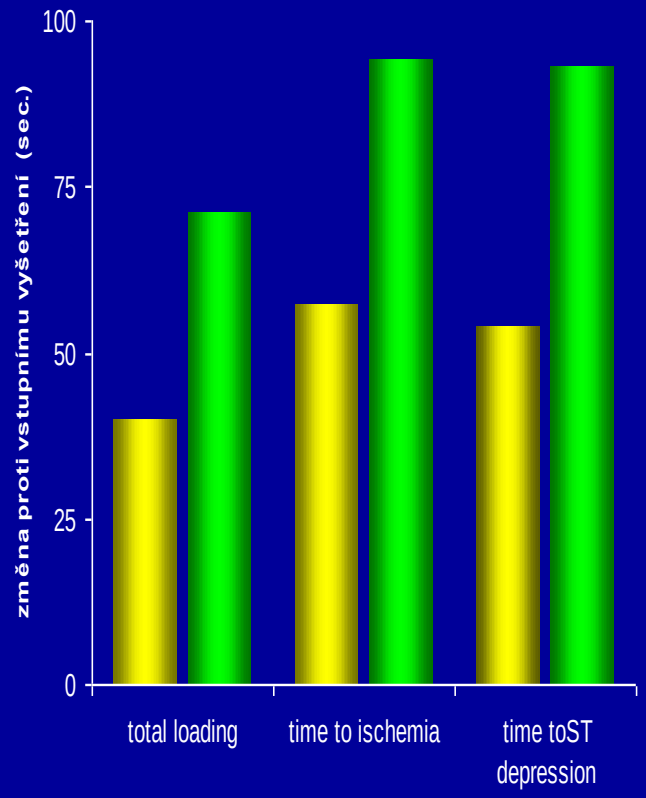
Stress ECG – increase time to ischemia



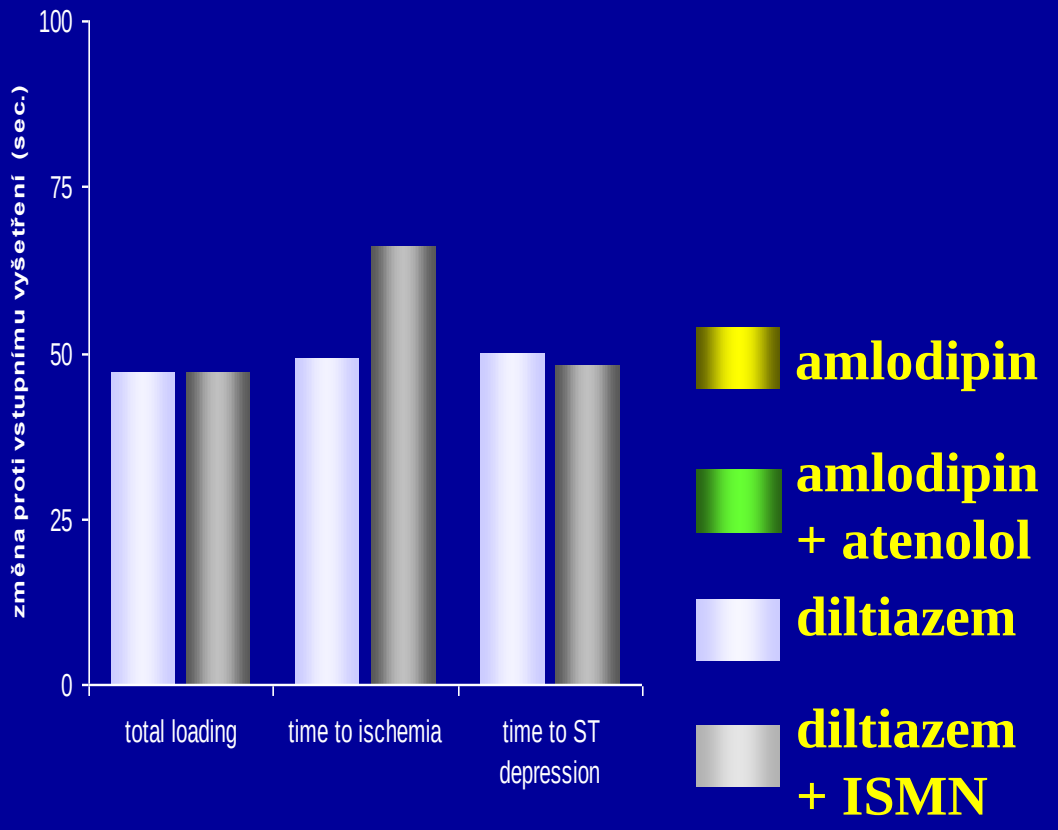
CAPE II: monoterapy x combination

amlodipine + BB against diltiazem + nitrates

stress ECG

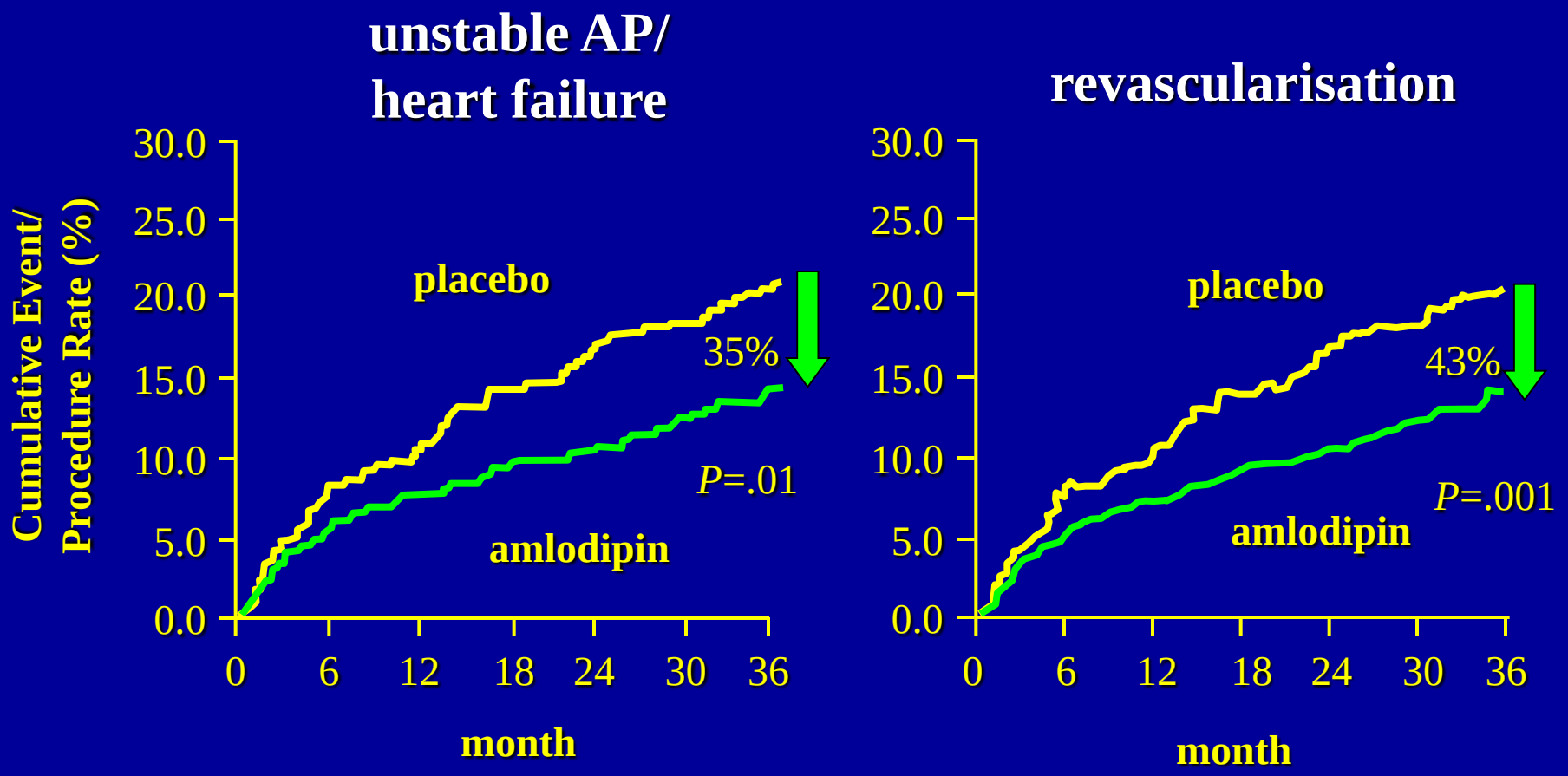


amlodipine + BB



