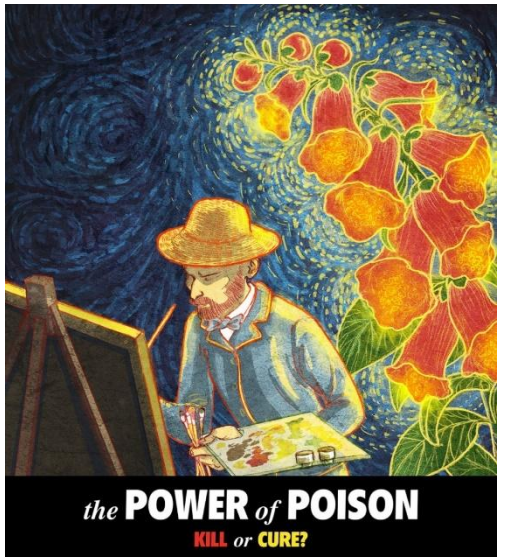
DIGOXIN V LÉČBĚ SRDEČNÍHO SELHÁNÍ - PRO

J. Krejčí



Historické okénko

AN

ACCOUNT OF THE FOXGLOVE,

AND

Some of its Medical Uses:

with

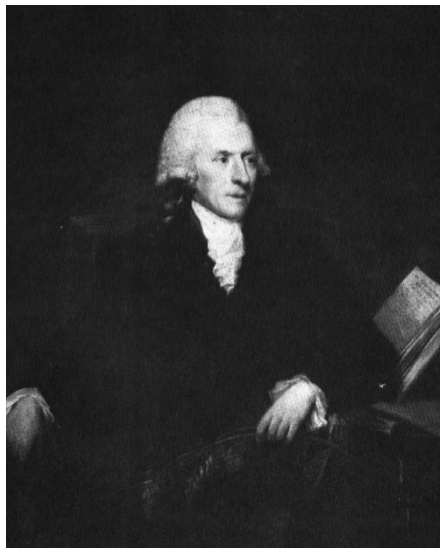
PRACTICAL REMARKS ON DROPSY,
AND OTHER DISEASES.

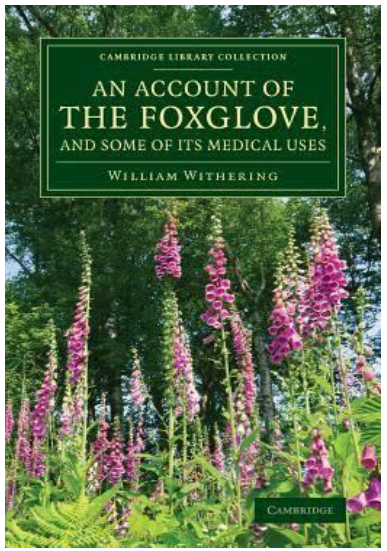
By

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





After all, in spite of opinion, prejudice, or error,
time will fix the real value upon this discovery.
—Sir William Withering,
Birmingham, United Kingdom, July 1, 1785 (1)

Proč máme u Sv. Anny rádi digoxin?

A tak roku 1785 začíná rozsáhlá přeměna kláštera v nemocnici. "Císařsko-královský všeobecný zaopatřovací ústav" zahájil u svaté Anny provoz 2.ledna 1786, do funkce ředitele byl jmenován Tomáš Pötzl. Spravoval 80 lůžek v nemocnici, po dvaceti lůžkách v porodnici, nalezinci a sirotčinci a pět lůžek oddělení pro pomatené. Základ nemocnice tvořily dva velké sály, upravené z budov hraničících s Pekařskou ulicí

Je za tímto vztahem opravdu jen historická paralela a nostalgie?

Srdeční selhání a digoxin

The Use of Digoxin in Patients With Worsening Chronic Heart Failure

Reconsidering an Old Drug to Reduce Hospital Admissions

Andrew P. Ambrosy, MD,* Javed Butler, MD, MPH,† Ali Ahmed, MD,‡ Muthiah Vaduganathan, MD, MPH,§ Dirk J. van Veldhuisen, MD,|| Wilson S. Colucci, MD,¶ Mihai Gheorghiade, MD#

Stanford, California; Atlanta, Georgia; Birmingham, Alabama; Boston, Massachusetts; Groningen, the Netherlands; and Chicago, Illinois

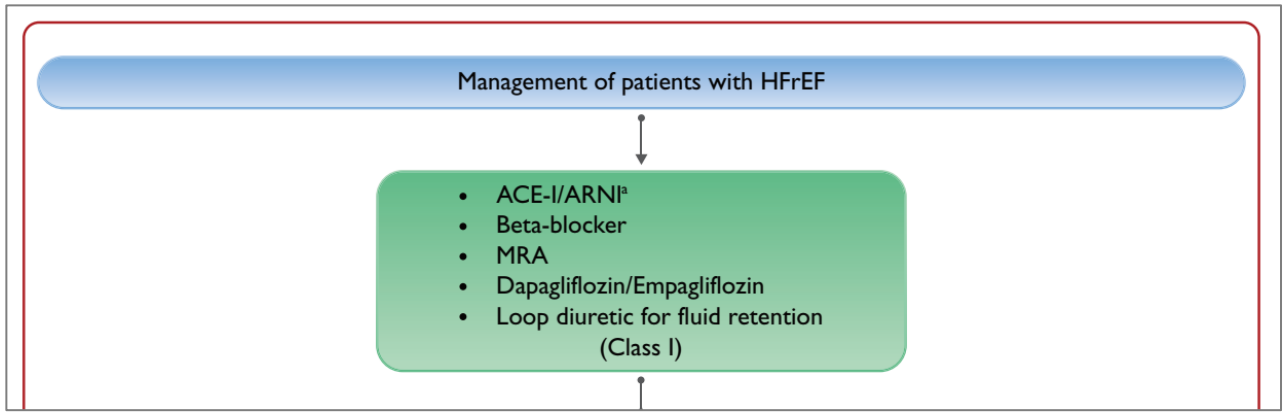
Table 2 Physiologic Effects of Digoxin Therapy

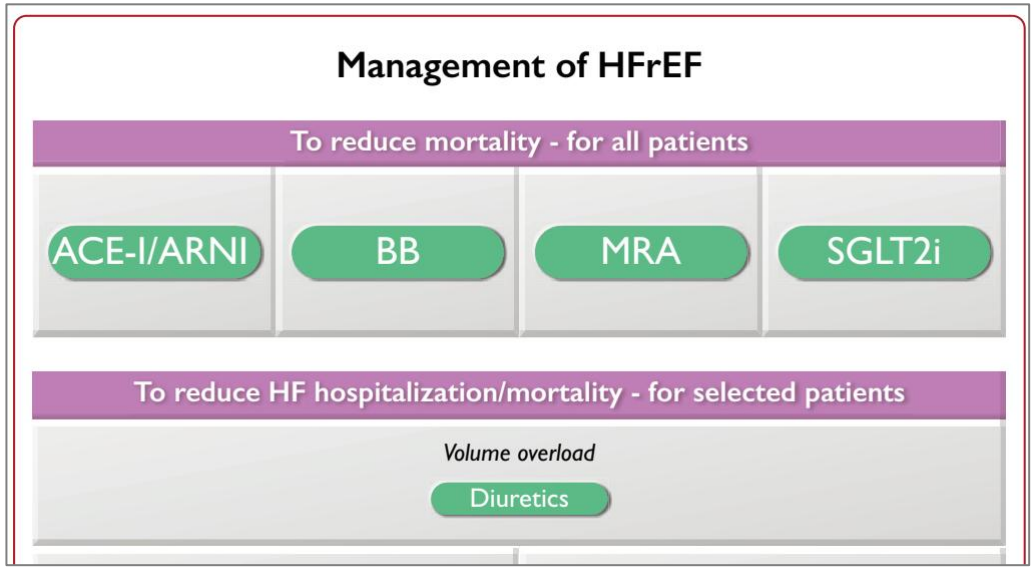
Hemodynamic	Neurohormonal	Electrophysiological
↑ LVEF	↑ Parasympathetic	SA node: slows sinus rate
↑ CO	↓ Sympathetic	AV node: prolongs conduction
↓ HR, ↔ BP	↓ RAAS	
↓ PCWP		

(J Am Coll Cardiol 2014;63:1823–32)

