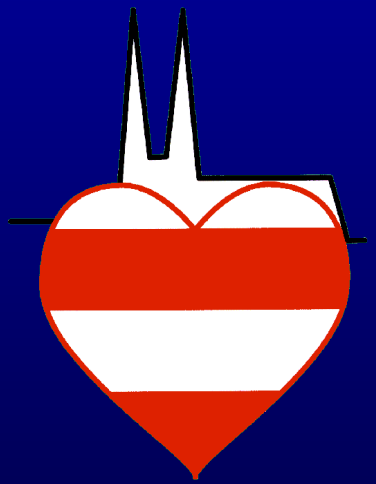
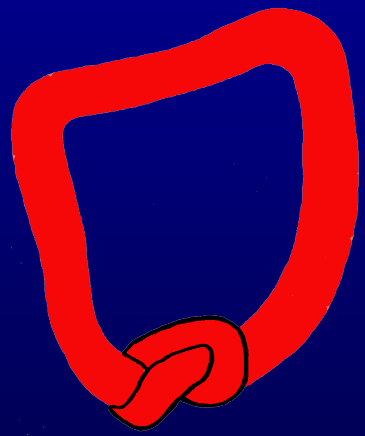
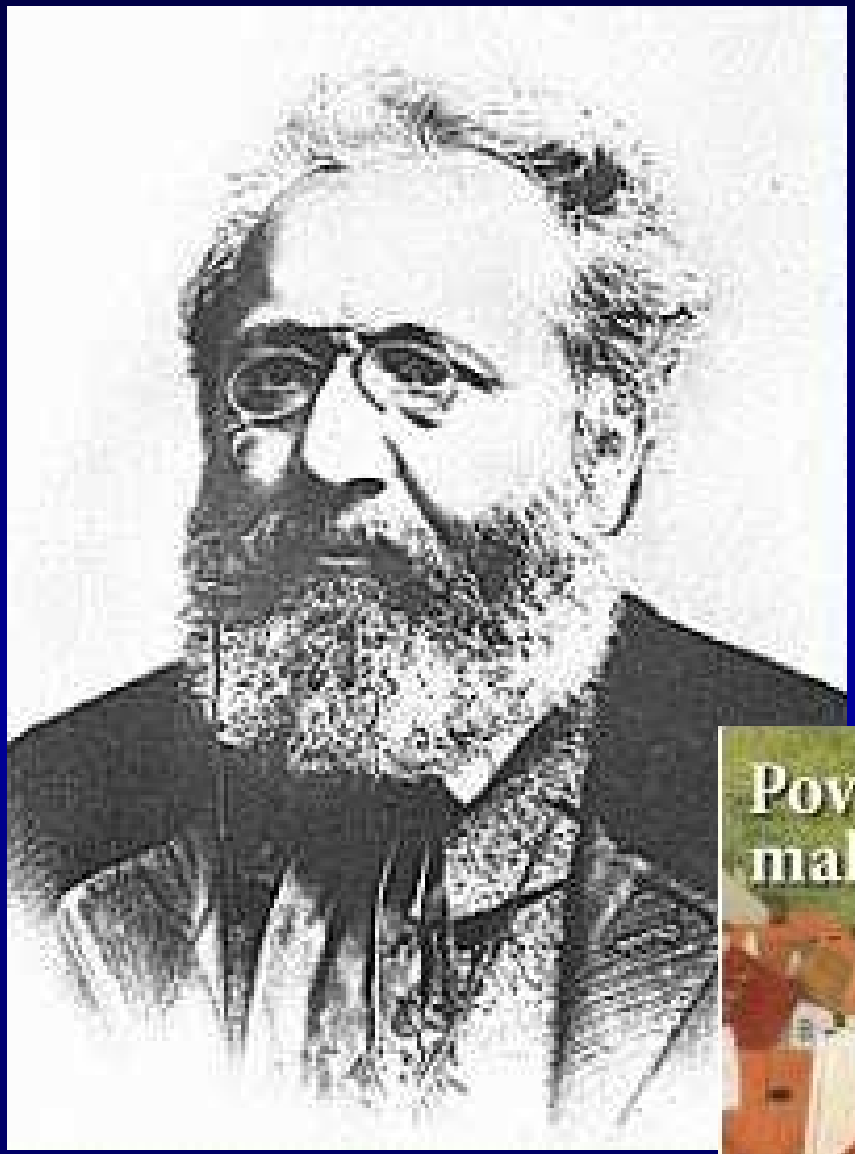
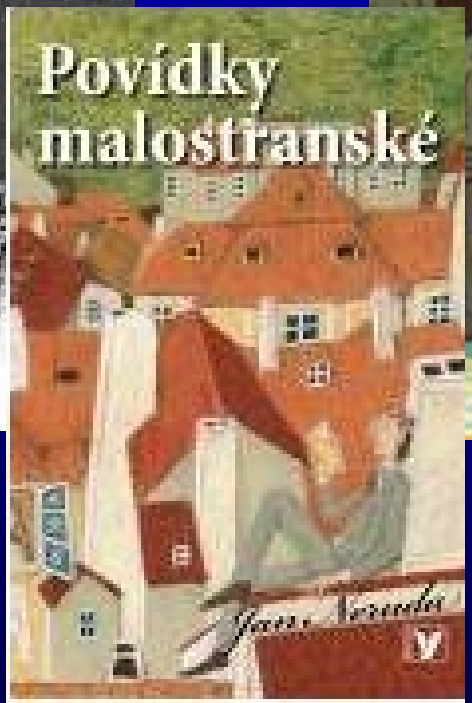
Význam blokády RAAS a postavení sartanů v léčbě kardiovaskulárních onemocnění

Jiří Vítovec

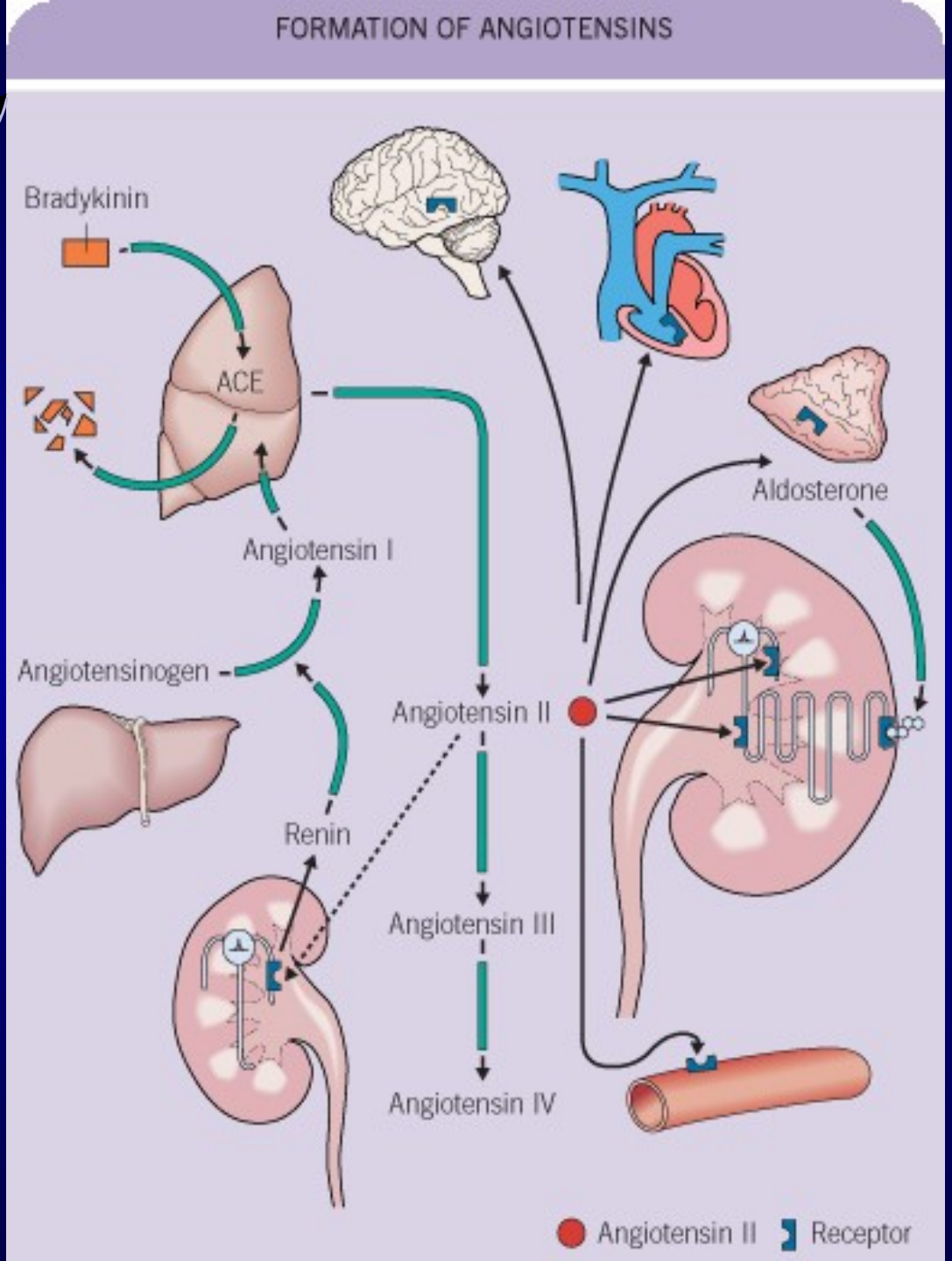







Povídky
malostranské
Jan Neruda


Jos. Lada
52


FORMATION OF ANGIOTENSINS
Bradykinin
ACE
Angiotensin I
Angiotensinogen
Renin
Angiotensin II
Angiotensin III
Angiotensin IV
Aldosterone
Angiotensin II
Receptor

