Pozitivně inotropní léky: mýty a fakta

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Jindřich a Lenka Špinarovi

LF MU a ICRC FN u sv.Anny

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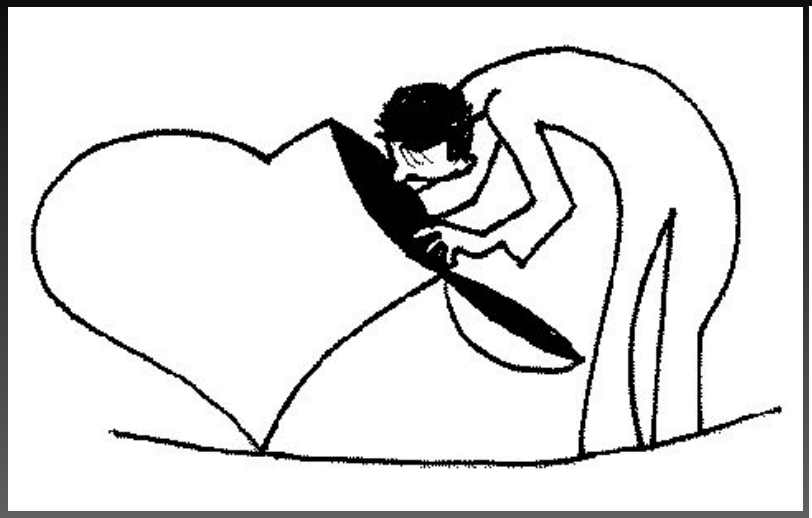
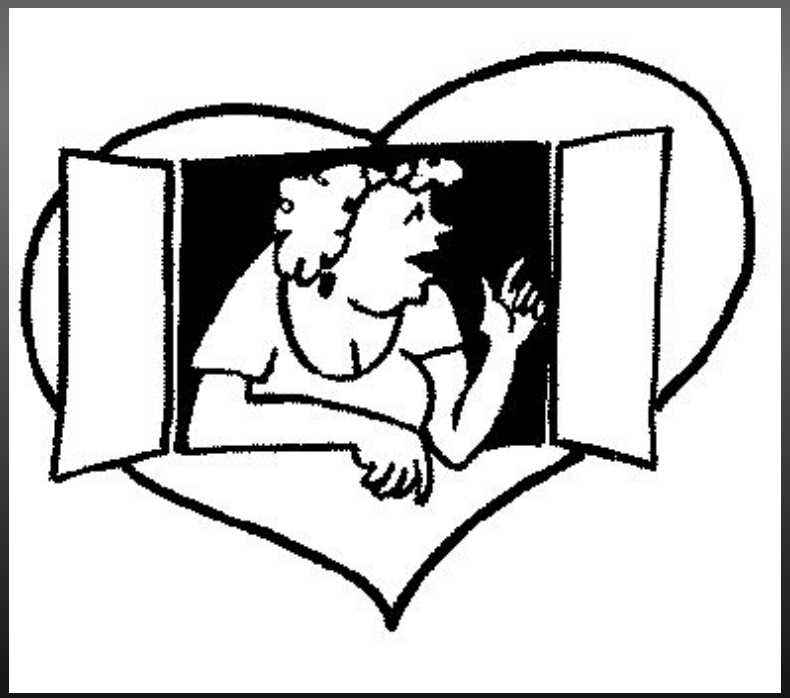
Stažlivost myokardu a její stupňování na buněčné úrovni

Příteli Jiřímu Vítovcovi
vděčně
Bravený

AVICENUM, zdravotnické nakladatelství, n. p.,
Praha 1974





Ca^{2+} MOVEMENTS

Opie 2004

Ca^{2+} 10^{-3} M

β-agonist

Ca^{2+} channel

α-agonist

Na^+

β

α

SR

Ca^{2+} pump

cAMP

"opens"

PL

Ca^{2+} leaves

Calcium values
Diastole 10^{-7} M
Systole 10^{-6} M

FREE Ca^{2+}

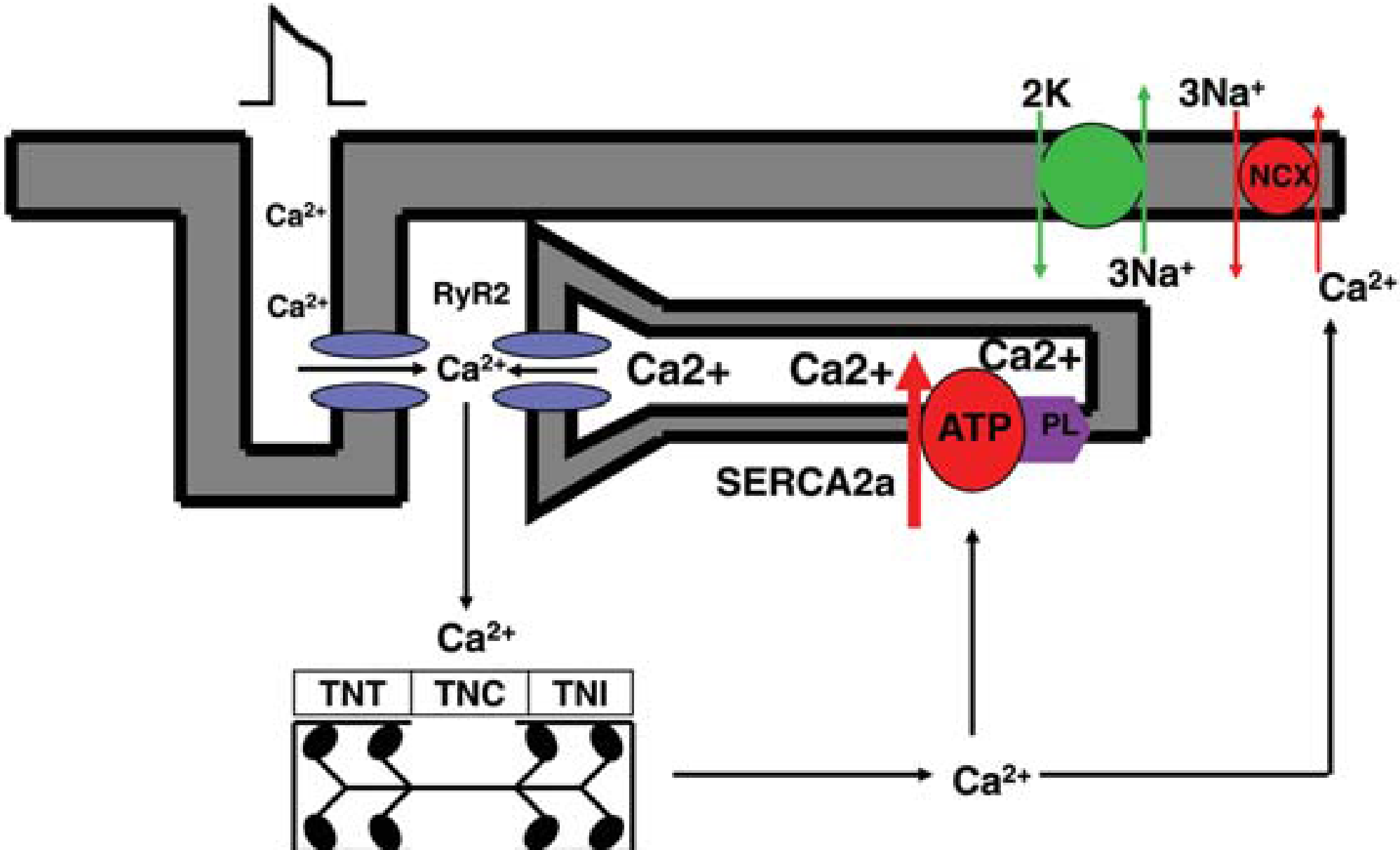
Relaxation

Mitochondrial metabolism

ATP

Contraction

Excitace-kontrakce



Počátky použití inotropik

v léčbě srdečního selhání

Toad alias Žbluňk

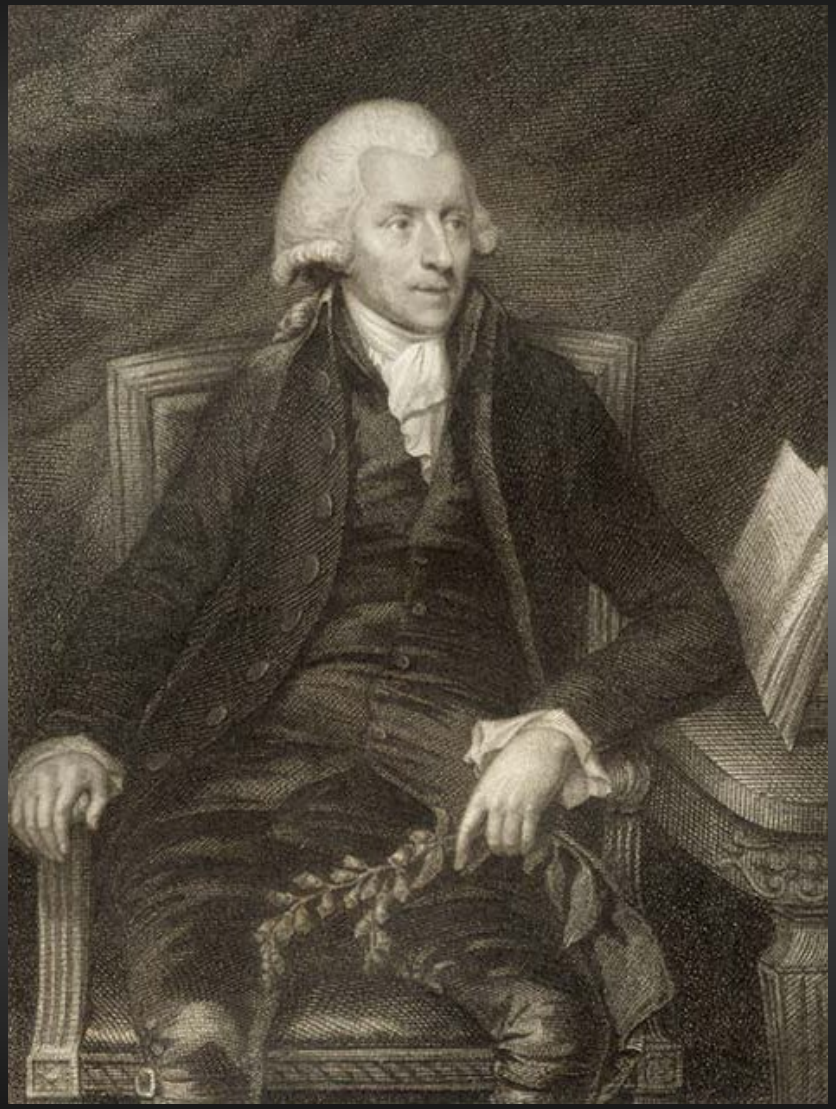
Bufo Bufo gargarizans.

Čína 2735 před n.l.

sušená kůže

Lukas D.S. Of Toads and Flowers. Circulation 1972; 66: 1-4

William Withering 1741-1799



William Withering

PURPLE FOXGLOVE or FOLKSGLOVE.
(*Digitalis Purpurea.*)

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.

