Léčba srdečního selhání

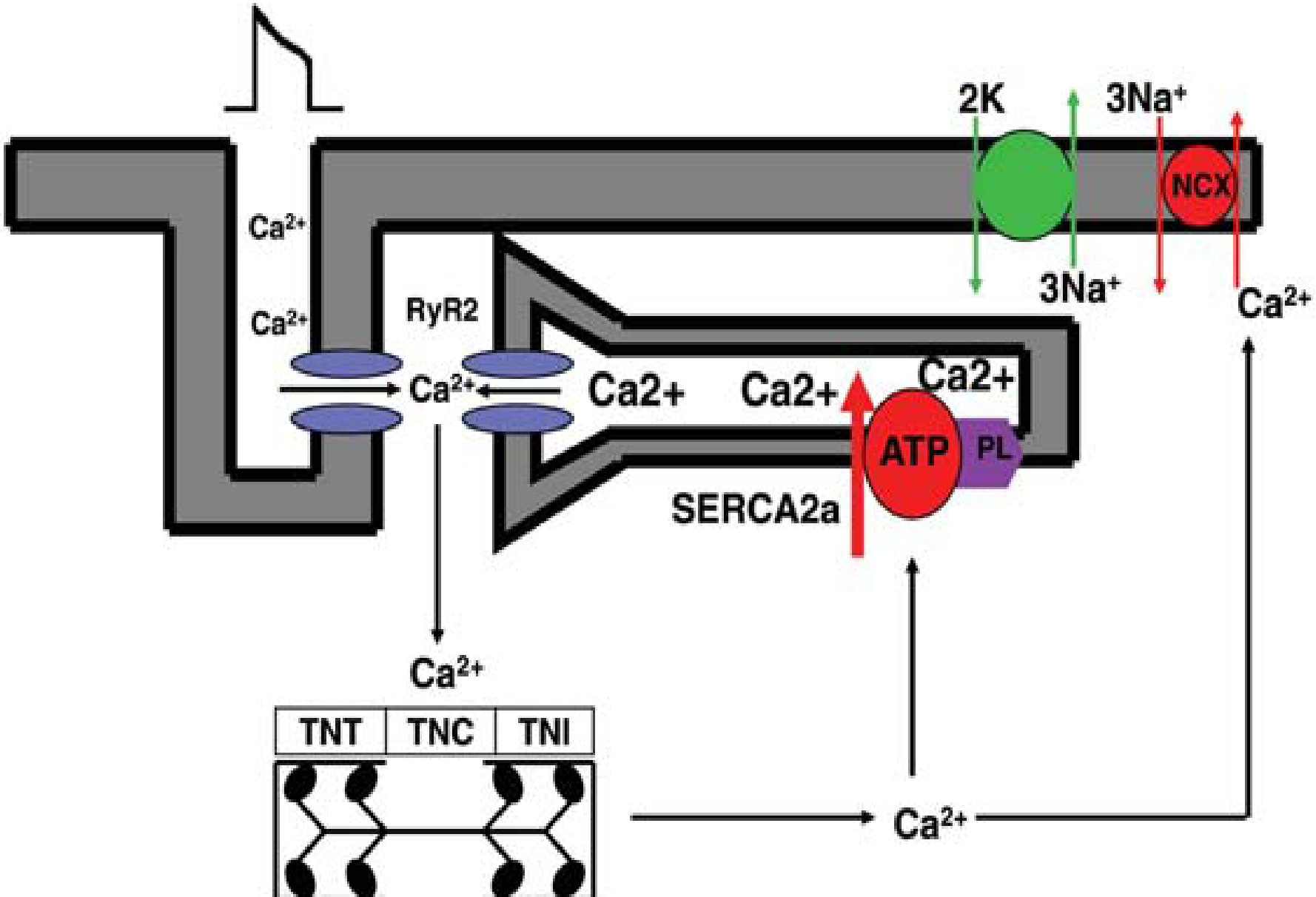
digitalis a inotropní látky

Jiří Vítovec
1.interní kardioangiologická klinika LF MU

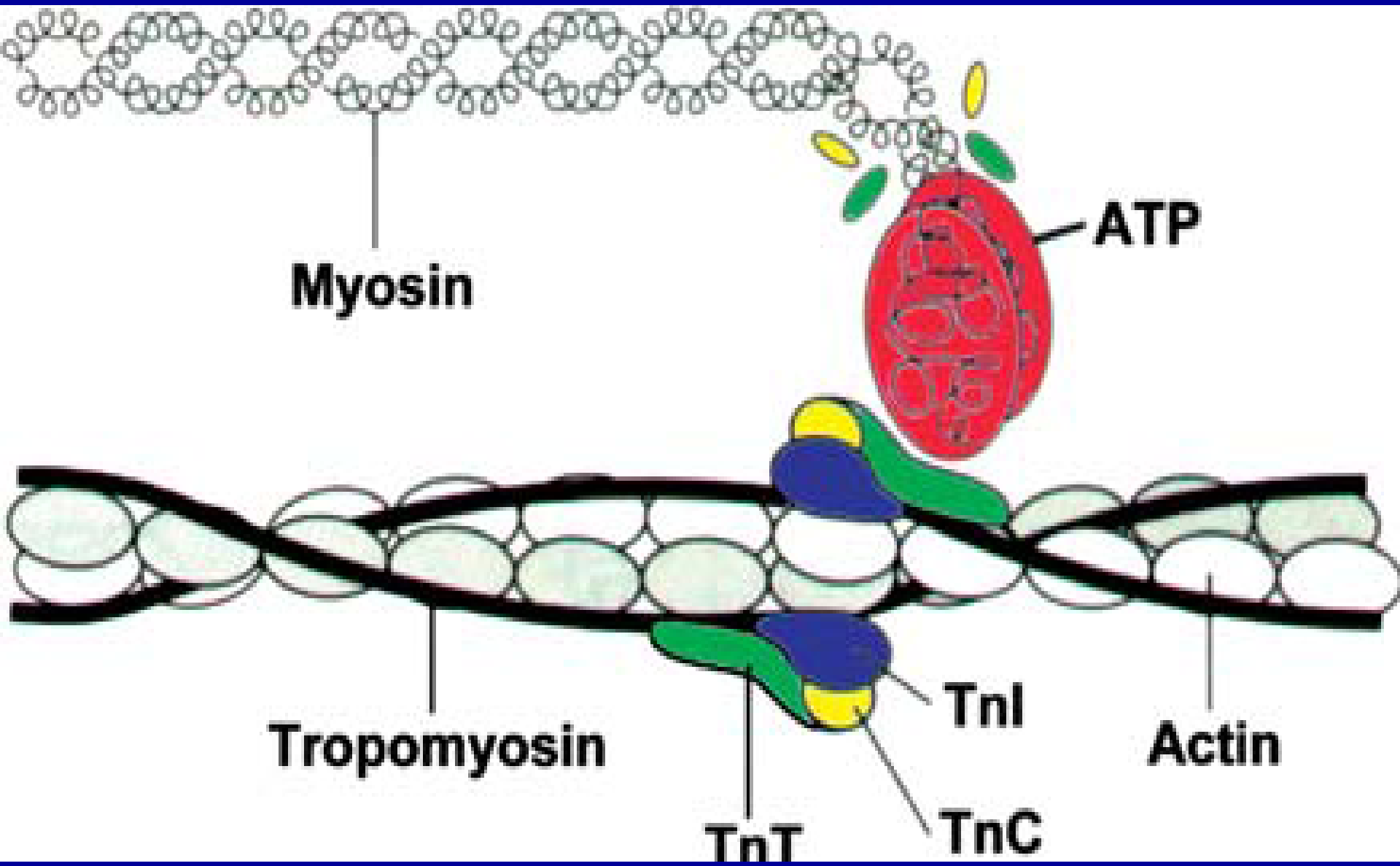
Léčba srdečního selhání

NYHA I	NYHA II	NYHA III	NYHA IV
ACEi/ARB	ACEi/ARB	ACEi/ARB	ACEi/ARB
BetaBlok	BetaBlok	BetaBlok	BetaBlok
	Diu	Diu	Diu
		Digoxin	Digoxin
		BRA	BRA
	CRT+ICD	CRT+ICD	CRT?
			Inotropika iv
			LVAD
			HTx

Excitace-kontrakce



Actino-myosinová interakce



William Withering

AN

ACCOUNT OF THE FOXGLOVE,

AND

Some of its Medical Uses:

with

PRACTICAL REMARKS ON DROPSY,
AND OTHER DISEASES.

By

WILLIAM WITHERING, M. D.
Physician to the General Hospital at Birmingham.

nonumque prematur in annum.
Horace.

BIRMINGHAM: PRINTED BY M. SWINNEY;
FOR C.G.J. AND J. ROBINSON, PATERNOSTER ROW, LONDON.
MDCCLXXXV

Birmingham, England:M.Swinney, 1785: X, V.

