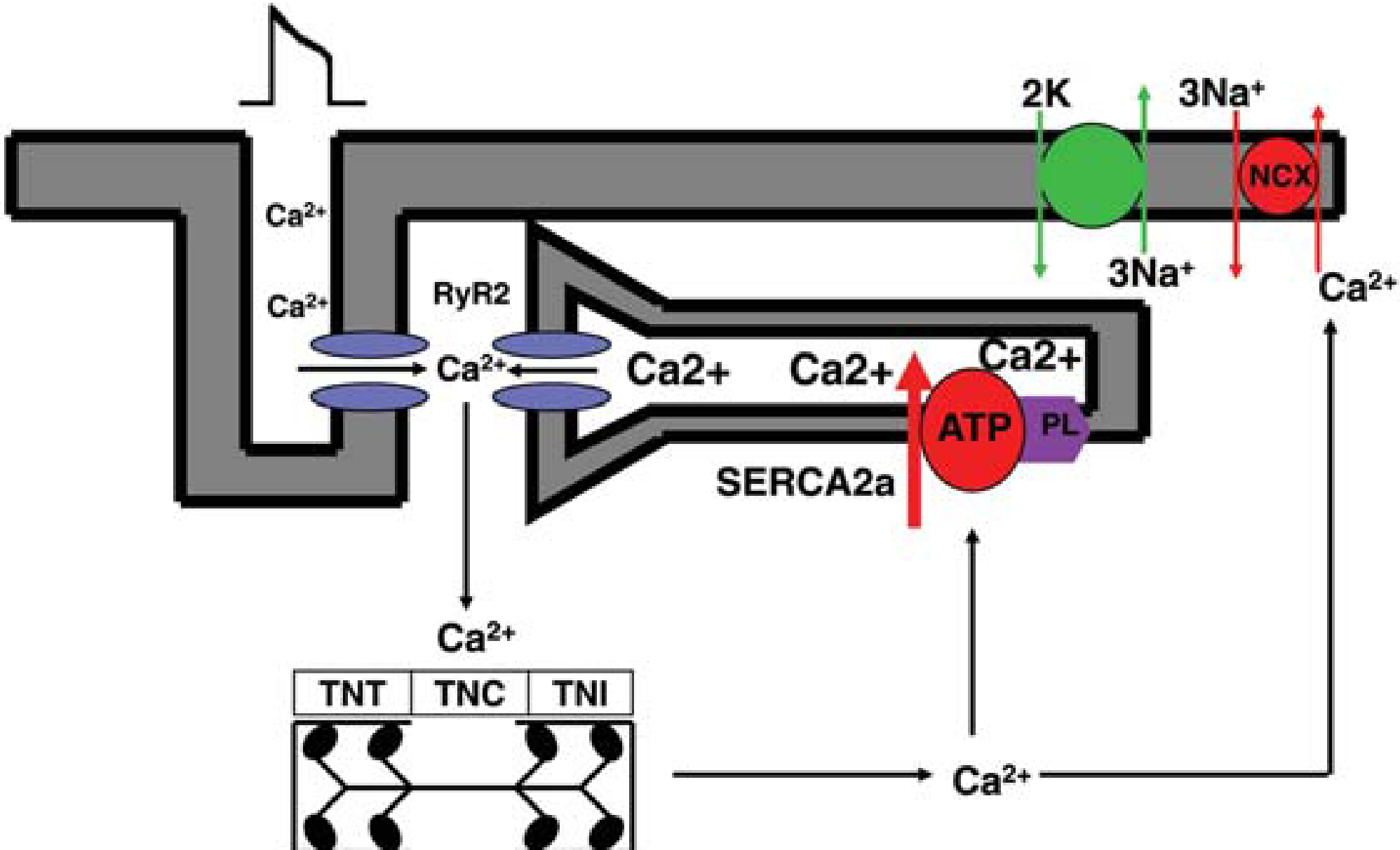
Pozitivně inotropní léky

Jiří Vítovec,

LF MU a FN u sv.Anny v Brně

Excitace-kontrakce



William Withering 1741-1799

AN

ACCOUNT OF THE FOXGLOVE,

AND

Some of its Medical Uses:

with

PRACTICAL REMARKS ON DROPSY,
AND OTHER DISEASES.

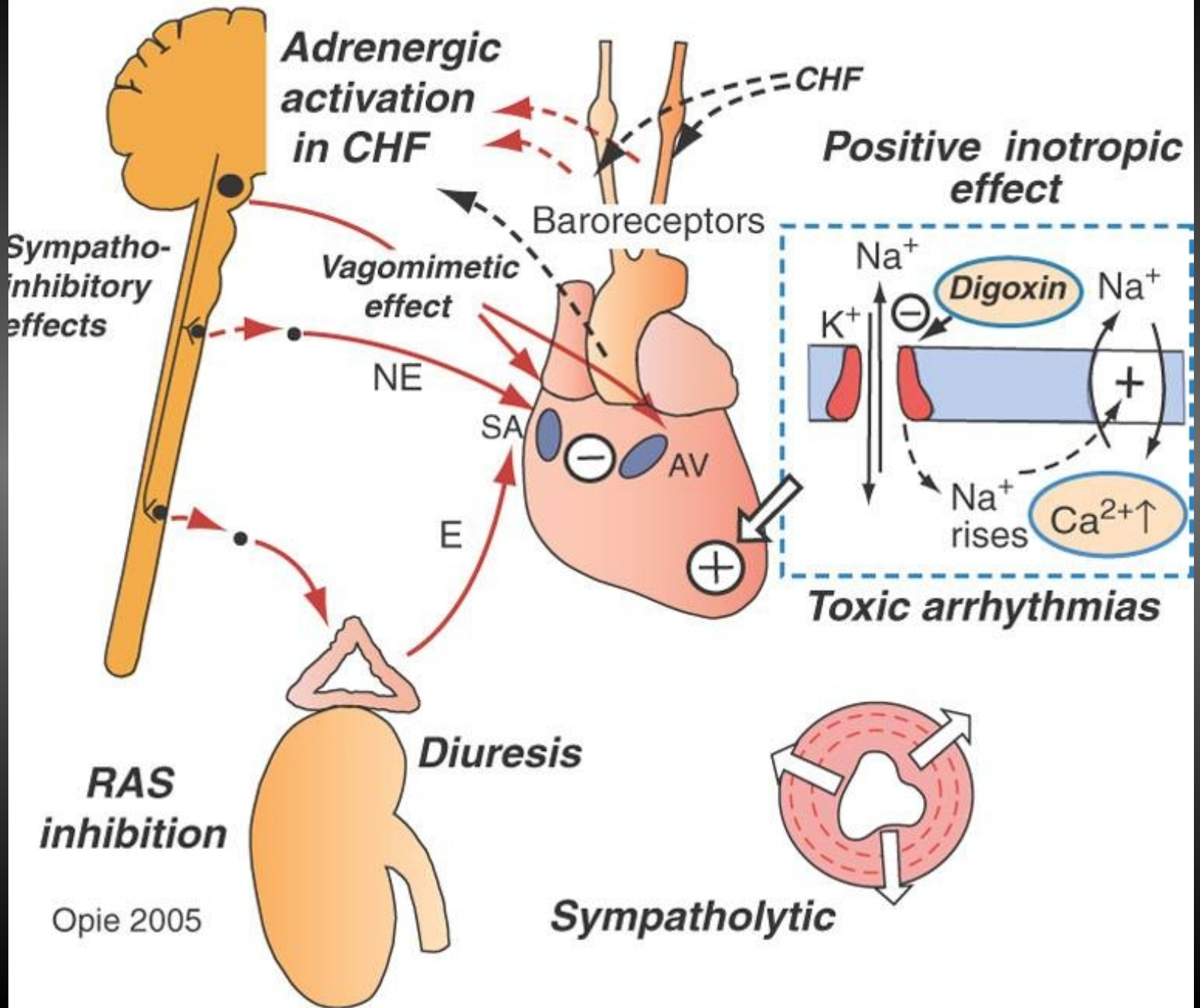
By

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.