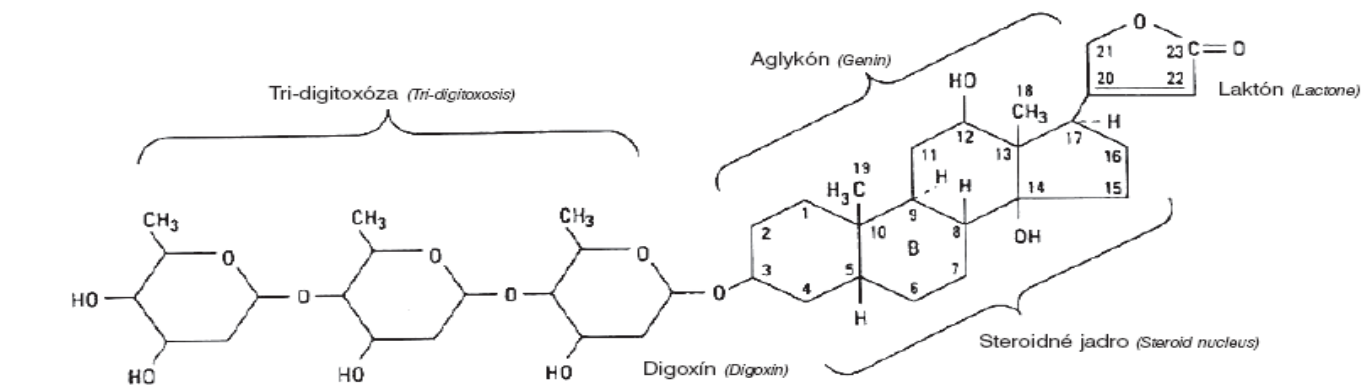
nonumque prematur in annum.
Horace.

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

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

Digitalis - trochu historie

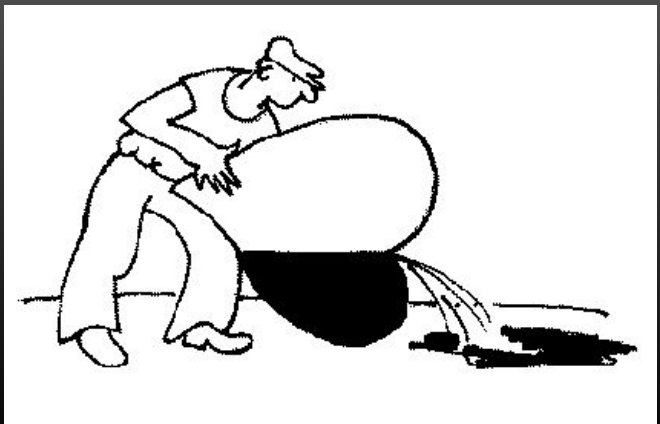
- **2735 AC Čína** **užití sušené ropuší kůže**
- **1000 AC Chikitsa** **kakadani – bud vyléčí nebo zabije**
- 1785 Withering diuretický a tonický vliv na srdce
- **1835 Bouillaud** **narkotický a bradykardický vliv**
- **1914 Mackenzie** **stimulace vagu a zpomalení fi.si.**
- 1928 Windaus chemická struktura digoxinu
- **1930 Smith** **izolace digoxinu z D.lanata** Burroughs Wellcome



Obrázok 4 Štruktúra digoxínu
Figure 4 *Structure of digoxin*

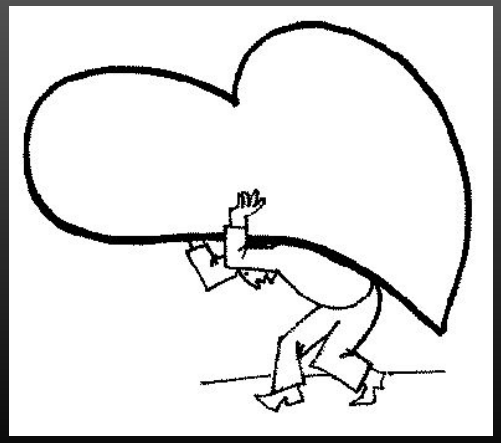
Digitalis - trochu historie

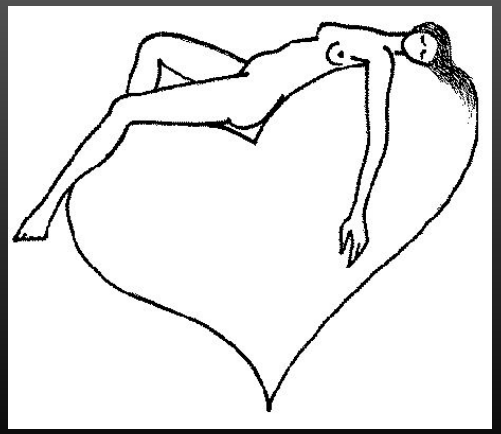
- **1953 Schatzmann** — **Na-K ATP receptory pro digitalis**
- 1961 Braunwald — přímá cévní vasokonstrikce
- **1972 Schon et al.** — **úloha vápníku pro zvýšení inotropie**
- 1983 Covit et al. — potlačení RAS
- 1988 Poole-Wilson — digoxin se stává nepotřebným lékem

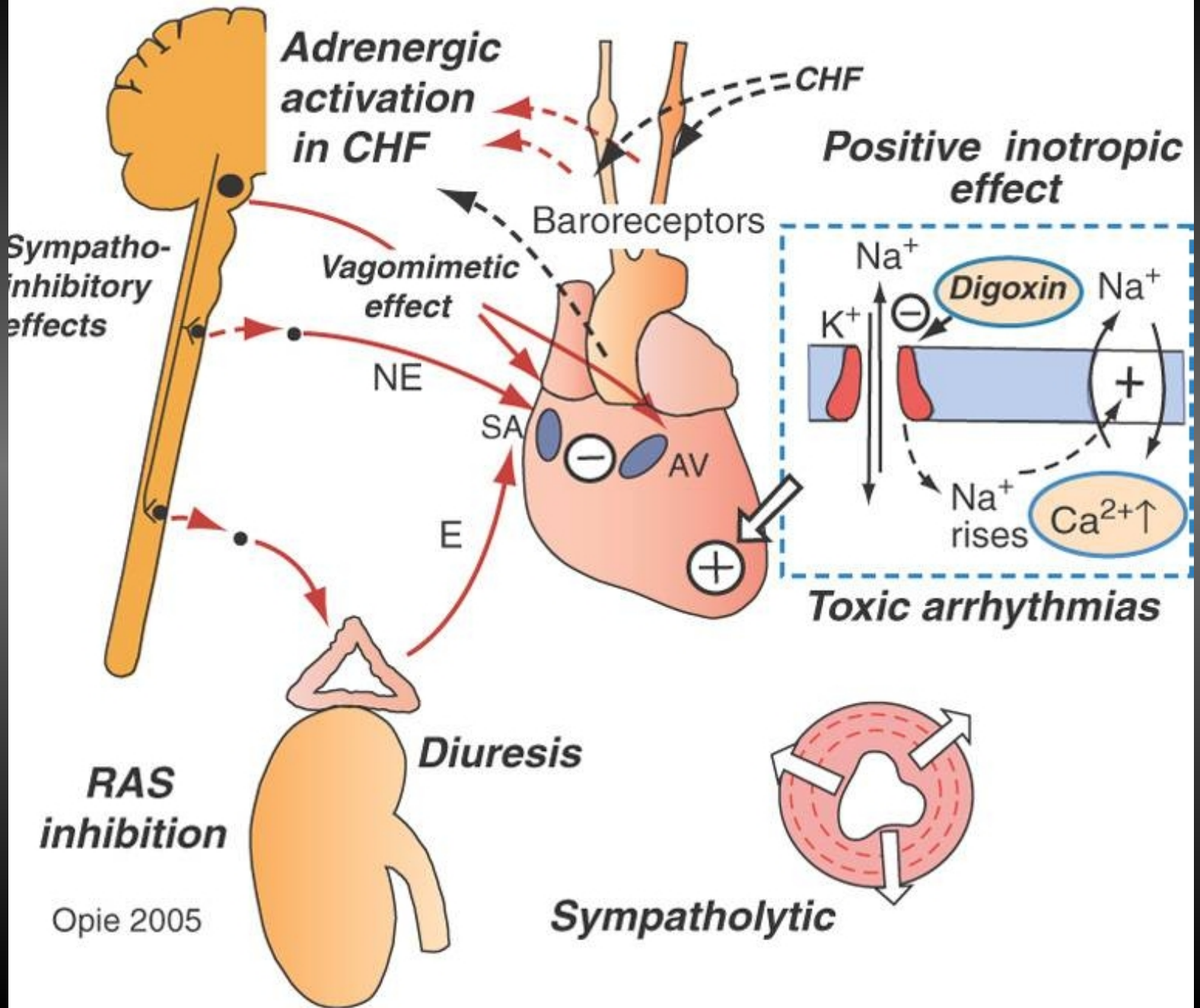


Digitalis - trochu historie

- **1997 DIG study** — **první a jediná klinická random.studie**
- 1997 Packer — digoxin's inability to substantially influence morbidity and mortality eliminates any ethical mandate for its use
- 2002 DIG subanal. — ženy mají vyšší riziko úmrtí
- **2002 DIG subanal.** — **bezpečné plazmat.koncentrace 0,5-0,9ng/ml**
- **2005 J.B.Young** — **Long live Withering´s Legacy**
- **2012** — ☺☺☺☺☺






Adrenergic activation in CHF
CHF
Positive inotropic effect
Baroreceptors
Sympatho-inhibitory effects
Vagomimetic effect
NE
SA
AV
E
Na+
Digoxin
Na+
K+
Na+ rises
Ca2+↑
Toxic arrhythmias
RAS inhibition
Diuresis
Sympatholytic
Opie 2005

Some Effects of Digoxin on the Heart and Circulation in Man

Digoxin in Enlarged Hearts Not in Clinical Congestive Failure

By RÉJANE M. HARVEY, M.D., M. IRENÉ FERRER, M.D., RICHARD T. CATHCART, M.D., AND JAMES K. ALEXANDER, M.D.

The early effect of intravenous Digoxin was observed in 12 patients with cardiac enlargement in whom there was no clinical or physiologic evidence of failure. There was either a fall or no change in the cardiac output and the intracardiac pressures did not alter following administration of the drug. The reaction to Digoxin in this type of patient with heart disease was in no way different from the response seen in two normal subjects included in the study but is in sharp contrast to the response elicited in patients in congestive heart failure.

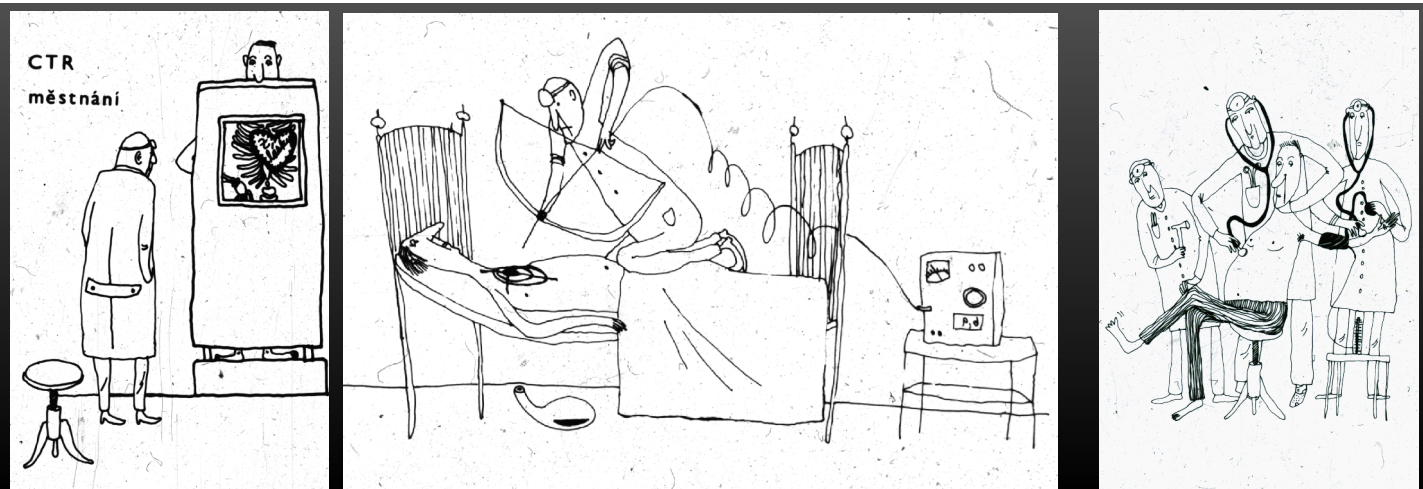
Circulation 1951; 60: 366-377

HEART FAILURE IN OUTPATIENTS

A Randomized Trial of Digoxin versus Placebo

DANIEL CHIA-SEN LEE, M.D., ROBERT ARNOLD JOHNSON, M.D., JOHN B. BINGHAM, M.D., MARIANNE LEAHY, R.N., ROBERT E. DINSMORE, M.D., ALLAN H. GOROLL, M.D., JOHN B. NEWELL, B.A., H. WILLIAM STRAUSS, M.D., AND EDGAR HABER, M.D.