Léčba HFrEF v Guidelines

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

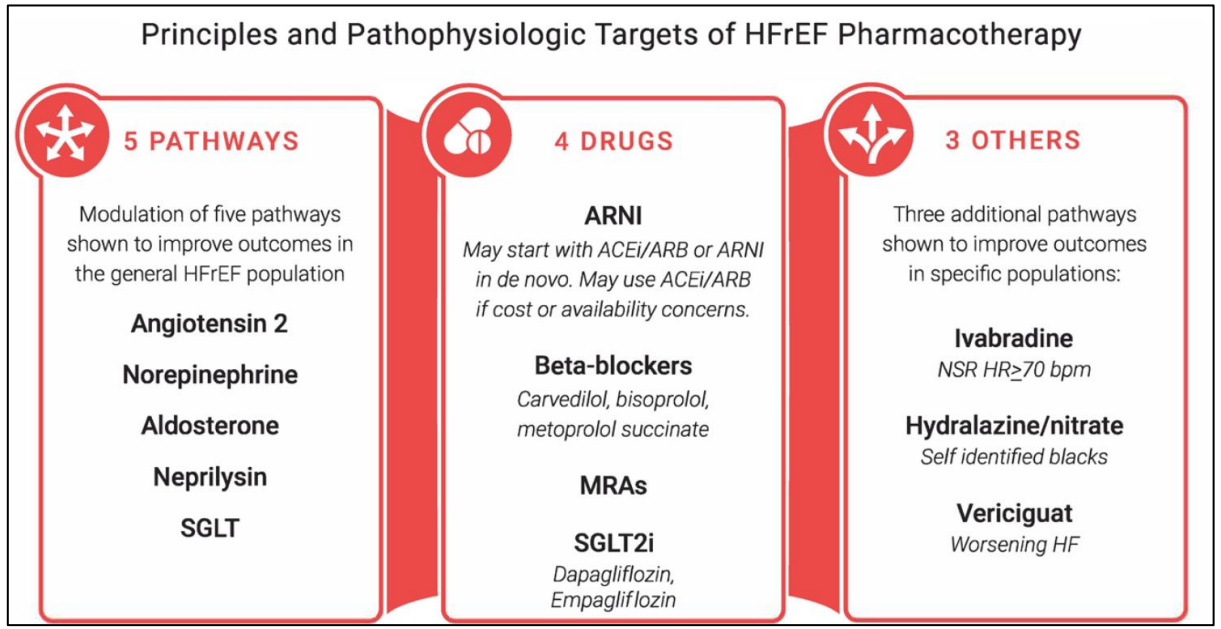




Eur Heart J. 2021;42(36):3599-3726.

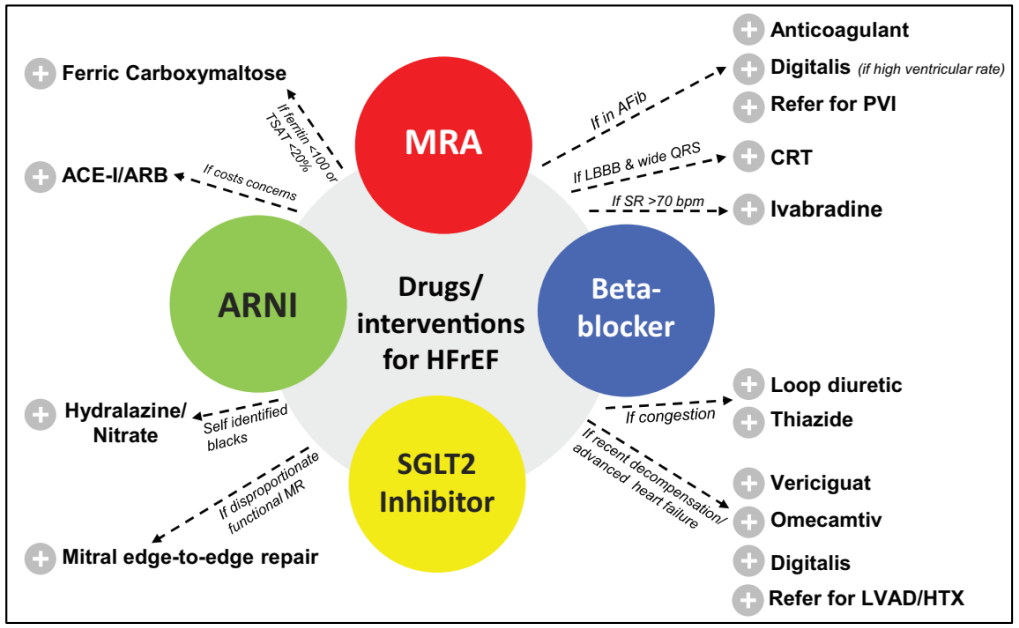
Léčba HFrEF v roce 2023

Victims of Success in Failure



Circulation. 2020;142:1129–1131.

Heart failure drug treatment: the fantastic four



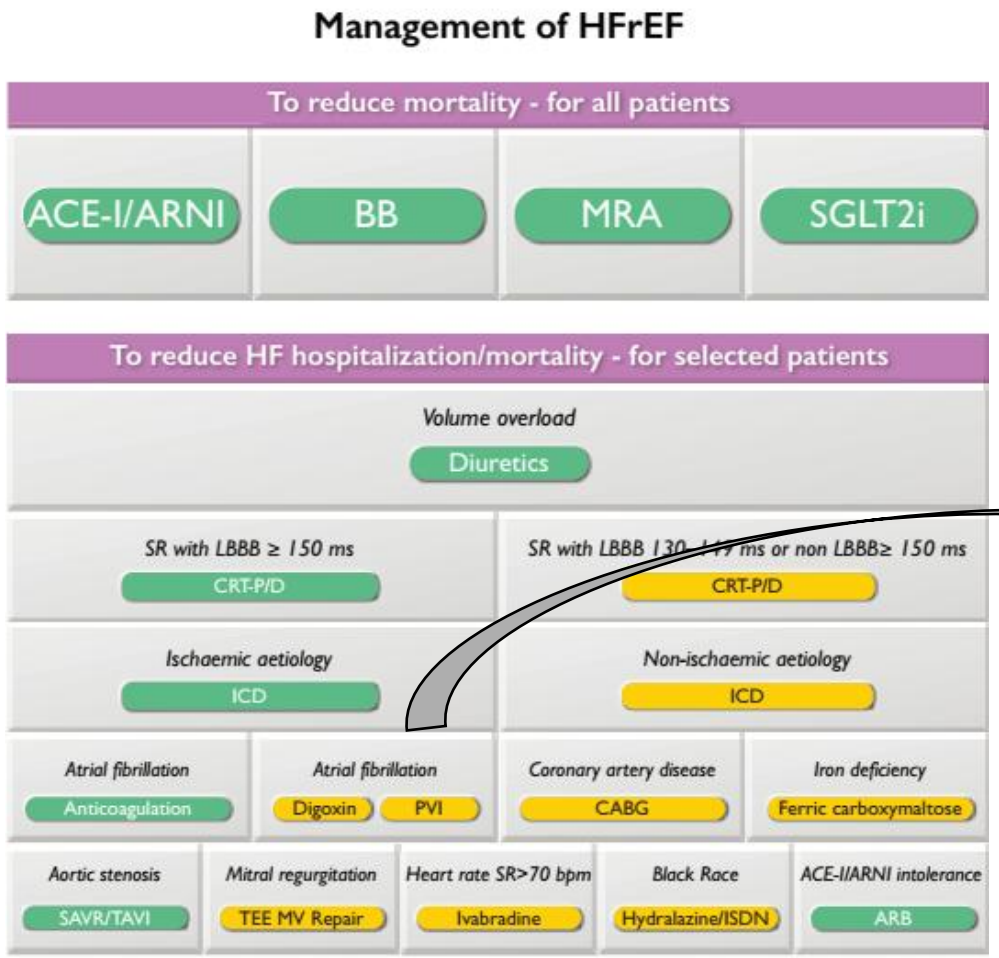
European Heart Journal (2021) **42**, 681–683

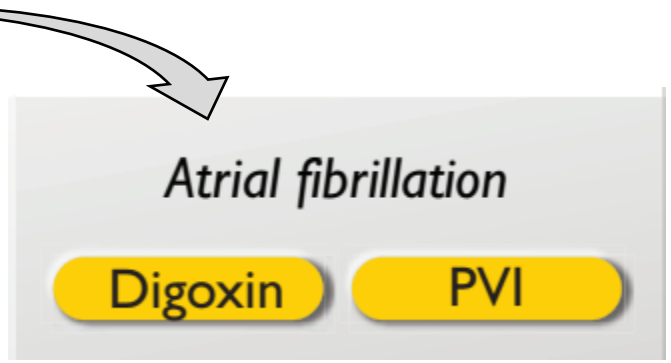
„Děláš-li si nové přátele, nezapomínej na staré.“

Erasmus Rotterdamský

28. říjen 1466 - 12. červenec 1536

Léčba HFrEF v Guidelines





Eur Heart J. 2021;42(36):3599-3726.

Léčba HFrEF v Guidelines

Rate control		
Beta-blockers should be considered for short- and long-term rate control in patients with HF and AF.[535]	IIa	B
Digoxin should be considered when the ventricular rate remains high, despite beta-blockers, or when beta-blockers are contraindicated or not tolerated.[536]	IIa	C

Digoxin		
Digoxin may be considered in patients with symptomatic HFrEF in sinus rhythm despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF hospitalizations).[144]	IIb	B

Eur Heart J. 2021;42(36):3599-3726.

Léčba HFrEF v Guidelines

Rate control		
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Digoxin should be considered when the ventricular rate remains high, despite beta-blockers, or when beta-blockers are contraindicated or not tolerated.[536]	IIa	C

Je redukce hospitalizací „malým cílem“?

Digoxin		
Digoxin may be considered in patients with symptomatic HFrEF in sinus rhythm despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF hospitalizations).[144]	IIb	B

Eur Heart J. 2021;42(36):3599-3726.