Patofyziologický efekt A II

Vazokonstrikce

↑PAI-1/ trombosa

↑Kontraktilita

destičková agregace

Aktivace SNS

Angiotensin II

↑Aldosteron

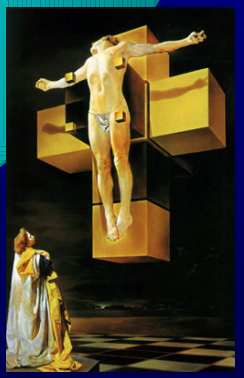
Hypertrofie cévní stěny

↑Vasopressin

Hypertrofie myocytů

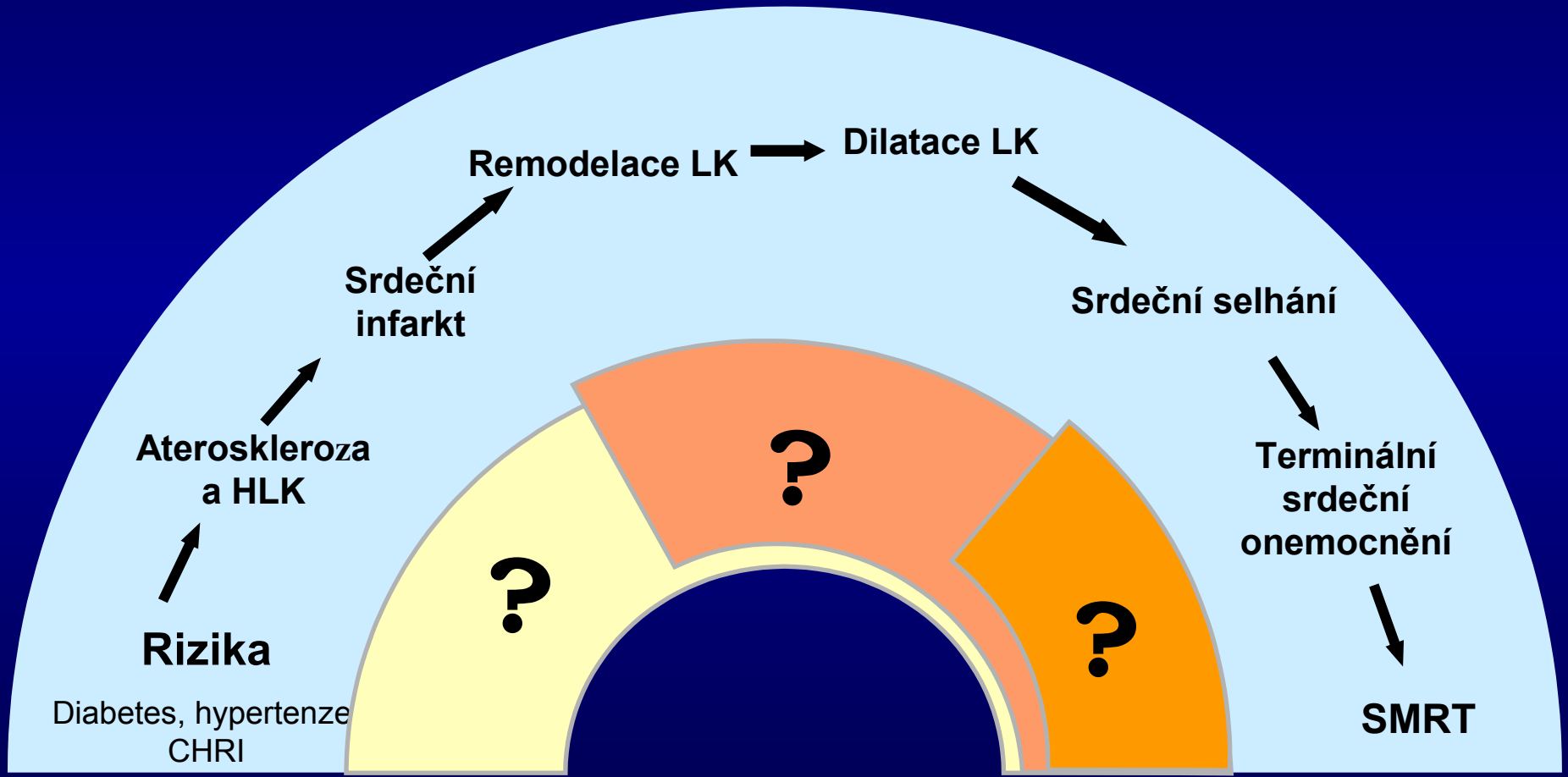
↑Endothelin

↑Collagen

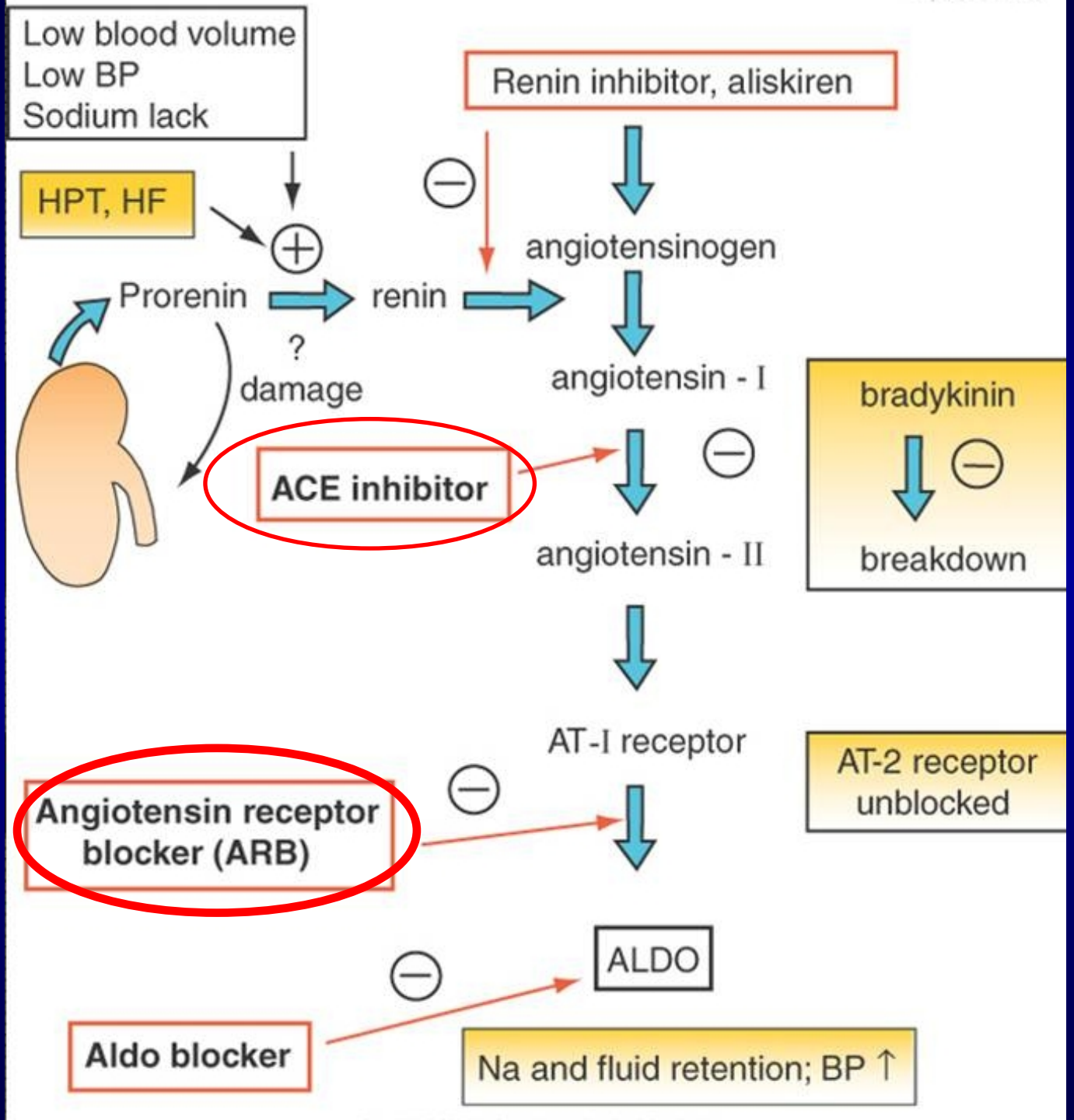


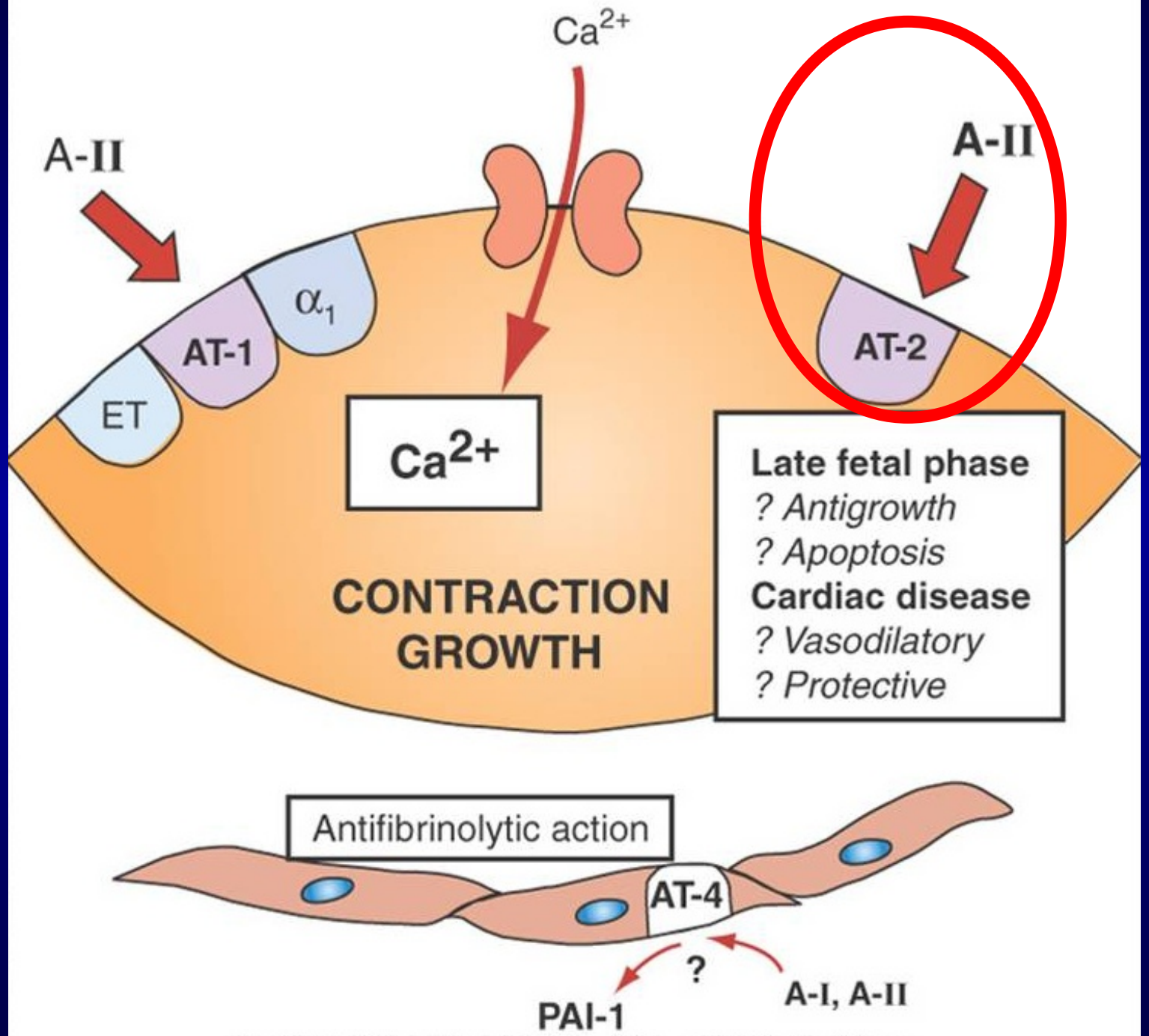
Modified after Burnier & Brunner Lancet 2000

Kardiovaskulární spojitost



Adapted from Dzau V, Braunwald E. *Am Heart J*. 1991;121:1244-1263.