Abstract The view that digitalis clinically benefits patients with heart failure and sinus rhythm lacks support from a well-controlled study. Using a randomized, double-blind, crossover protocol, we compared the effects of oral digoxin and placebo on the clinical courses of 25 outpatients without atrial fibrillation. According to a clinicoradiographic scoring system, the severity of heart failure was reduced by digoxin in 14 patients; in nine of these 14, improvement was confirmed by repeated trials (five patients) or right-heart catheterization (four patients). The other 11 patients had no detectable improvement from digoxin. Patients who responded to digoxin had more chronic and more severe heart failure, greater left ventricular dilation and ejection-fraction depression, and a third heart sound. Multivariate analysis showed that the third heart sound was the strongest correlate of the response to digoxin ($P<0.0001$). These data suggest that long-term digoxin therapy is clinically beneficial in patients with heart failure unaccompanied by atrial fibrillation whose failure persists despite diuretic treatment and who have a third heart sound. (N Engl J Med. 1982; 306:699-705.)



Dvojitě slepé studie
(s vysazením digoxinu)

RADIANCE

Packer (NEJM 1993)

178 pts,s.r., NYHA II-III,EF< 35%,Rx ACEI,diuretika

Závěr: Po vysazení digoxinu zhoršení stavu srd.selhání.

PROVED

Uretsky (JACC 1993)

88 pts,s.r., NYHA II-III,EF< 35%,Rx pouze,diuretika

Závěr: Po vysazení digoxinu zhoršení stavu srd.selhání.

DIG

Cíl: Určit vliv digoxinu na úmrtnost a hospitalisaci u nemocných se srdečním selháním a sinusovým rytmem

Pts: Digoxin 3397, Placebo 3403, EF< 0,45

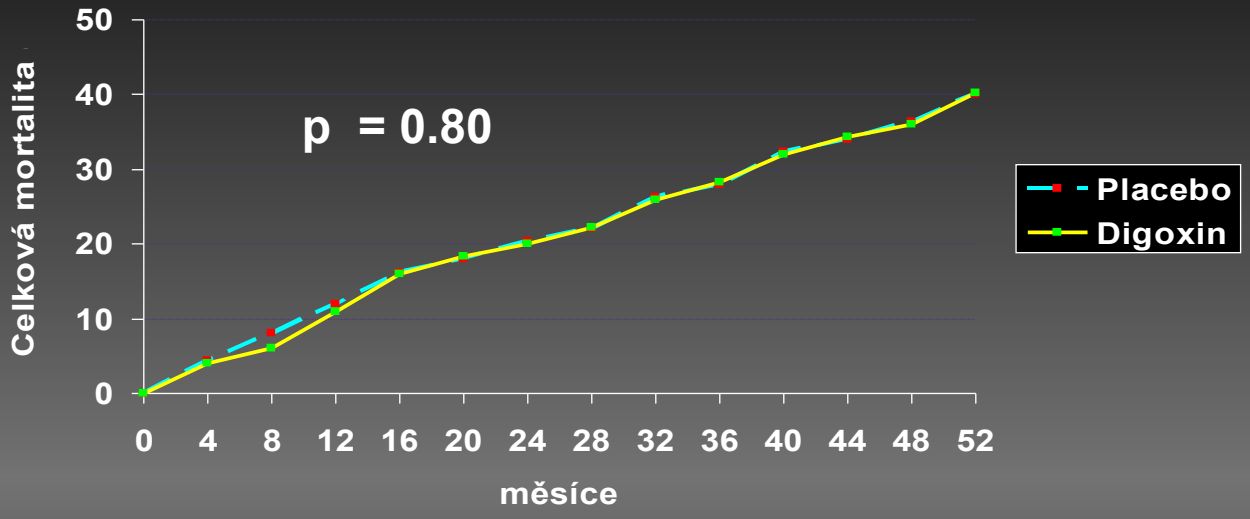
Rx: ACE-I 94%, diuretika 82%, nitráty 43%

Dg: ICHS 71%, DKM 29%

NYHA: I 14%, II 53%, III 31%. IV 2%

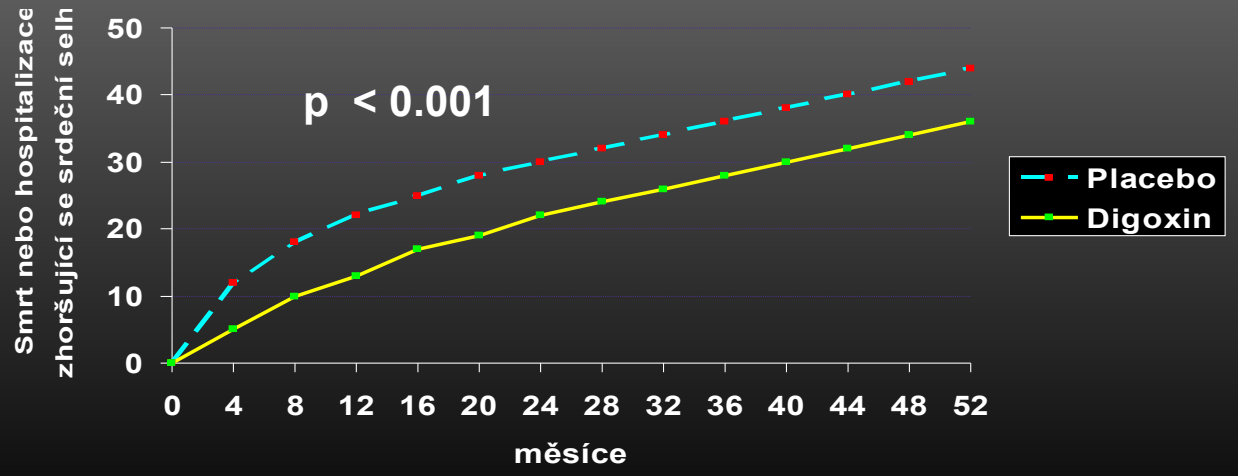
N Engl J Med 1997;336:525-33

DIG



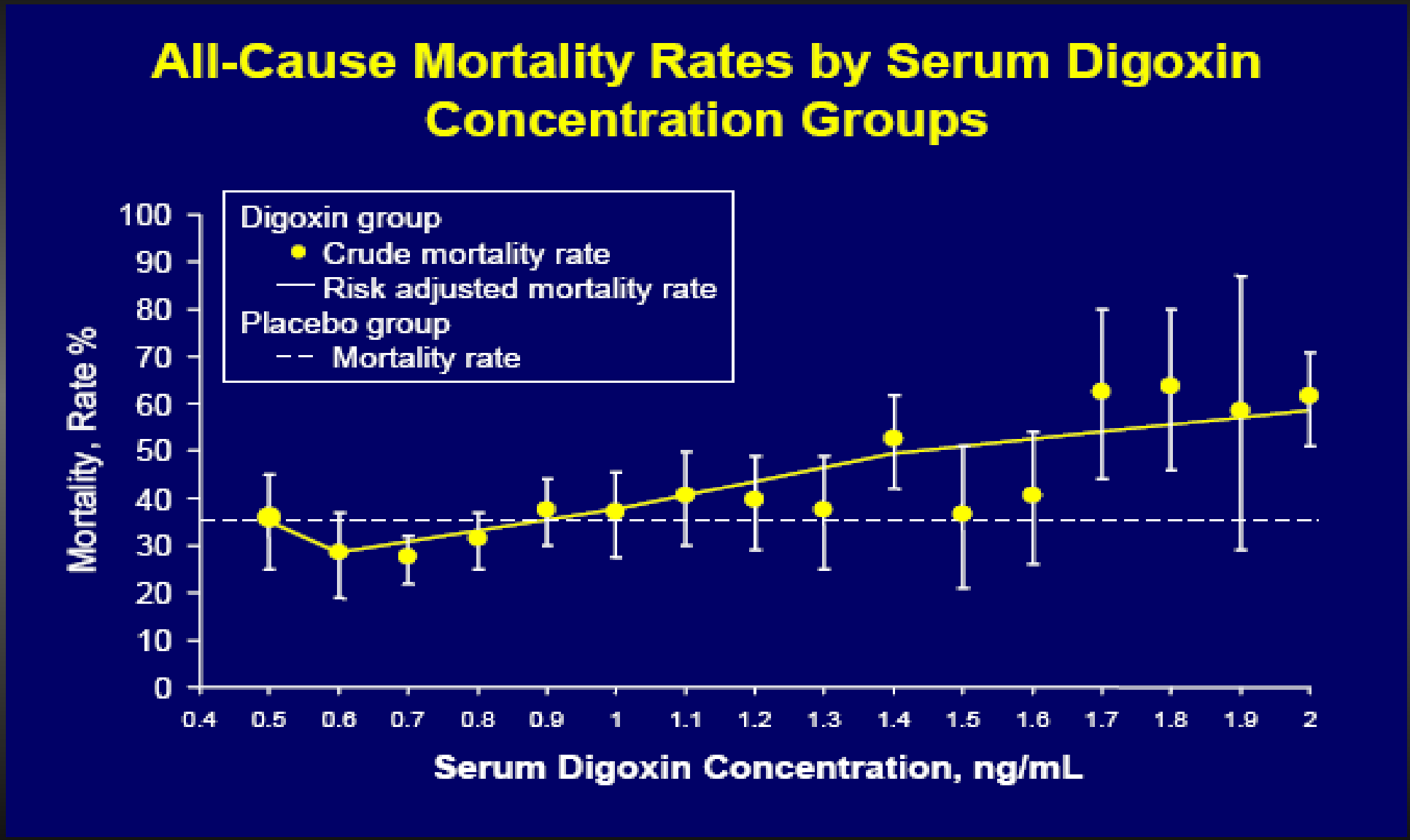
Celková mortalita

Mortalita a hospitalisace pro zhoršení srdečního selhání



N Engl J Med 1997;336:525-33

DIG



J Am Coll Cardiol 2005;46:497-504

Mýty o digoxinu

Komu?

každému po IM či se srdečním selhání, dříve dokonce po 60 roku

Dávka?

tak aby plazm.koncentrace byla mezi 1,1-2 nmol/L

Kdy?

lék 1.volby

Další názory:

jed, zvyšuje mortalitu, obsolentní lék

Digoxin in the Crazy World

" We love Digoxin! Give us more"

Fakta o digoxinu

Jaký?

vyřešeno - digoxin

Dávka?

tak aby plazm. [0,55 - 0,9 ng/ml = 0,6-1,1 nmol/L]

Kdy?

lék 3.volby

po ACEi/ARB,BB ev.diu

Myslet na předávkování!!