Digoxin a rehospitalizace

Digoxin Reduces 30-day All-cause Hospital Admission in Older Patients with Chronic Systolic Heart Failure

Robert C. Bourge, MD,[a] Jerome L. Fleg, MD,[b] Gregg C. Fonarow, MD,[c] John G. F. Cleland, MD,[d] John J. V. McMurray, MD,[e] Dirk J. van Veldhuisen, MD, PhD,[f] Mihai Gheorghiade, MD,[g] Kanan Patel, MBBS, MPH,[a] Inmaculada B. Aban, PhD,[a] Richard M. Allman, MD,[h,a] Connie White-Williams, RN, PhD,[a] Michel White, MD,[i] Gerasimos S. Filippatos, MD, PhD,[j] Stefan D. Anker, MD, PhD,[k] Ali Ahmed, MD, MPH[a,h]

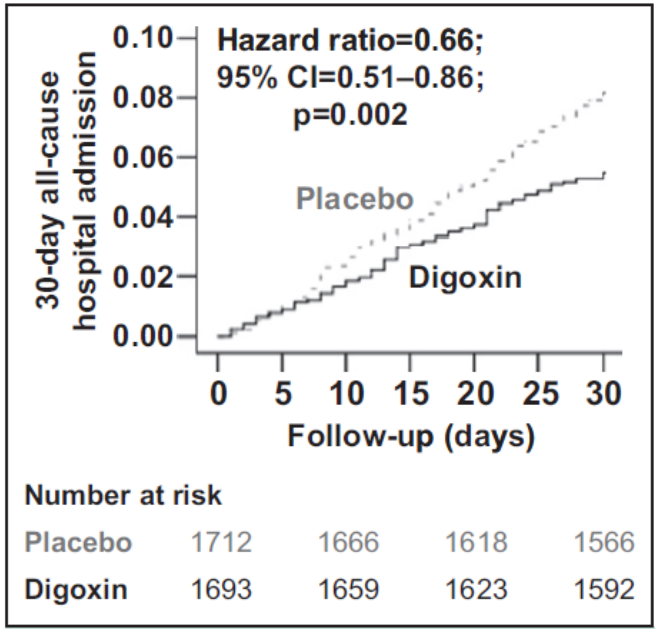


Table 3 Effect of Digoxin on Outcomes During 30 Days After Randomization in All 6800 Ambulatory Patients with Chronic Heart Failure and Reduced Ejection Fraction in the Main Digitalis Investigation Group Trial

	% (events)				
Outcomes	Placebo (n = 3403)	Digoxin (n = 3397)	Absolute Risk Difference* (%)	Hazard Ratio† (95% CI)	*P* Value
30-d all-cause hospitalization	7.9% (270)	5.5% (187)	−2.4	0.69 (0.57-0.83)	<.001
30-d cardiovascular hospitalization	6.1% (209)	3.6% (122)	−2.5	0.58 (0.46-0.72)	<.001
30-d heart failure hospitalization	4.1% (140)	1.6% (55)	−2.5	0.39 (0.29-0.53)	<.001
30-d all-cause mortality	1.1% (36)	0.7% (23)	−0.4	0.64 (0.38-1.08)	.093
30-d cardiovascular mortality	0.9% (32)	0.6% (21)	−0.3	0.66 (0.38-1.14)	.134
30-d heart failure mortality	0.4% (15)	0.1% (5)	−0.3	0.33 (0.12-0.92)	.033
30-d all-cause hospitalization or all-cause mortality	8.5% (288)	6.0% (204)	−2.5	0.70 (0.59-0.84)	<.001

CI = confidence interval.
*Absolute risk differences were calculated by subtracting percent events in patients receiving placebo from those receiving digoxin.
†HRs comparing patients receiving digoxin with those receiving placebo.

The American Journal of Medicine (2013) 126, 701-708

DIG trial

THE EFFECT OF DIGOXIN ON MORTALITY AND MORBIDITY IN PATIENTS WITH HEART FAILURE

THE DIGITALIS INVESTIGATION GROUP*

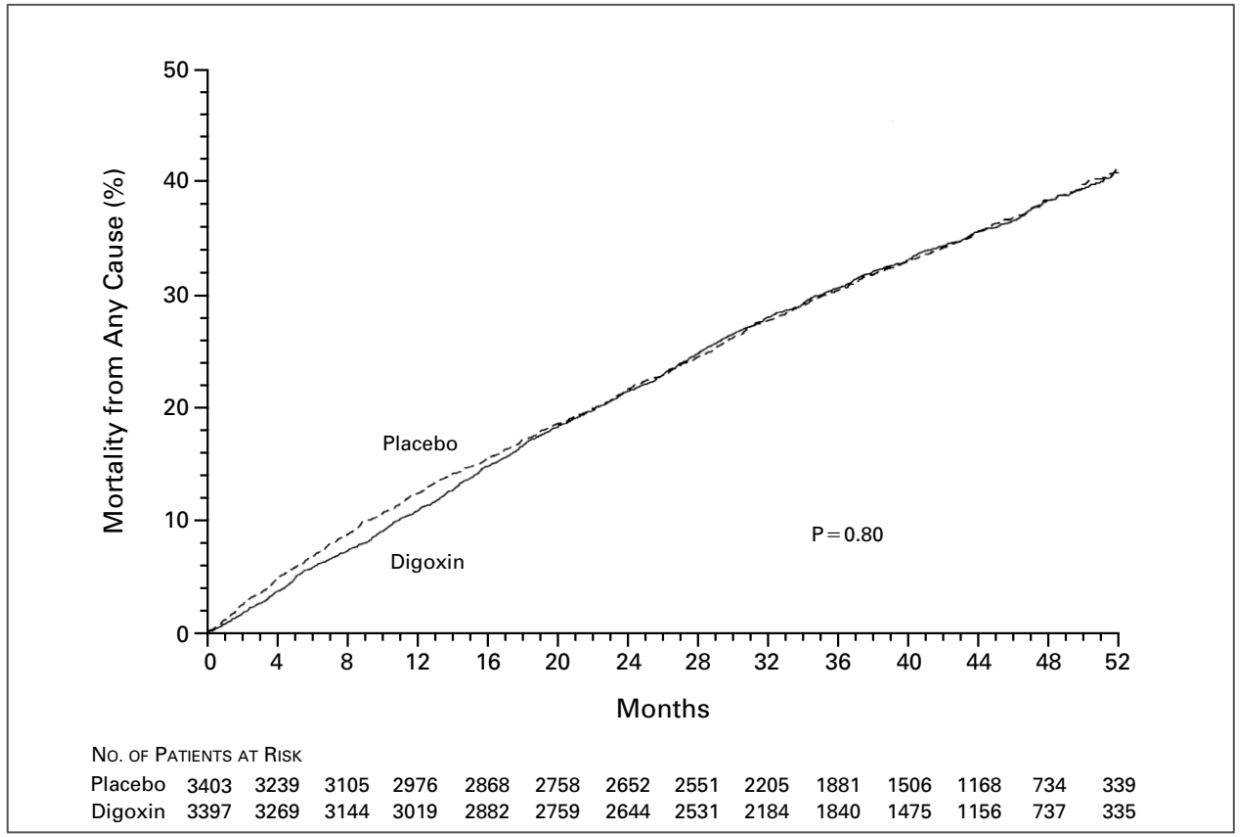
- 6800 nemocných, z nich 5812 mělo EF ≤ 45%
- léčba diuretikum, ACEI, nitráty
- bez betablokátorů!

- Primárním cíle byla celková mortalita.

Concomitant medications		
Diuretics	81.2	82.2
ACE inhibitors	94.1	94.8
Nitrates	42.1	43.1
Other vasodilators§	0.9	1.5