A Fond Farewell to the Foxglove? The Decline in the Use of Digitalis

Weisse AB. Journal of Cardiac Failure 2010; 16: 45-47

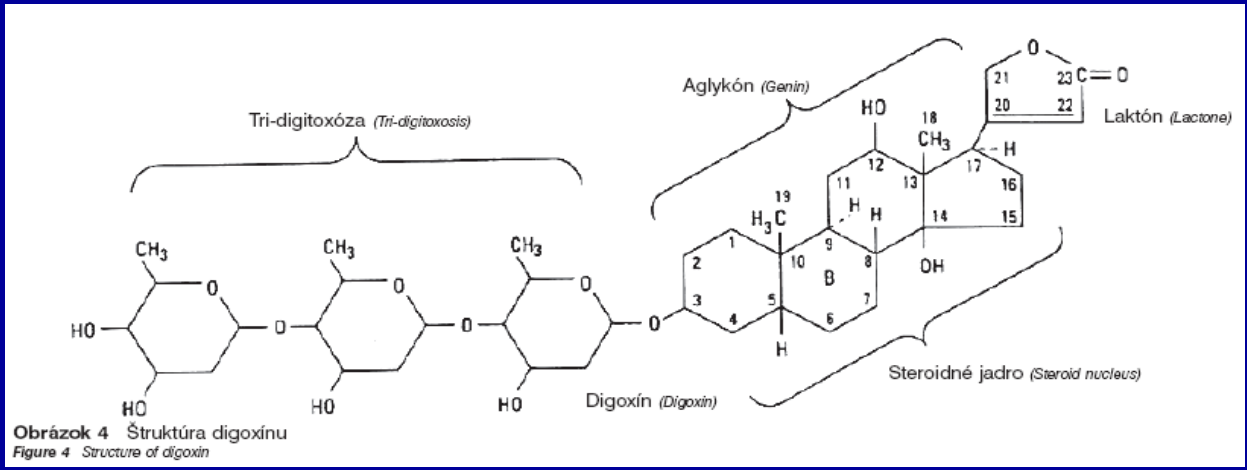
152 pts.	Success (%)	Failure	Total
Definitive cardiac	39 (89)	5	44
Others	59 (55)	49	108

Were such data presented in an article submitted to any modern journal, they would no doubt be immediately rejected. What did Withering know about a randomized, prospective, double blind study to determine therapeutic efficacy? **Fortunately for millions of patients over the last 200 years, this was no impediment to his wonderful contribution.**

Whither Withering´s Legacy?

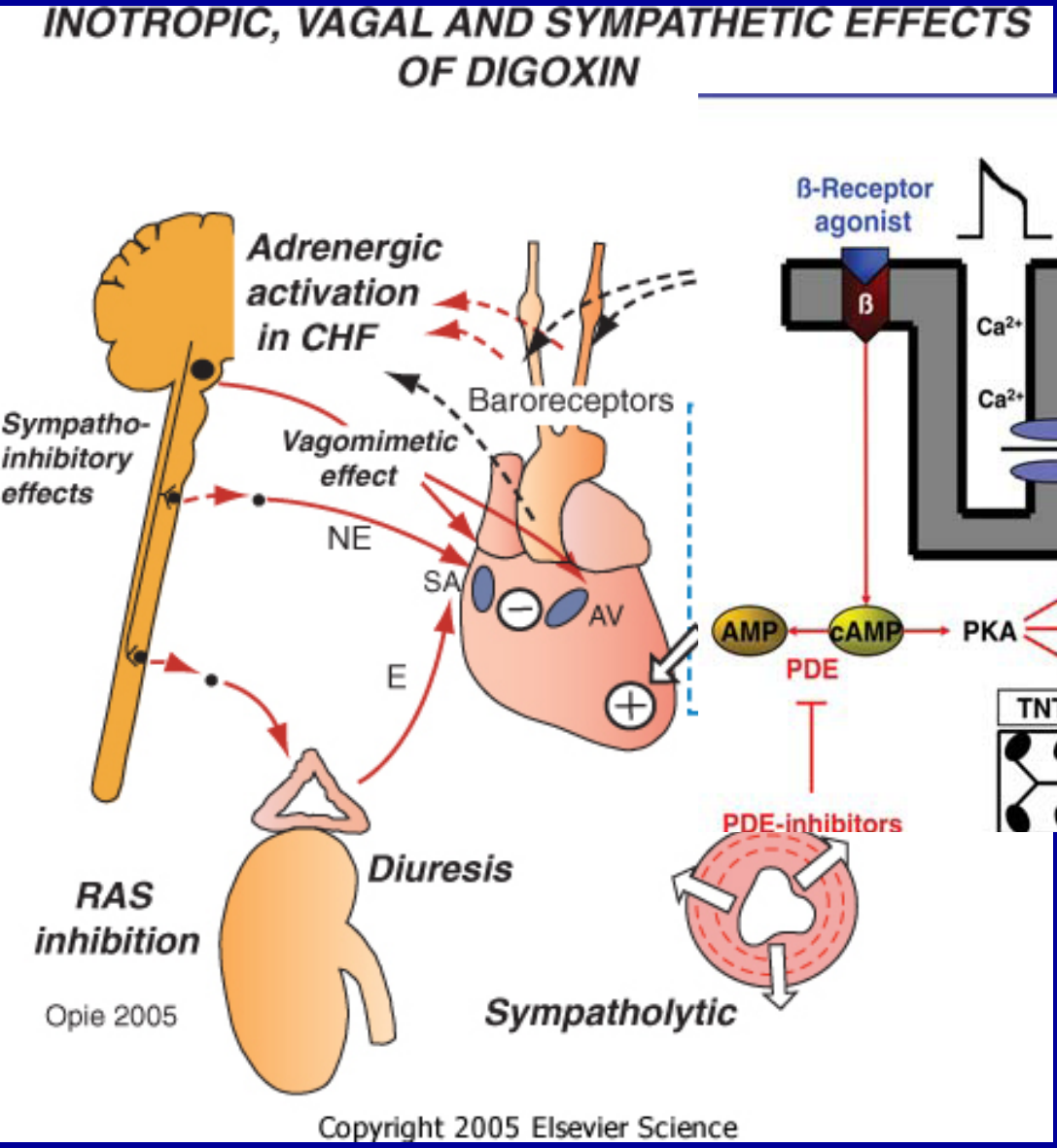
DIGITALIS LANATA

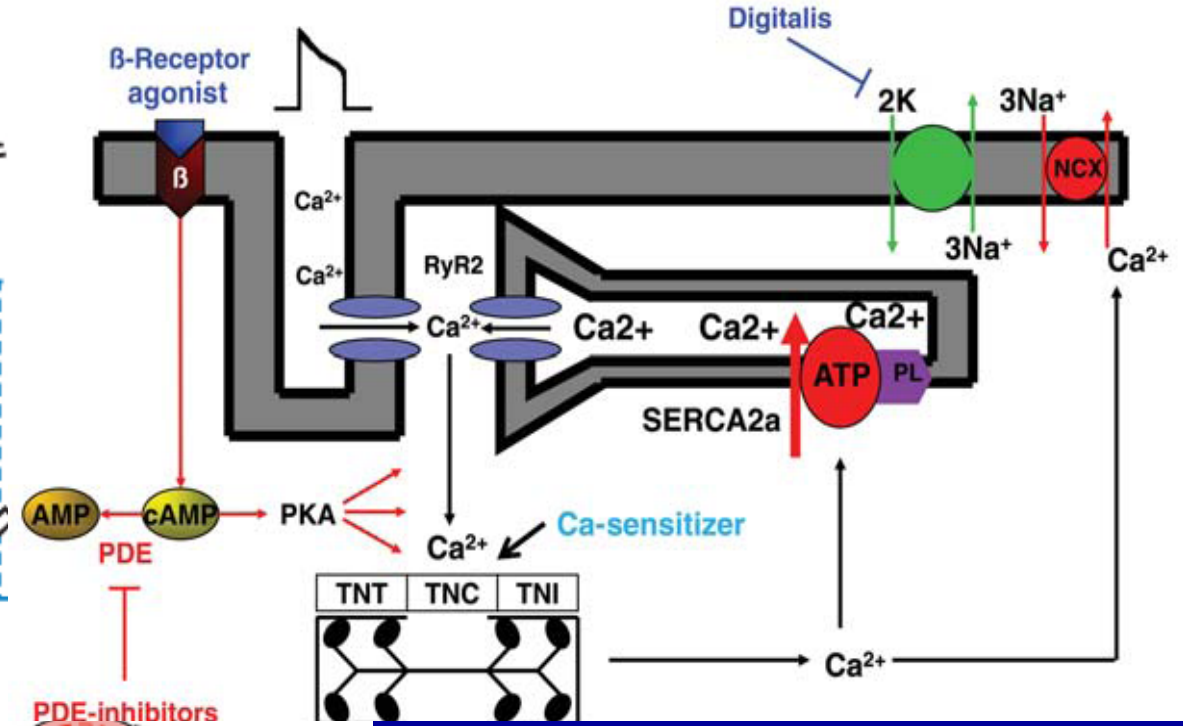
digoxin



Obrázok 4 Štruktúra digoxínu
Figure 4 *Structure of digoxin*

Srdeční glykosidy účinky





Farmakokinetika digoxinu

- 60 - 75% absorbováno z GIT
- t 1/2 = 36 hodin
- 75% renální eliminace (GF i TEx)
- therap.plazm.[0,5-0,9 ng/ml=0,6-1,1 nmol/L]
- vazba na albumin 20 - 40 %
- metabolizován < 20%