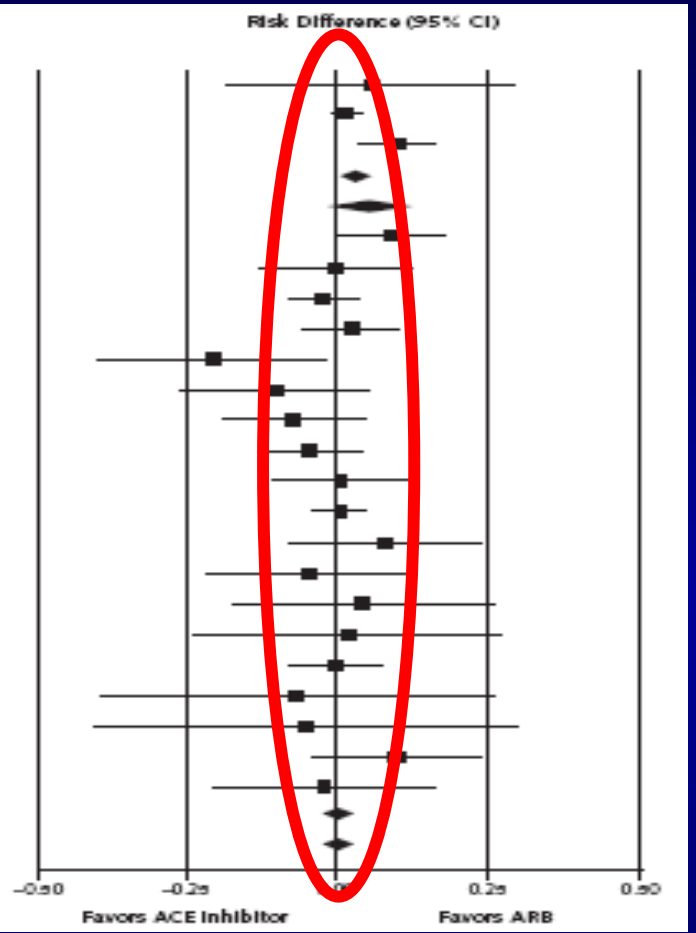

Low blood volume
Low BP
Sodium lack
HPT, HF
Renin inhibitor, aliskiren
angiotensinogen
Prorenin
renin
?
damage
angiotensin - I
ACE inhibitor
bradykinin
breakdown
angiotensin - II
AT-I receptor
AT-2 receptor unblocked
Angiotensin receptor blocker (ARB)
ALDO
Aldo blocker
Na and fluid retention; BP ↑


Ca2+
A-II
A-II
α1
AT-1
ET
AT-2
Ca2+
CONTRACTION
GROWTH
Late fetal phase
? Antigrowth
? Apoptosis
Cardiac disease
? Vasodilatory
? Protective
Antifibrinolytic action
AT-4
?
A-I, A-II
PAI-1

HYPERTENZE

Srovnání ACE-I a ARB u HT

Study, Year (Reference)	Time Point, wk	Events/Total, n/n	
		ARB	ACE Inhibitor
Verdecchia et al., 2000 (68)	172	12/22	32/66
Mazzaglia et al., 2005 (83)	52	348/1382	1072/4602
Hasford et al., 2002 (80)	52	394/754	140/333
Fixed			
Random			
Saito et al., 2004 (60)	26	66/200	51/214
Cuspidi et al., 2002 (34)	48	53/115	57/124
Rullopo et al., 2001 (59)	12	153/168	152/163
Larochelle et al., 1997 (47)	12	11/121	4/61
Lacourcière et al., 2000 (46)	52	20/52	30/51
Ruff et al., 1996 (69)	12	3/50	4/25
Townsend et al., 1995 (66)	12	62/132	72/136
Neutel et al., 1999 (55)	48	169/385	93/193
Karlberg et al., 1999 (43)	26	89/139	88/139
Malacco et al., 2004 (49)	16	479/604	479/609
Fogari et al., 2004 (73)	16	45/75	39/75
Rosei et al., 2005 (58)	24	39/66	40/63
Ghiadoni et al., 2003 (42)	26	29/29	21/28
Uchiyama-Tanaka et al., 2005 (67)	52	14/18	19/25
Argenziano and Trimarco, 1999 (27)	26	182/264	182/264
Robles et al., 2004 (82)	12	10/15	11/15
Kavgaci et al., 2002 (44)	26	13/20	7/10
Mogensen et al., 2000 (53)	24	54/66	46/64
Eguchi et al., 2008 (37)	12	29/37	29/36
Fixed			
Random			



61 srovnávajících malých ale bez dlouhodobé, multicentrické, dvojitě slepé studie

Malý nebo žádný rozdíl mezi oběma skupinami

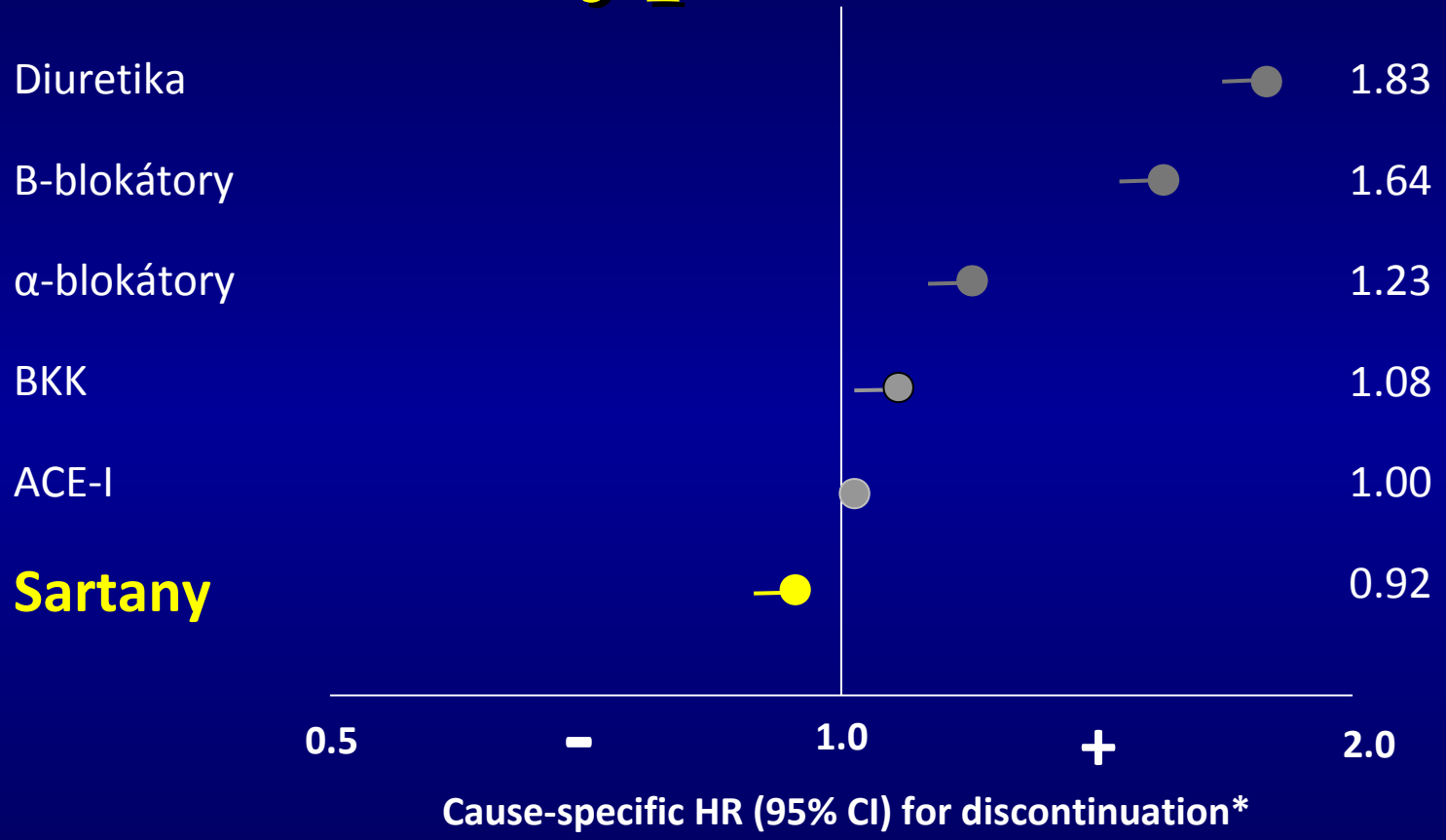
Ignorování jednotlivých léků i dávek

ACEi jsou spojeny s více kašlem a angioedémem

Výhody blokády AT_1 léčbě hypertenze

- nejsou negativní metabolické účinky
- regrese zmnoženého vaziva v myokardu
- zpomalení progrese diabet. i nediabet. nefropatie
- snížení inzulinová rezistence
- zamezení ztrát draslíku při diuretické terapii
- výrazné snížení výskytu dráždivého kašle

Adherence k antihypertenzivům



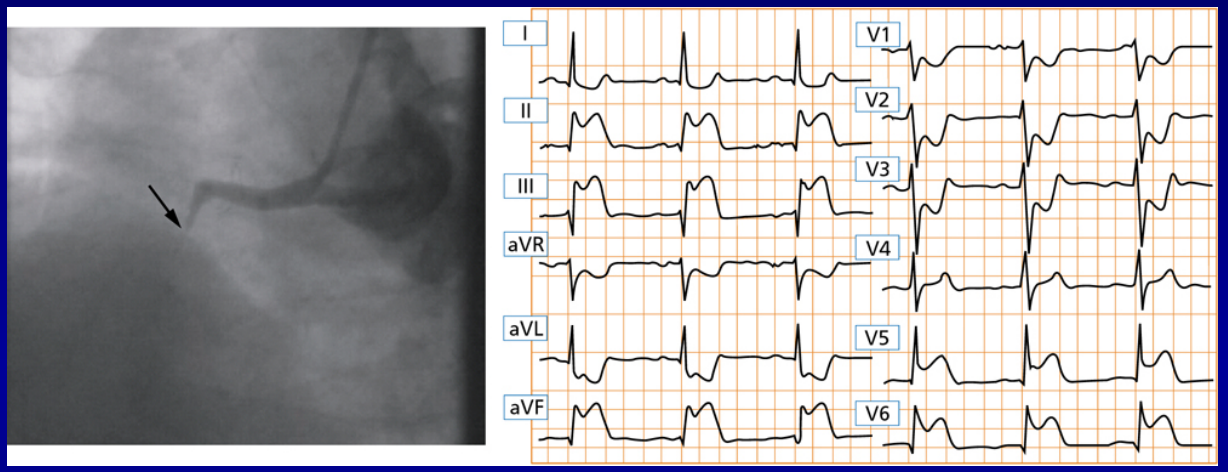
* Relative to ACE-I after 1 year of treatment

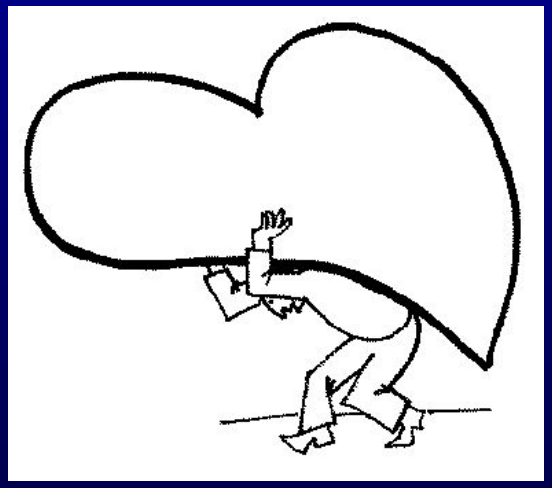
Corrao et al. *J Hypertens.* 2008;26:819–824.