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.**

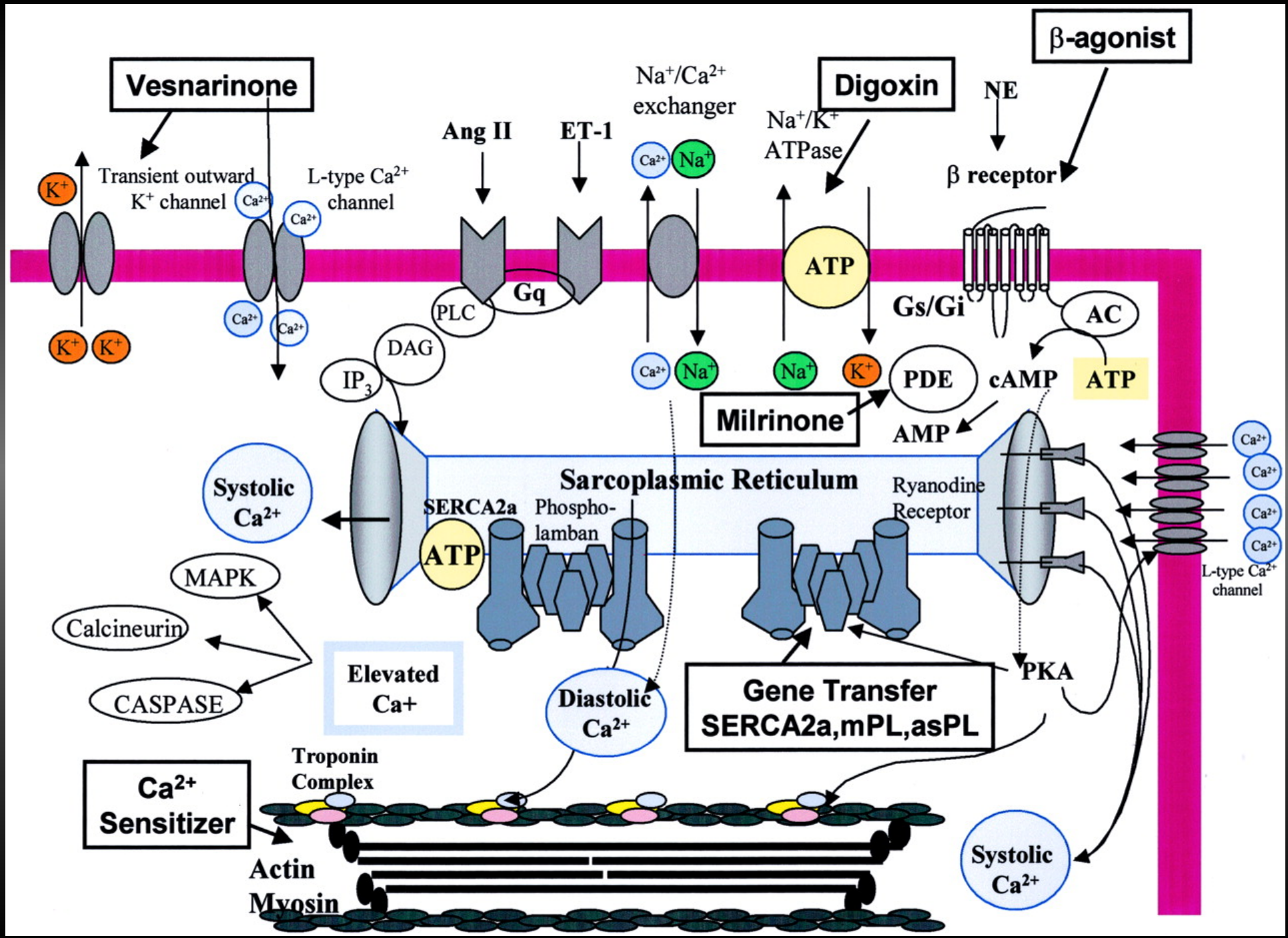
Long live Withering´s Legacy!!

“After all, in spite of opinion, prejudice or error, Time will fix the real value upon this discovery, and determine whether I have imposed upon myself and others, or contributed to the benefit of science and mankind ”

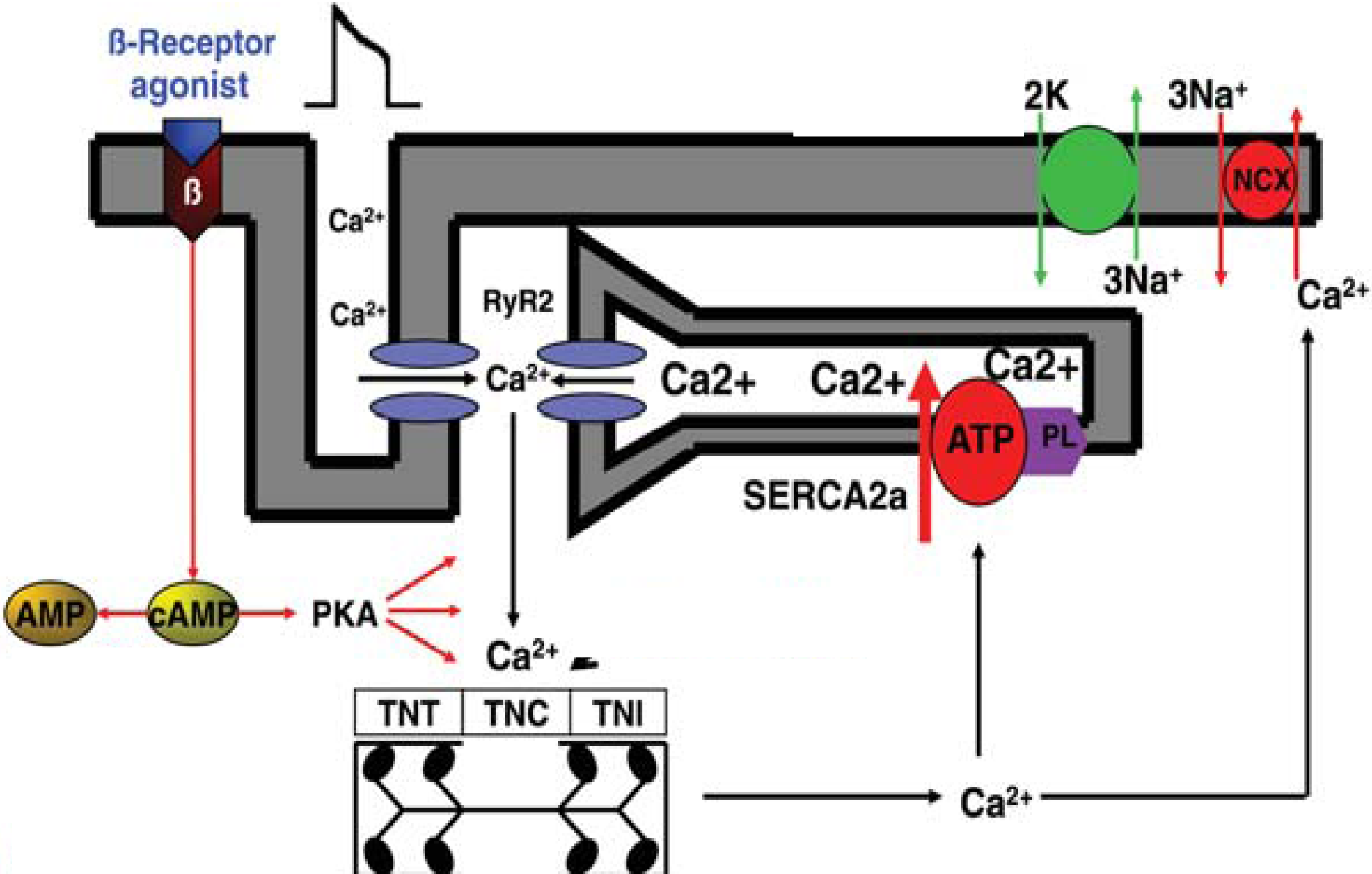
Konec konců, i přes názor, předsudek a omyl, čas ukáže skutečnou hodnotu tohoto objevu a určí, zda jsem ošidil sebe i ostatní nebo jsem prospěl vědě a lidstvu.

Digoxin Google 9 920 000

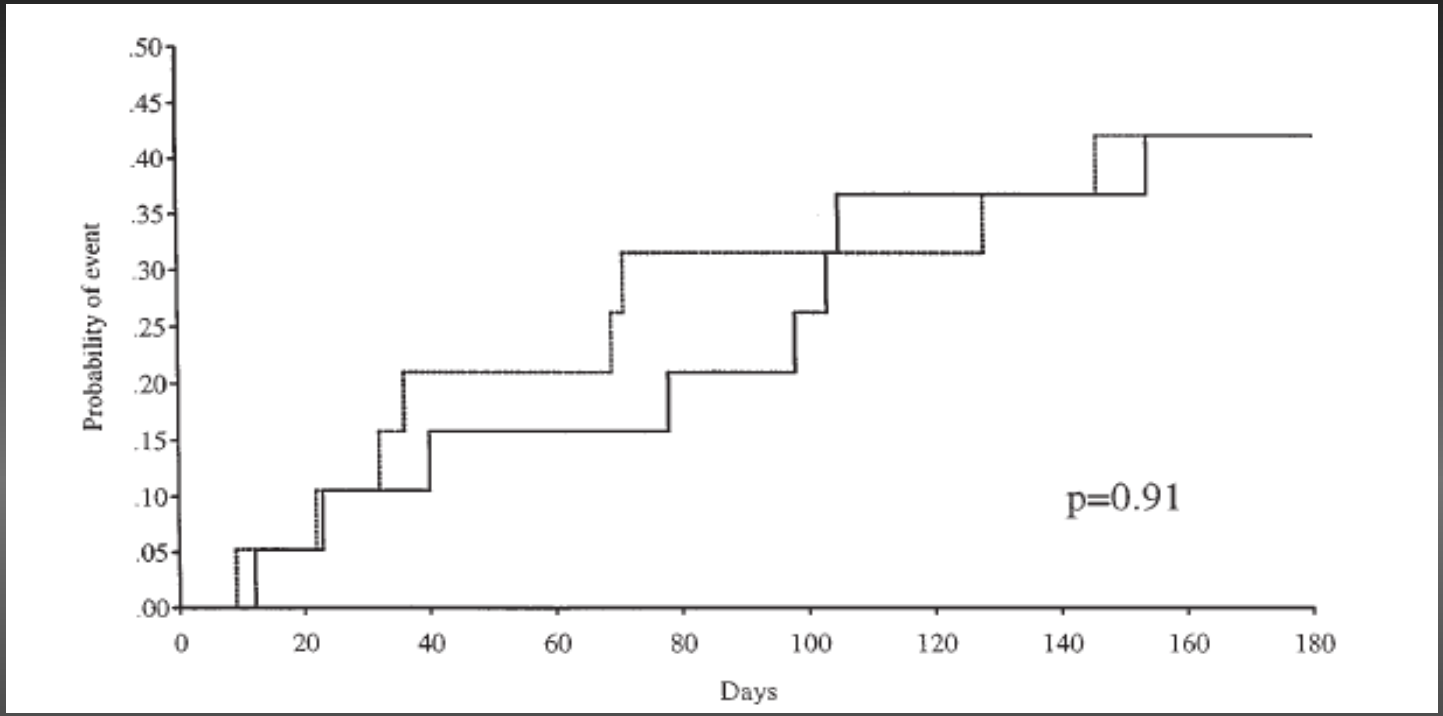
Sir William Withering, Birmingham, July 1, 1785


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
Sodium-potassium-ATPase inhibition	Digoxin
Beta-1-adrenoceptor stimulation	**Dobutamine, dopamine**
Phosphodiesterase III inhibition	**Enoximone, milrinone**
Calcium sensitization	**Levosimendan**
Sodium-potassium-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 receptor stabilizer; S44121
Energetic modulation	Etomoxir, pyruvate


ß-Receptor agonist
ß
2K
3Na+
NCX
3Na+
Ca2+
Ca2+
Ca2+
RyR2
Ca2+
Ca2+
Ca2+
Ca2+
ATP
PL
SERCA2a
AMP
cAMP
PKA
Ca2+
TNT
TNC
TNI
Ca2+