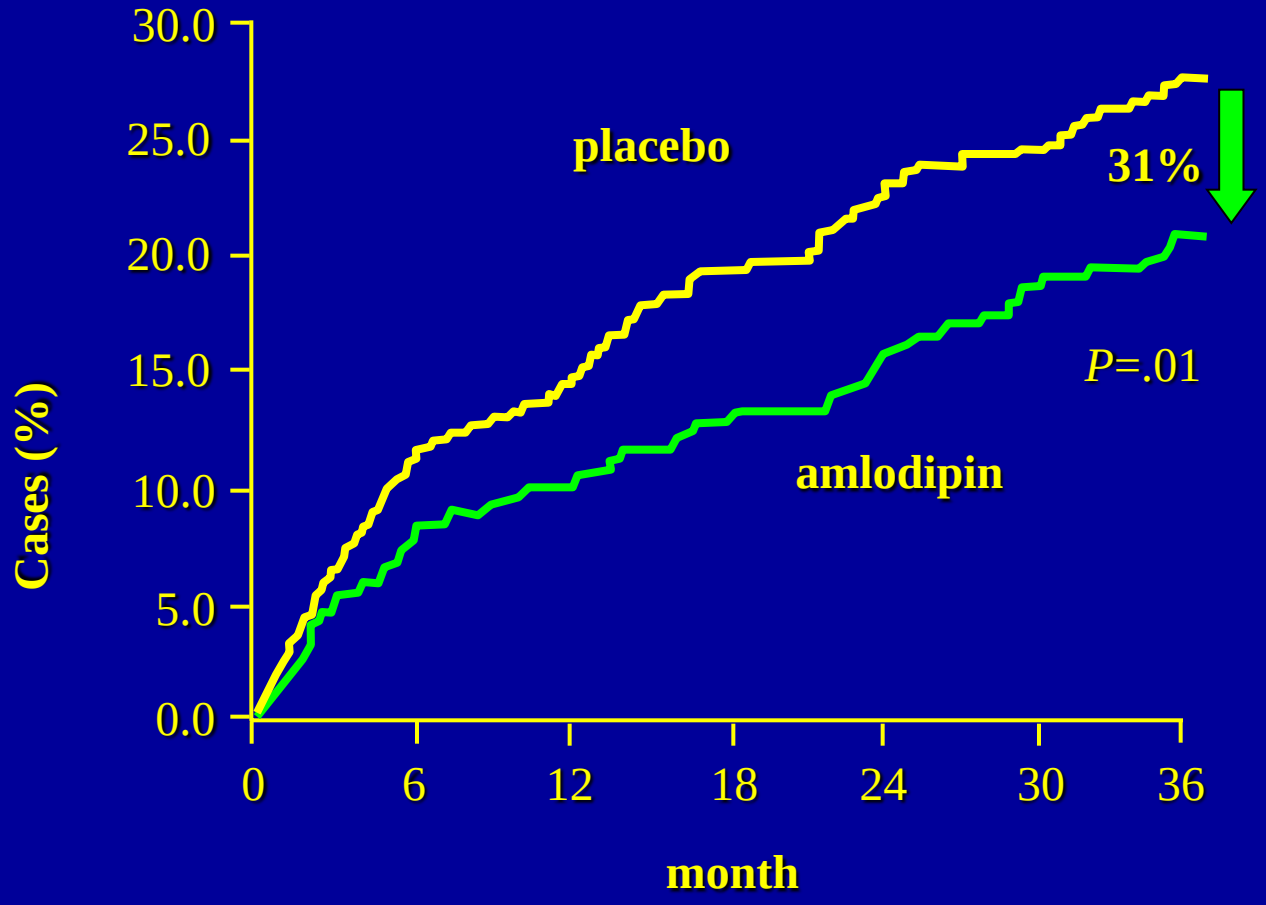
diltiazem + ISMN

PREVENT: unstable AP and invazive interventions



Pitt et al. *Circulation*. 2000.

PREVENT: important CV events



Pitt et al. *Circulation*. 2000.

Contraindications and AR

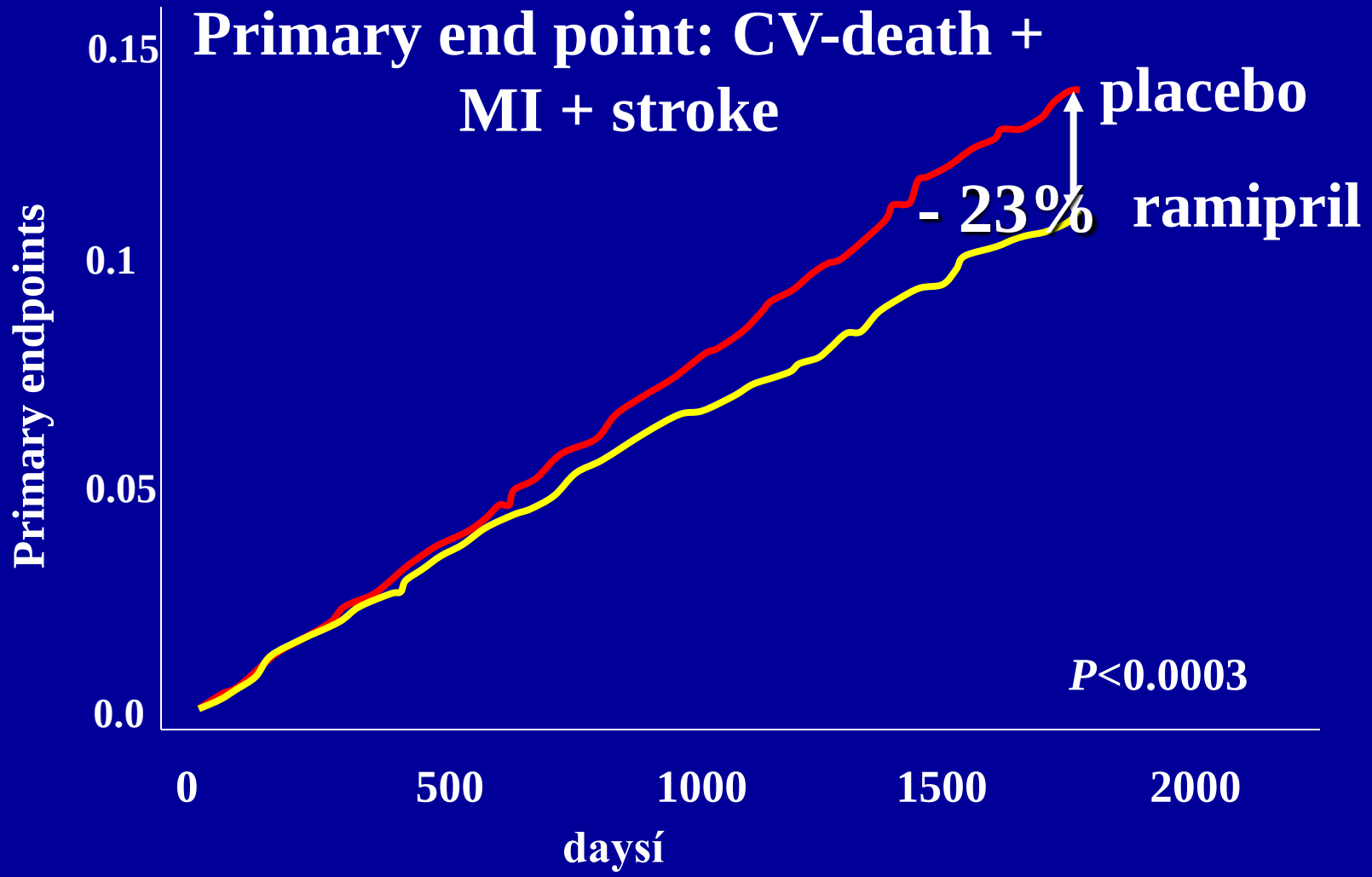
- **Non-dihydropyridine CCB**
- **AR – bradycardia, negative innotropic effect, hypotension, obstipation**
- **CI – srdeční selhání, převodní poruchy, hypotenze**
- **Dihydropyridine CCB**
- **AR – frequent perimaleolar oedema, hypotension, reflex tachykardia**
- **CI – only hypotension**