N Engl J Med 1997; 336:525-533

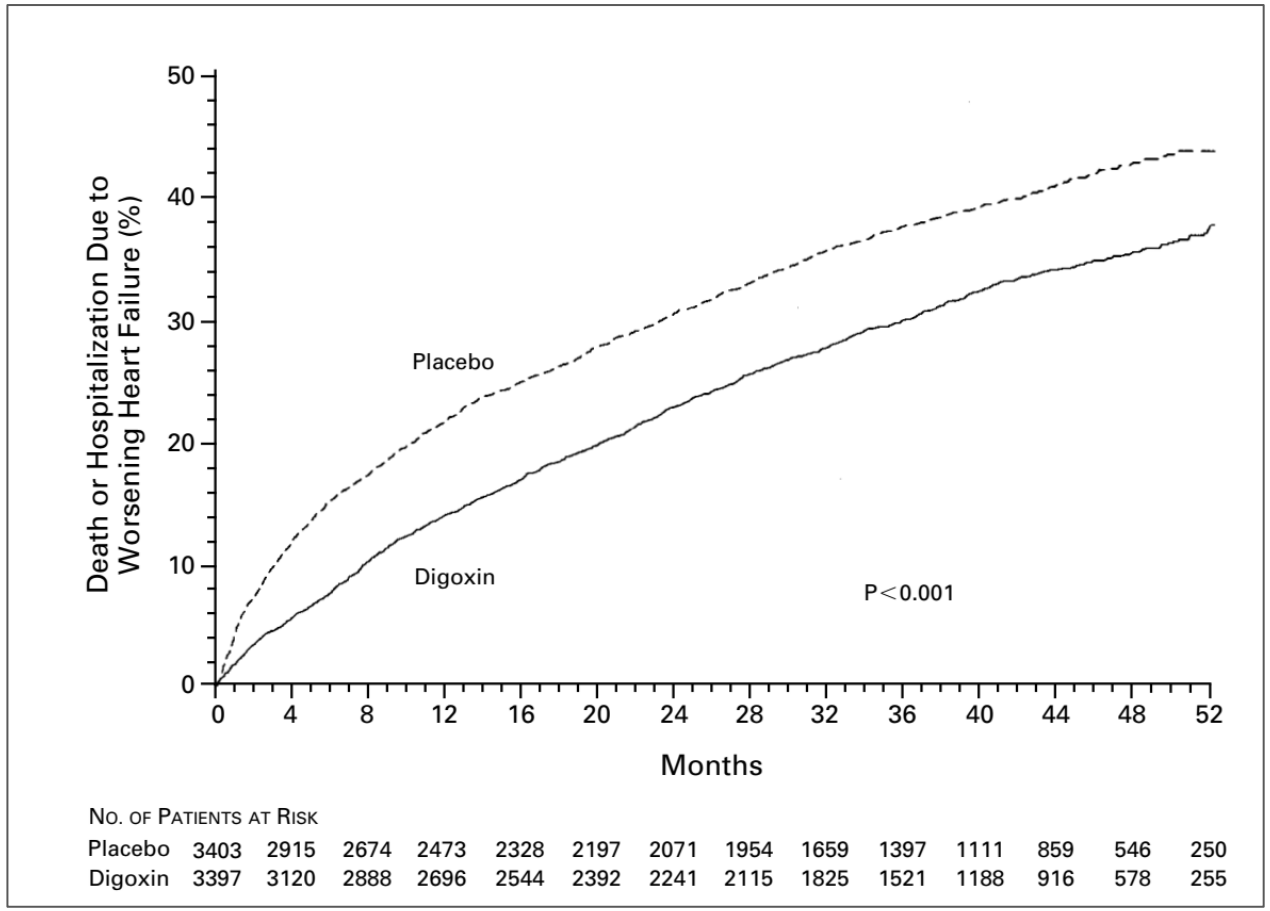
DIG trial



In conclusion, digoxin had no effect on overall mortality in patients receiving diuretics and angiotensin-converting–enzyme inhibitors, but it did reduce the overall number of hospitalizations and the combined outcome of death or hospitalization attributable to worsening heart failure. In clinical practice, digoxin therapy is likely to affect the frequency of hospitalization, but not survival.

N Engl J Med 1997; 336:525-533

DIG trial



(risk ratio, 0.75; 95 percent confidence interval, 0.69 to 0.82; P<0.001)

In conclusion, digoxin had no effect on overall mortality in patients receiving diuretics and angiotensin-converting–enzyme inhibitors, but it did reduce the overall number of hospitalizations and the combined outcome of death or hospitalization attributable to worsening heart failure. In clinical practice, digoxin therapy is likely to affect the frequency of hospitalization, but not survival.

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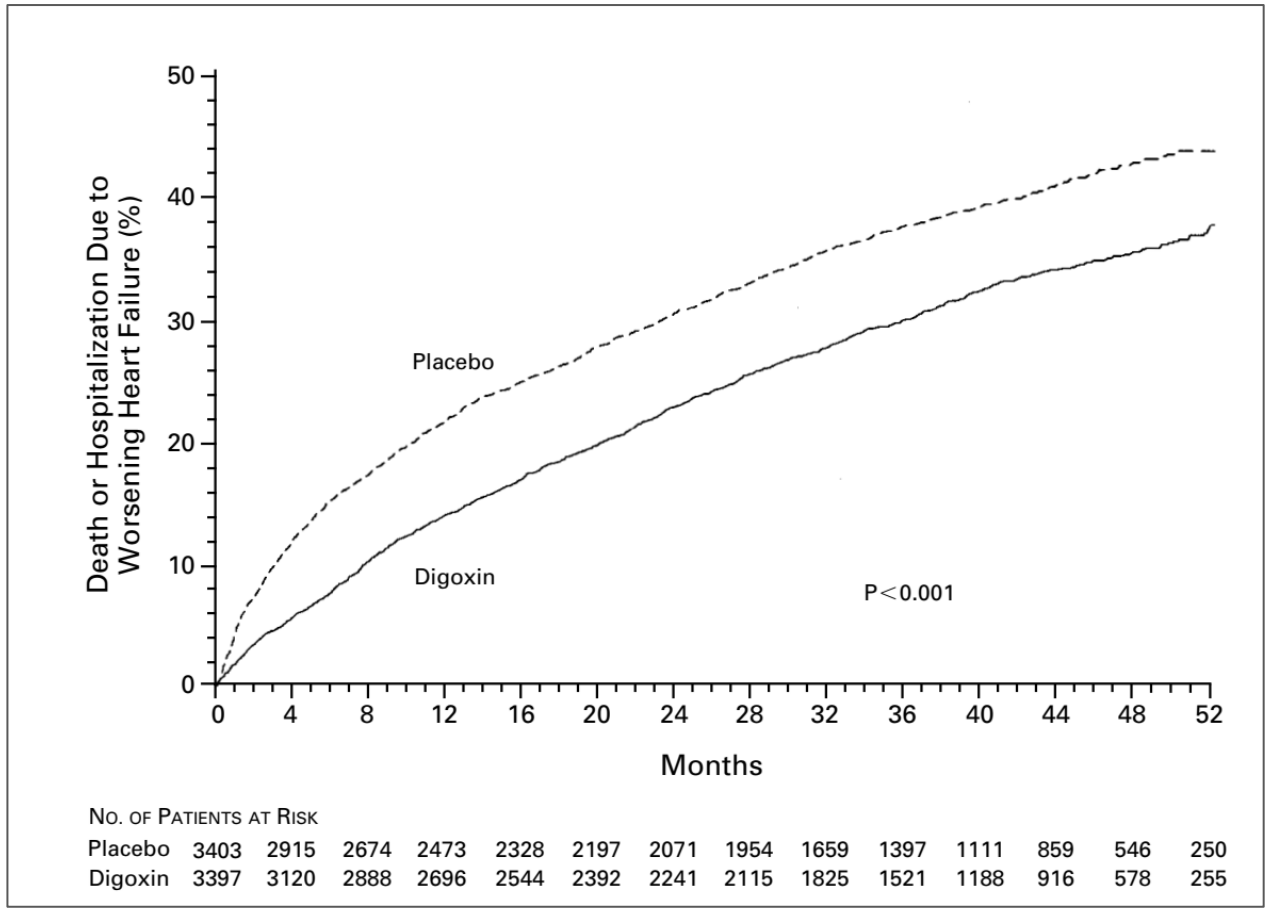
DIG trial



Je to tak bezvýznamný výsledek?

In conclusion, digoxin had no effect on overall mortality in patients receiving diuretics and angiotensin-converting–enzyme inhibitors, but it did reduce the overall number of hospitalizations and the combined outcome of death or hospitalization attributable to worsening heart failure. In clinical practice, digoxin therapy is likely to affect the frequency of hospitalization, but not survival.

N Engl J Med 1997; 336:525-533

Jen pro srovnání…

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

Primary composite outcome — no. (%)				
Death from cardiovascular causes or first hospitalization for worsening heart failure	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

Efficacy outcomes						
Primary composite outcome — no. (%)†	386 (16.3)	11.6	502 (21.2)	15.6	0.74 (0.65 to 0.85)	<0.001
Hospitalization or an urgent visit for heart failure	237 (10.0)	7.1	326 (13.7)	10.1	0.70 (0.59 to 0.83)	NA
Hospitalization for heart failure	231 (9.7)	6.9	318 (13.4)	9.8	0.70 (0.59 to 0.83)	NA
Urgent heart-failure visit	10 (0.4)	0.3	23 (1.0)	0.7	0.43 (0.20 to 0.90)	NA
Cardiovascular death	227 (9.6)	6.5	273 (11.5)	7.9	0.82 (0.69 to 0.98)	NA

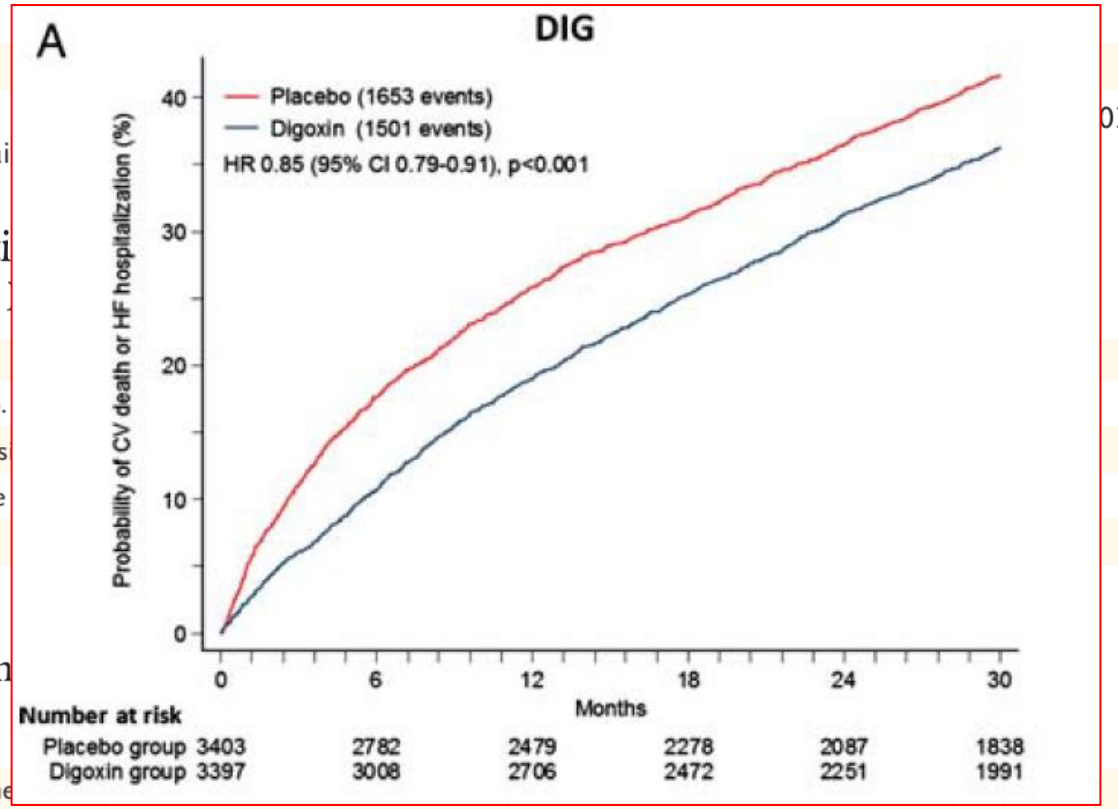
Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