Známky intoxikace digoxinem

G I T

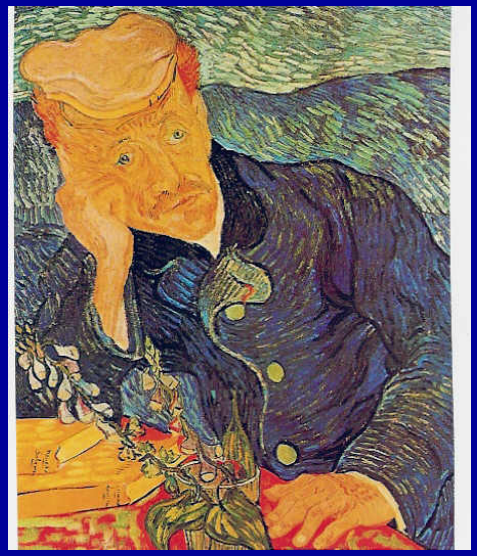
- anorexie, nausea, zvracení, průjem

CNS

- únava, deprese, žluté vidění

SRDEČNÍ

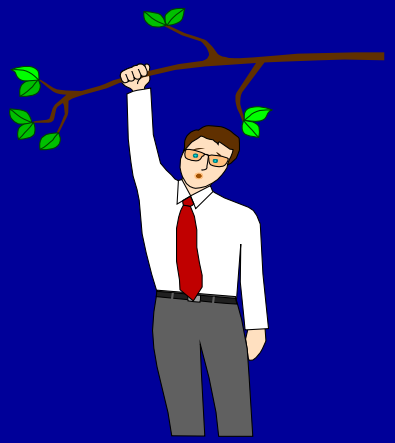
- arytmie



Arytmie při léčbě digoxinem

- KES (bigeminie)
- síňová tachykardie s blokádou
- AV junkční tachykardie
- SA i AV blokády (SAB,AVB)

Rizikové stavy při léčbě digoxinem



- st.p. IM
- thyreopatie
- hypoxemie (plicní onem.)
- lék.interakce (CAA, ATB)
- vyšší věk (nižší GF a sval.hmota)
- změny koncentrace K a Ca
- jiné - obezita, ren.selhání

D I G

The Digitalis Investigation Group

The effect of digoxin on mortality and morbidity in patients with heart failure

N.Eng.J.Med.1997, 336:525-533

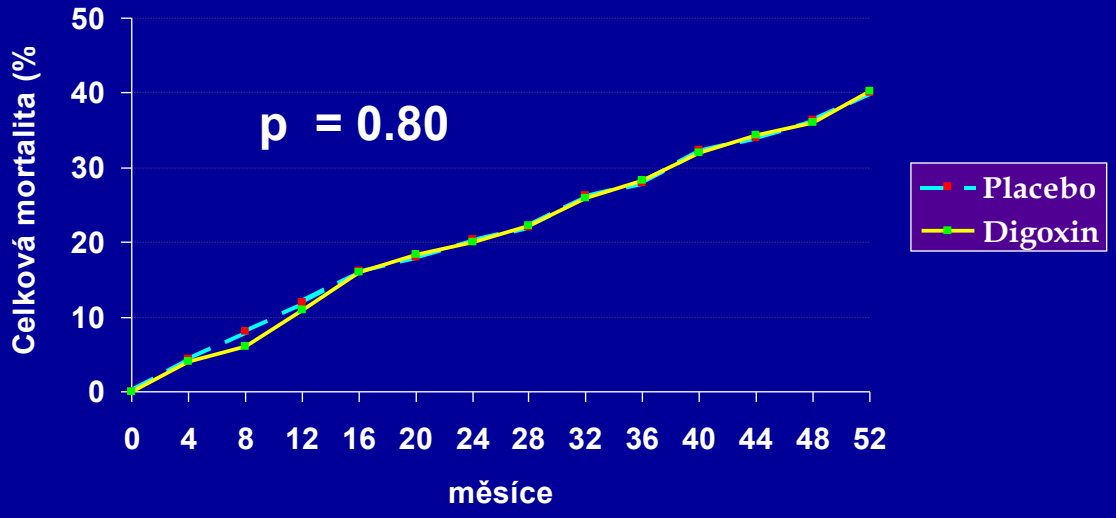
DIG : Cíl studie

Určit vliv digoxinu na úmrtnost a hospitalisace u nemocných se srdečním selháním a sinusovým rytmem