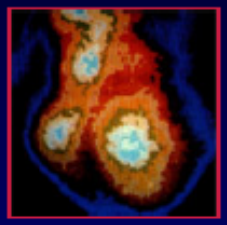
Kdy ARB u HT?

- při srovnání nevýznamný trend k většímu poklesu TK při léčbě ACE-I *(analýza 9 st.)*
- významně nižší výskyt AE po sartanech a tím větší adherence k léčbě
- významně nižší progrese nefropatie u HT s DM při kombinaci obou lékových skupin

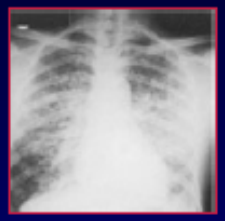
AKS & ICHS



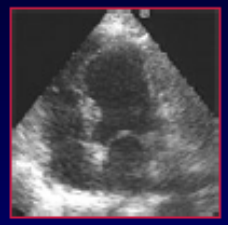




SAVE
RadNukl
EF ≤ 40%

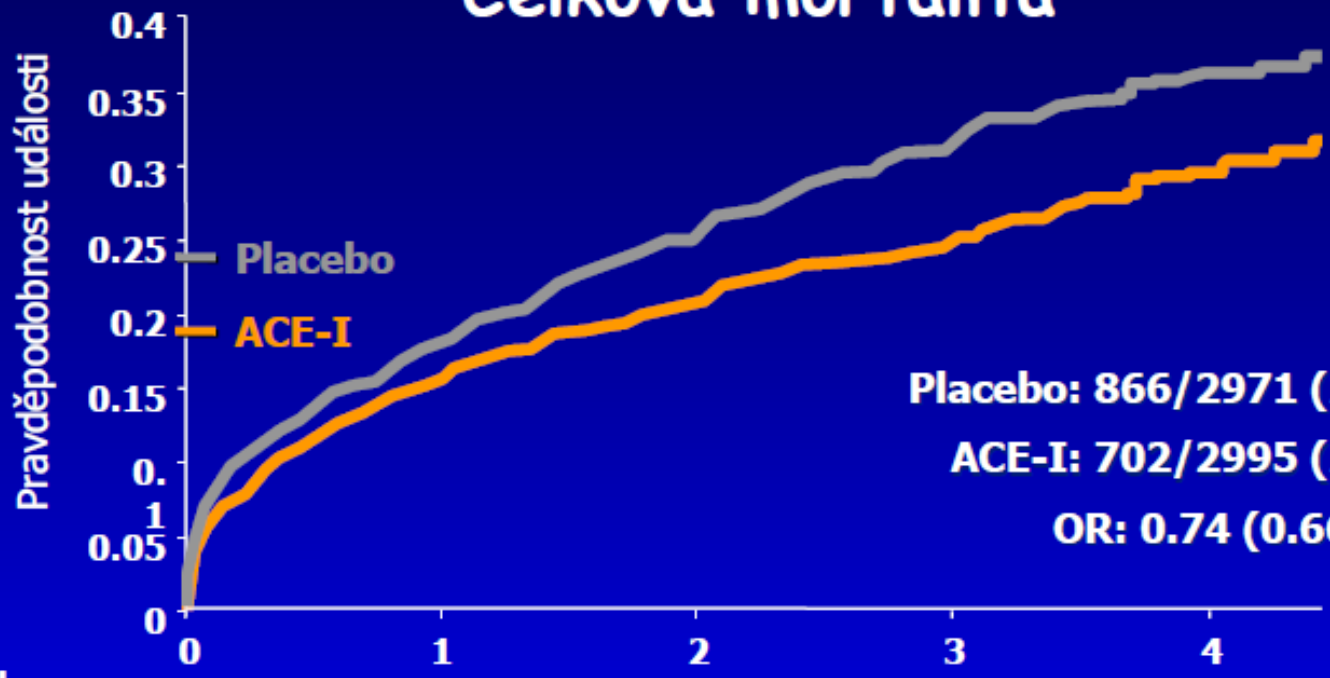


AIRE
Klin a/nebo
RTG známky
CHSSF



TRACE
Echo
EF ≤ 35%

Celková mortalita



Placebo: 866/2971 (29.1%)

ACE-I: 702/2995 (23.4%)

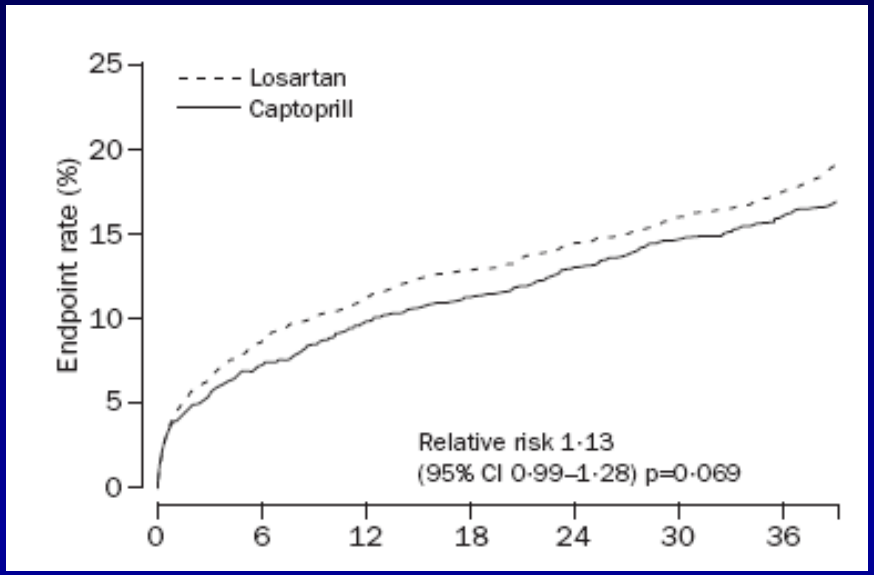
OR: 0.74 (0.66–0.83)

Roky					
ACE-I	2995	2250	1617	892	223
Placebo	2971	2184	1521	853	138

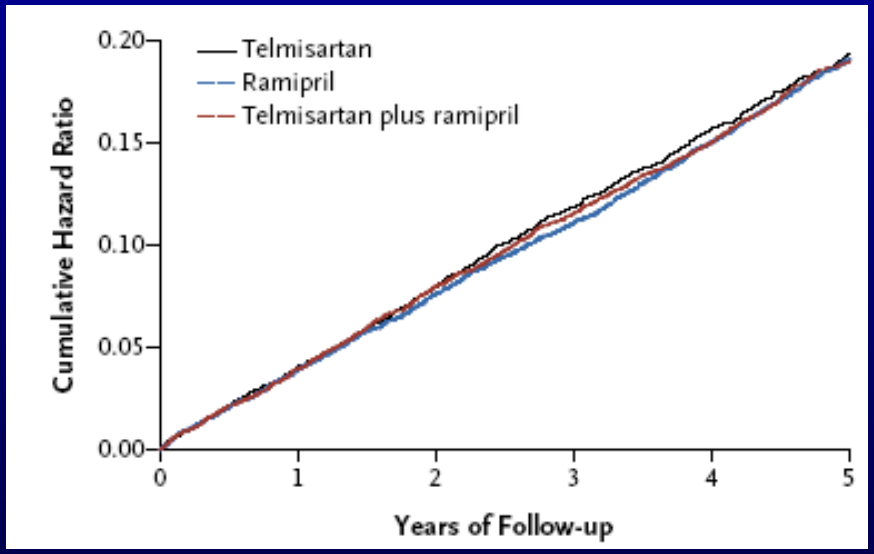
Flather MD, et al. *Lancet*. 2000;355:1575–1581