Primary composite outcome — no. (%)	361 (19.4)	15.8	462 (24.7)	21.0	0.75 (0.65 to 0.86)	<0.001
Hospitalization for heart failure	246 (13.2)	10.7	342 (18.3)	15.5	0.69 (0.59 to 0.81)	
Cardiovascular death	187 (10.0)	7.6	202 (10.8)	8.1	0.92 (0.75 to 1.12)	

Jen pro srovnání…

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

Primary composite outcome — no. (%)					
Death from cardiovascular causes or first hospitalization for worsening heart fai				01	



Dapagliflozin in Pati… and Reduced …

Efficacy outcomes					
Primary composite outcome — no.				15.6	0.74 (0.65 to 0.85) <0.001
Hospitalization or an urgent vis				10.1	0.70 (0.59 to 0.83) NA
Hospitalization for heart failure				9.8	0.70 (0.59 to 0.83) NA
Urgent heart-failure visit				0.7	0.43 (0.20 to 0.90) NA
Cardiovascular death				7.9	0.82 (0.69 to 0.98) NA

Cardiovascular an…

Primary composite outcome				21.0	0.75 (0.65 to 0.86) <0.001
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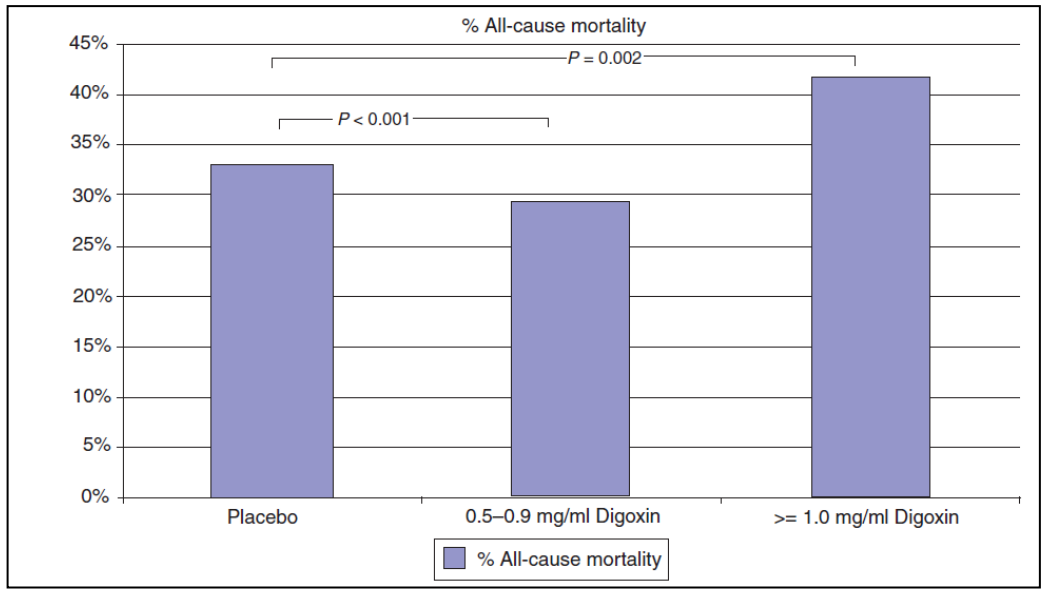
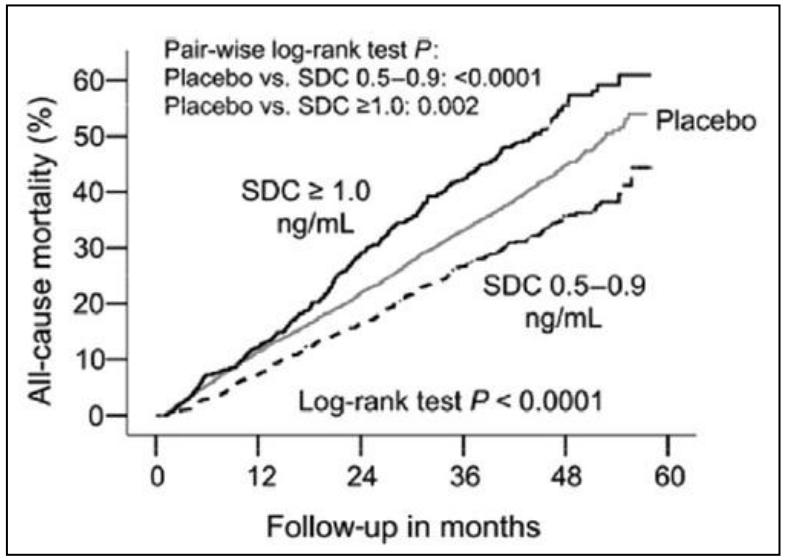
Cardiovascular death	187 (10.0)	7.6	202 (10.8)	8.1	0.92 (0.75 to 1.12)

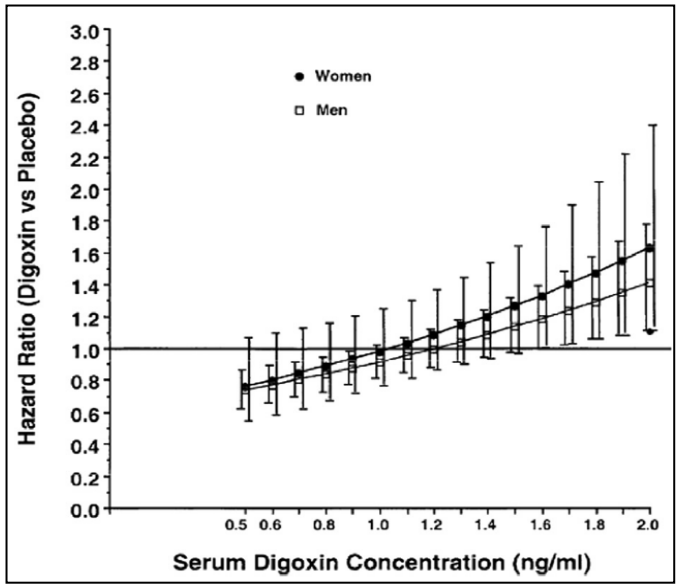
DIG trial

Digoxin for patients with atrial fibrillation and heart failure: paradise lost or not?†

Dirk J. van Veldhuisen[1]*, Isabelle C. Van Gelder[1], Ali Ahmed[2], and Mihai Gheorghiade[3]







European Heart Journal (2013) **34**, 1468–1470

DIG trial

Effect of oral digoxin in high-risk heart failure patients: a pre-specified subgroup analysis of the DIG trial†

Mihai Gheorghiade[1], Kanan Patel[2], Gerasimos Filippatos[3], Stefan D. Anker[4], Dirk J. van Veldhuisen[5], John G.F. Cleland[6], Marco Metra[7], Inmaculada B. Aban[2], Stephen J. Greene[1], Kirkwood F. Adams[8], John J.V. McMurray[9], and Ali Ahmed[2,10]*

- EF < 25%
- NYHA III-IV
- CT-ratio > 55%

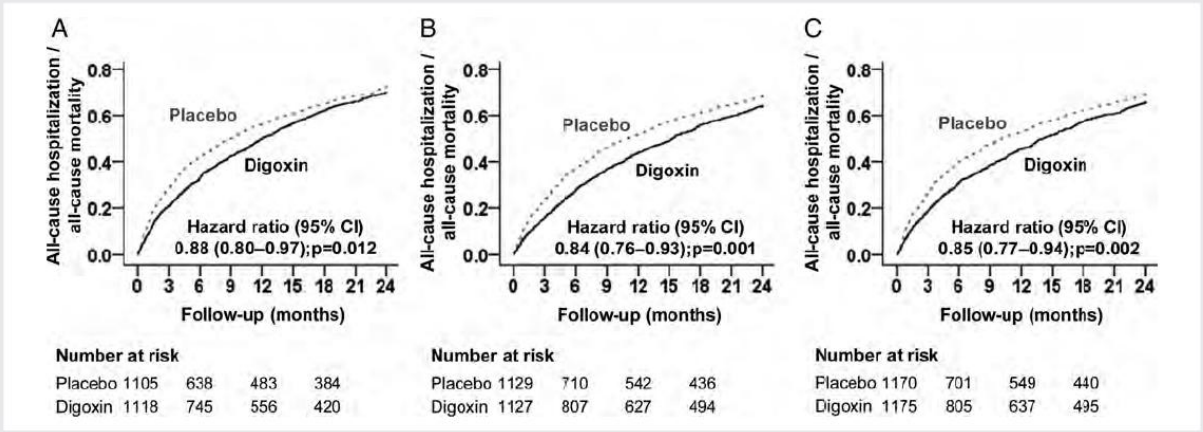


Figure 2 Kaplan–Meier plots for all-cause mortality or all-cause hospitalization by treatment groups in high-risk patients with chronic heart failure (HF) in the DIG trial: (*A*) NYHA class III–IV, (*B*) LVEF <25%, and (*C*) cardiothoracic ratio >55%. CI, confidence interval.