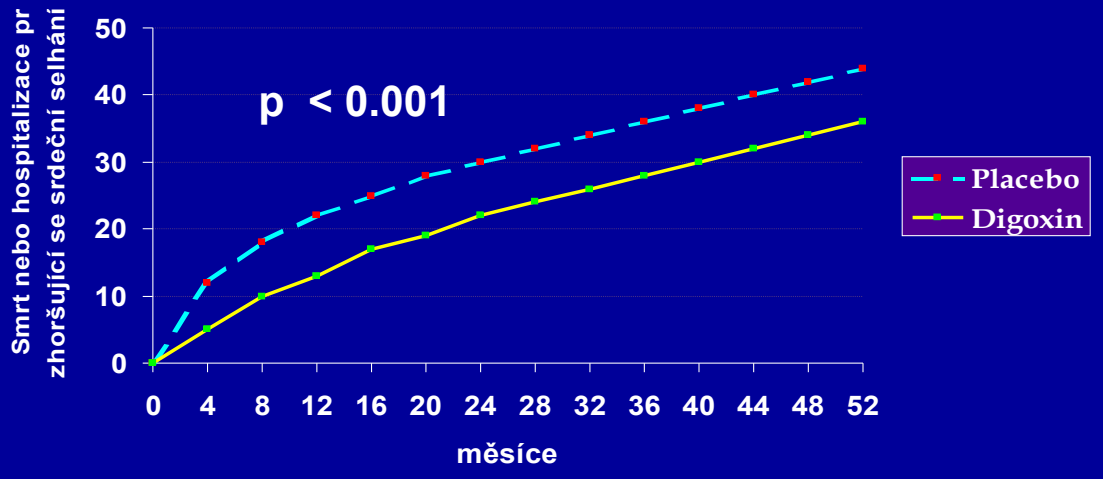
NEJM 1997

DIG

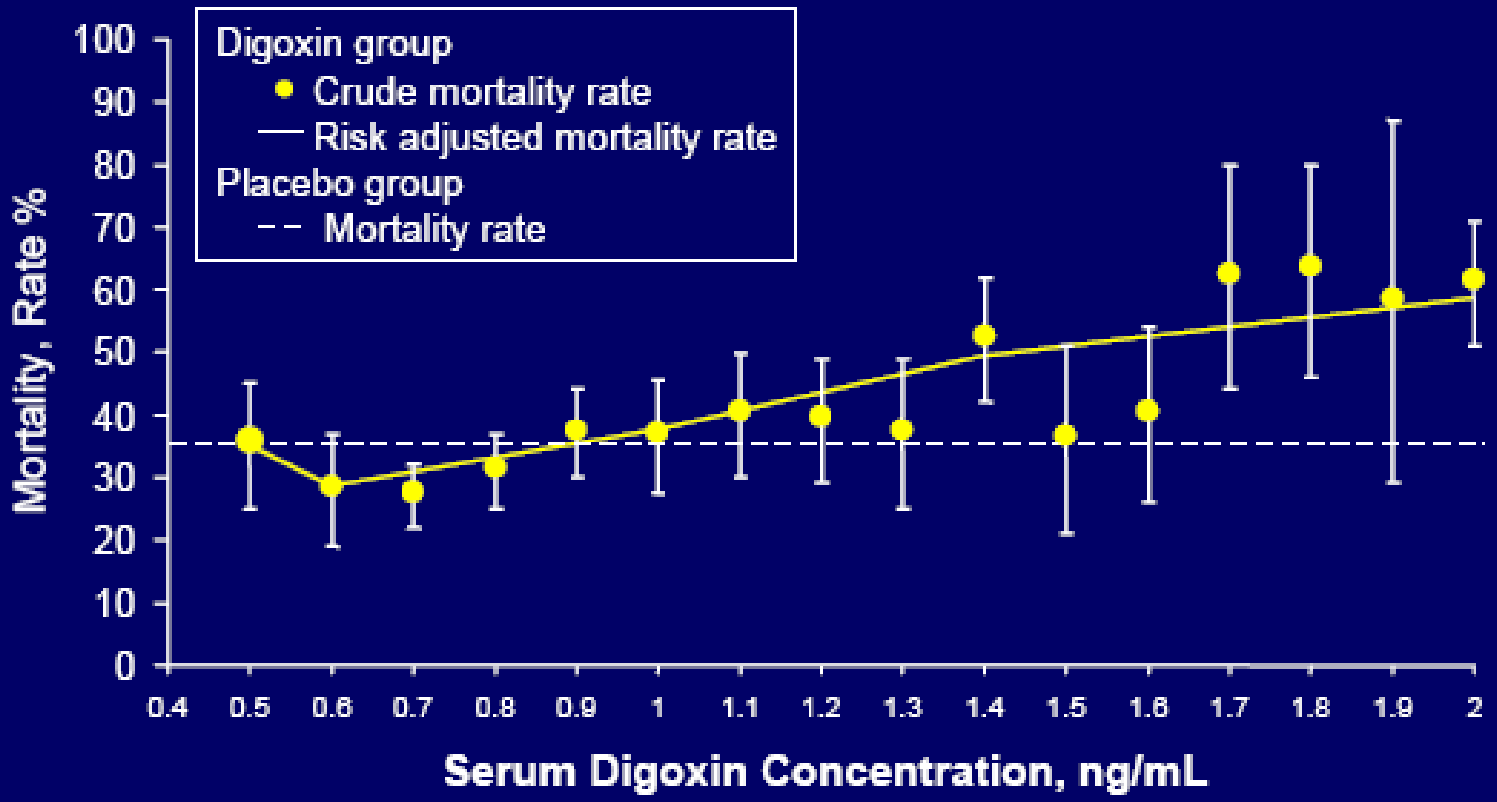
Celková mortalita



Mortalita a hospitalisace pro zhoršení srdečního selhání



All-Cause Mortality Rates by Serum Digoxin Concentration Groups



Indikace digoxinu

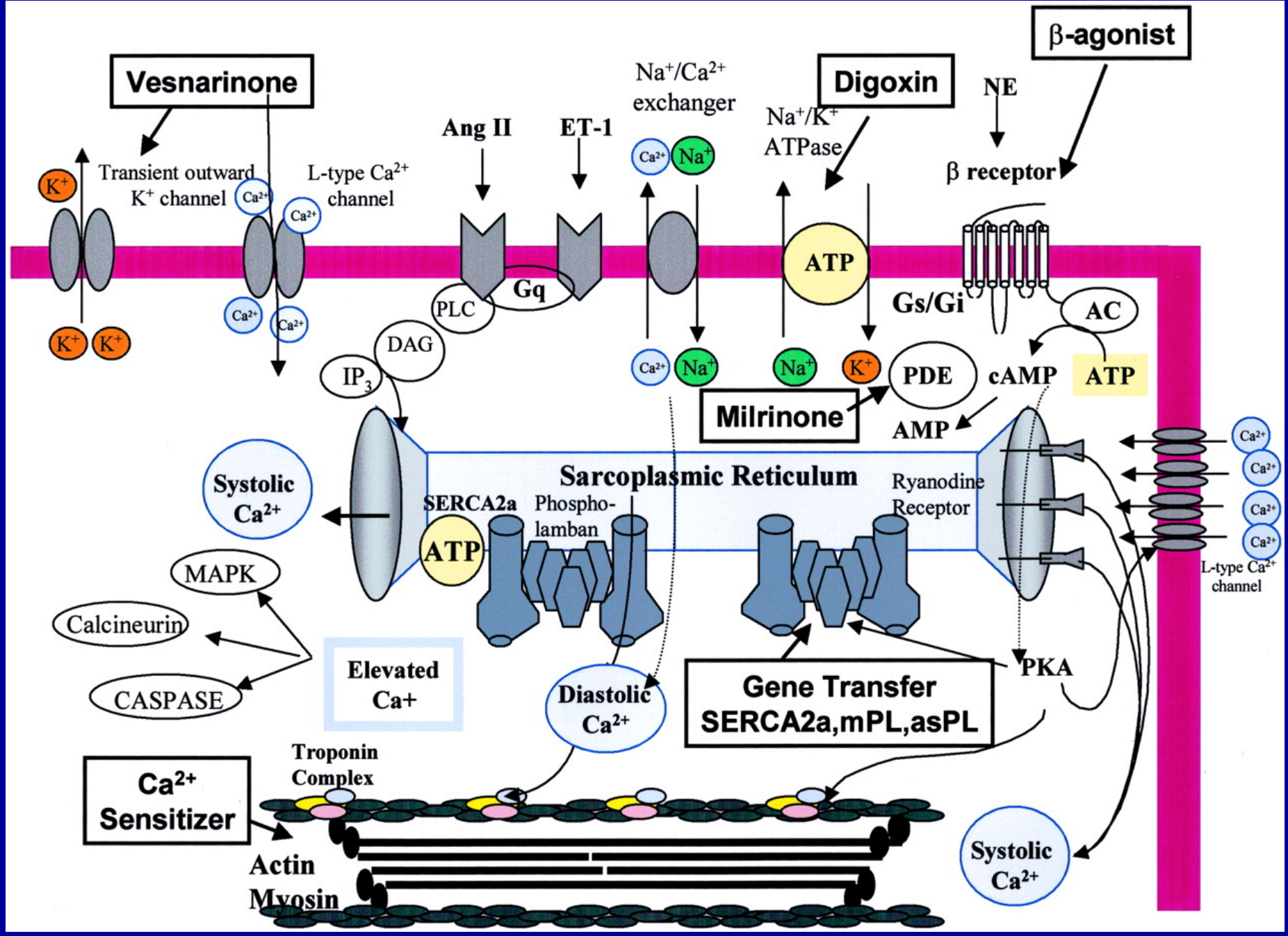
lék 3.volby (po ACE-I/ARB , BB ev.diu) u symptomatických nemocných

[0,5- 0,9 ng/ml = 0,6-1,1 nmol/L]

fi.si. s rychlou odp.komor

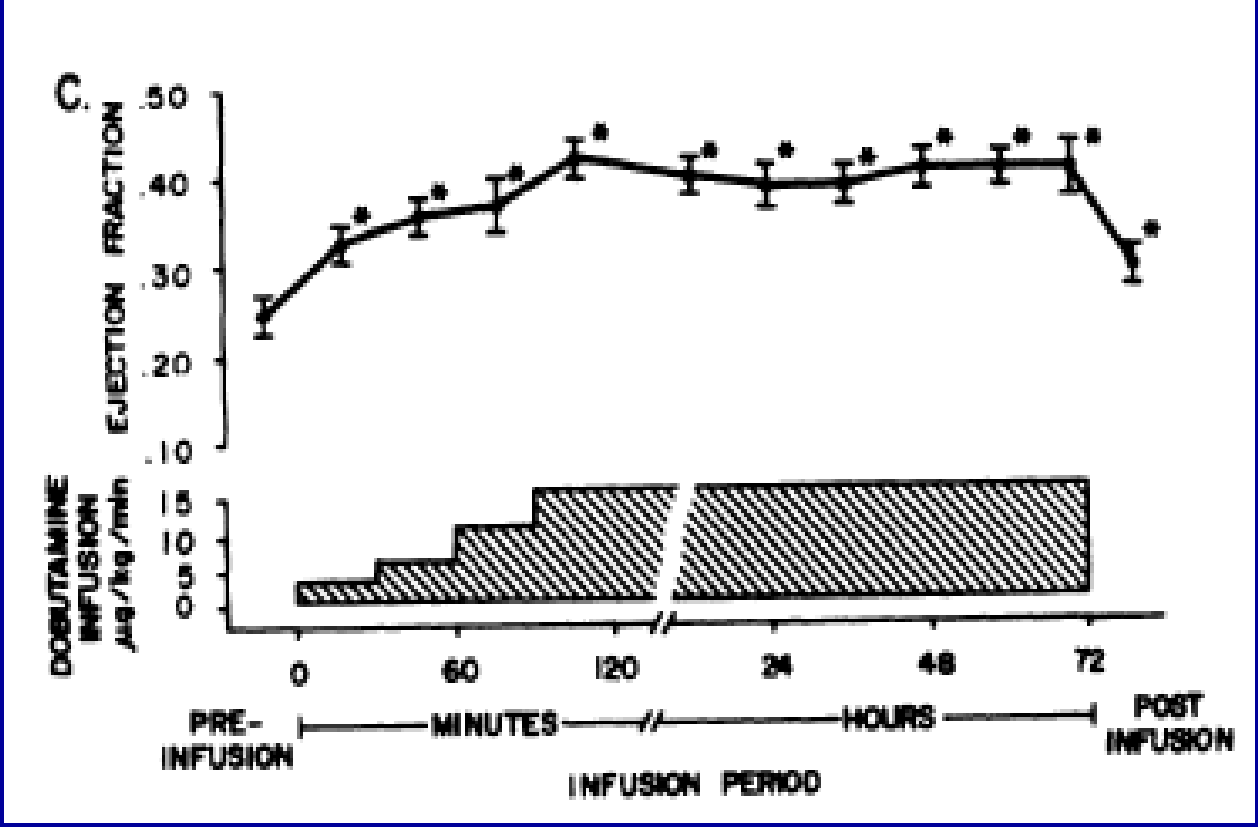
kardiomegalie

cval


Vesnarinone
β-agonist
Digoxin
NE
Na+/Ca2+ exchanger
Na+/K+ ATPase
Ang II
ET-1
Transient outward K+ channel
L-type Ca2+ channel
β receptor
ATP
Gq
PLC
Gs/Gi
AC
DAG
IP3
PDE
cAMP
ATP
Milrinone
AMP
Sarcoplasmic Reticulum
Systolic Ca2+
SERCA2a
Phospho-lamban
ATP
Ryanodine Receptor
L-type Ca2+ channel
MAPK
Calcineurin
CASPASE
Elevated Ca+
Diastolic Ca2+
PKA
Gene Transfer SERCA2a,mPL,asPL
Troponin Complex
Ca2+ Sensitizer
Actin
Myosin
Systolic Ca2+

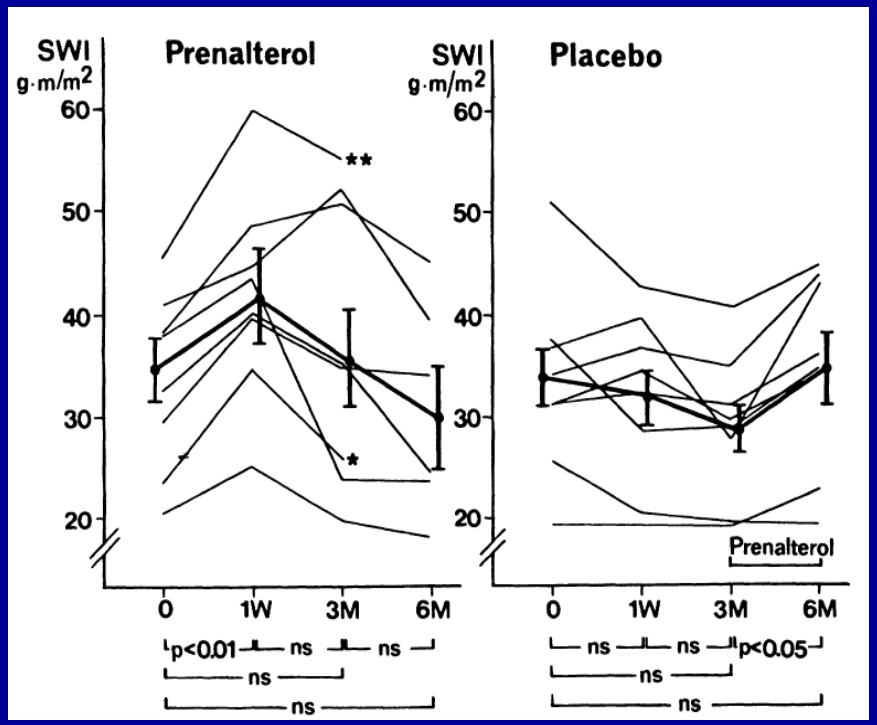
Inotropic mechanism	Drugs
Na-K -ATPase inhibition	**Digoxin**
Beta-1-adrenoceptor stimulation	**Dobutamine, dopamine**
Phosphodiesterase III inhibition	**Enoximone, milrinone**
Calcium sensitization	**Levosimendan**
Na-K-ATPase inhibition plus SERCA activation	**Istaroxime**
Acto-myosin cross-bridge activation	**Omecamtiv mecarbil**
SERCA activation	Gene transfer
SERCA activation plus vasodilation	Nitroxyl donor; CXL-1020
Ryanodine receptor stabilization	Ryanodine r. stabilizer; S44121
Energetic modulation	Etomoxir, pyruvate