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

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

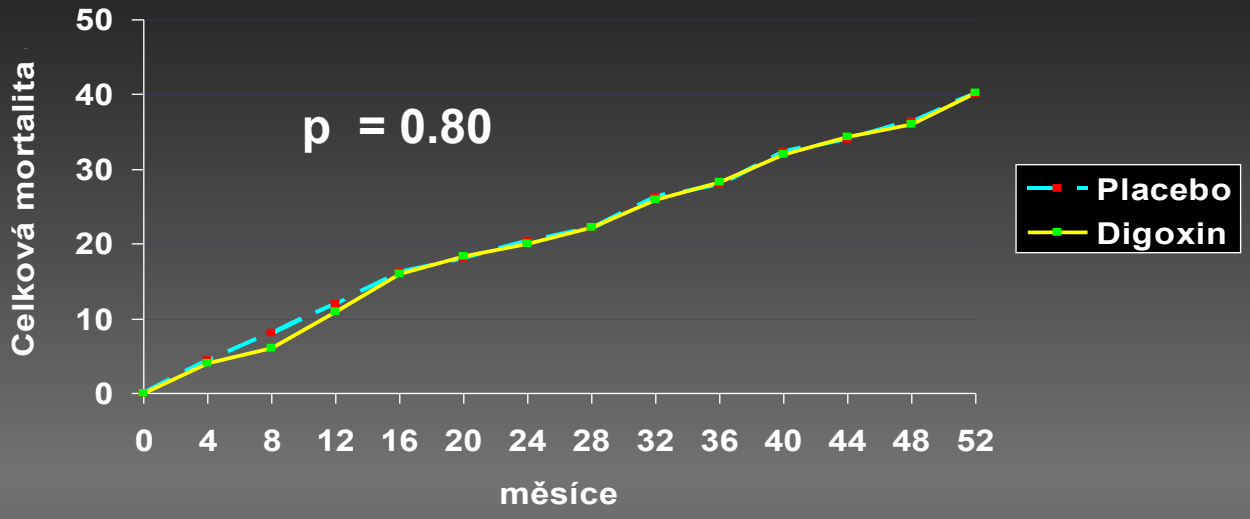
Rx: ACE-I 94%, diuretika 82%, nitráty 43%

Dg: ICHS 71%, DKM 29%

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

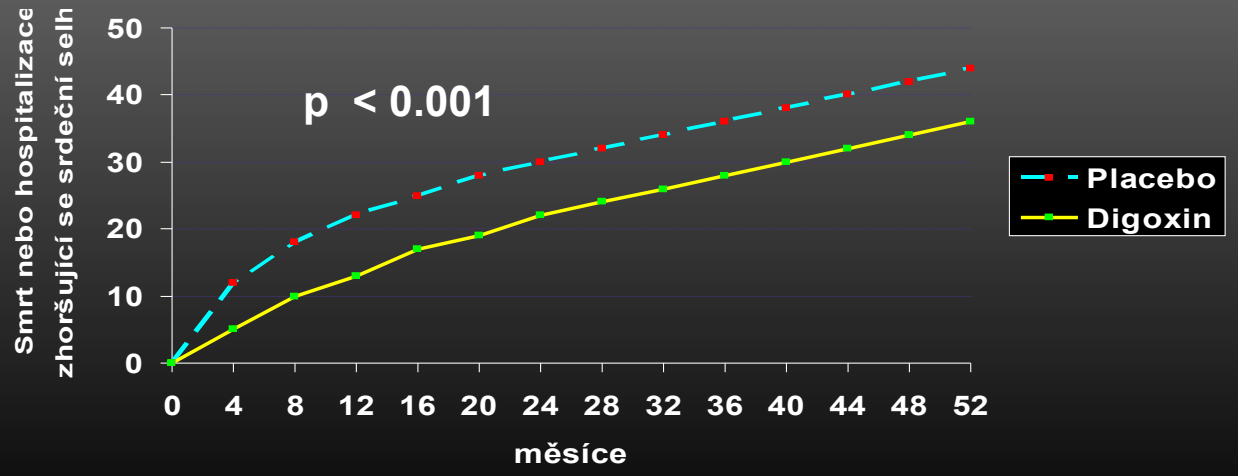
N Engl J Med 1997;336:525-33

DIG



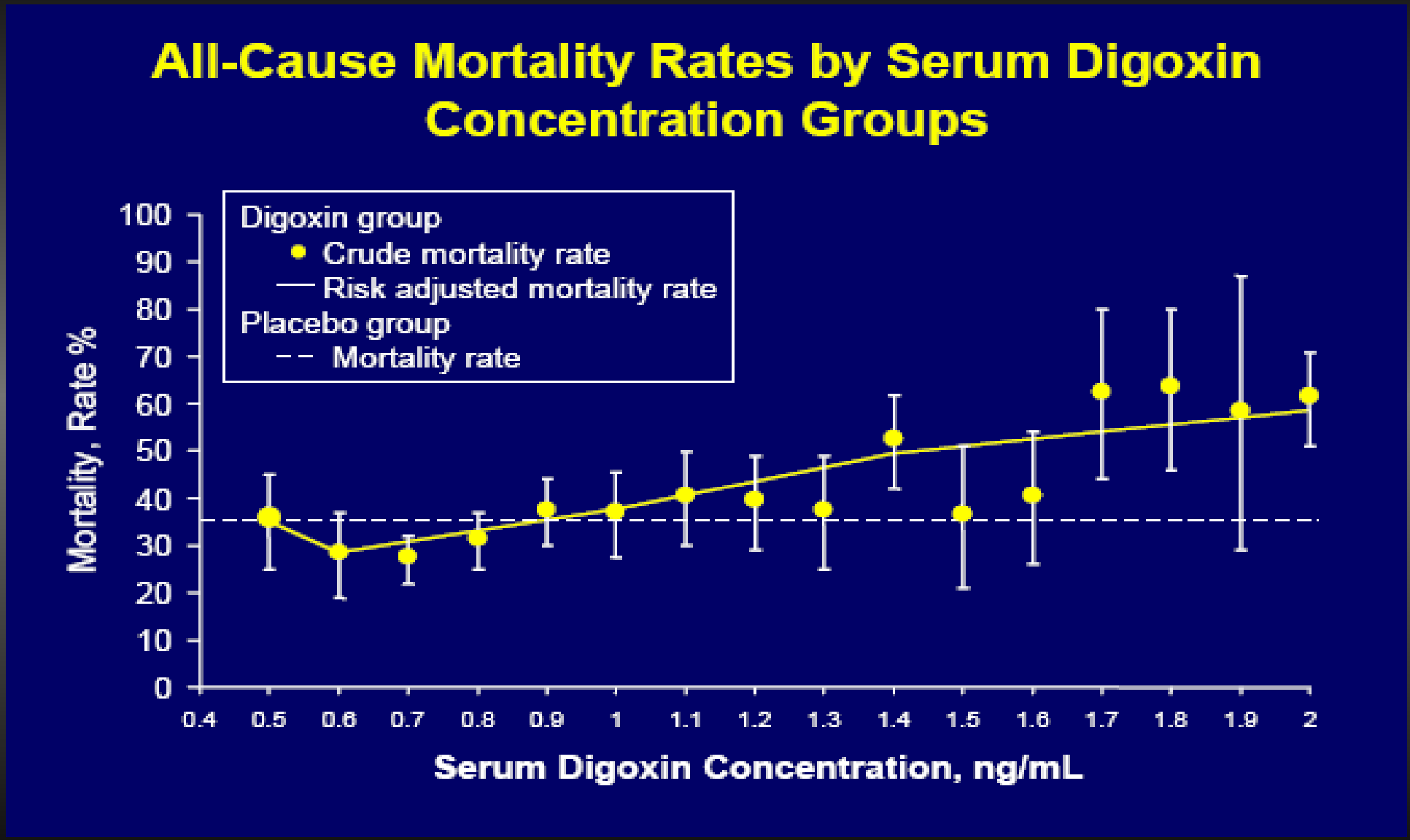
Celková mortalita

Mortalita a hospitalisace pro zhoršení srdečního selhání



N Engl J Med 1997;336:525-33

DIG



J Am Coll Cardiol 2005;46:497-504

Fakta o digoxinu

Jaký?

vyřešeno - digoxin

Dávka?