ACE INHIBITORS

IHD ACE INHIBITORS

- Significant improvement of prognosis for secondary prevention - even for patients wih normal LV functon (study HOPE, EUROPA)
- Not clear - that improvement during secondary prevention is due to ACE inhibition or decreased BP only

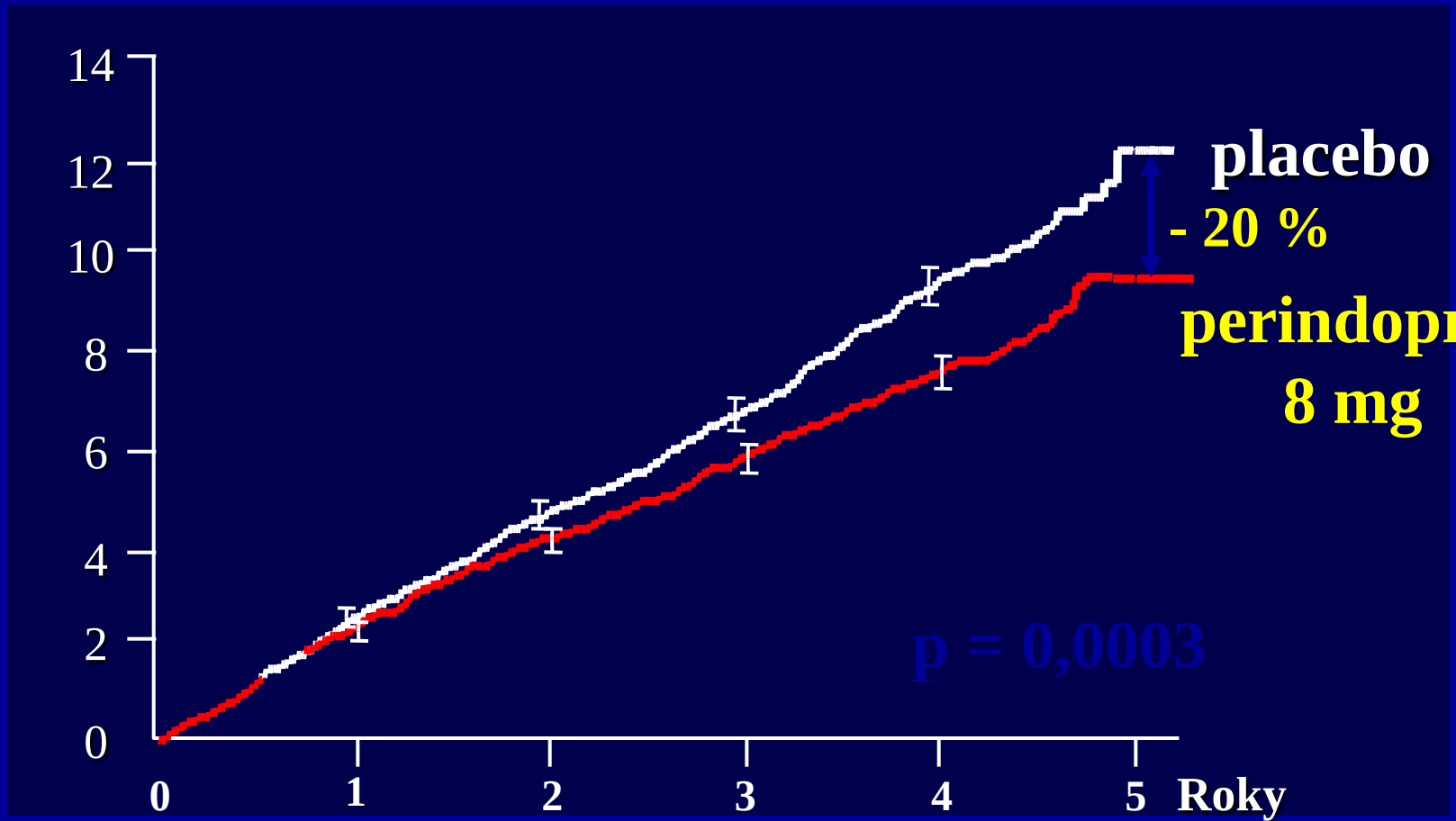
STUDY HOPE



Yusuf S et al. NEJM 2000;342:154-160.

STUDY EUROPA

Primary endpoint - mortality + MI + resuscit.