The cardiovascular effects of the continuous infusion of dobutamine in patients with severe cardiac failure



Circulation 1977, 56:468-472

Long-term hemodynamic effects of prenalterol in patients with severe CHF

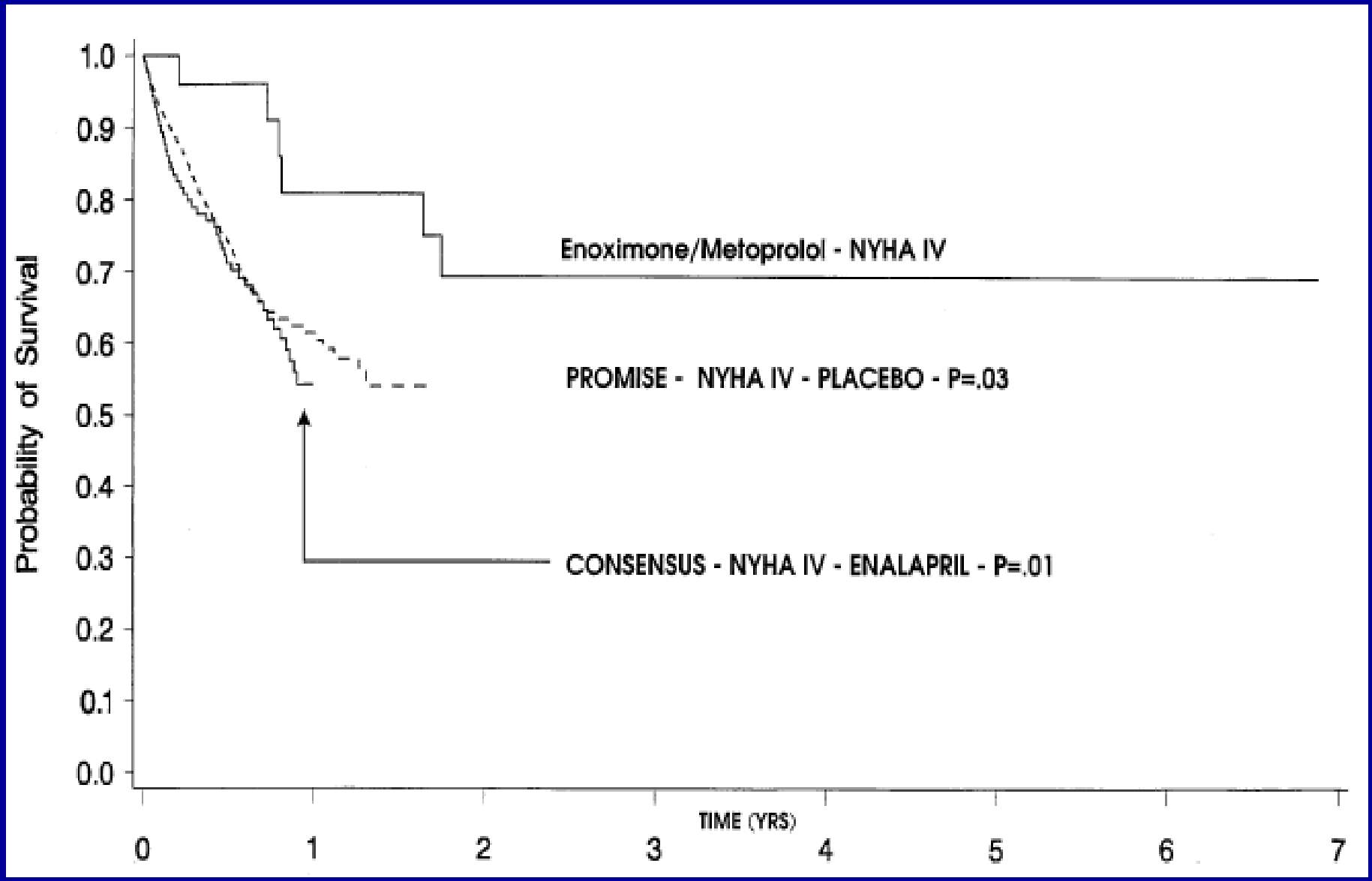


The results indicate that prenalterol is not an effective drug for the treatment of patients with heart failure, because its effects are not sustained during long-term administration.

Circulation 1984 ;69, 298-305

Katecholaminy

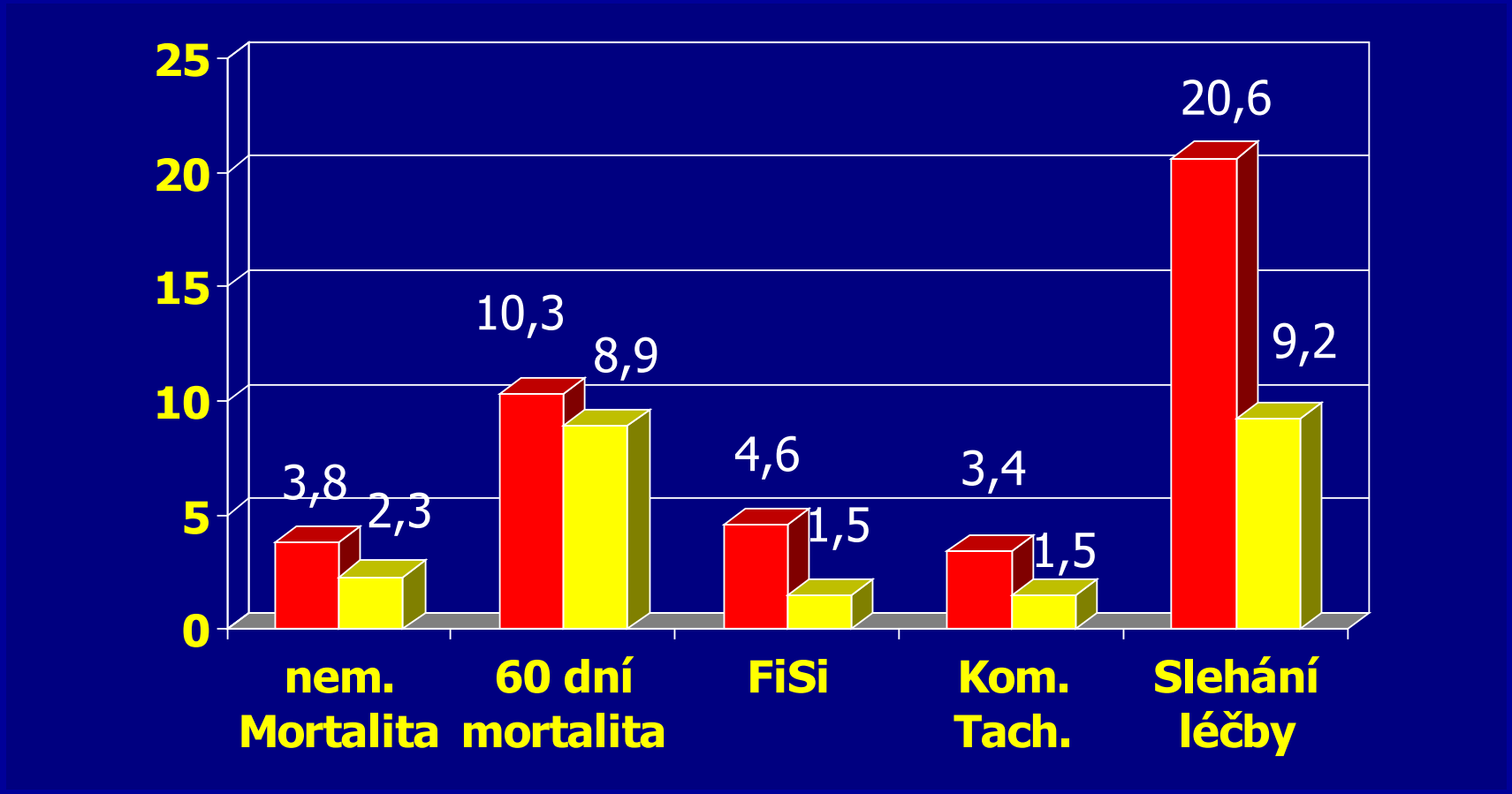
Stav	Látka	Dávka	Poznámka
Oligourie Hypotenze	Dopamin	2-5-20 ug/kg/min	DA,VD, ren?? β i α st.inotropní
Hypotenze + ⇓ CI	Dobutamin	1-20 ug/kg/min	β st., inotrop
Šokový stav	Noradrenalin	0,01-0,1 ug/kg/min	α,β st., inotrop



J Am Coll Cardiol 1998;31:1336–40)