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

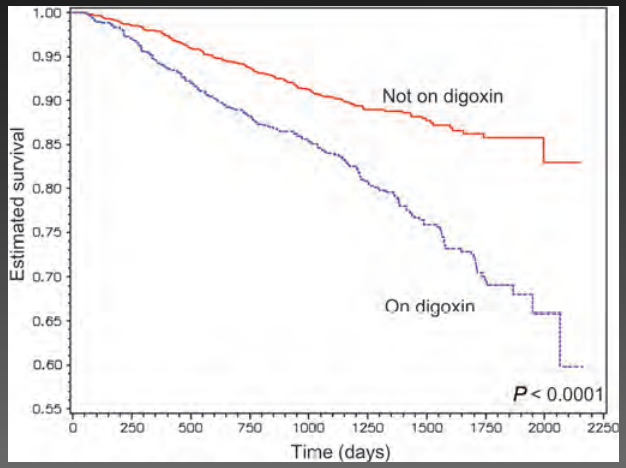
Kdy?

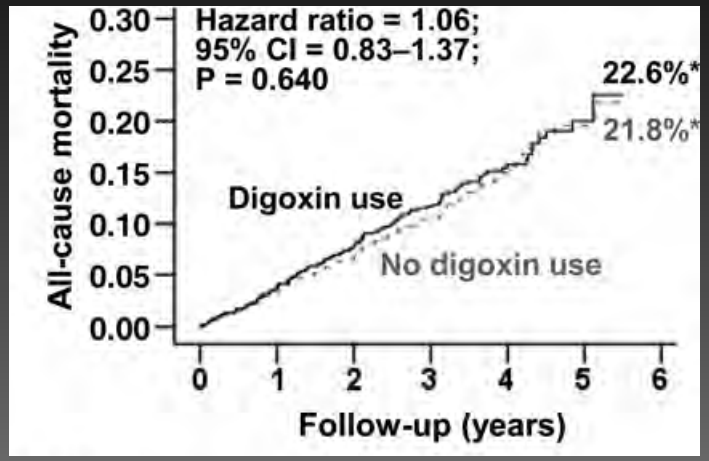
lék 3.volby

po ACEi/ARB,BB ev.diu

Myslet na předávkování!!

AFFIRM

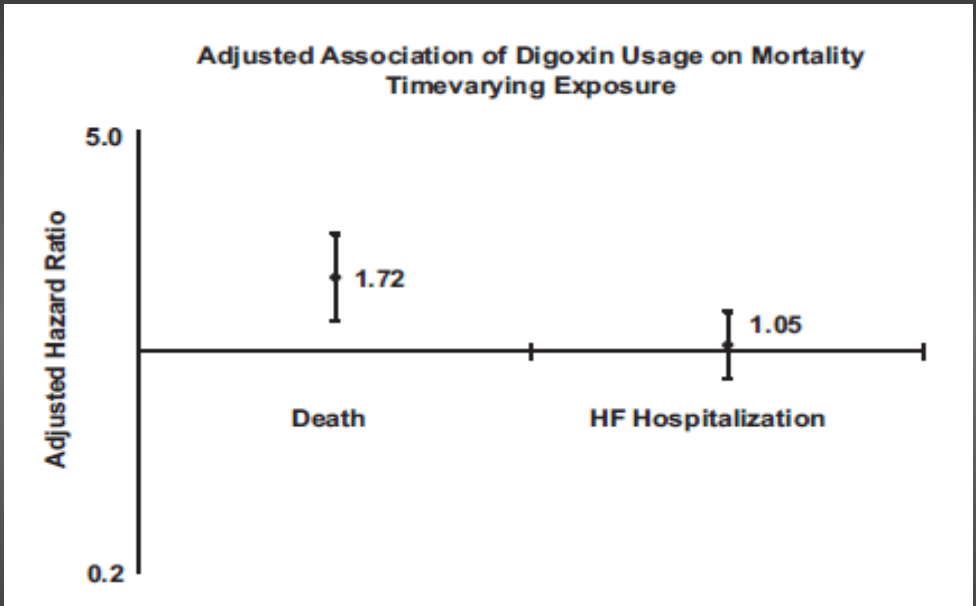




	Whitbeck *et al.*	Gheorghiade *et al.*
Study design	Non-randomized, observational analysis using data from randomized AFFIRM trial	Non-randomized, observational analysis using data from randomized AFFIRM trial
Time point digoxin used assessed	Time-varying covariate, throughout study	Fixed, at baseline only
Cohort	Full cohort ($n = 4058$)	Selected cohort ($n = 1756$)
Propensity method	Adjustment	Matching[a]
Primary HR for digoxin and all-cause mortality association	HR 1.41, 95% CI 1.19–1.67; $P < 0.001$	HR 1.06, 95% CI 0.83–1.37; $P = 0.640$
Main conclusion from authors	Digoxin associated with significant increase in all-cause mortality in patients with AF	No evidence of increased mortality associated with digoxin use as baseline initial therapy in patients with AF

European Heart Journal (2013) 34, 1481–1488 **a** 1489–1497

Freeman et al looked at 2891 digoxin-naive adults with recently diagnosed systolic heart failure from 2006 to 2008, 18% of whom were started on digoxin; they were followed for a median of 2.5 years. Hazard ratio* (95% CI) for Outcomes, Digoxin (n=529) vs No Digoxin (n=2362) for Recent-Onset Systolic HF



Conclusions—Digoxin use in patients with incident systolic HF was independently associated with a higher risk of death but no difference in HF hospitalization

Freeman JV, Yang J, Sung SH, et al. .*Circ Cardiovasc Qual Outcomes* 2013; 6:525-533

Doporučení digoxinu

Jaký?

digoxin

Dávka?

tak aby plazm.

[0,55 - 0,9 ng/ml = 0,6-1,1 nmol/L] !!

Kdy?

lék 3-4.volby

po ACEi/ARB,BB ev.diu

Myslet na předávkování a používat klinický náhled!!