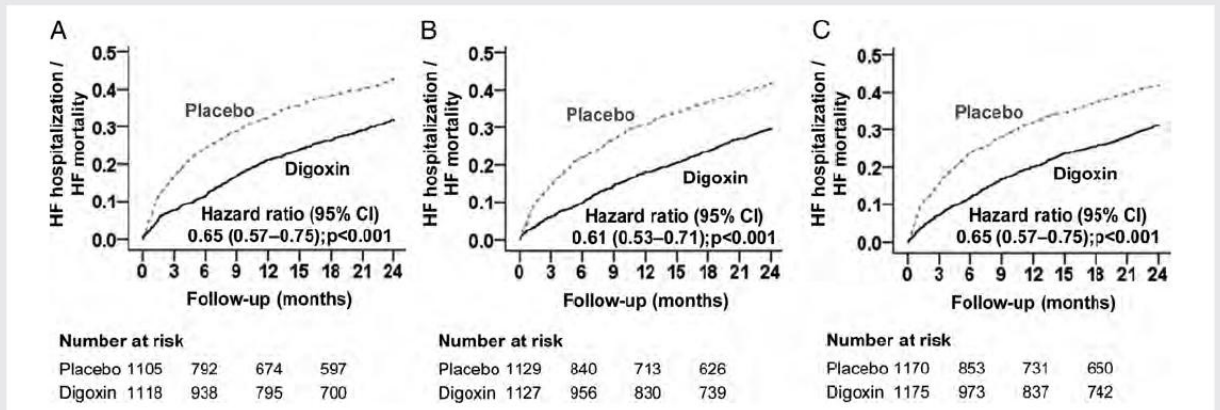


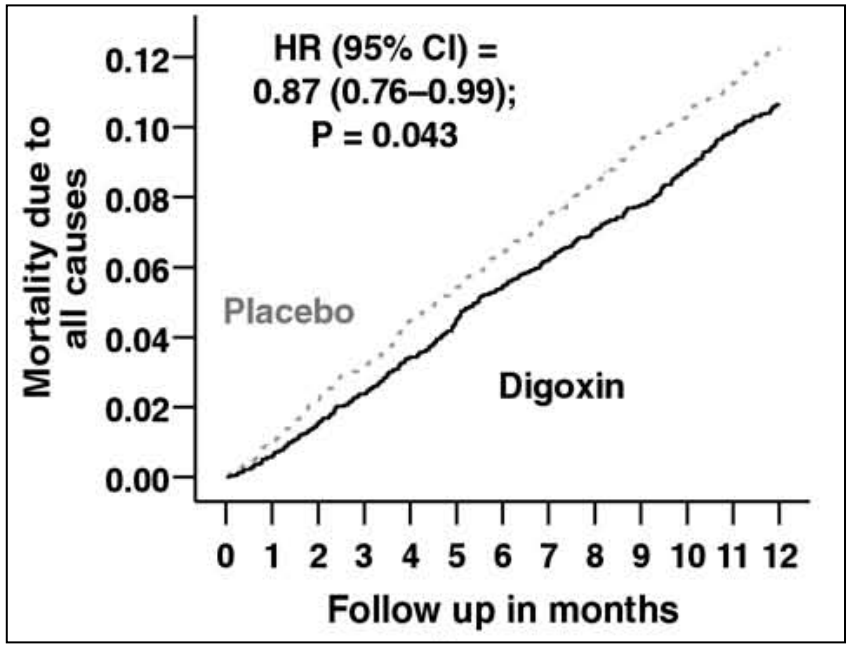
Figure 1 Kaplan–Meier plots for heart failure (HF) mortality or HF hospitalization by treatment groups in high-risk patients with chronic HF in the DIG trial: (*A*) NYHA class III–IV, (*B*) LVEF <25%, and (*C*) cardiothoracic ratio >55%. CI, confidence interval.

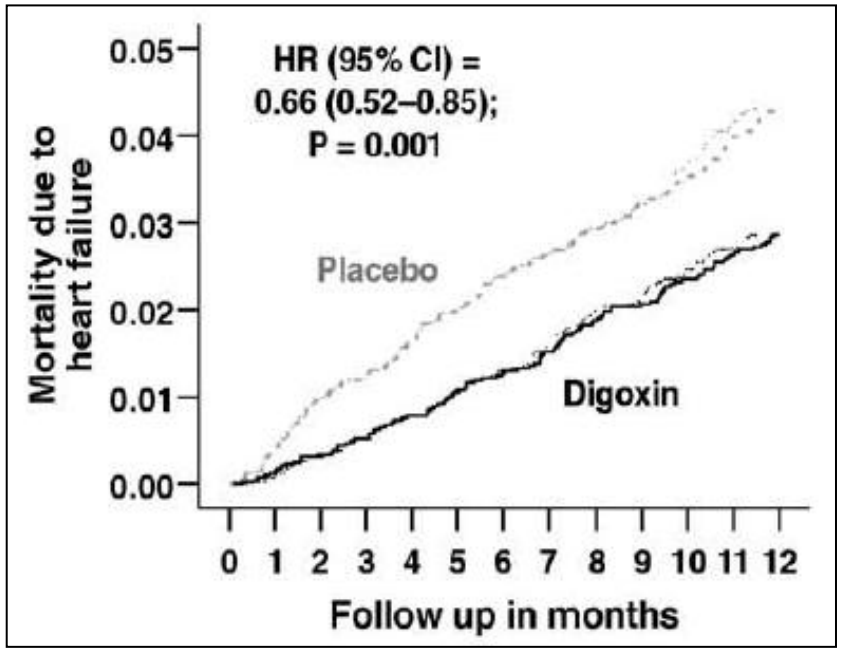
DIG trial

Effectiveness of Digoxin in Reducing One-Year Mortality in Chronic Heart Failure in the Digitalis Investigation Group Trial

Ali Ahmed, MD, MPH[a,b,*], Finn Waagstein, MD[c], Bertram Pitt, MD[d], Michel White, MD[e], Faiez Zannad, MD, PhD[f], James B. Young, MD[g], and Shahbudin H. Rahimtoola, MD[h]

- **Pokud zkrátíme follow-up na 1 rok…**
- **Řada nemocných v placebové větvi začala užívat digoxin**
- **Dlouhodobá expozice a progrese onemocnění vedly k vzestupu hladin DIG a tím k vyššímu riziku NÚ**



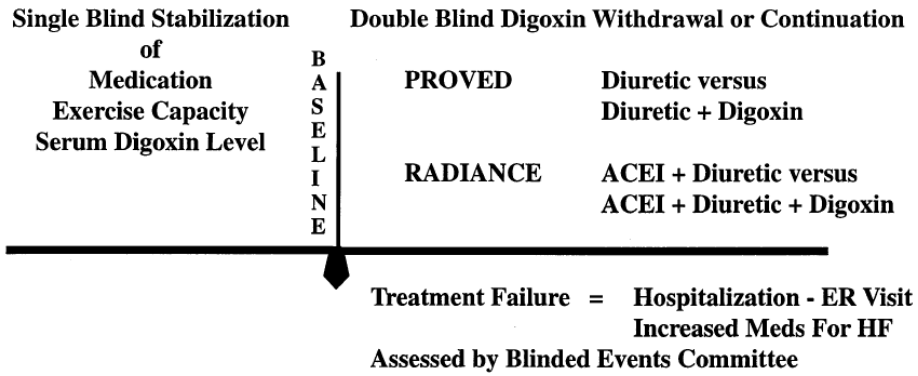


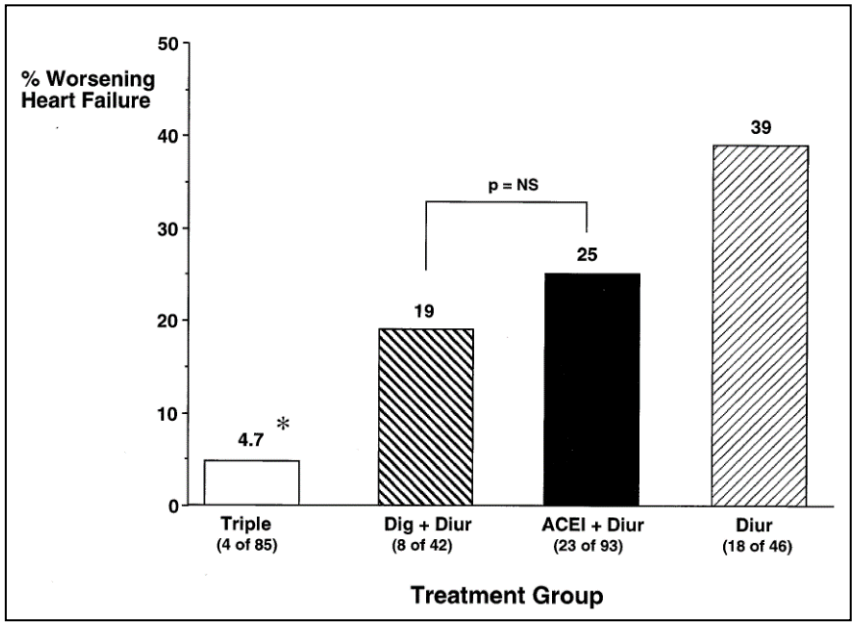
Am J Cardiol 2009;103:82–87

Vysazení digoxinu u stabilních nemocných

Superiority of "Triple" Drug Therapy in Heart Failure: Insights from the PROVED and RADIANCE Trials