OPTIME CHF

951 pts s TKs > 80 mmHg a TF < 110/min
diuretika ACE-I, betabl., digitalis povoleny



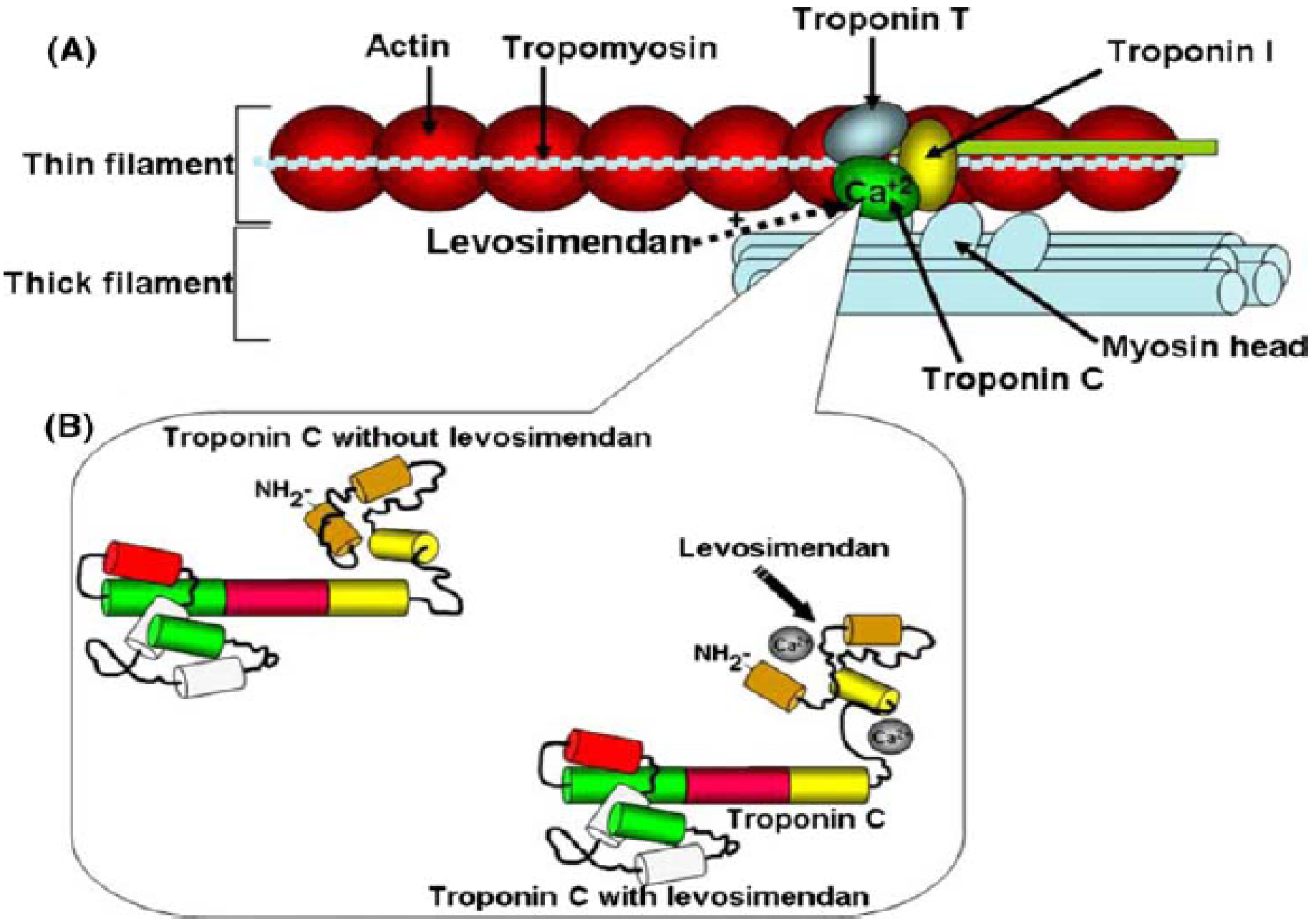
Milrinon 72 hod vs placebo

JAMA 2002;287:1541–7

Inhibitory PDE III

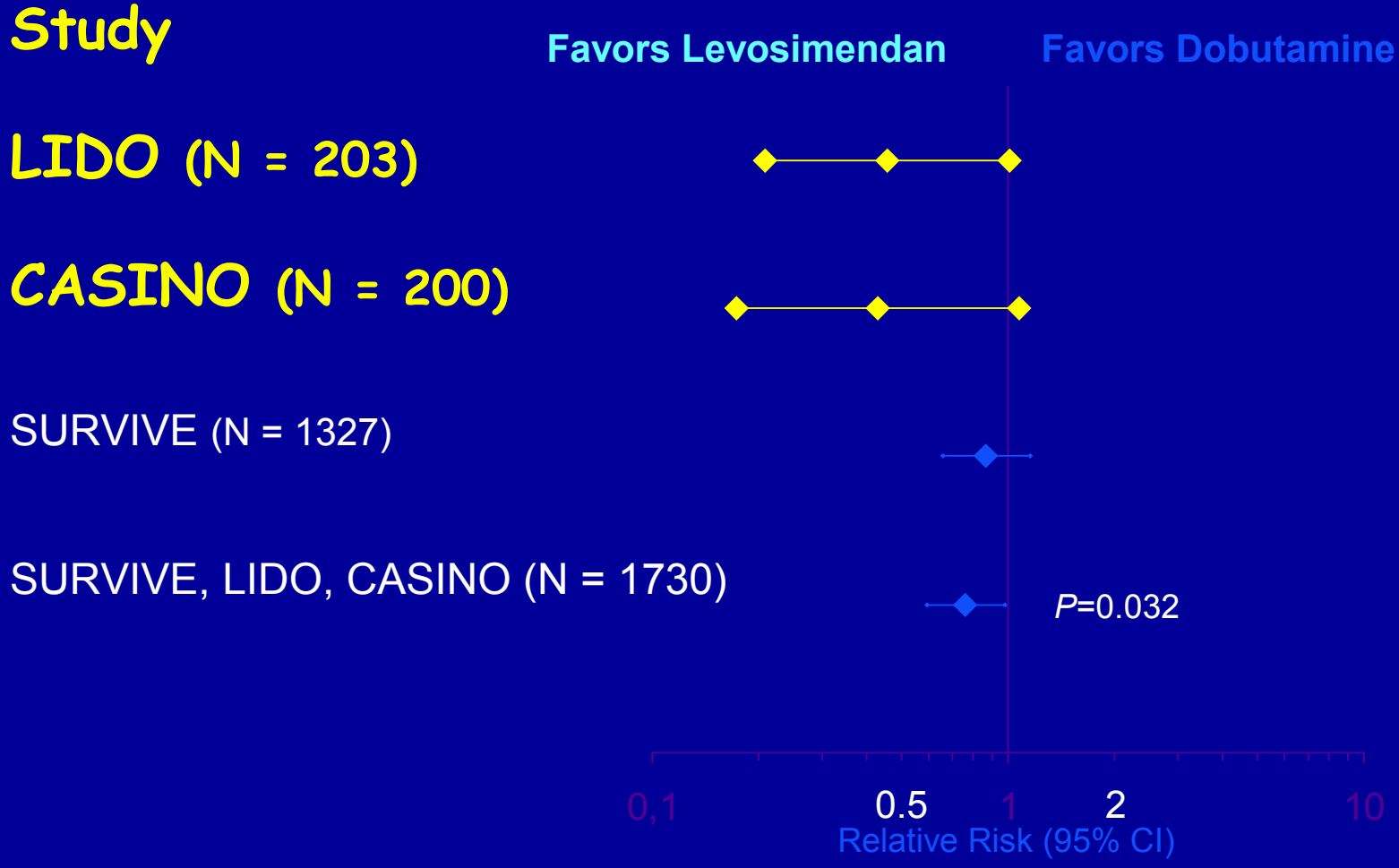
Stav	Látka	Dávka
Selhání dobutaminu	**Milrinon**	0,5-1 ug/kg/min
Selhání dobutaminu	**Amrinon**	5-10 ug/kg/min
Selhání dobutaminu	**Enoximon**	1,2- 7,5 ug/kg/min

Podávání inhibitorů fosfodiesterázy nemá průkaz na snížení mortality (IIb).