Placebo cases per year - 2,4 %

Remme P et al., NEJM 2003

POTASSIUM CHANNELS ACTIVATORS

NICORANDIL

CLINICAL EFFECTS

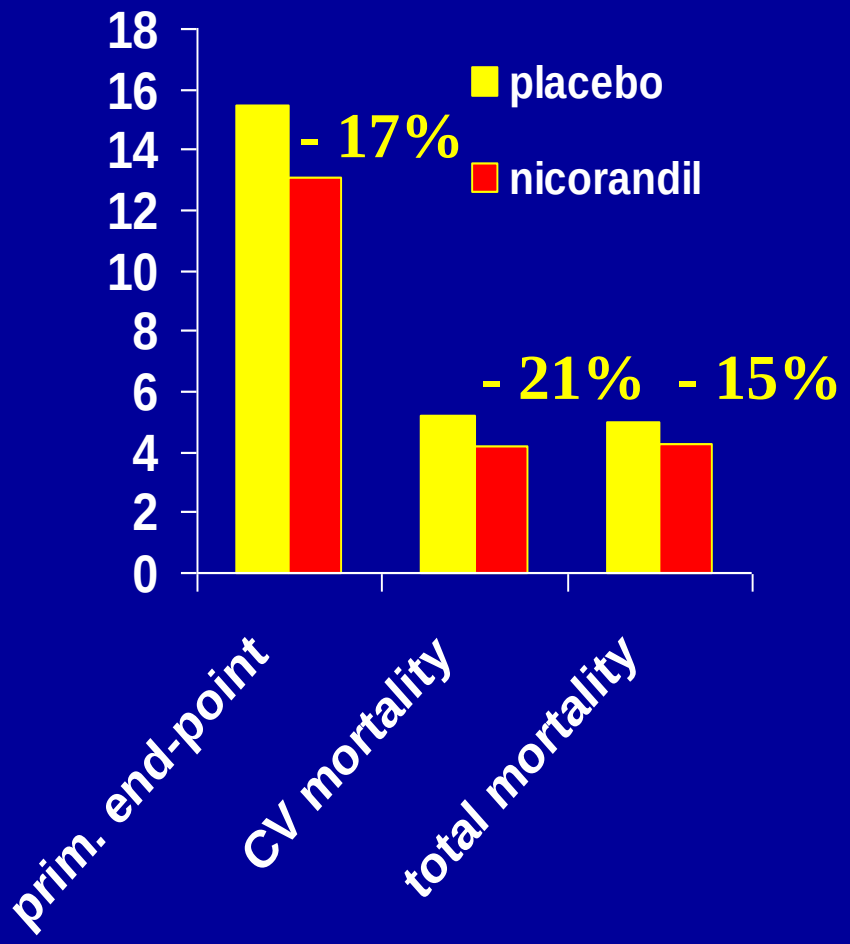
- **antiangina effectiveness comparable to BB, CCB and nitrates**
- **Alternative choice - BB a CCB when contraindicated or side effects**
- **Combination with BB possible**

additive effect for „preconditioning“

NICORANDIL - IONA Trial

- 5126 patients with CHD and stable AP – optimal treatment
- follow up 1-3 y, ø 1,6 ± 0,5
- Randomization nicorandil 10 mg b.i.d. → 20mg b.i.d vs. placebo
- Primary end-point: CV-mortality + nonfatal MI + hospitalization for angina attack

Lancet 2002;359:1269-75



BETA-BLOCKERS

BETA-BLOCKER CLINICAL EFFECTS

- **negative innotropic effect:**
  - **LV filling time – prolongation**
  - **coronary bed perfusion - improvememt**
- **negative innotropic effect**
- **metabolic demand decreased**
- **BP decrease**
- **antiarrythmic properties (increased fibrilation treshold)**

BETA-BLOCKER CLINICAL EFFECTS

- β blockade$_1$ juxtaglomerular receptor → renin production decreased
- Catecholamine release in CNS - decreased
- Antioxidand properties ??
- cytoprotektive efect – even at high catecholamine level
- Apoptoses inhibition