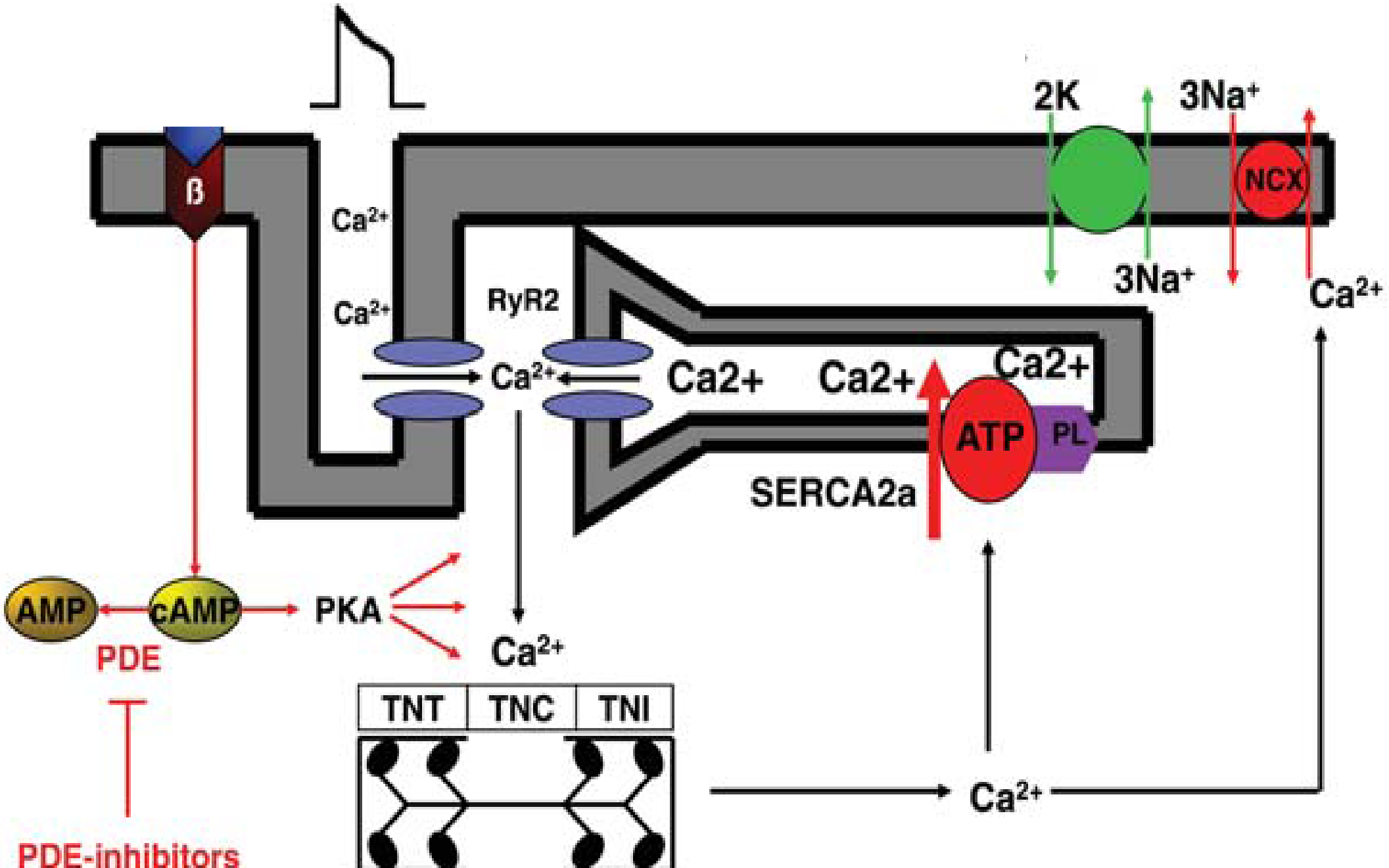
Intermittent 6-month low-dose dobutamine infusion in severe heart failure: DICE Multicenter Trial



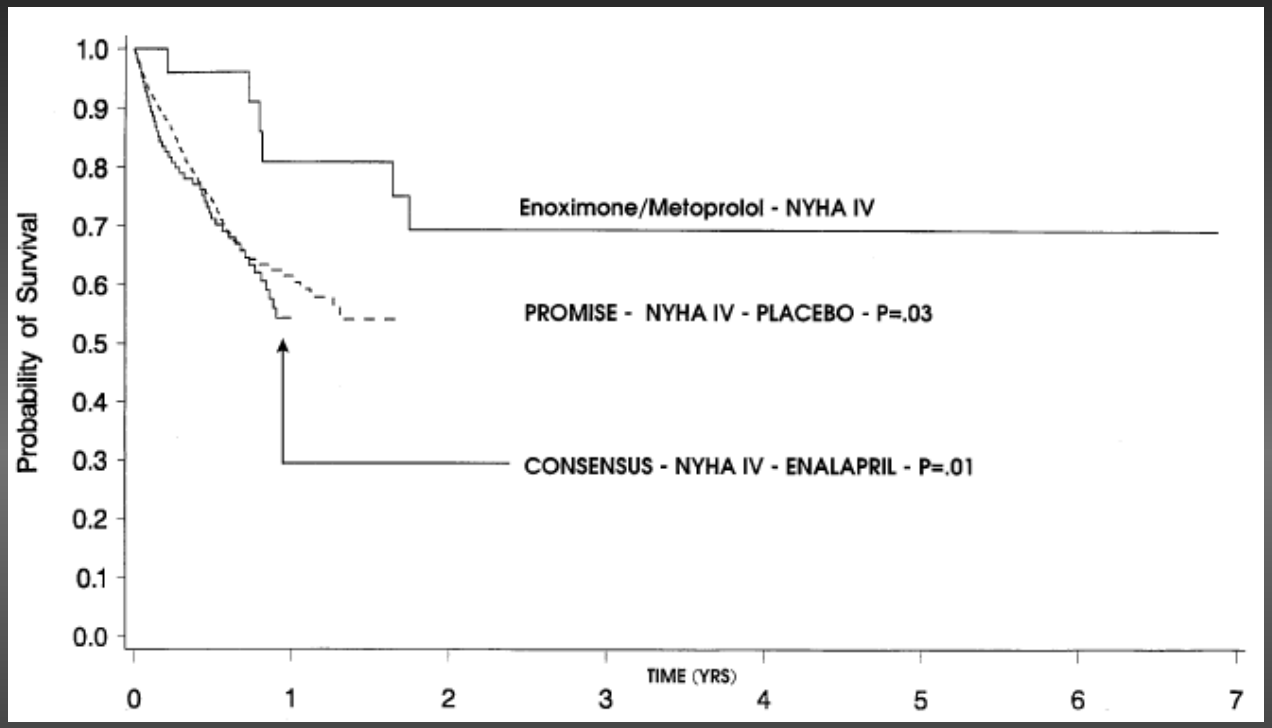
Conclusions Six-month intermittent low-dose dobutamine administration was well tolerated by patients with severe CHF; it did not improve the functional status and did not significantly increase the mortality rate as found with higher dobutamine doses in other studies. Hospitalizations for all causes and for worsening of CHF tended to be fewer in the dobutamine group.
(Am Heart J 1999;138:247-53.)

Indikace betamimetik

Stav	Beta mimetika	Dávka	Poznámka
Oligourie Hypotenze	Dopamin	2-5 ug/kg/min	DA,VD, ren??
		5-20 ug/kg/min	β i α st. inotropní
Hypotenze + ⇓ CI, ESHF bridging před OTS,	Dobutamin	1-20 ug/kg/min	β st., inotrop


2K
3Na+
NCX
β
Ca2+
Ca2+
RyR2
3Na+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
ATP
PL
SERCA2a
AMP
cAMP
PKA
PDE
Ca2+
TNT
TNC
TNI
Ca2+
PDE-inhibitors

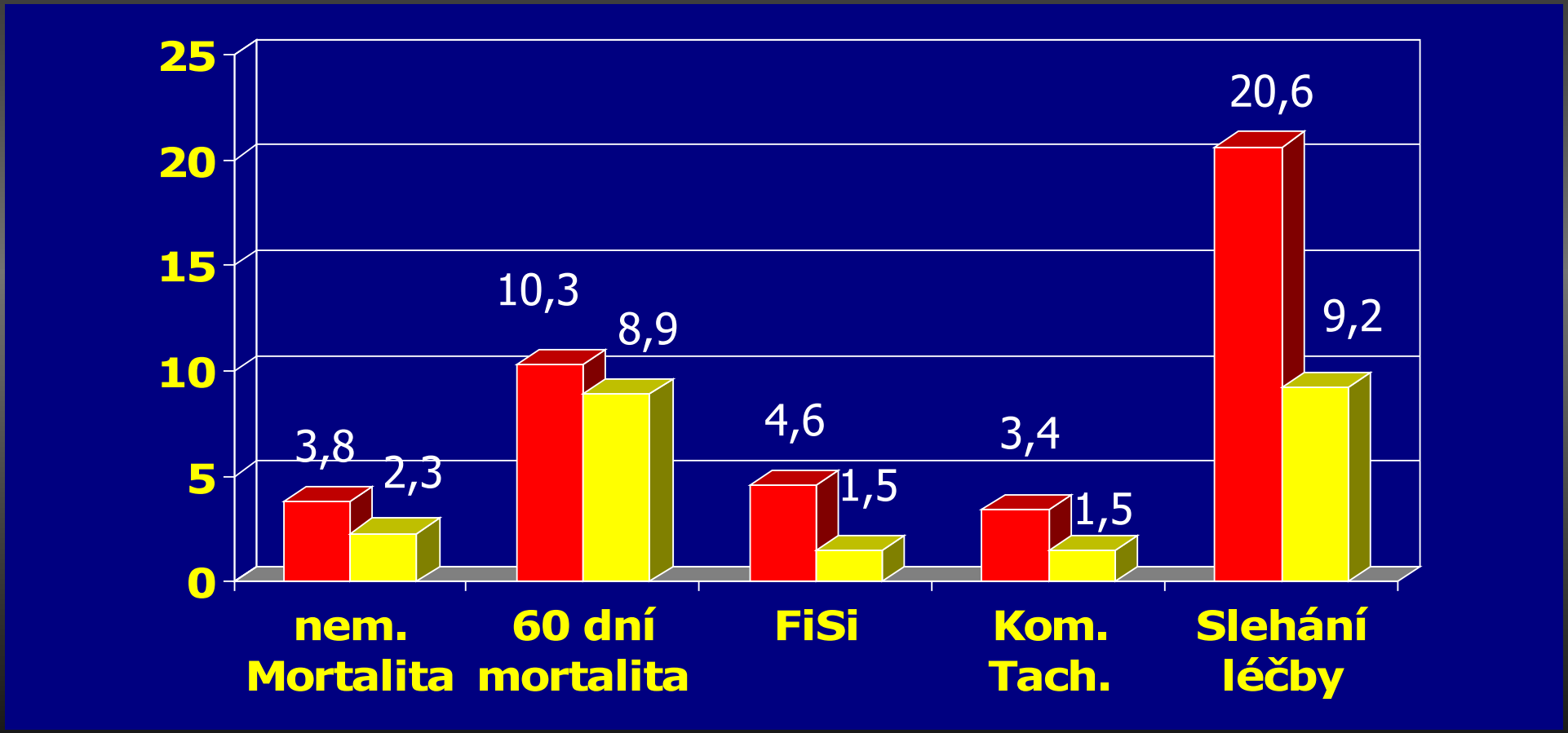
Combined Oral Positive Inotropic and Beta-Blocker Therapy for Treatment of Refractory Class IV Heart Failure



Conclusions. Combination therapy with a positive inotrope and a beta-blocker appears to be useful in the treatment of severe, class IV heart failure. It may be used as a palliative measure when transplantation is not an option or as a bridge to heart transplantation.Further study of this form of combined therapy is warranted. (J Am Coll Cardiol 1998;31:1336–40)