(A)
Actin
Tropomyosin
Troponin T
Troponin I
Thin filament
Thick filament
Levosimendan
Troponin C
Myosin head
(B)
Troponin C without levosimendan
NH2-
Levosimendan
NH2-
Troponin C
Troponin C with levosimendan

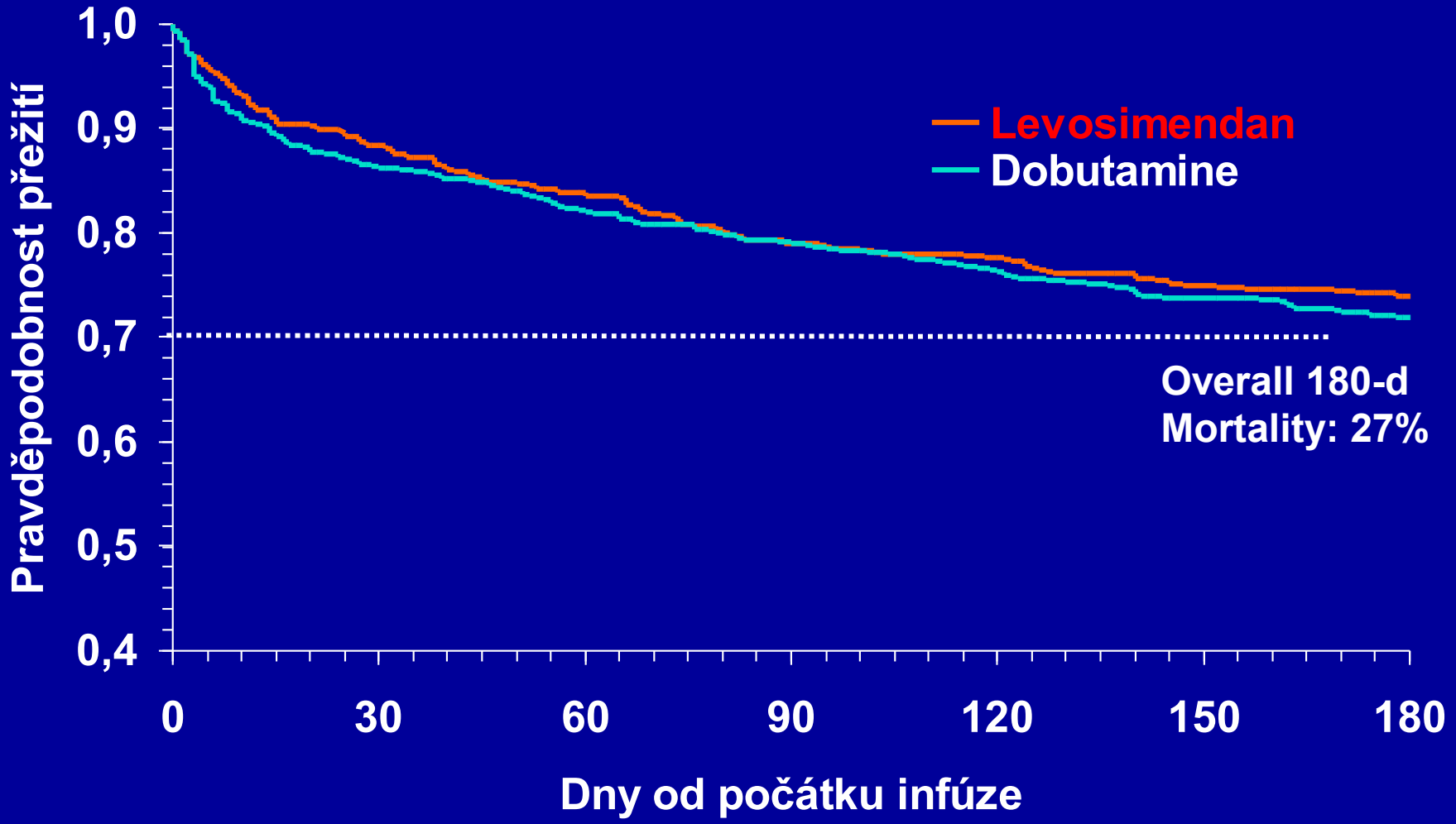
Studie s levosemindanem

Mortality Comparison - 31 Days



SURVIVE

180-denní celková mortalita



Klinická kriteria určující odpověd na levosimendan u ASS

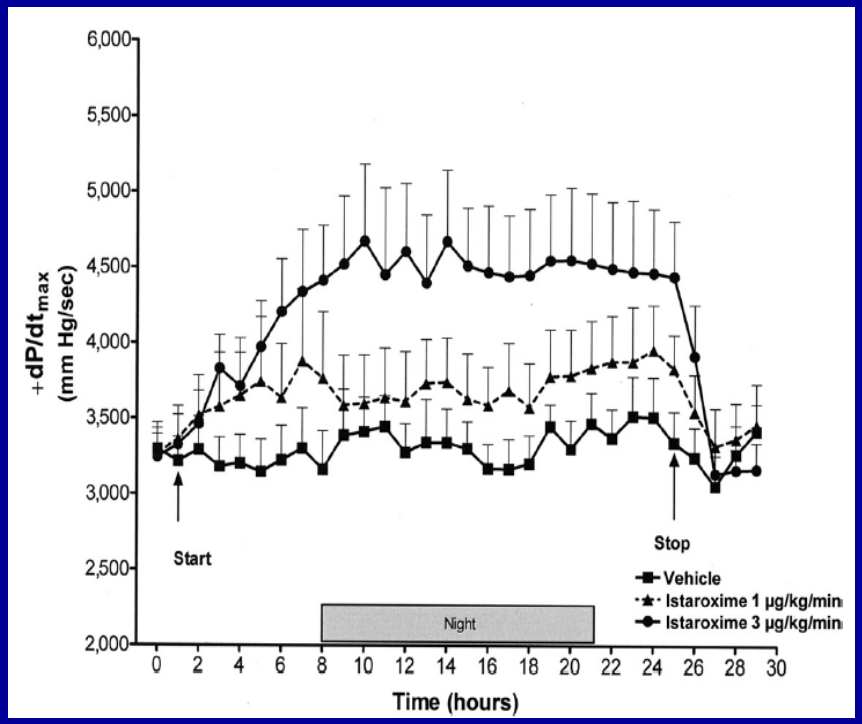
Respondeři	Non respondeři
ADCHSS NYHA III/IV	ASS de novo a ESHD
ICHS etiol	DKM
sTK > 100	sTK < 100
Bez hypotenziv a arytmogenních léků	S hypotenzivy a arytmogenními léky
BNP > 50%↓ /< 700 pg/ml při propuštění	BNP < 50%↓ / > 700 pg/ml při propuštění
Rychlí acetylátoři (geneticky podmíněné)	Pomalí acetylátoři (geneticky podmíněné)

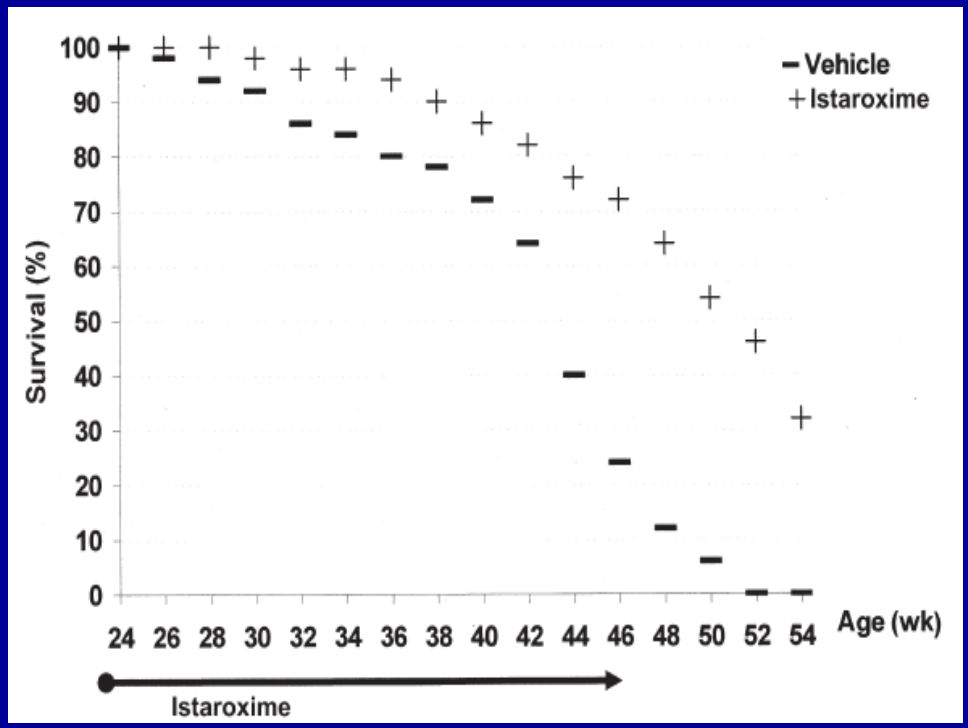
Parissis J.T et al. Am J Cardiol doi:101016/j.amjcard.2006.10.007

Istaroxim

Istaroxim inhibuje aktivitu Na-K ATPasy a současně stimuluje SR Ca ATPase (SERCA) isoform 2a (SERCA2a).