Srovnání ACE-I a ARB po IM a ICHS

OPTIMAAL

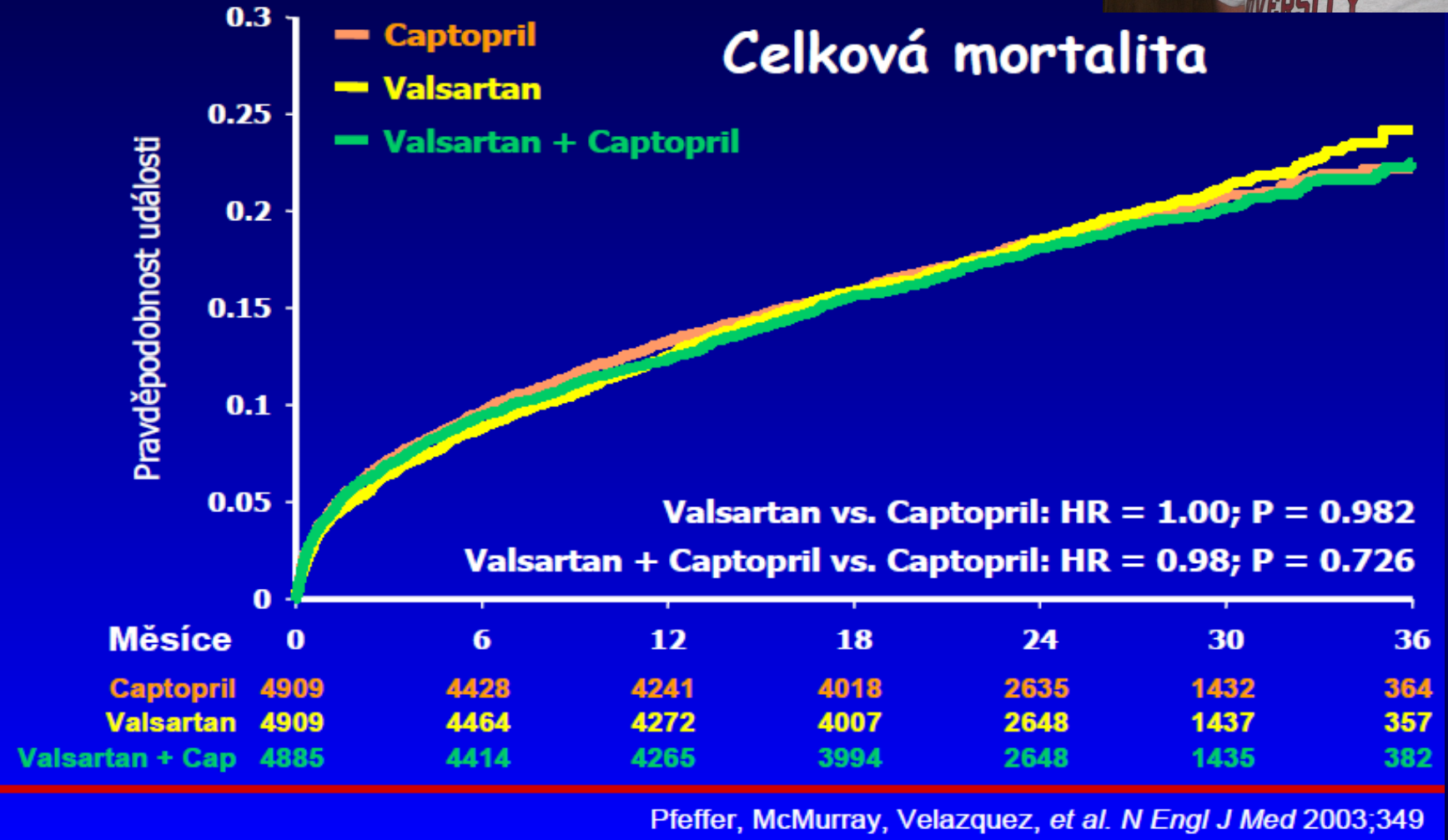


ONTARGET



VALIANT

ACE I vs ARB vs kombinace



Měsíce	0	6	12	18	24	30	36
Captopril	4909	4428	4241	4018	2635	1432	364
Valsartan	4909	4464	4272	4007	2648	1437	357
Valsartan + Cap	4885	4414	4265	3994	2648	1435	382

Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349

Kdy ARB u ICHS a po IM?

- patří mezi učinné léky v sek.prevenci ICHS – studie ONTARGET
- jasná data o prevenci remodelace po IM, srovnatelná s ACEi
- výrazně nižší výskyt NÚL
- nekombinovat s ACEi !!

SRDEČNÍ SELHÁNÍ

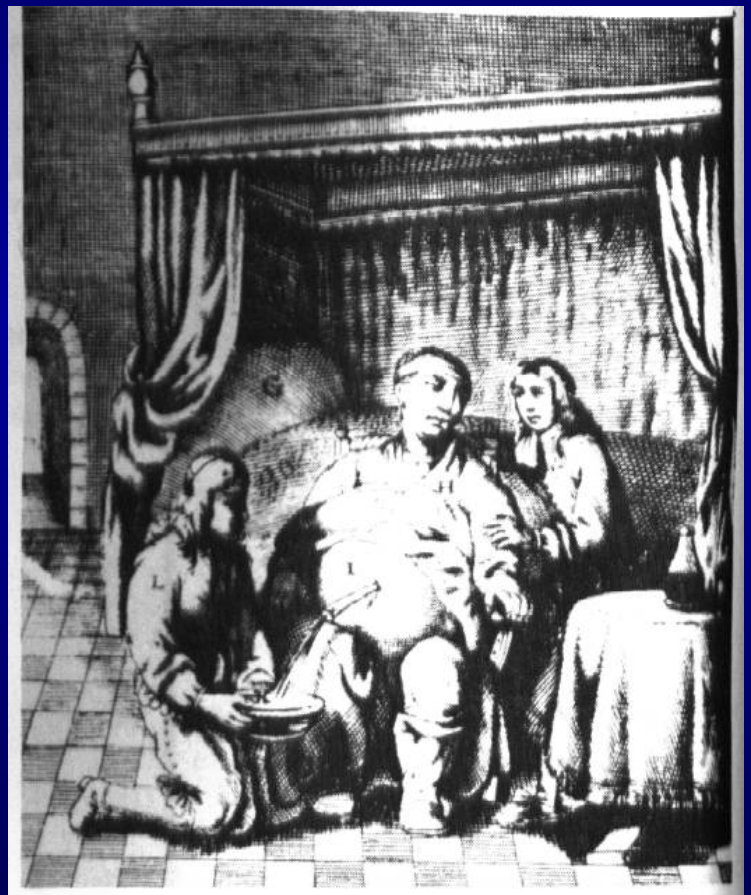


Figure 7-1 Relief of dropsy (P Barbette, 1672).

Blokáda receptorů AT_1 u CHSS

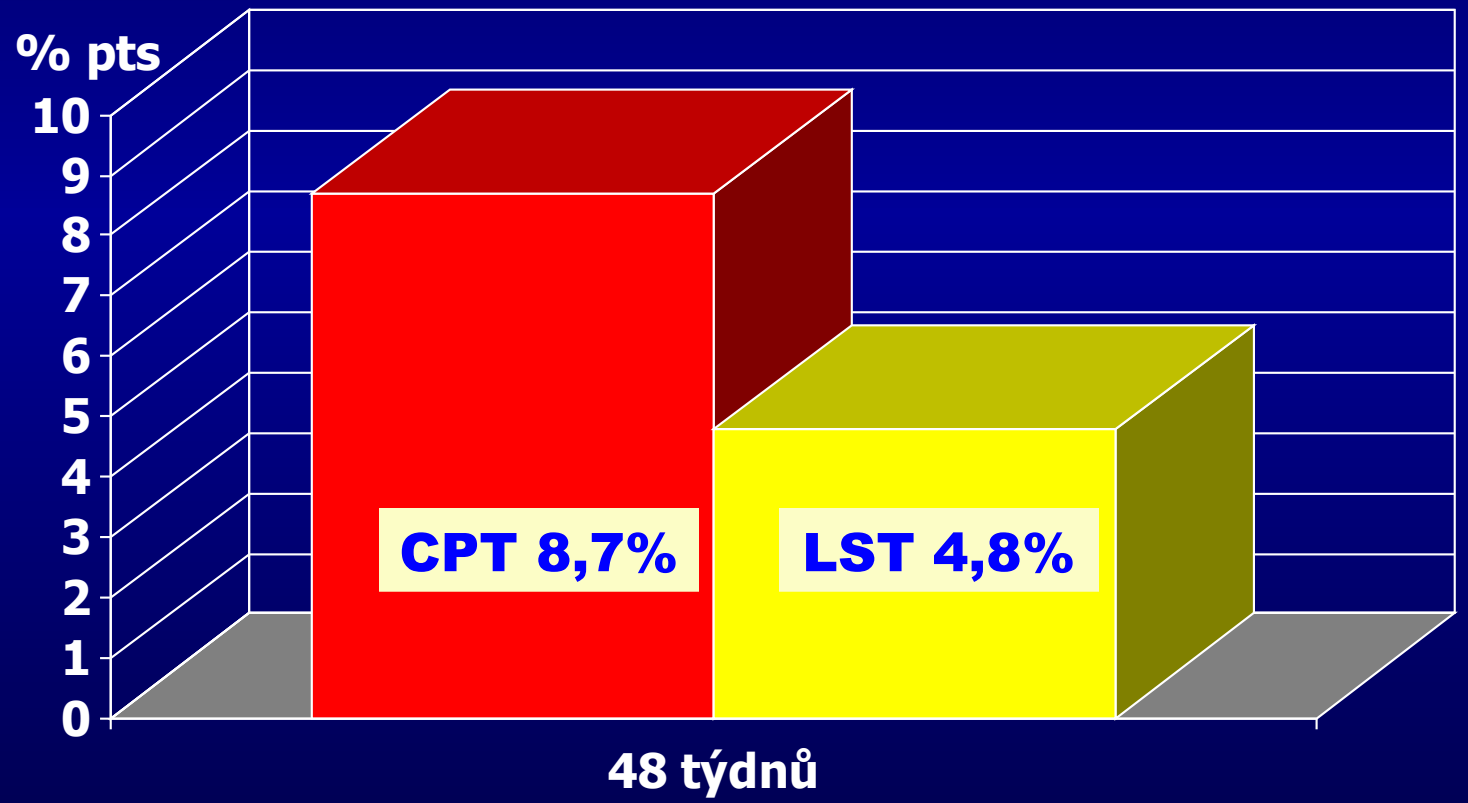
- prevence proliferace fibroblastů v LK – zlepšení poddajnosti
- prevence remodelace (dilatace LK) a ↓ progrese selhání
- ↓ aktivace sympatiku

ELITE (722 pts)

losartan (1x 50 mg) vs captopril (3x 50 mg)