Efekt ß-blockers

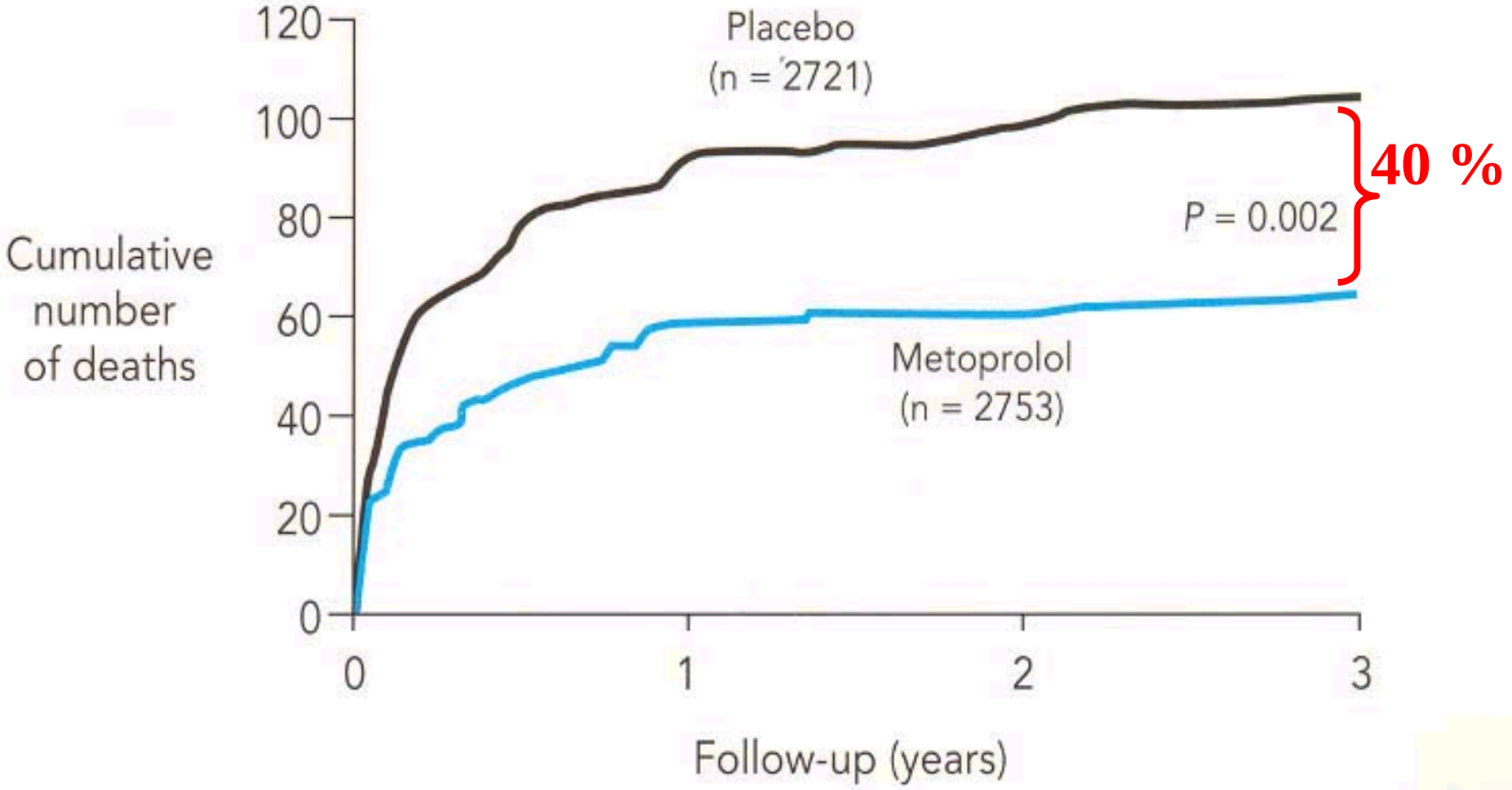
1) antiischemic effect ***(better myocardial perfusion, decreased metabolic denand)***

2) antiarrhytmic effect

3) inhibition of hyperactive regulations:

- ***catecholamine release***
- ***renin-angiotensin-aldosteron activation***
- ***apoptosis***

ACUTE DEATH REDUCTION FOR MI BETA-BLOCKERS (meta-analysis)



Olsson et al. *Eur Heart J.* 1992;13:28-32.

FAVORITS

BETAXOLOL, BISOPROLOL

•- high cardioselectivity without ISA, hydrofilic

- long halflife (15-20 hours)

- small biodegradation variability

METOPROLOL

•- high cardioselectivity without ISA, lipophilic

- short and variable halflive

- exelent clinical trials – widely used BB

SINUSE NODE INHIBITORS (BRADINES)

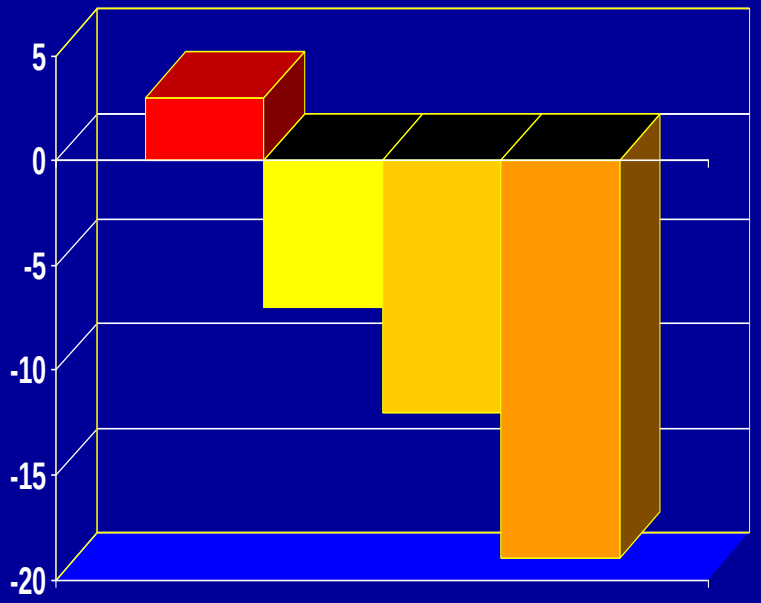
I_f current inhibitors
(hyperpolarisation) bradycardia only