hemodynamika u psů **přežití u křečků**

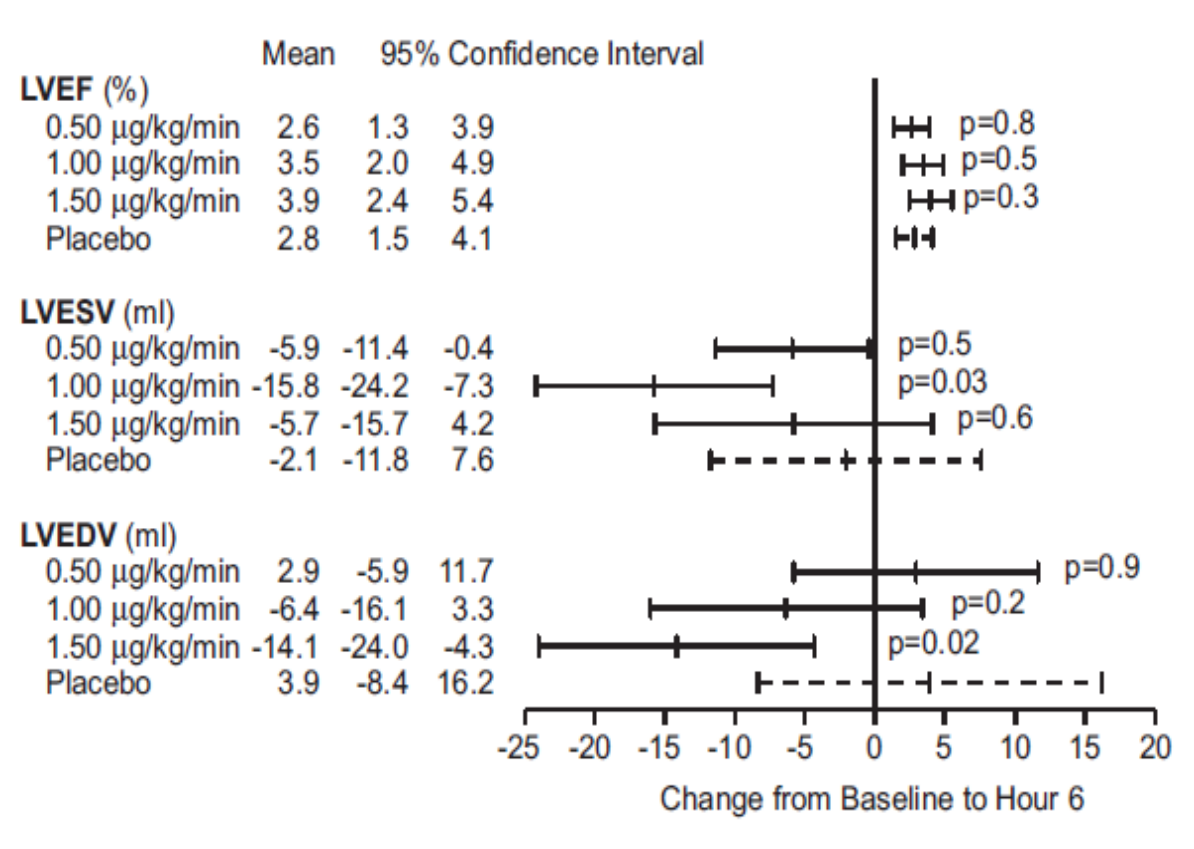




Heart Fail Rev (2009) 14:277–287

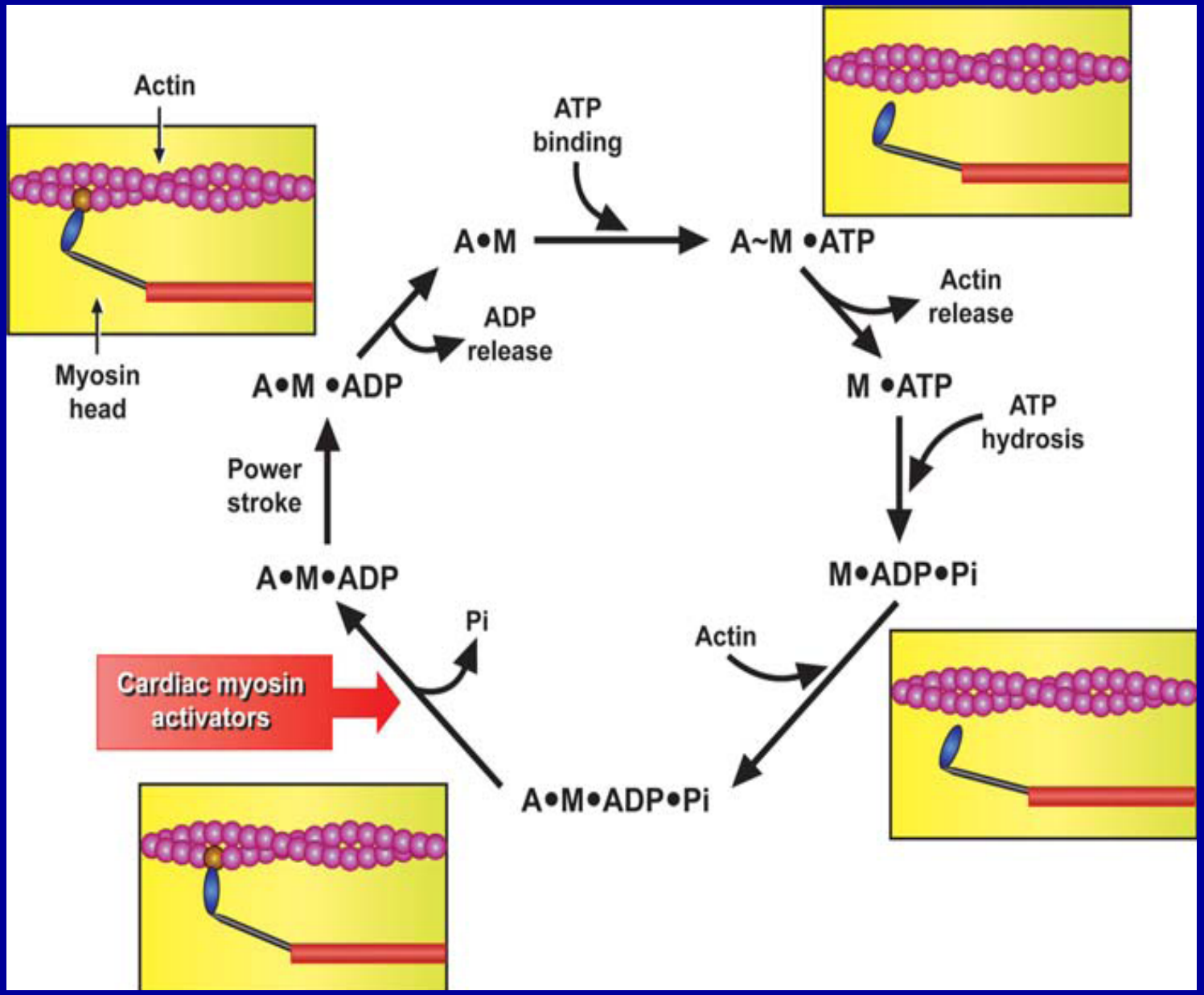
HORIZON-HF

Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime,a Novel Intravenous Inotropic and Lusitropic Agent

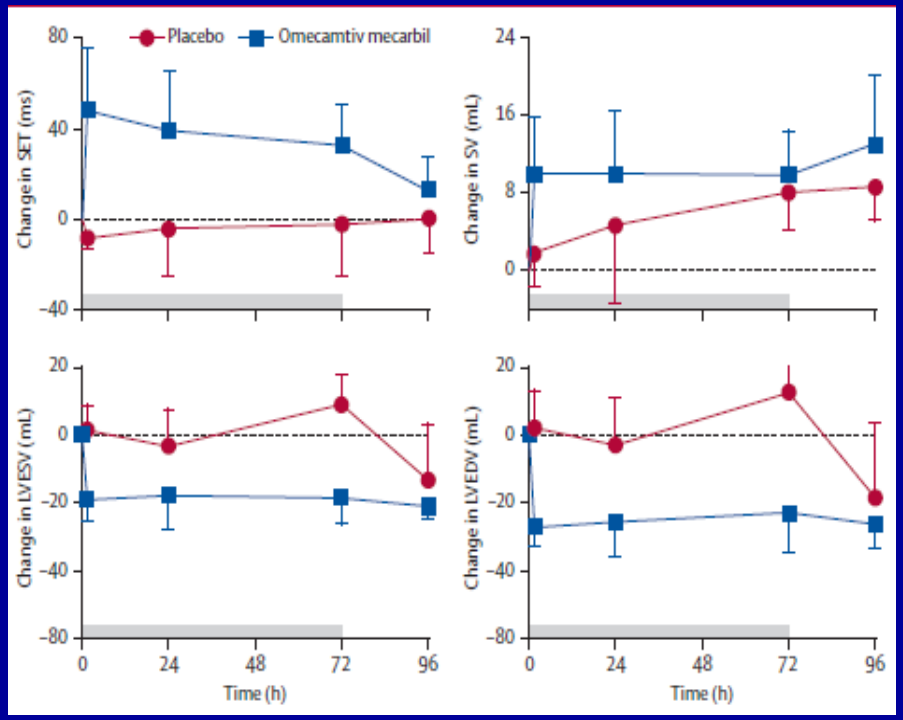


In patients hospitalized with HF, istaroxime improved PCWP and possibly diastolic function. In contrast to available inotropes, istaroxime increased SBP and decreased HR J Am Coll Cardiol 2008;51:2276–85

Omecamtiv mecarbil



The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure:



Interpretation Omecamtiv mecarbil improved cardiac function in patients with heart failure caused by left ventricular dysfunction and could be the first in class of a new therapeutic agent

Lancet 2011; 378: 676–83

Indikace inotropik

1.Hemodynamické zhoršení s nízkým MO (př. CI pod 2 l/min/m2) a zvýšení plnícího tlaku LK či PK (př. PCWP nad 18–20 mmHg a RAP nad10–12 mmHg)

2. Optimalní farmakologická léčba, včetně inhibitorů RAA, diuretik event. s nitráty

3. Kriticky nemocný na podkladě abnormalní hemodynamiky a:

a. Závažná limitace zátěže

b. Převodnění s rezistencí na diuretika

c. Renální či hepatální postižení (zvýšení krea, urea, JT, bili apod.)

Using IV inotropes is still controversial among doctors because they increase your risk of death. However, if a CHFer suffers severe symptoms that standard drugs don't help, he might want inotropes anyway. Keep in mind that using IV inotropes will probably shorten your life. On the other hand, they may greatly improve your quality of life, even if only for a short while. It's your body, your life, and your call.

Study	Inotropic	Result
Xamoterol	Xamoterol	Increase mortal
Enoximone	Enoximone	Increase mortal
PROMISE	Milrinone	Increase mortal
PROFILE	Flosequinan	Increase mortal
OPTIME-CHF	Milrinone	Increase mortal
VEST I	Vesnarinone	Increase mortal
VEST II	Vesnarinone	Increase mortal
PICO	Pimobendan	Increase mortal
PRIME 2	Ibopamine	Increase mortal
SURVIVE/REVIVE	Levosimendan	Neutral effects