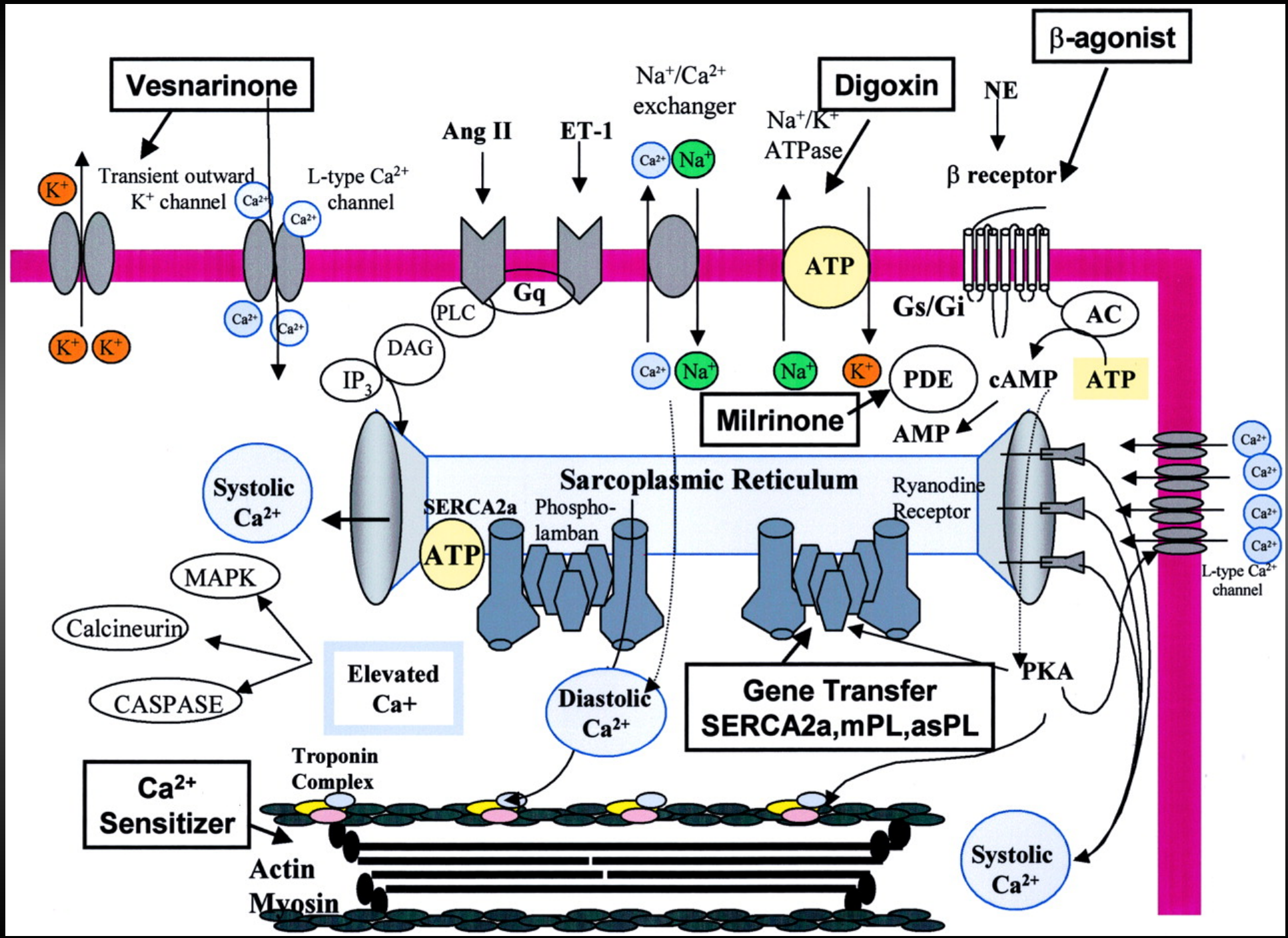
A Fond Farewell to the Foxglove?

ALLEN B. WEISSE, Journal of Cardiac Failure Vol. 16 No. 1 2010

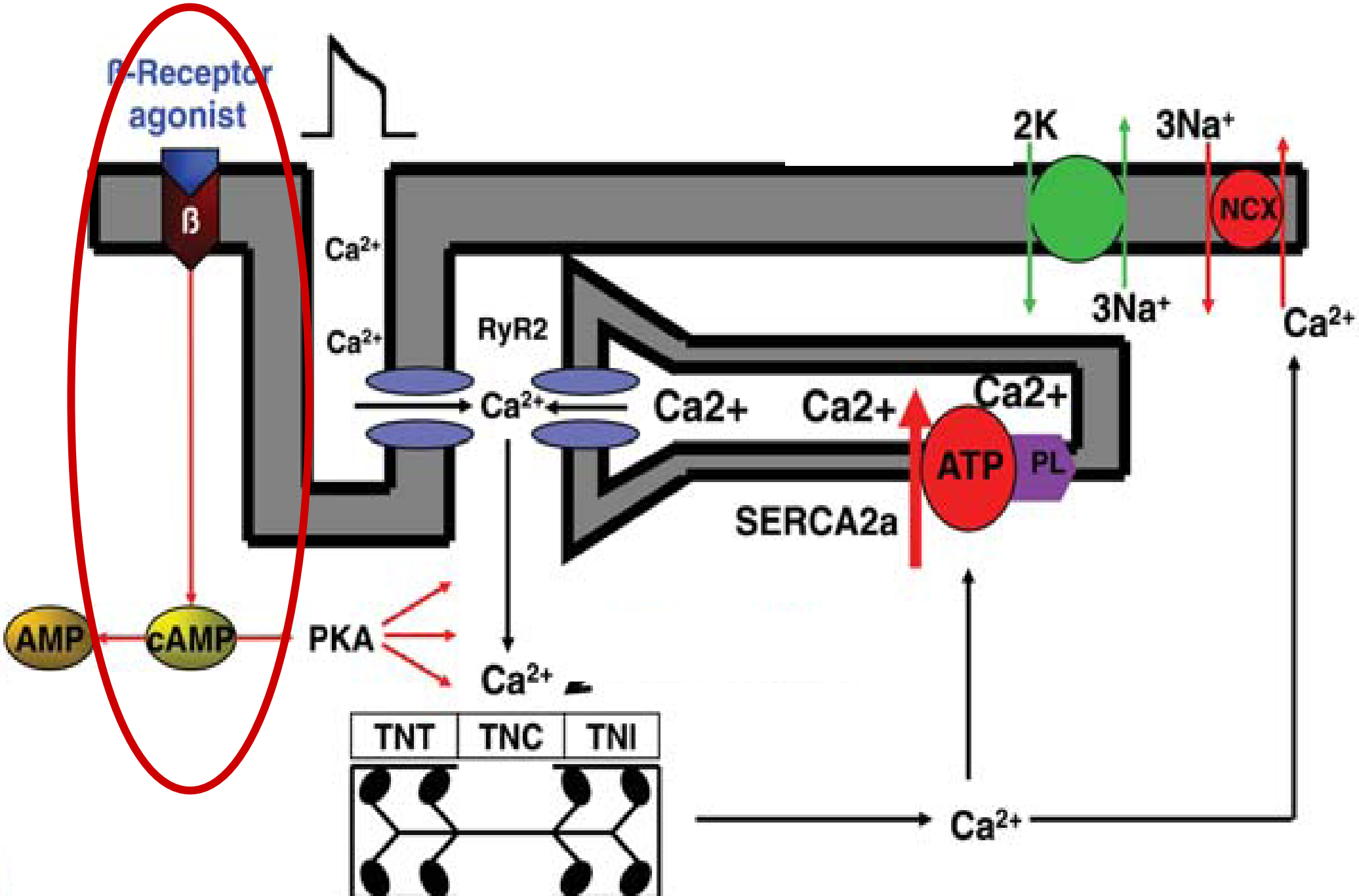
Table 1. Withering's Success in Treating Dropsy: 152 Cases

Patients	Success (%)	Failure	Total
Definite cardiac	39 (89)	5	44
Others	59 (55)	49	108