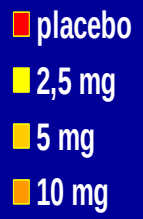
IVABRADIN

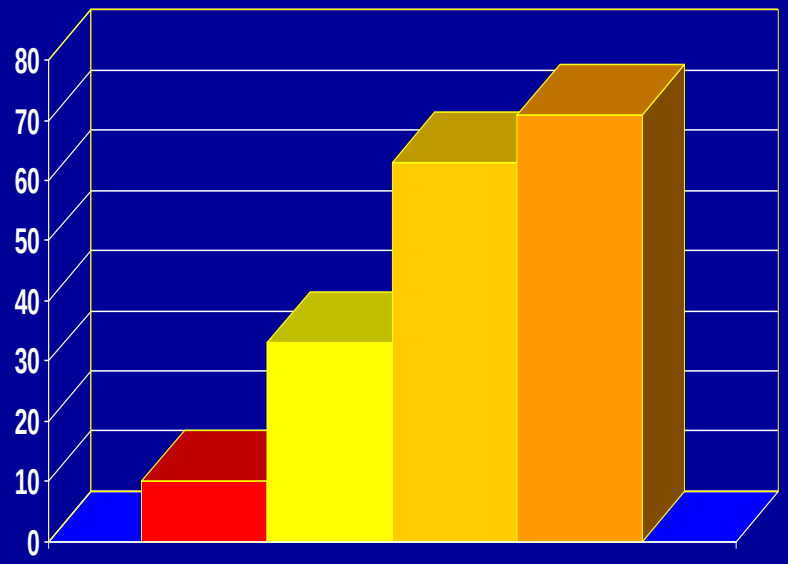
↓ heart rate (min^{-1})

↑ work-load tolerance (s)