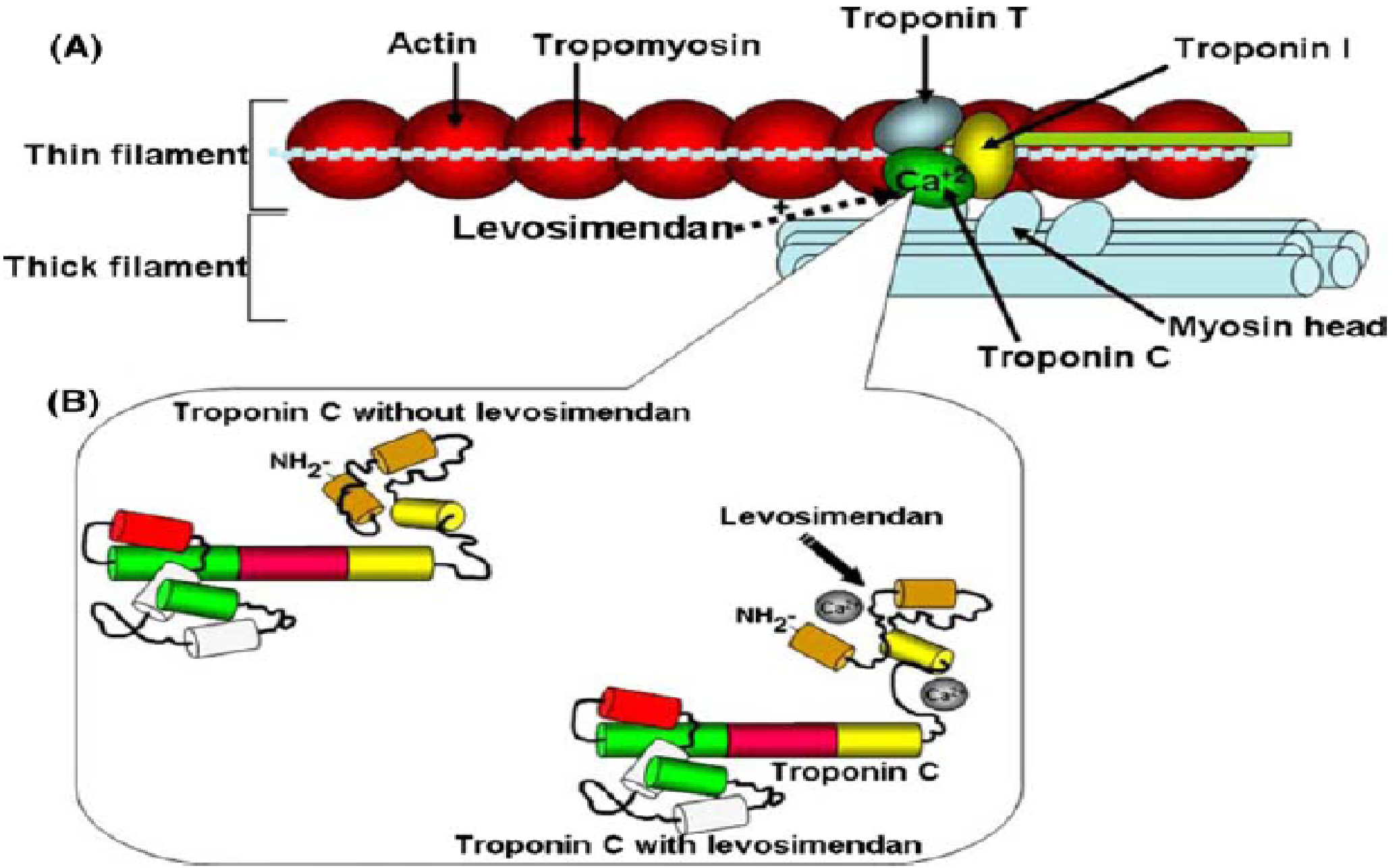
OPTIME CHF

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



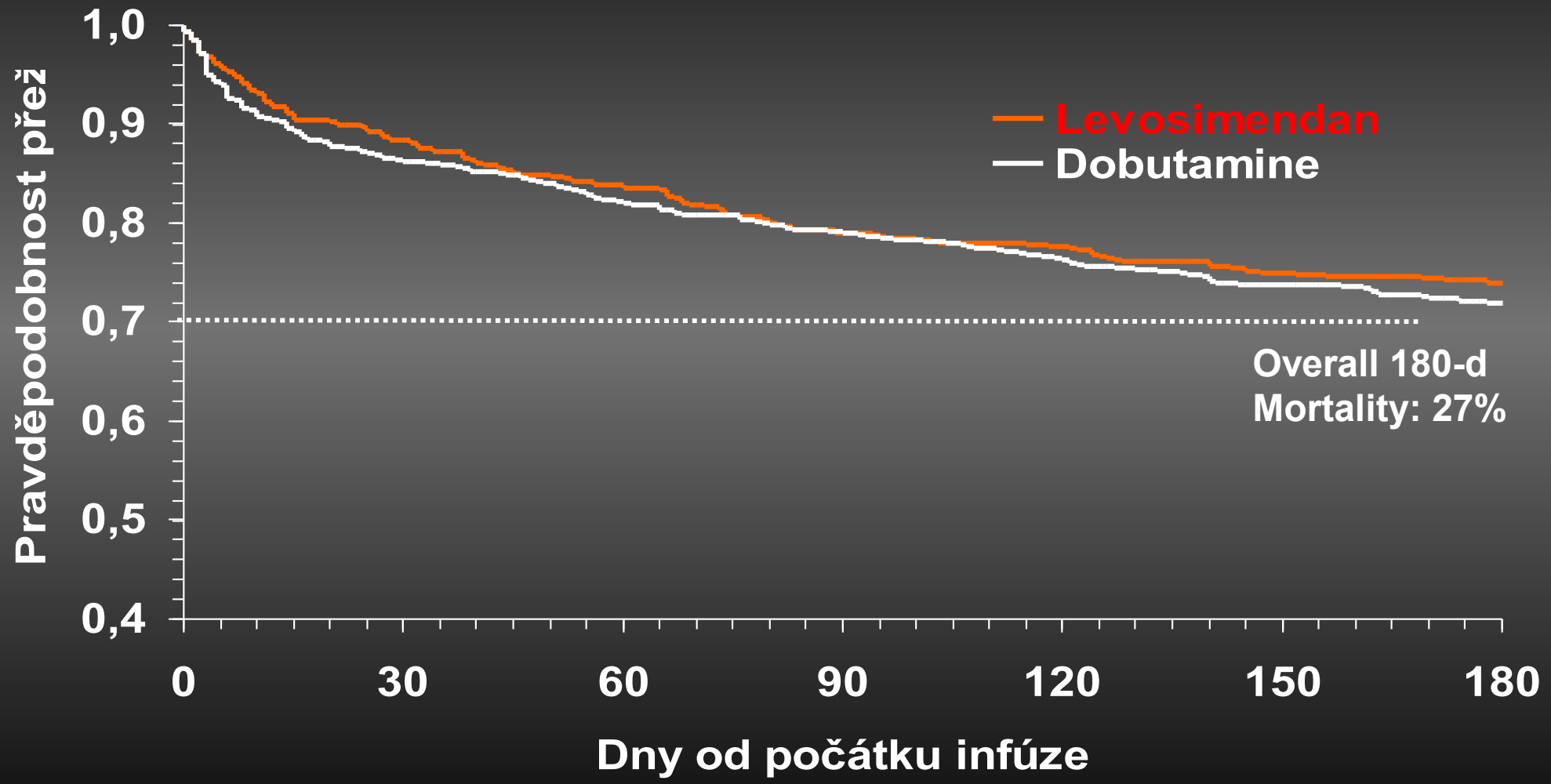
Milrinon 72 hod vs placebo

JAMA 2002;287:1541–7


(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

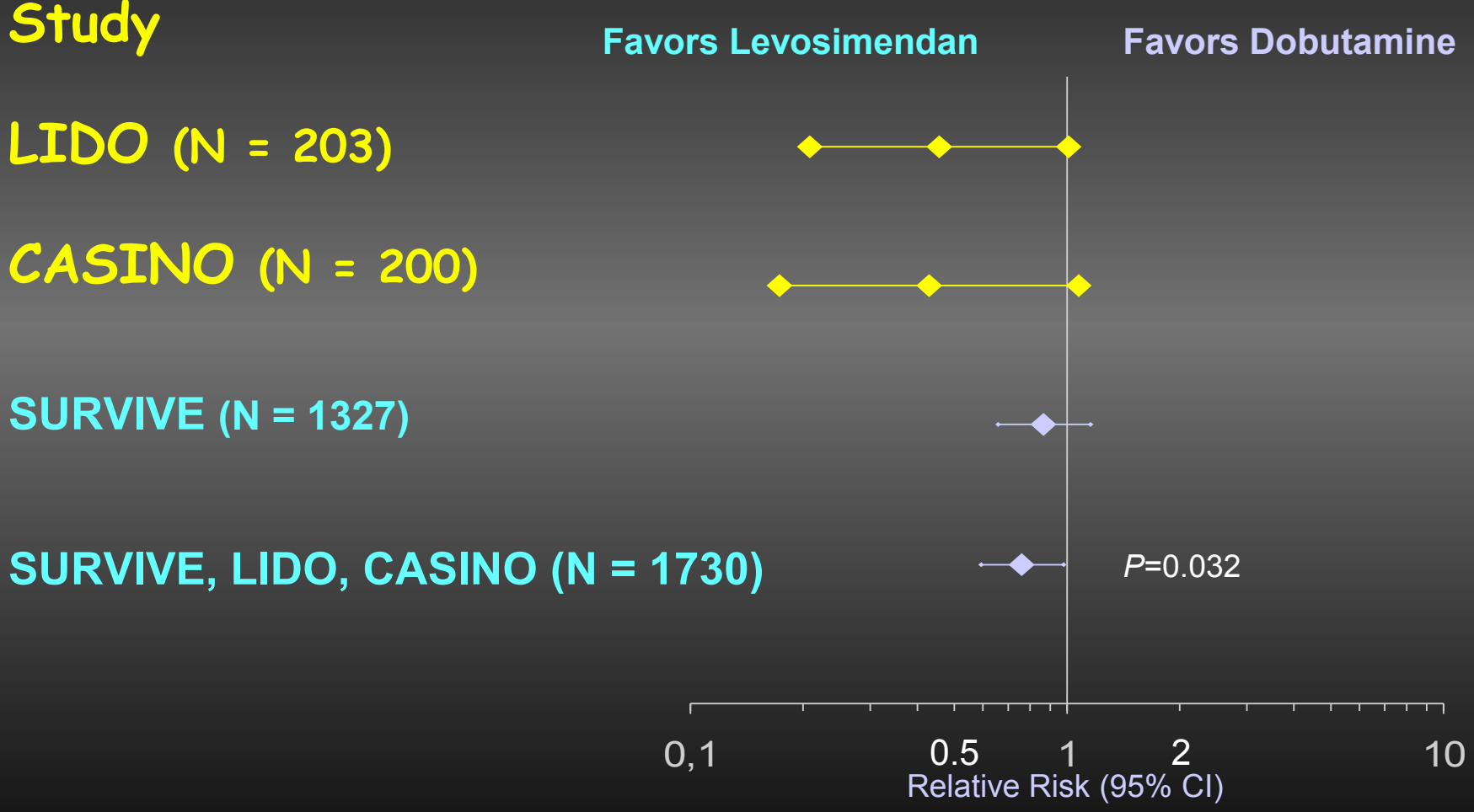