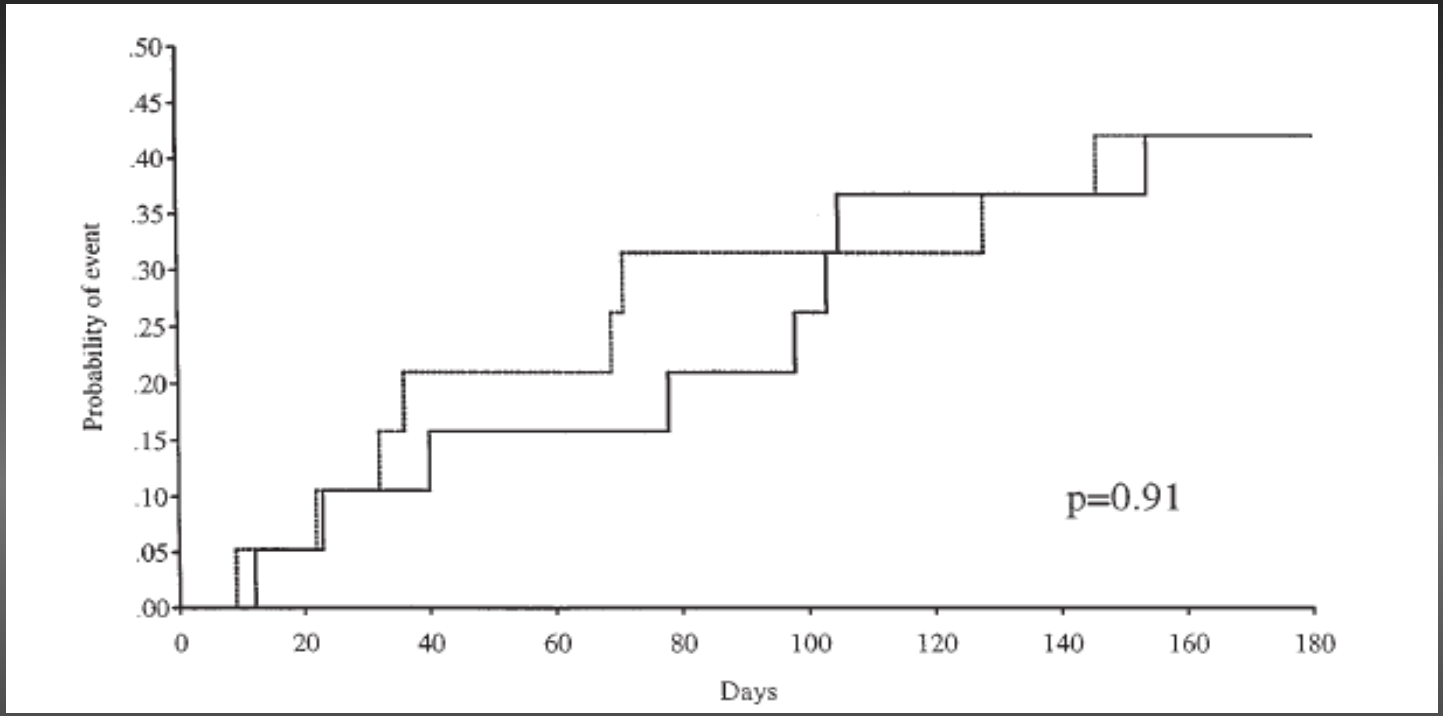
Were such data presented in an article submitted to any modern journal, they would no doubt be immediately rejected. What did Withering know about a randomized, prospective, double blind study to determine therapeutic efficacy? Fortunately for millions of patients over the last 200 years, this was no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


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


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

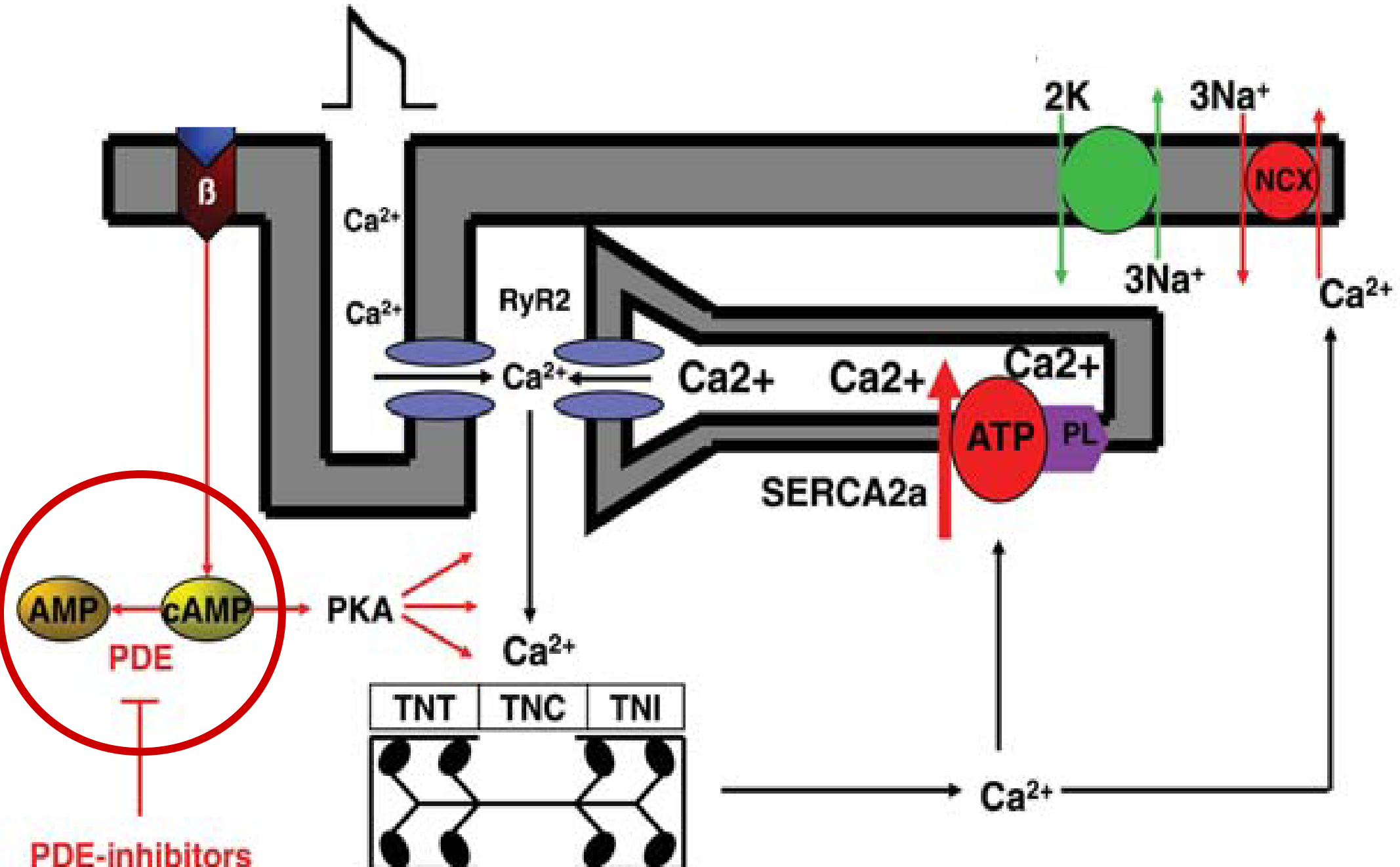
Intermittent 6-month low-dose dobutamine infusion in severe heart failure: DICE Multicenter Trial



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.)