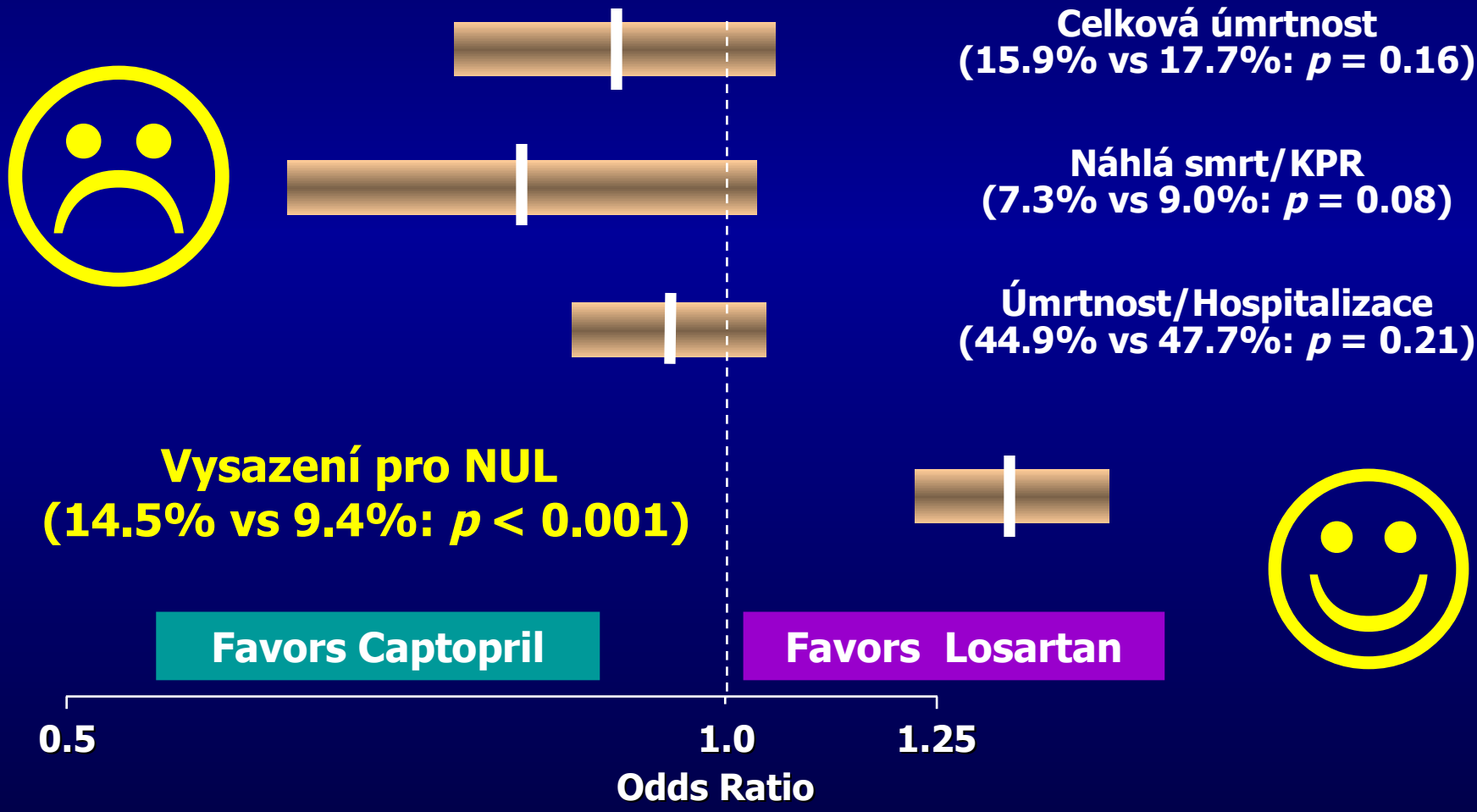
Prim.cíl: vliv na renální funkce stejný

Sek. cíl: ↓ mortalita (p=0,035, RR 0,54)



ELITE II (3152 pts)

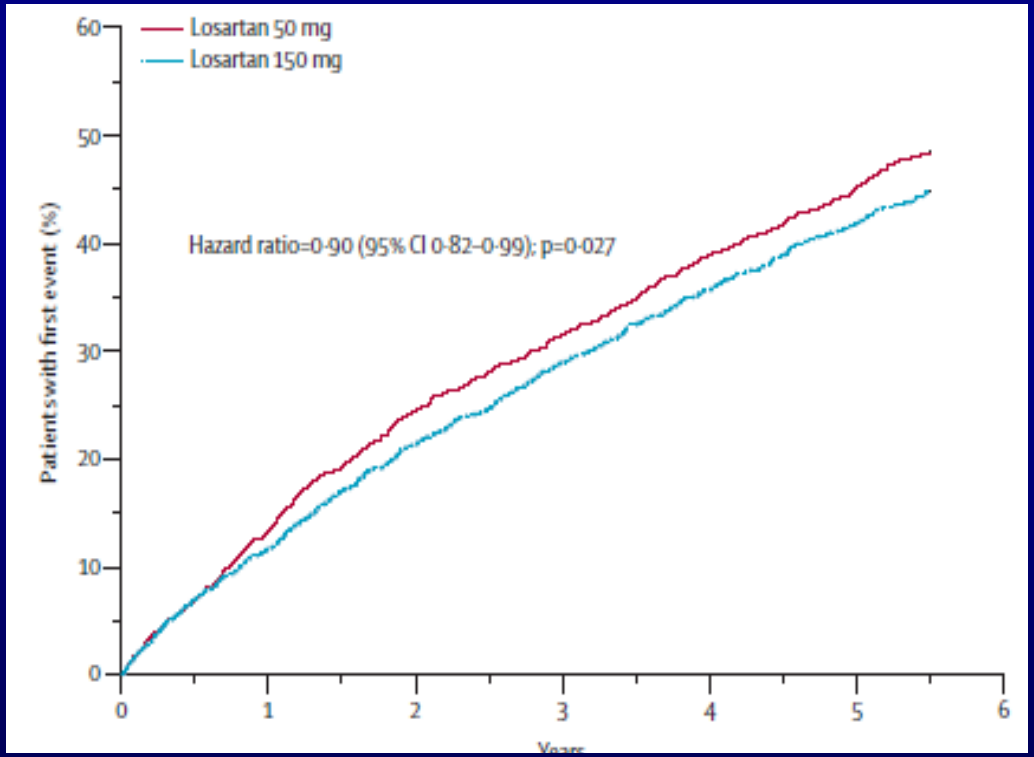
losartan (**1x 50 mg**) vs captopril (3x 50 mg)



Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial

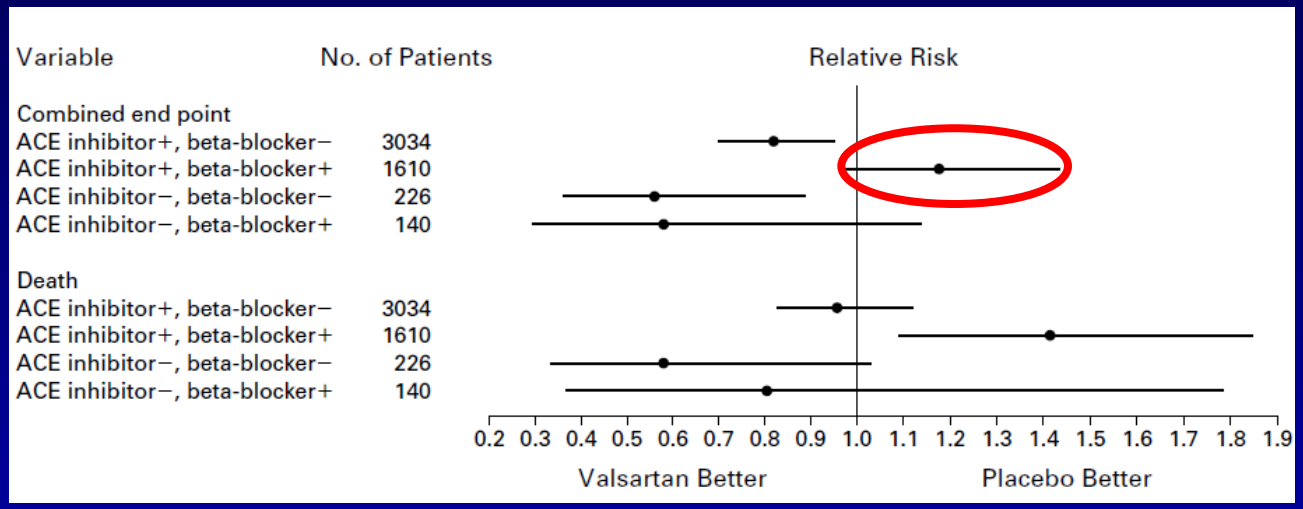
Marvin A Konstam, James D Neaton, Kenneth Dickstein, Helmut Drexler,* Michel Komajda, Felipe A Martinez, Gunter A J Riegger, William Malbecq, Ronald D Smith, Soneil Guptha, Philip A Poole-Wilson,† for the HEAAL Investigators‡

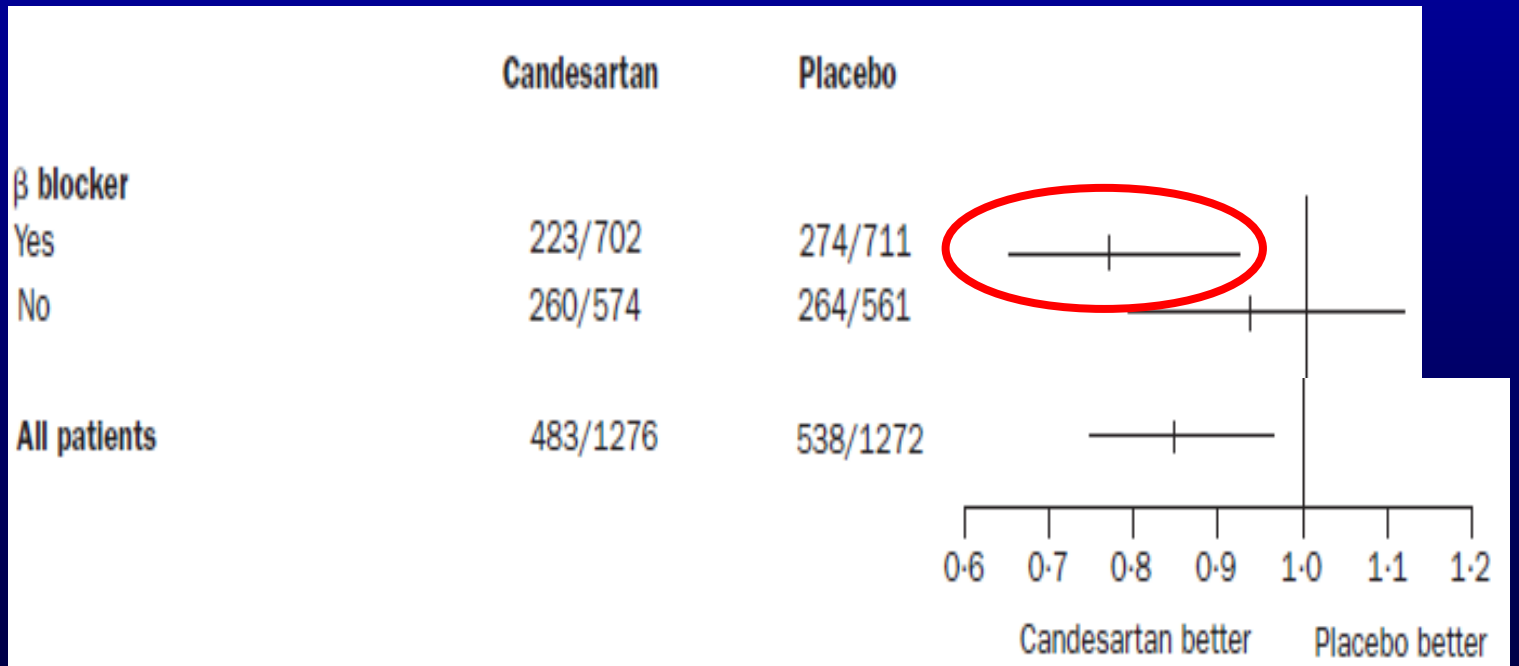
This double-blind trial. 3846 patients with heart failure of NYHA II–IV, LVEF 40% or less, and intolerance to ACE inhibitors were randomly assigned to losartan 150 mg (n=1927) or 50 mg daily (n=1919). The primary endpoint was death or admission for heart failure.