JAMES B. YOUNG, MD, FACC,* MIHAI GHEORGHIADE, MD, FACC,†
BARRY F. URETSKY, MD, FACC,‡ J. HERBERT PATTERSON, PHARMD,§
KIRKWOOD F. ADAMS, JR., MD, FACC‖





Závěry: vysazení digoxinu u původně stabilních jedinců s HFrEF je spojeno s vyšším rizikem progrese srdečního selhání, sníženou tolerancí námahy, poklesem LVEF a vzestupem tepové frekvence

Vysazení léčby srdečního selhání

Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial

Brian P Halliday, Rebecca Wassall, Amrit S Lota, Zohya Khalique, John Gregson, Simon Newsome, Robert Jackson, Tsveta Rahneva, Rick Wage, Gillian Smith, Lucia Venneri, Upasana Tayal, Dominique Auger, William Midwinter, Nicola Whiffin, Ronak Rajani, Jason N Dungu, Antonis Pantazis, Stuart A Cook, James S Ware, A John Baksi, Dudley J Pennell, Stuart D Rosen, Martin R Cowie, John G F Cleland, Sanjay K Prasad

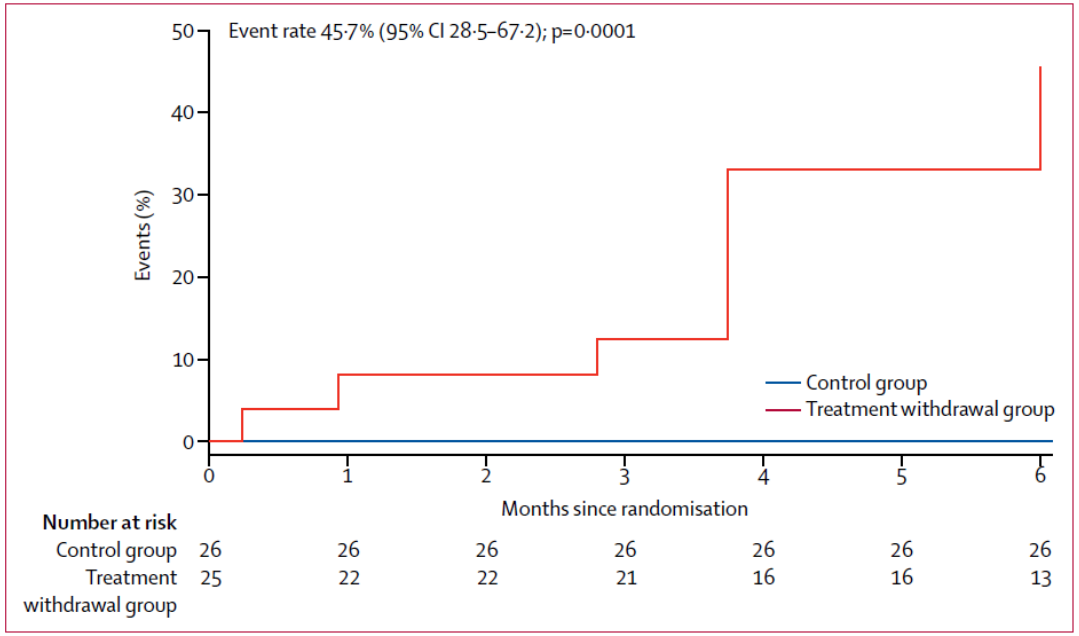


Figure 3: Kaplan-Meier curve of time to primary endpoint in randomised phase, according to treatment group

- **během prvních 6 měsíců 11 z 25 pts randomizovaných k ukončení léčby dosáhlo endpointu, zatímco ten se neobjevil u žádného z pokračujících v léčbě (Kaplan-Meier event rate 45.7%; p=0,0001)**
- **po 6 měsících 25 z 26 původně pokračujících ukončilo léčbu, u 9 z nich se objevil endpoint (Kaplan-Meier event rate 36.0%)**

Lancet 2019; 393: 61–73

Vysazení léčby srdečního selhání

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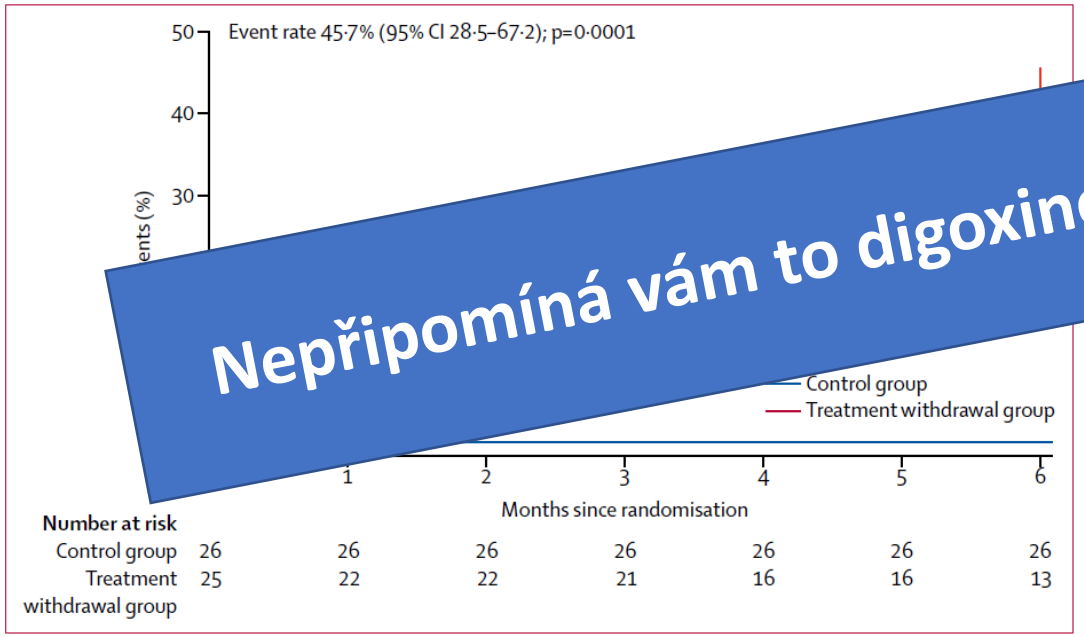


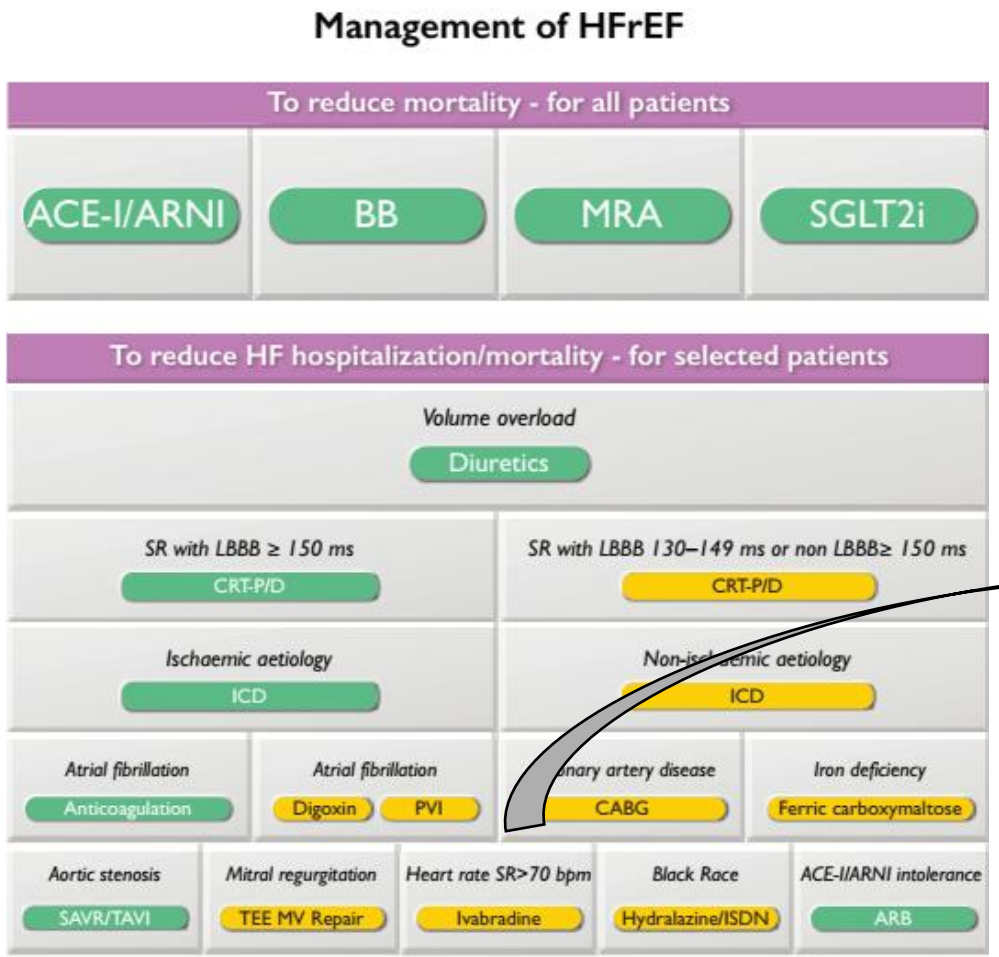
Figure 3: Kaplan-Meier curve of time to primary endpoint in randomised phase, according to treatment group

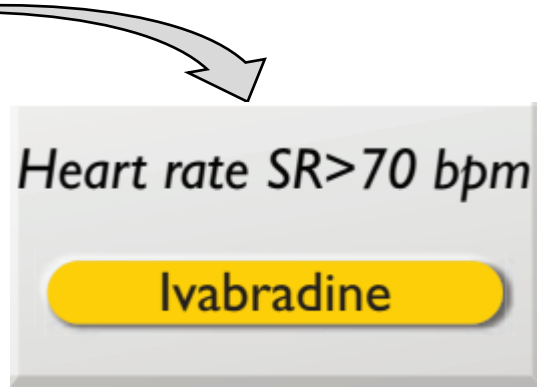
Nepřipomíná vám to digoxinovou story ze studií Proved a Radiance?