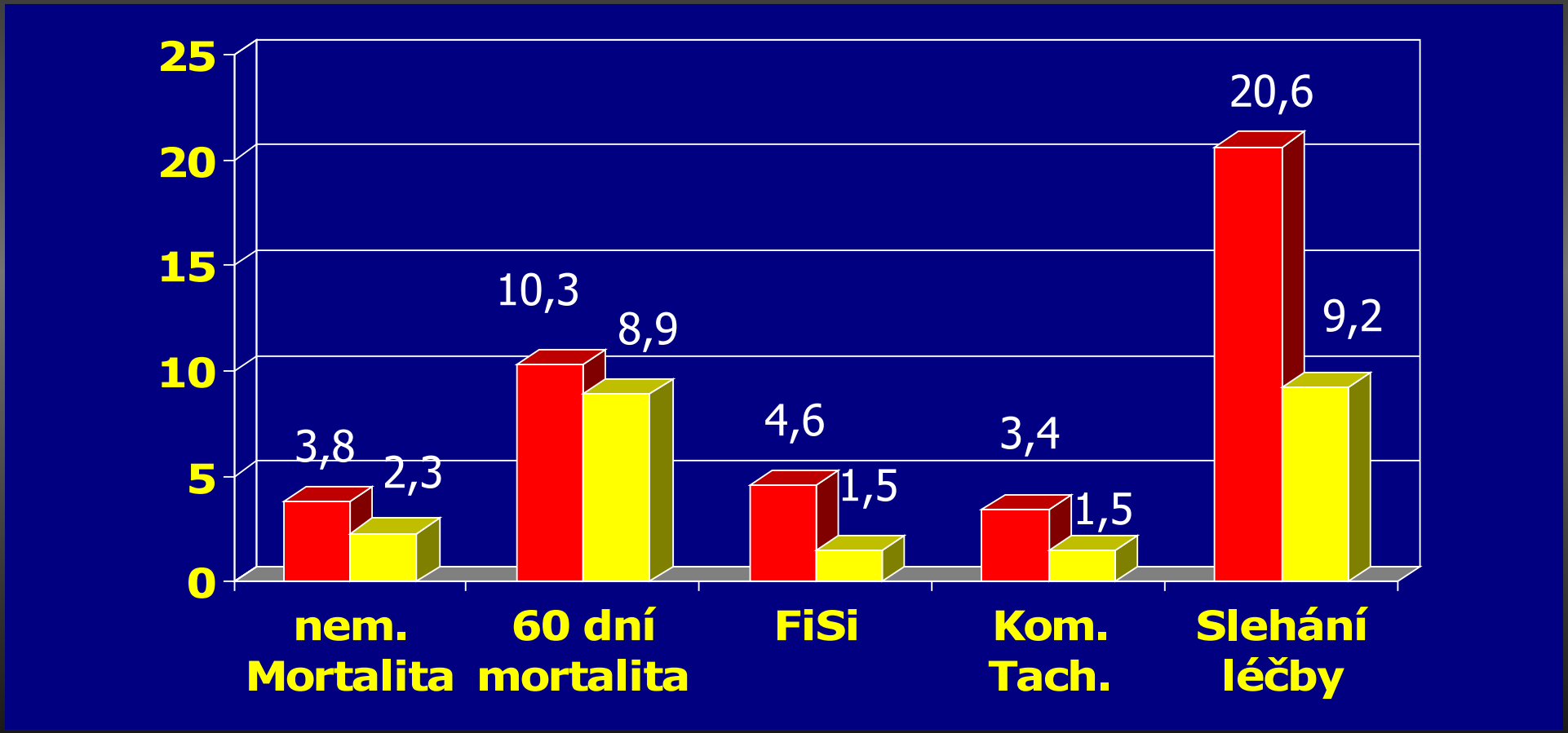
Indikace betamimetik

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

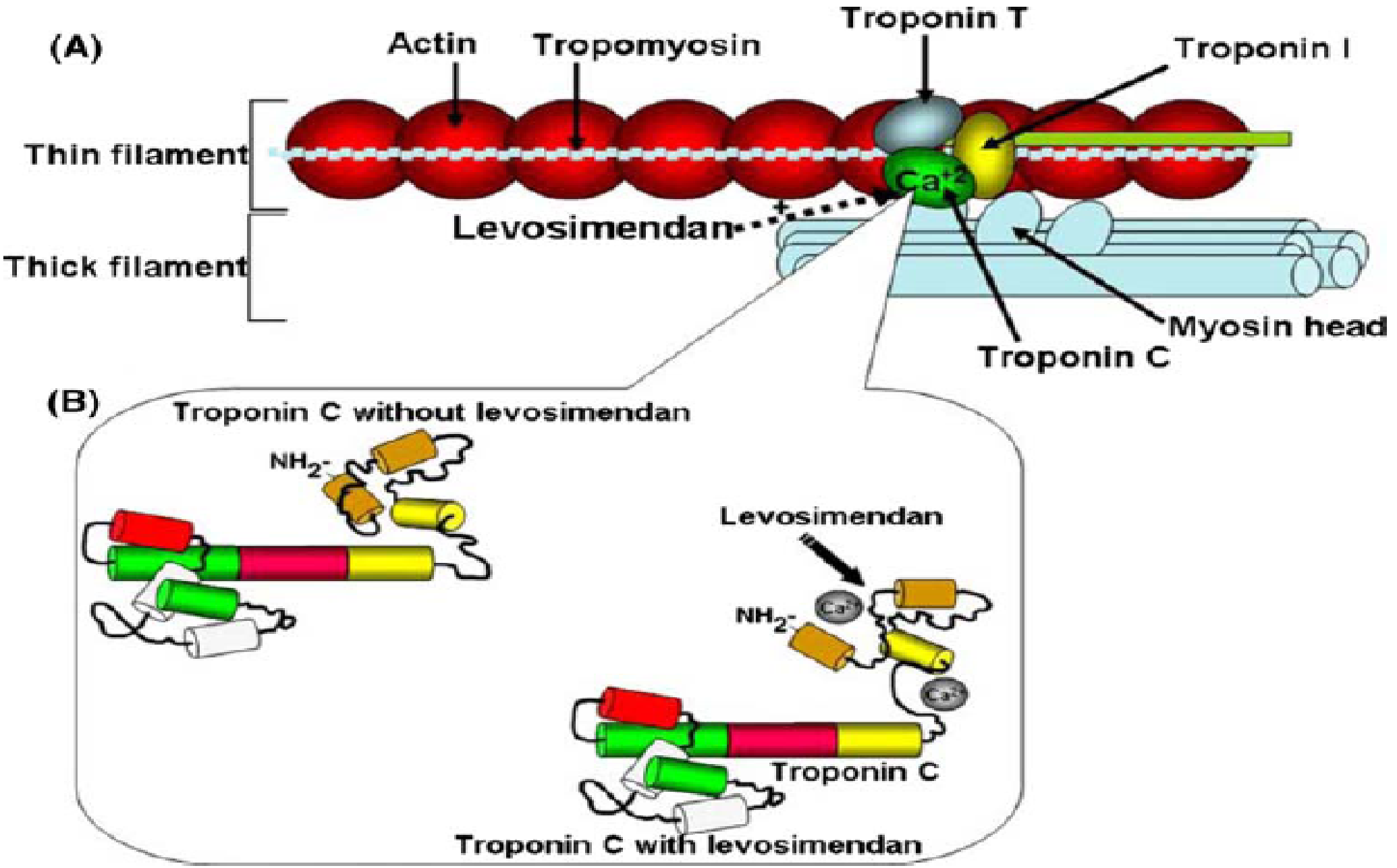
OPTIME CHF

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



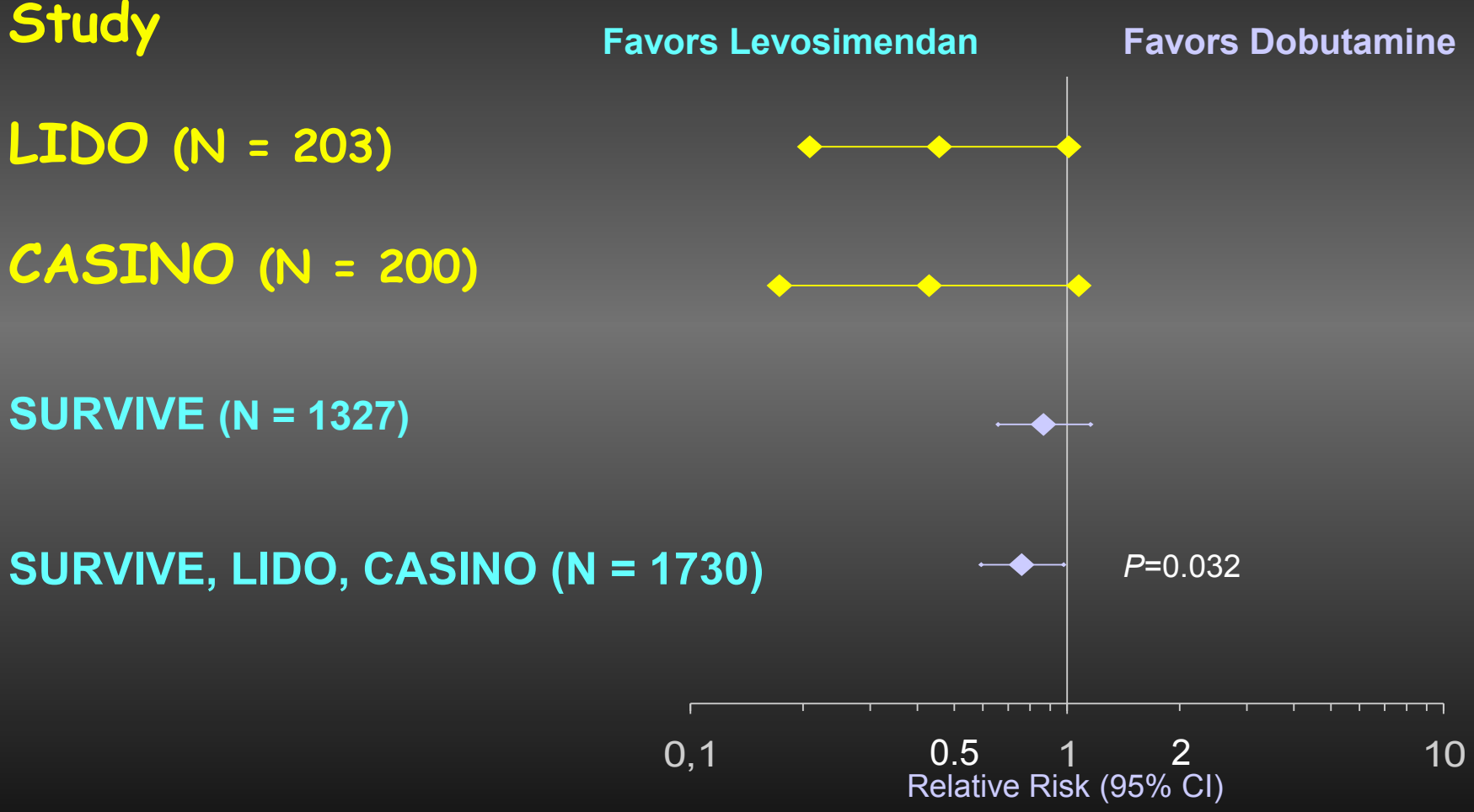
Milrinon 72 hod vs placebo