Lancet 2009; 374: 1840-48

Val-HeFT a CHARM





ARB u srdečního selhání

Recommended to reduce the risk of HF hospitalization and the risk of premature death in patients with an EF ≤40% and **unable to tolerate an ACE inhibitor because of cough** (patients should also receive a beta-blocker and an MRA)

I A

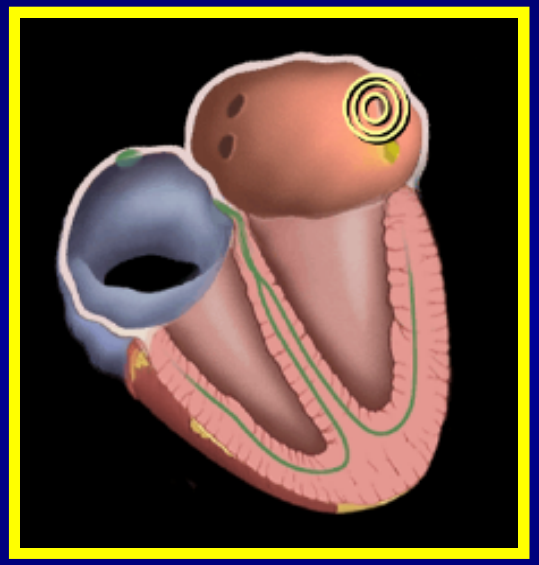
Recommended to reduce the risk of HF hospitalization in patients with an EF ≤40% and persisting symptoms (NYHA class II–IV) despite treatment **with an ACE inhibitor and a beta-blocker who are unable to tolerate an MRA**.

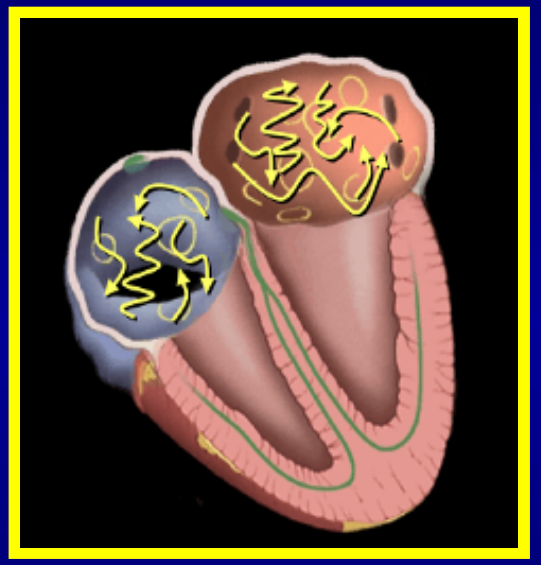
I A

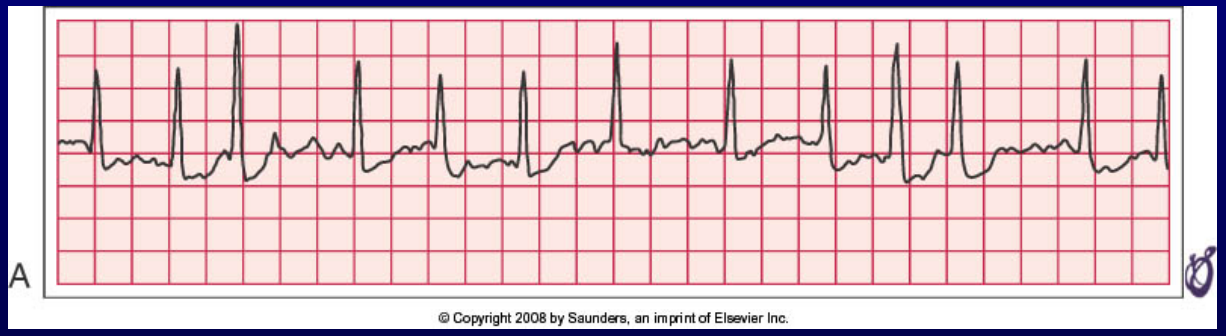
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 EHJ 2012