SURVIVE

180-denní celková mortalita

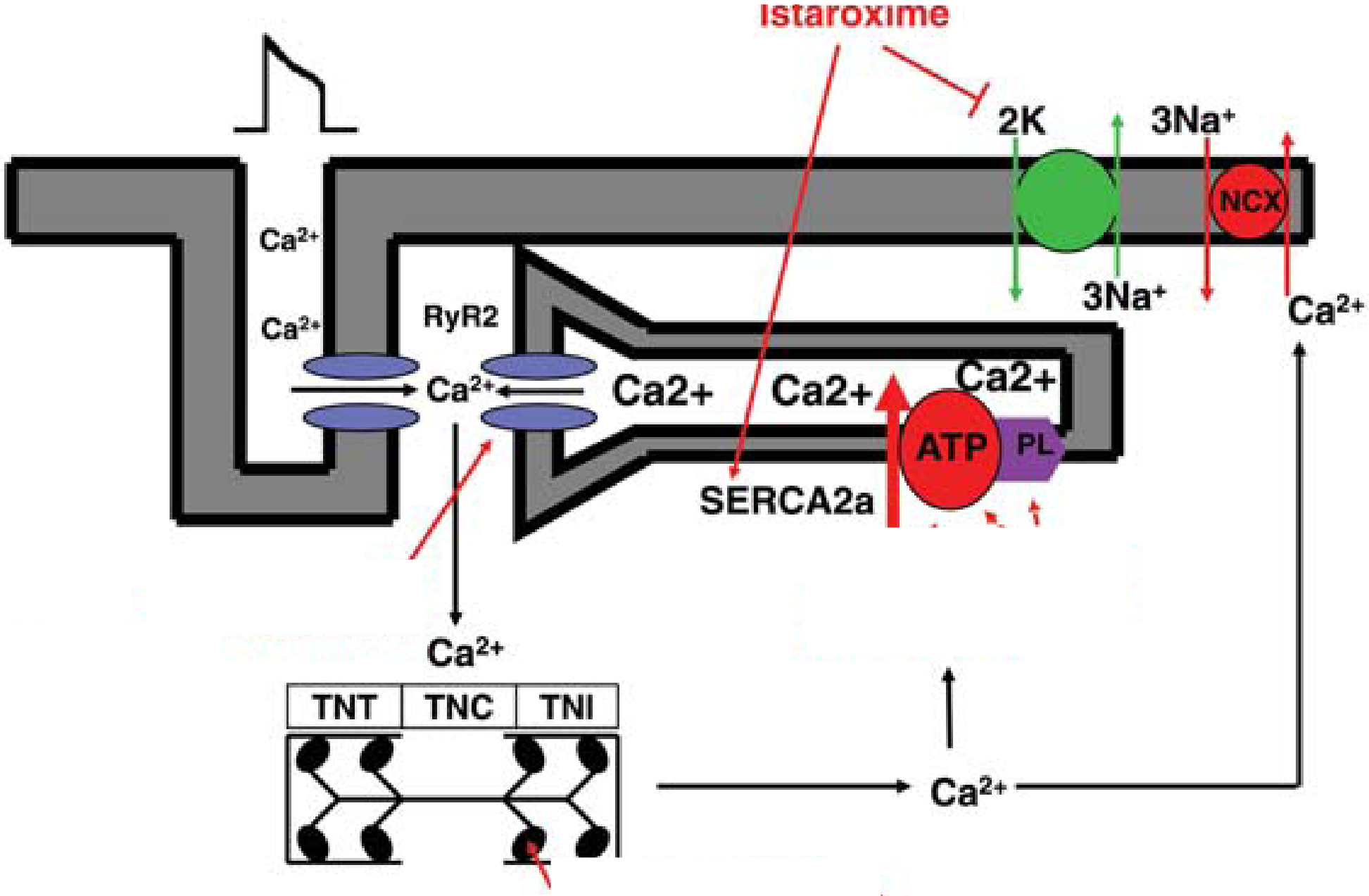


Studie s levosemindanem

Mortality Comparison - 31 Days

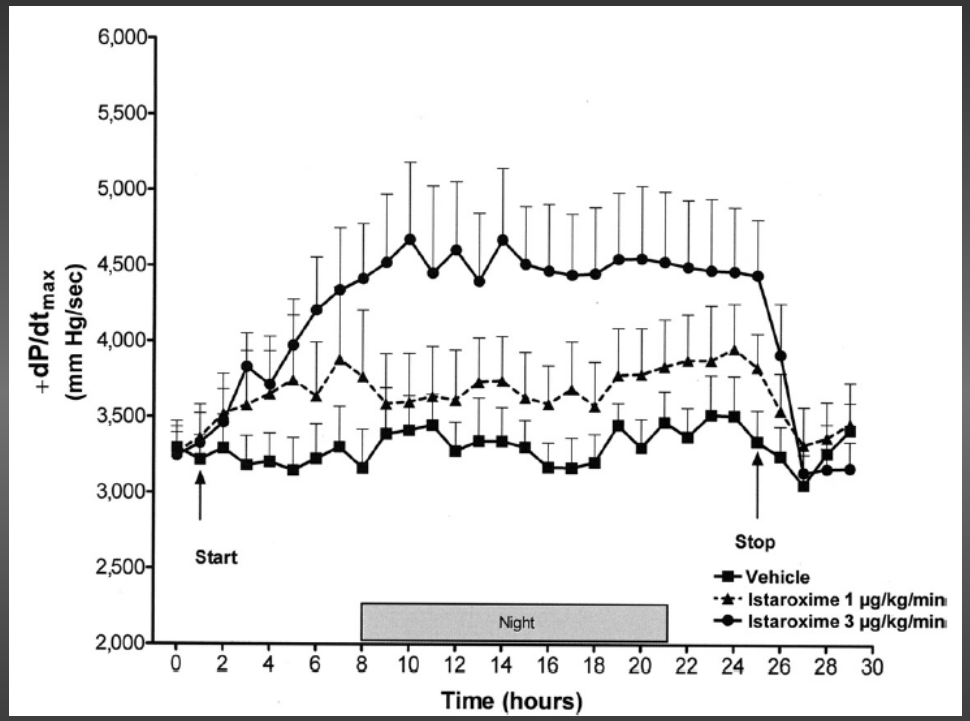


Istaroxim inhibuje aktivitu Na-K ATPasy a současně stimuluje SR Ca ATPase (SERCA) isoform 2a (SERCA2a).