JAMA 2002;287:1541–7

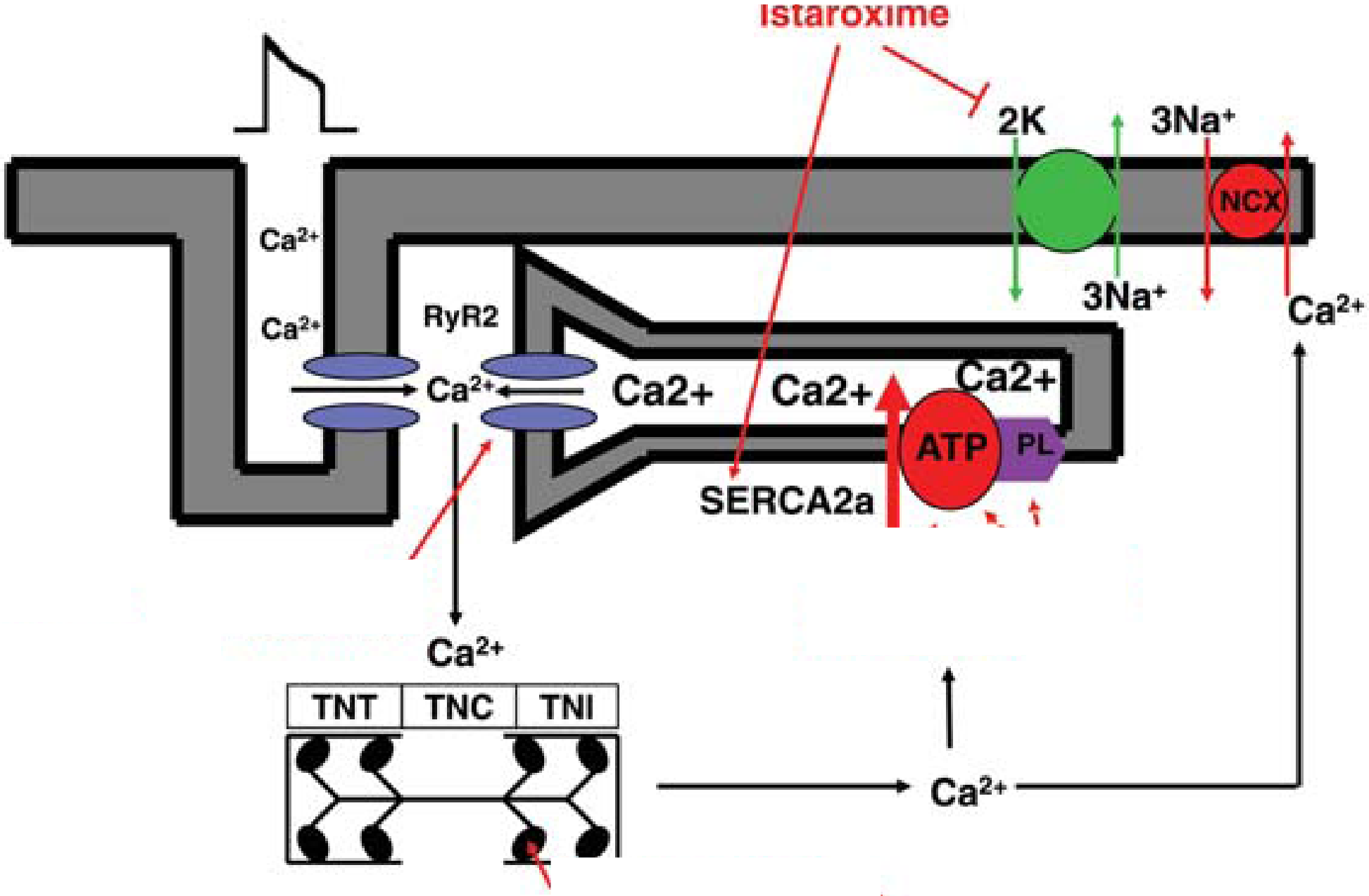

(A)
Actin
Tropomyosin
Troponin T
Troponin I
Thin filament
Thick filament
Levosimendan
Troponin C
Myosin head
(B)
Troponin C without levosimendan
NH2-
Levosimendan
NH2-
Troponin C
Troponin C with levosimendan