MOŽNÉ DALŠÍ KV INDIKACE ARB

Fibrilace a flutteru síní

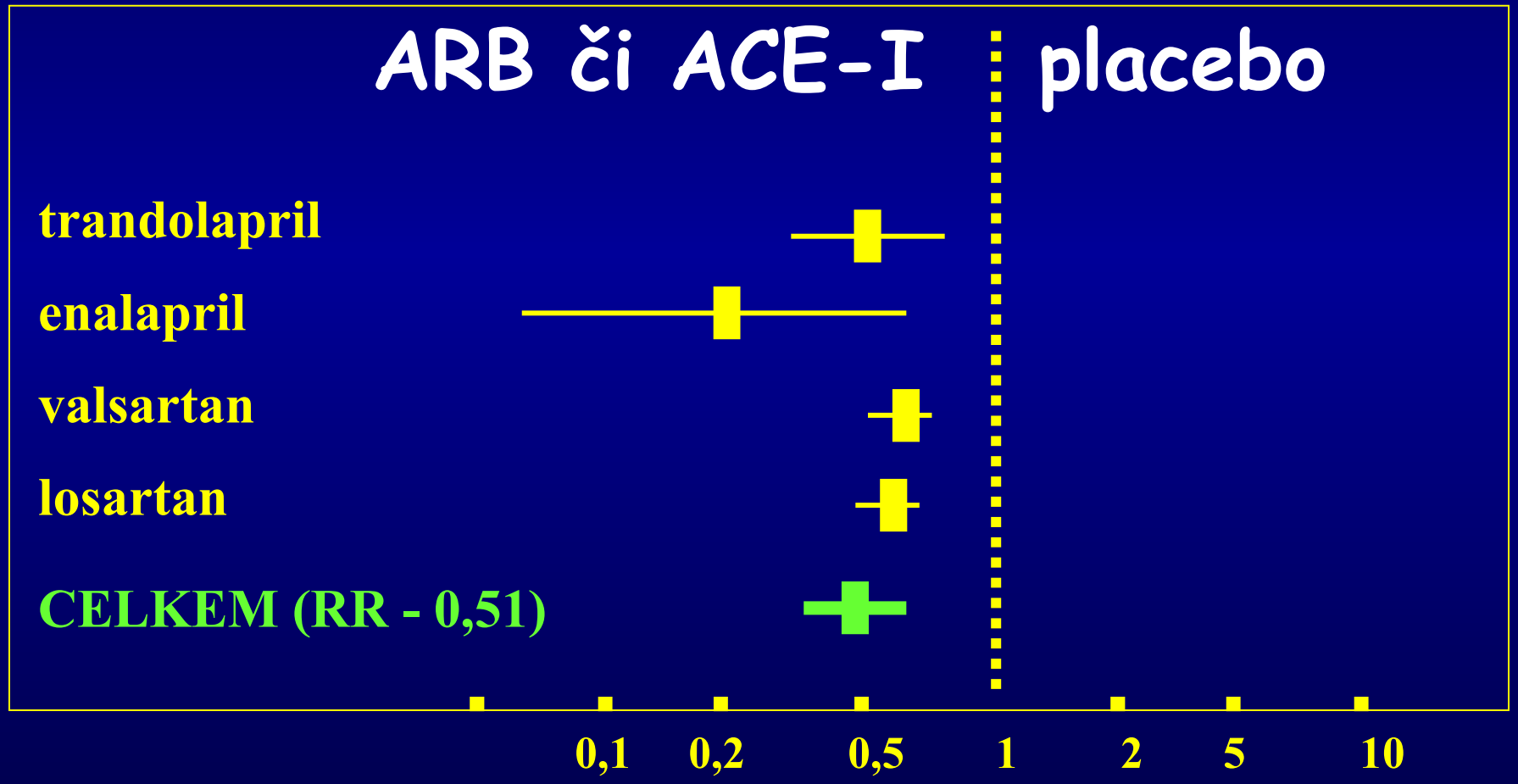






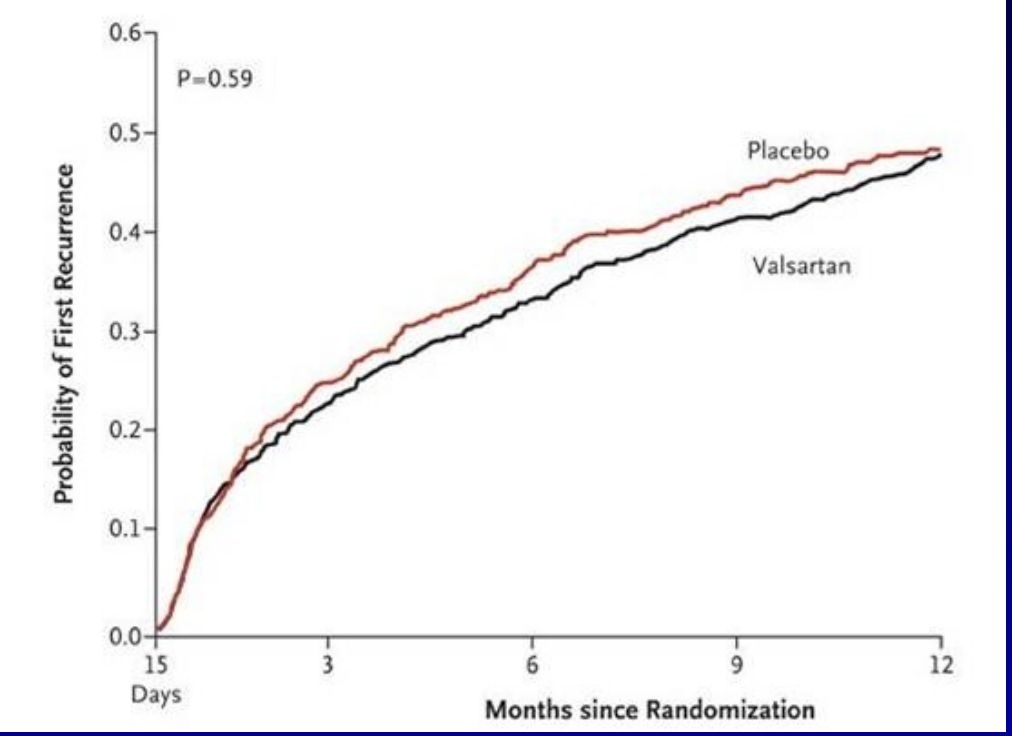
Incidence fibrilace síní

HR 0,51 (0,36-0,72), N-7342



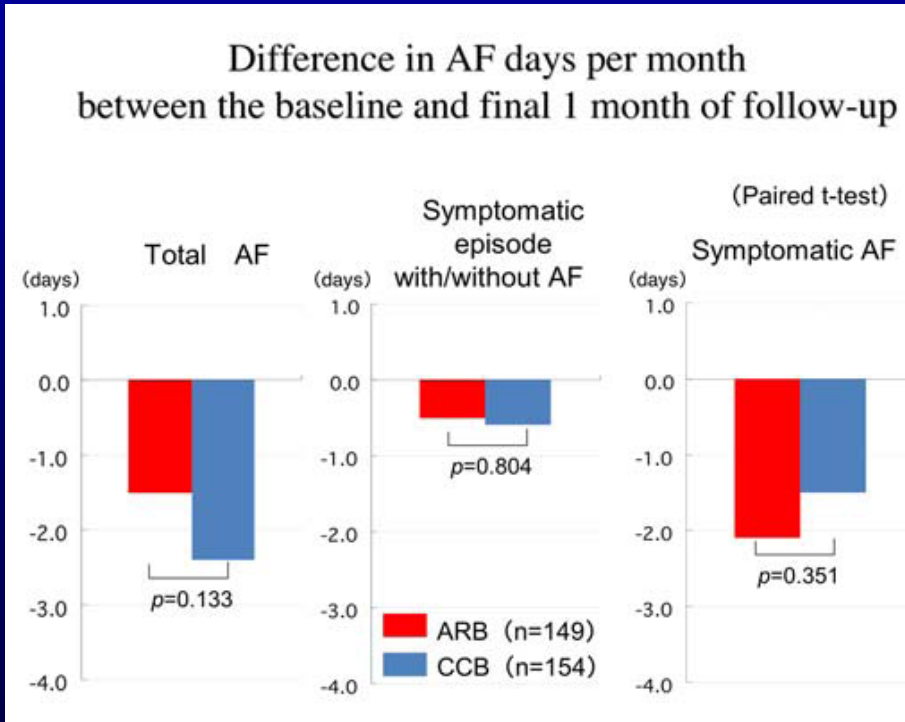
Blokáda RAA a fibrilace síní

- výrazná aktivace syst. RAA u fibrilace síní → proliferace fibrobl. v síních
- blokáda RAA snižuje progresi fibrózy síní
- **2 nezávislé meta-analýzy (Kalus JS, 2006 a Cochrane Inst., 2005) se shodují ve snížení incidence fibrilace asi o polovinu**
- Studie k ověření (GISSI-AF s valsartanem a J-RHYTHM II s cardesartanem)

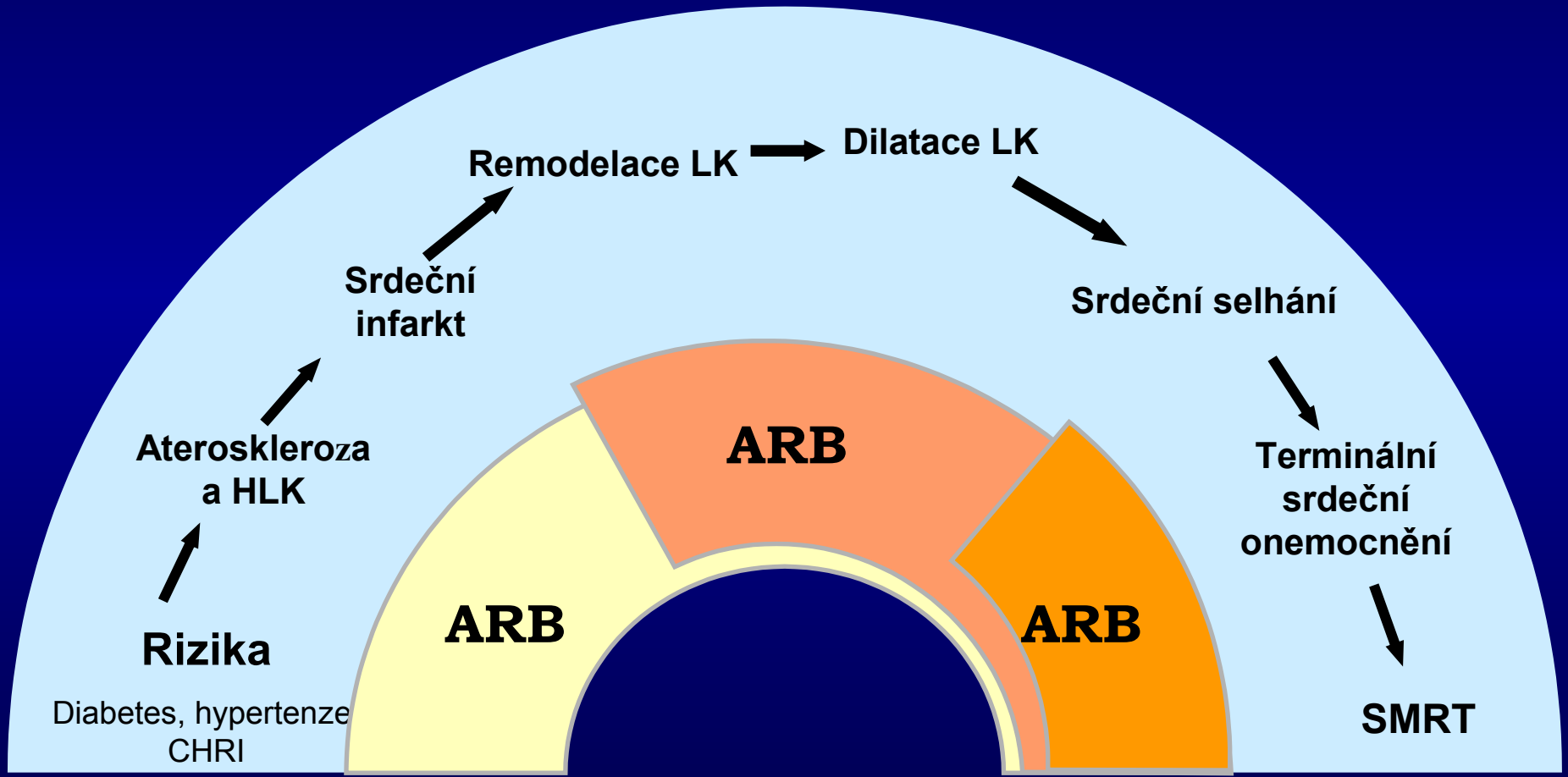


GISSI - AF

J-RHYTHM II



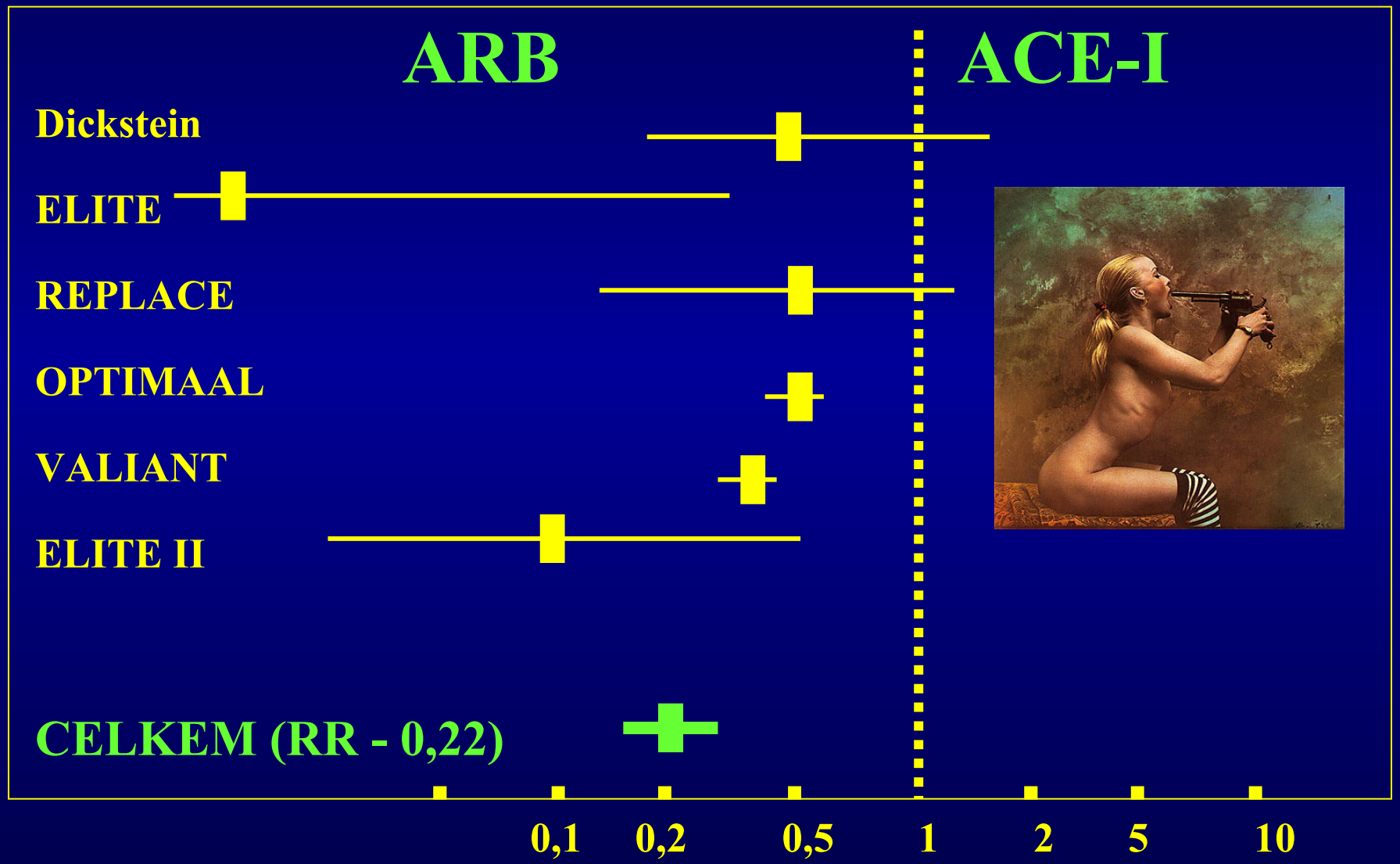
Kardiovaskulární spojitost



Adapted from Dzau V, Braunwald E. *Am Heart J*. 1991;121:1244-1263.

SROVNÁNÍ TOLERANCE ARB a ACE-I

Snížení rizika kašle u ARB a ACE-I *(n-20 143)*



Lakhard R, 2006

Jak mám si vybrat jednu,holky já mám všechny rád

candesartan, **epro**sartan, **irbe**sartan, **losa**rtan, **telmi**sartan, **val**sartan

Sartany dle biologického poločasu

Kakuta et al. *Int J Clin Pharmacol Res.* 2005;25:41–46

Indikace sartanů dle SPC

	cande	epro	irbe	losa	telmi	val
Hypertenze	ano	ano	ano	ano	ano	ano
Srdeční selhání	ano			ano		ano
KV prevence					ano	
Nefropatie			ano	ano		
Prevence CMP u HLK				ano		

Product information provided by EMA (http://www.emea.europa.eu) and eMC (http://emc.medicines.org.uk).

Děkuji za pozornost