N = 360



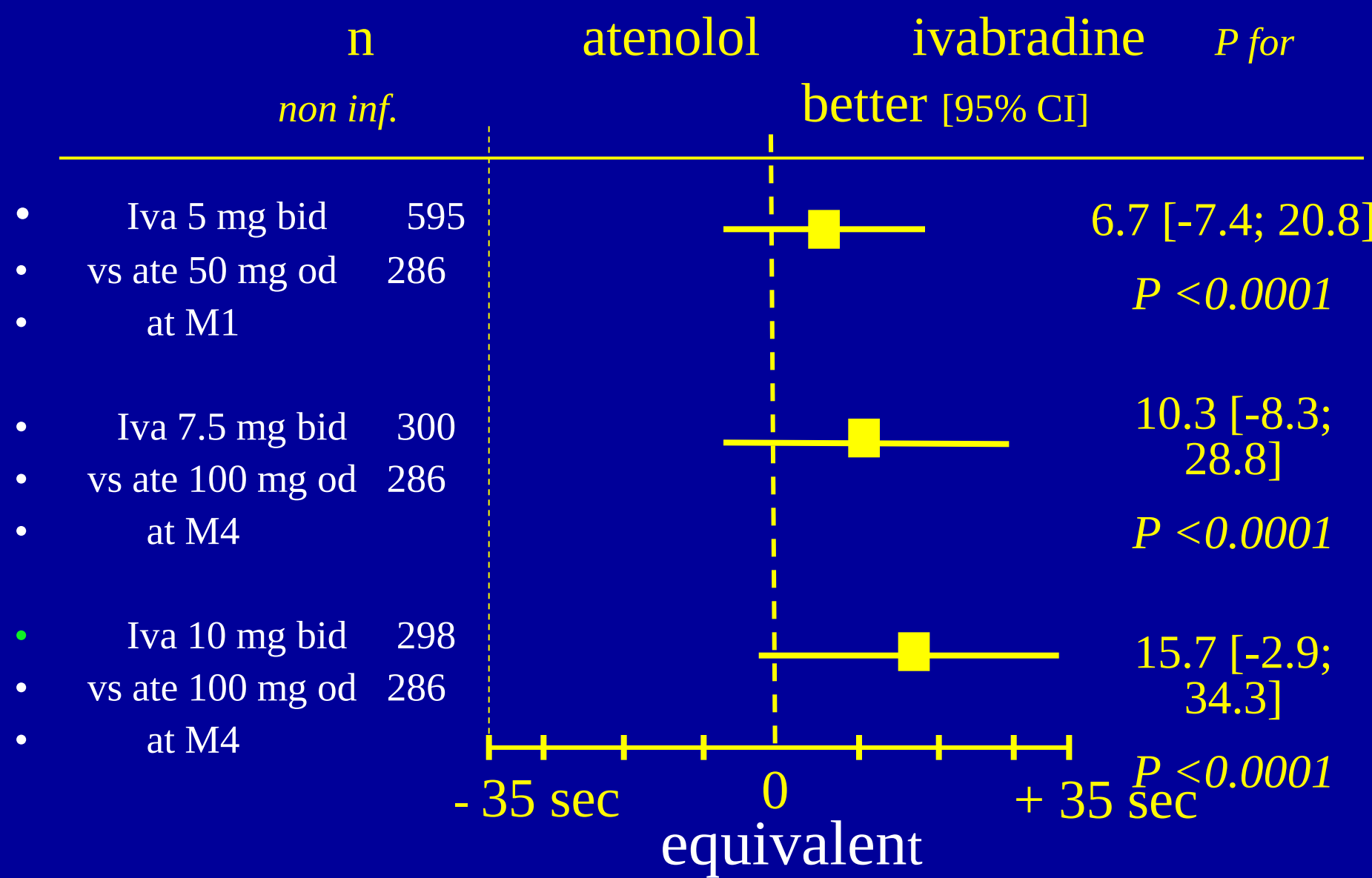




Borer J.S. et al., Circulation 2003;107:817-23

IVABRADIN vs ATENOLOL

PRIMARY END-POINT – LOADING TIME



METABOLIC MODULATORS

ENERGY OUTCOMES OPTIMALIZATION

- During ischemia – (pH decrease) inhibition of glycolysis

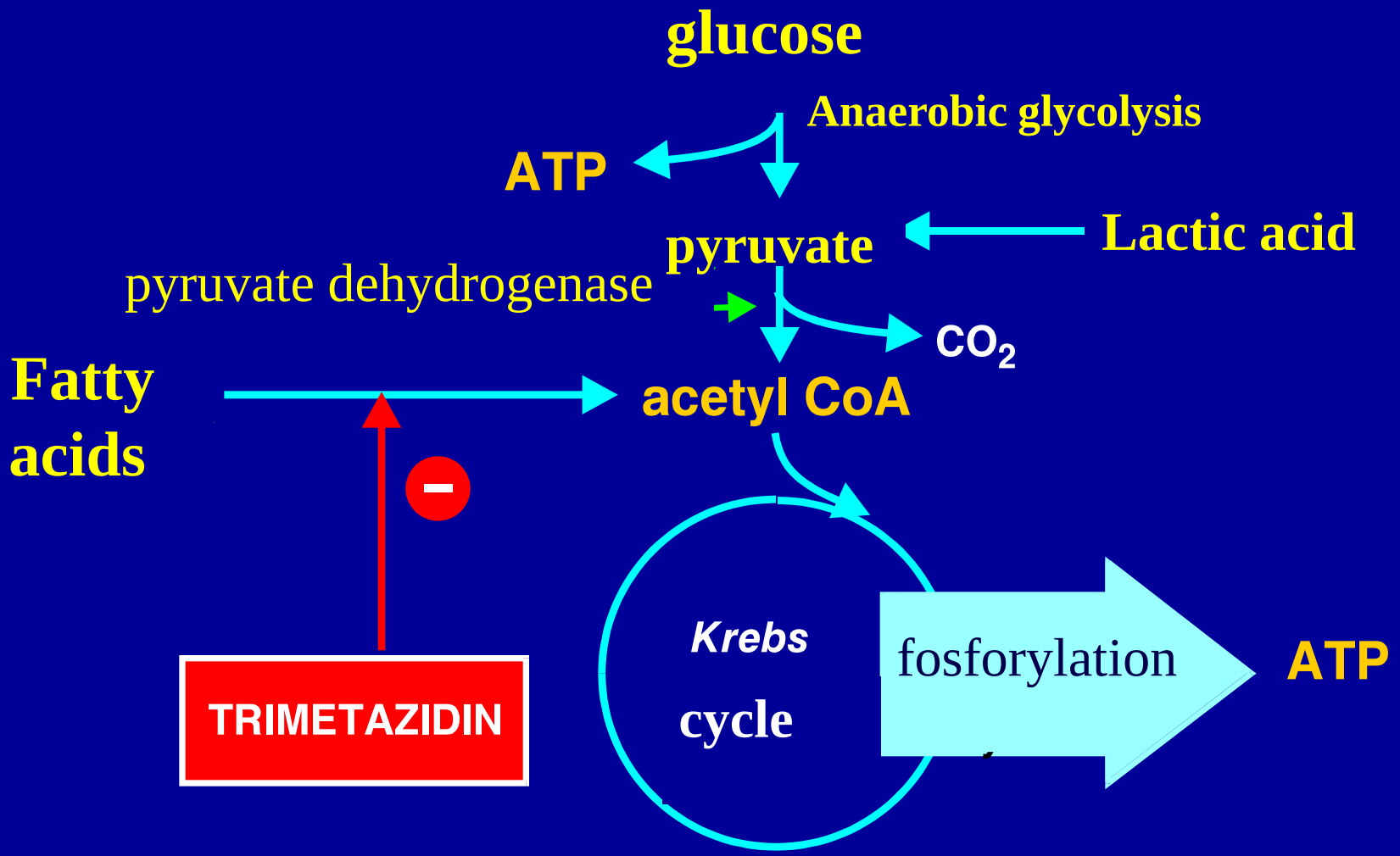
- FA ß-oxidation main source of energy
- switch from FA ß-oxidation to glycolysis by **trimetazidine or ranolazine**
  - 15% increase macroergic phosphates
  - membrane stabilization

TRIMETAZIDINE

- **Modulation (inhibition 3-KAT) during ischemic shift to glycolysis**
- **Optimalization of energetic metabolism of kardiomyocytes**
- **No change in hemodynamic**
- **Well tolerated**

3-KAT = 3-ketoacyl-CoA thioláza

METABOLIC MODULATORS
mechanism of action



TRIMETAZIDINE
clinical effectiveness

- **Combination with BB, CCB, nitrates**
- **Second choice therapy when BB or CCB contraindicated**
- **Additional therapy for all patients with non compensated stabile AP**

RECOMENDED COMBINATIONS

- **beta-blockers + dihydropyridine CCB**
- **beta-blockers + ISMN**
- **beta-blockers + trimetazidine**
- **CCB + trimetazidine**

- **Triple-combination: BB + CCB (DHP) + trimetazidine**

- **Acute attack: CCB + nitrates**

COMPLEX TREATMENT IHD:

- a) stop atherogenic progresion – plaque stabilization – elimination of endotelial dysfunktion
- b) avoid arterial thrombotic occlusion (ev. rapid restoration of perfuson)
- c) decrease of myocardial ischemia
  - improvement of flow through ischemic myocard
  - decrease myocardial metabolic requirements
  - optimalization of metabolic energy utilization
- d) prevention of arythmiaa
- e) prevention of myocardial remodelation and development of heart failure