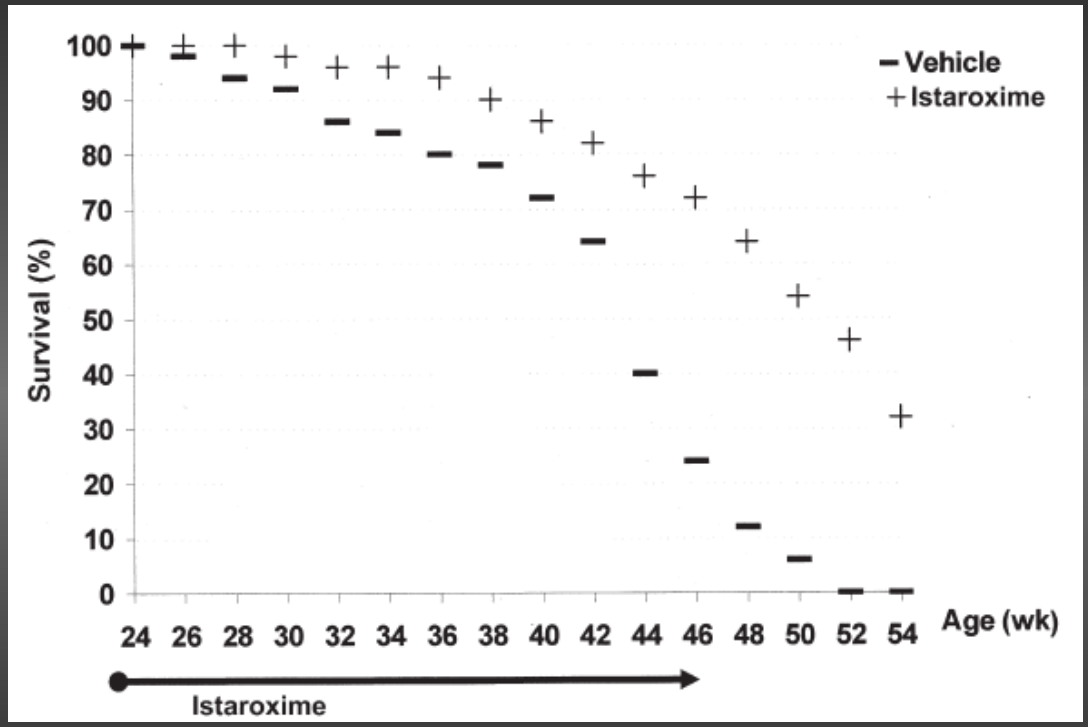


Istaroxim

hemodynamika u psů



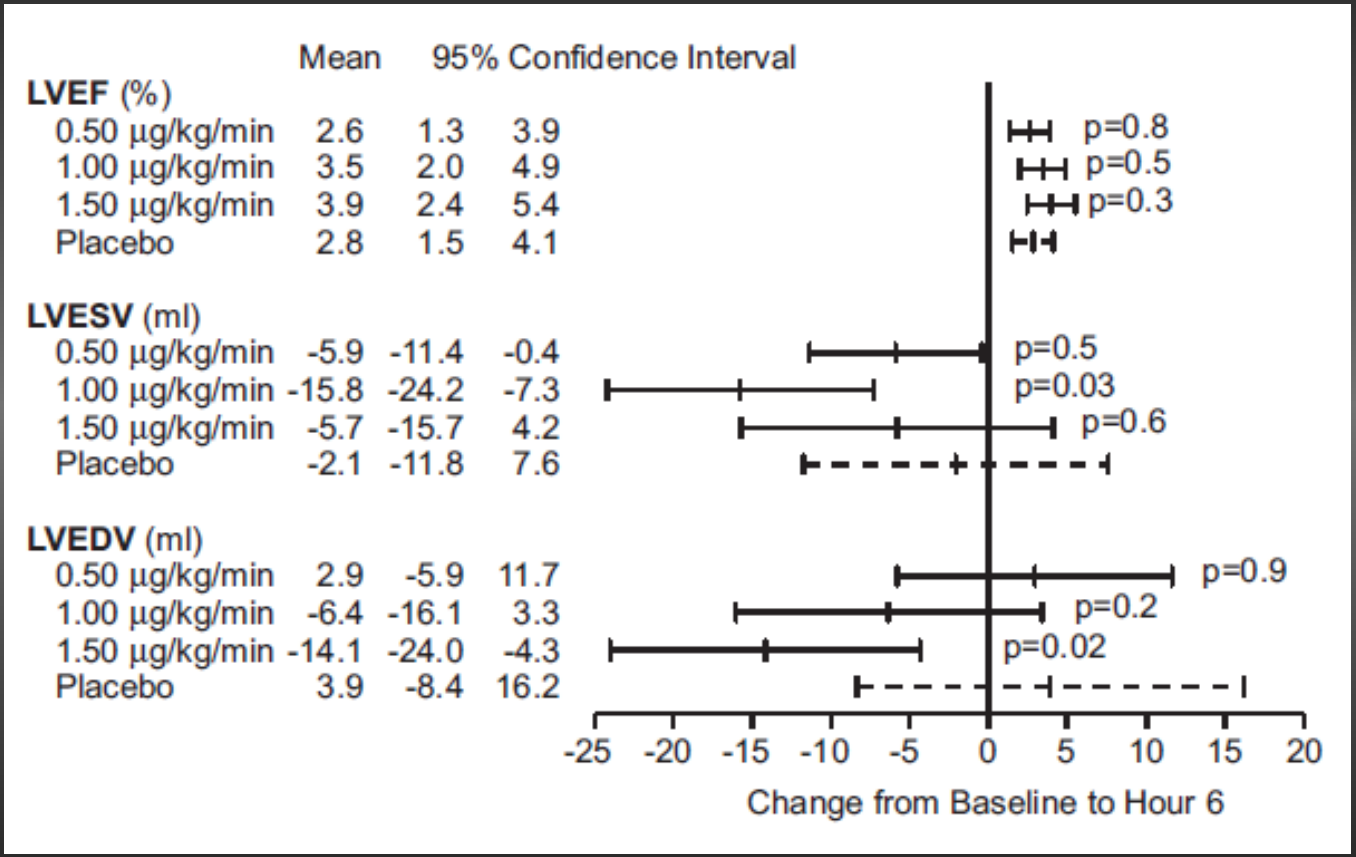
přežití u křečků



Heart Fail Rev (2009) 14:277–287

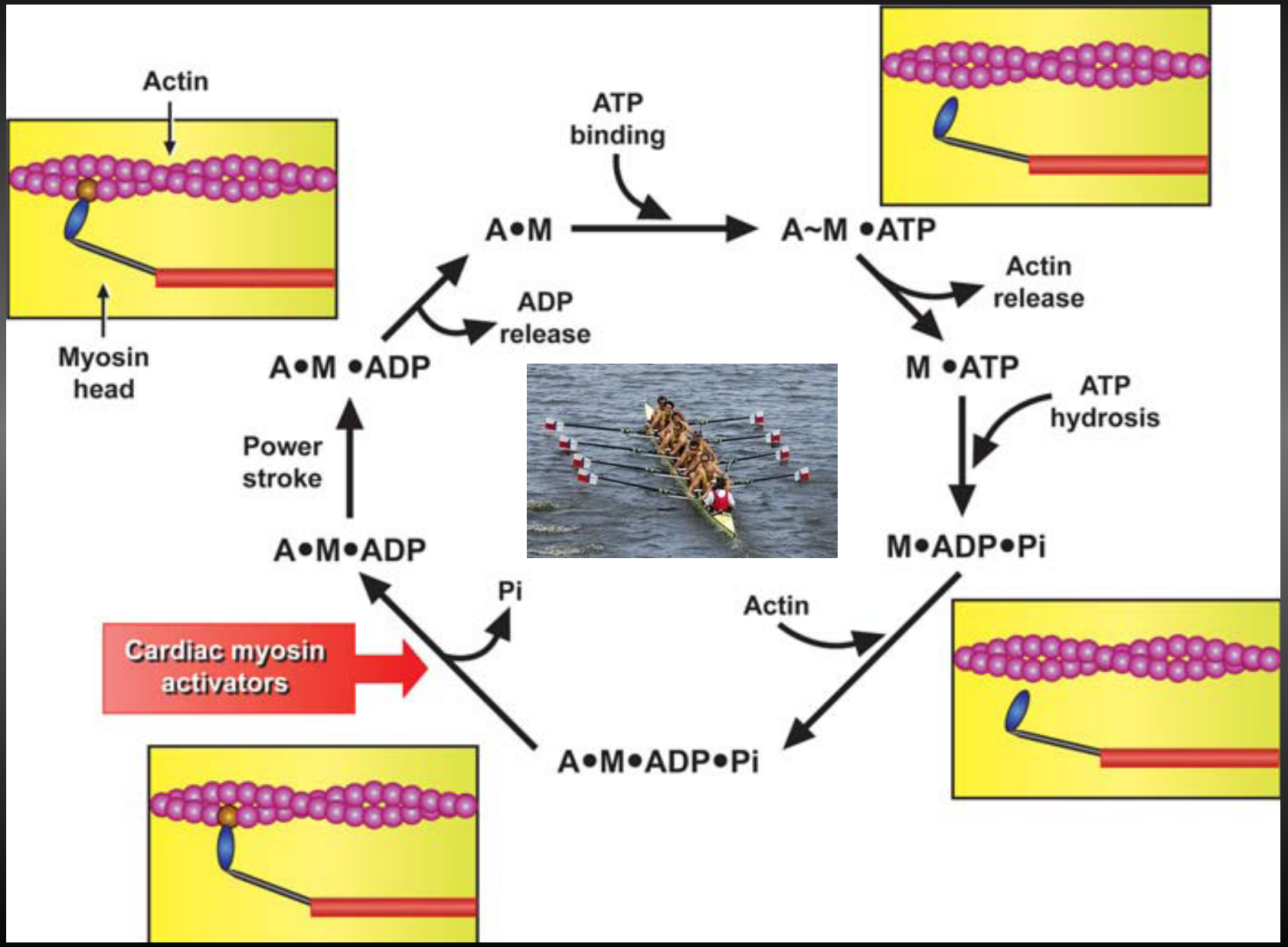
HORIZON-HF

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

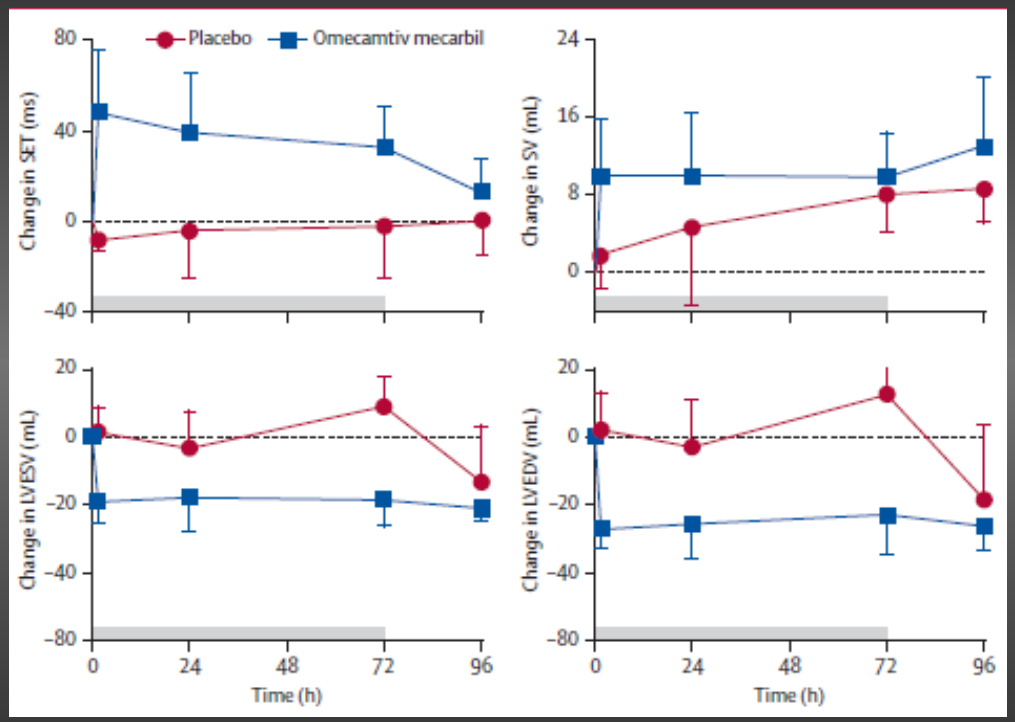


In patients hospitalized with HF, istaroxime improved PCWP and possibly diastolic function. In contrast to available inotropes, istaroxime increased SBP and decreased HR. (JACC 2008;51:2276–85)

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)

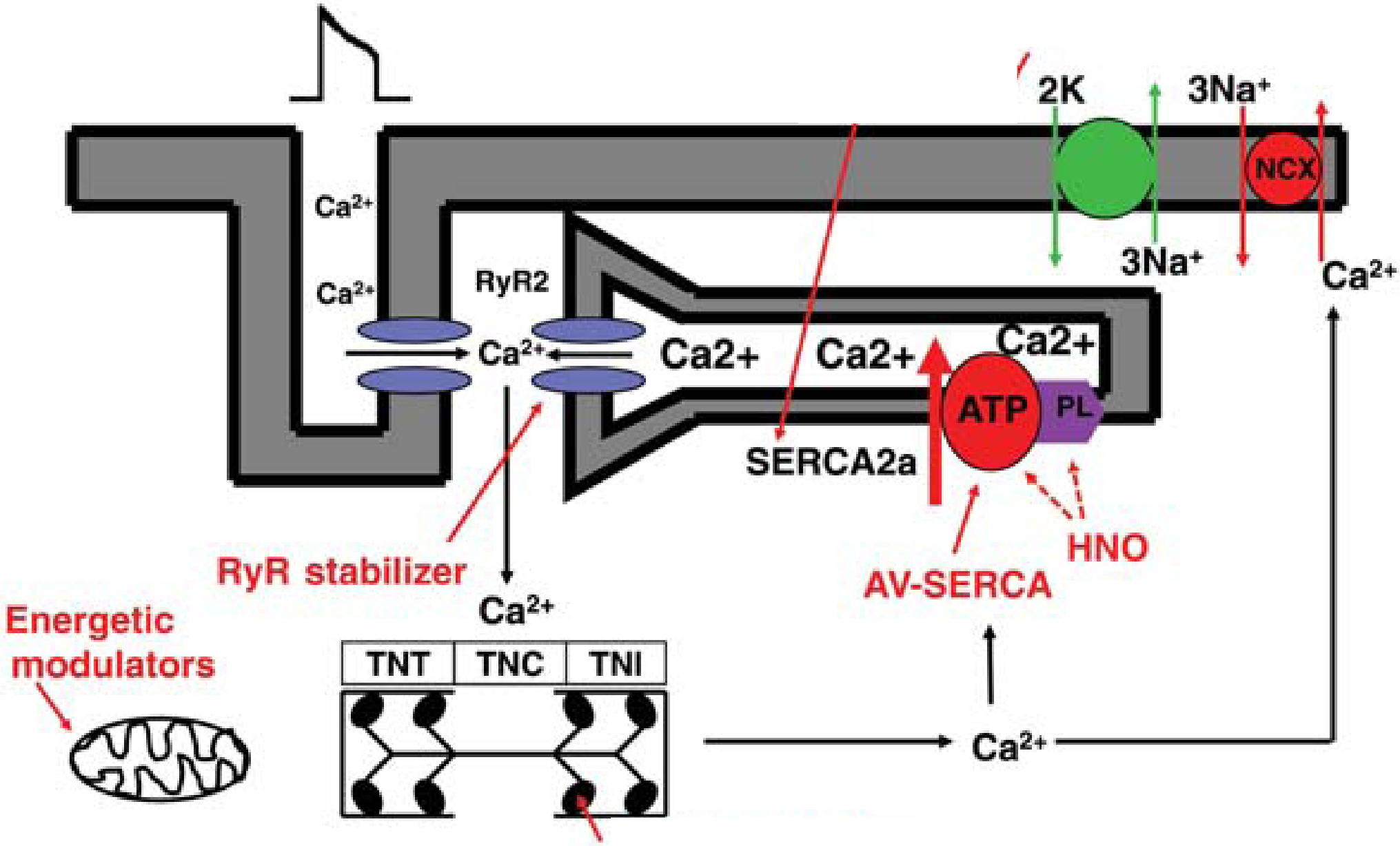
ATOMIC HF

Study to Evaluate the Safety and Efficacy of IV Infusion Treatment With Omecamtiv Mecarbil in Subjects With Left Ventricular Systolic Dysfunction Hospitalized for Acute Heart Failure

Primary Outcome Measures:

The primary objective of the study is to evaluate the effect of 48 hours of intravenous (IV) omecamtiv mecarbil compared with placebo on dyspnea in subjects with left ventricular systolic dysfunction hospitalized for acute heart failure.

New inotropes



Mýty o inotropicích

1. hledání zlatého grálu tzn. perorálního inotropika

2. zlepšení hemodynamiky sníží úmrtnost
3. kvalita života je méně významný cíl léčby než statisticky vyčíslitelná mortalita!

Fakta o inotropicích

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

Fakta o inotropicích

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.)
4. Tam, kde nelze použít LVAD - jako „bridging" před OTS

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

Digoxin vs ostatní inotropika v boji o chronické podávání u srdečního selhání

I poslední diapozitiv je nutno připravovat ve stavu střízlivém!!