Studie s levosemindanem

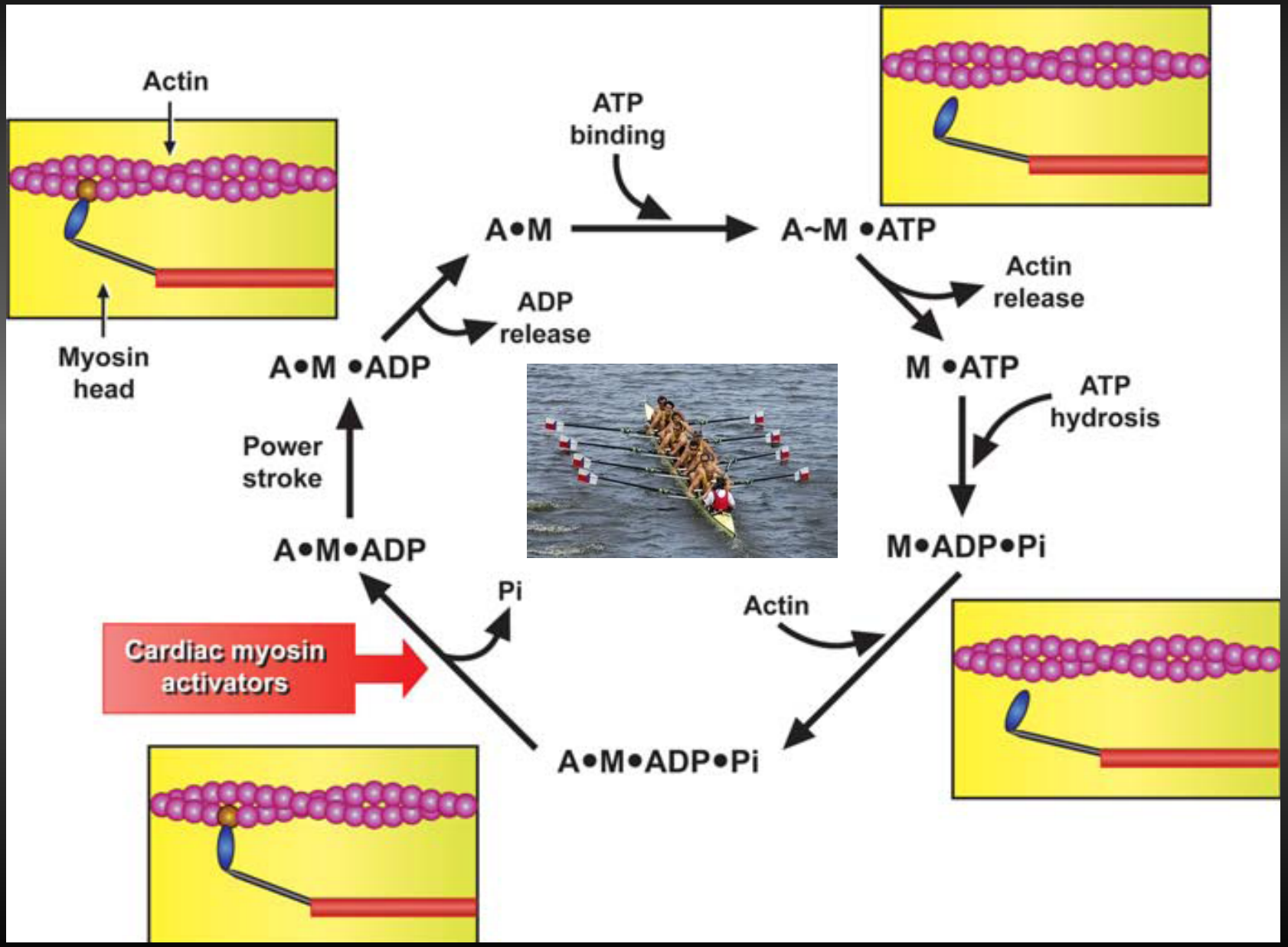
Mortality Comparison - 31 Days



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



Omecamtiv mecarbil



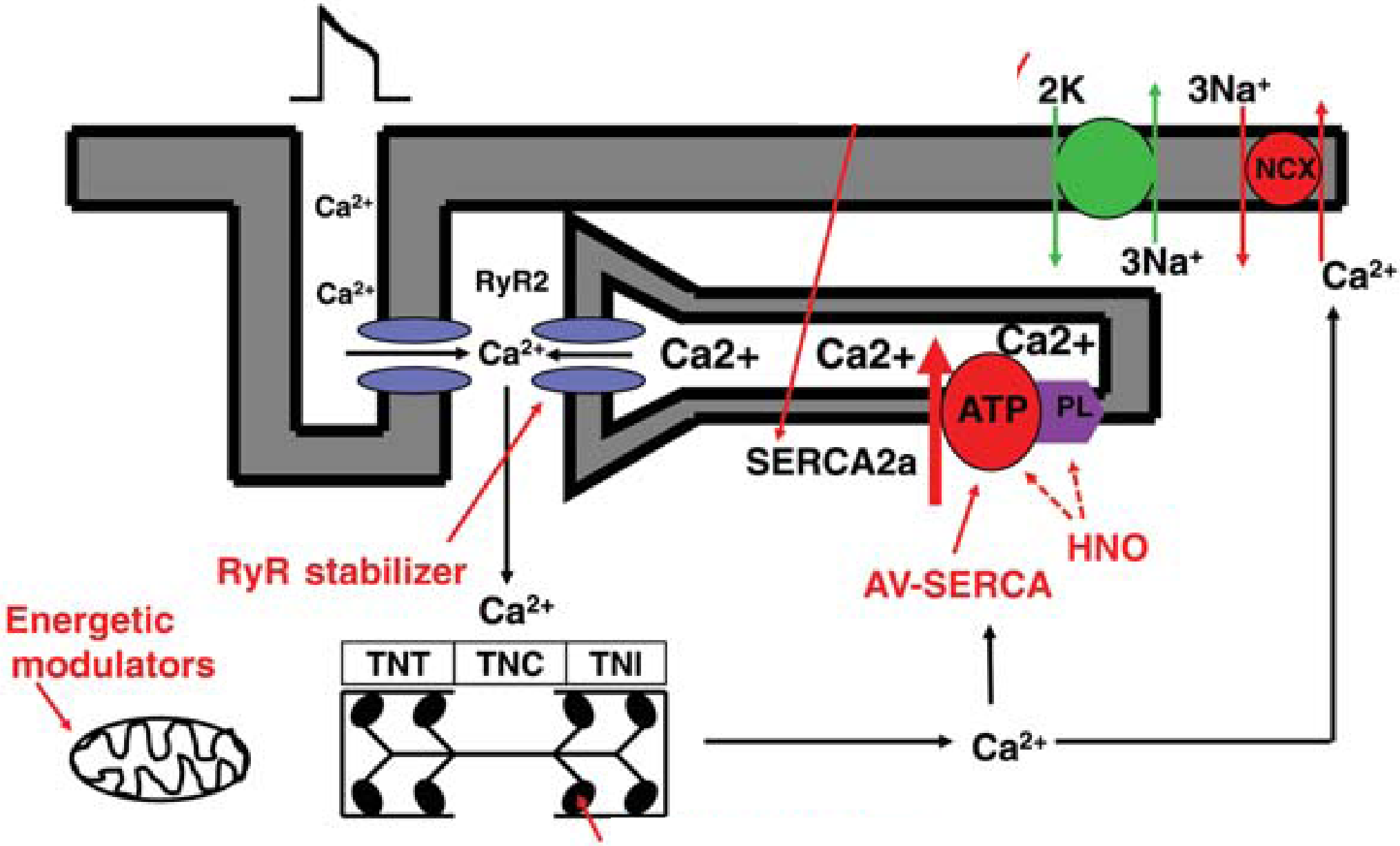
ATOMIC HF

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, který by nahradil digoxin
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.**