- **bě… …ých**
  …mico ten se
  …kračujících v léčbě (Kaplan-
  …nt rate 45.7%; p=0,0001)
- **po 6 měsících 25 z 26 původně pokračujících ukončilo léčbu, u 9 z nich se objevil endpoint (Kaplan-Meier event rate 36.0%)**

Lancet 2019; 393: 61–73

Léčba HFrEF v Guidelines



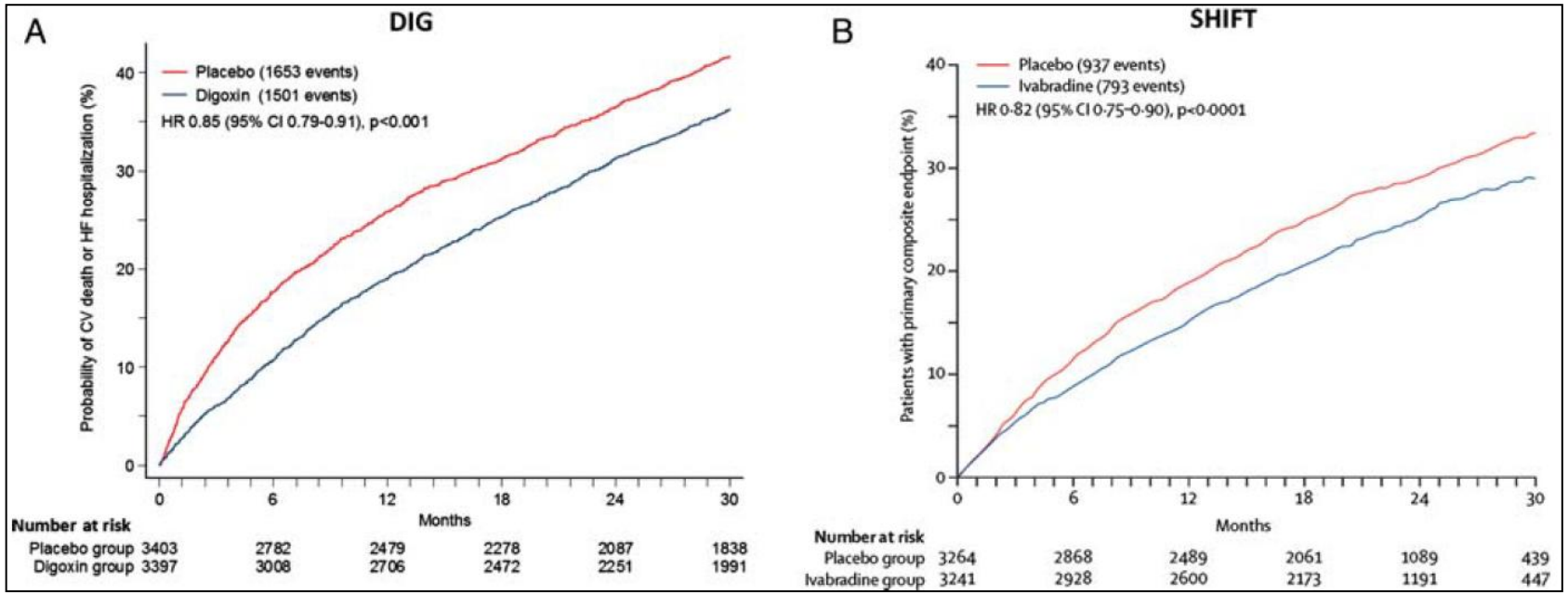


Eur Heart J. 2021;42(36):3599-3726.

Digoxin vs ivabradin

Should we SHIFT our thinking about digoxin? Observations on ivabradine and heart rate reduction in heart failure

Davide Castagno[1], Mark C. Petrie[2], Brian Claggett[3], and John McMurray[4]*



Methods and results In this short commentary, we retrospectively analyse the Digitalis Investigation Group (DIG) Trial looking at the primary composite endpoint used in SHIFT (i.e. cardiovascular death or hospital admission for worsening heart failure) and compare the effect of digoxin on this endpoint with that of ivabradine. A remarkably similar risk reduction in the composite outcome and in its components appears evident among patients receiving the active treatment in both studies (although ivabradine was added to a beta-blocker, whereas digoxin was not).

Conclusions This raises the question of whether the Cardiological community dismissed digoxin too readily and if we should re-appraise its potential role in the treatment of heart failure.

European Heart Journal (2012) **33**, 1137–1141

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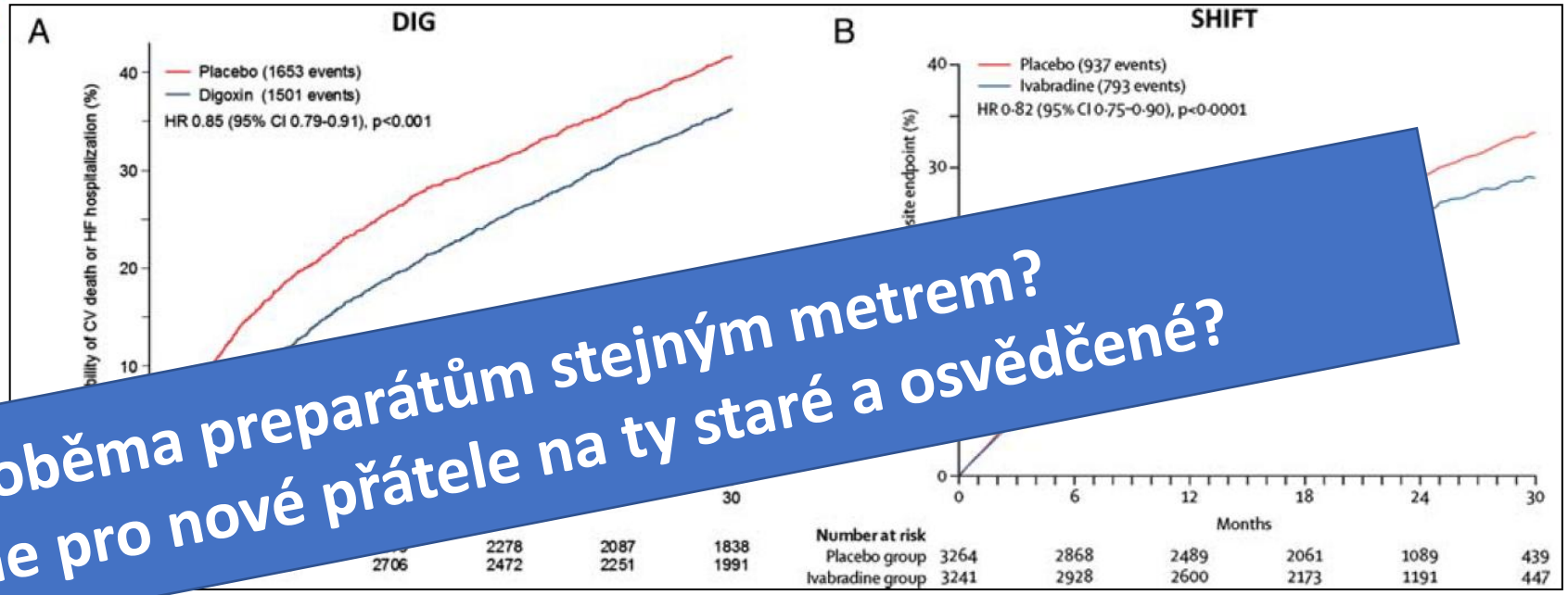

Měříme oběma preparátům stejným metrem?
Nezapomínáme pro nové přátele na ty staré a osvědčené?

Method and resu

…spectively analyse the Digitalis Investigation Group (DIG) Trial looking at the …endpoint used in SHIFT (i.e. cardiovascular death or hospital admission for worsening heart …ure) and compare the effect of digoxin on this endpoint with that of ivabradine. A remarkably similar risk reduction in the composite outcome and in its components appears evident among patients receiving the active treatment in both studies (although ivabradine was added to a beta-blocker, whereas digoxin was not).

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European Heart Journal (2012) **33**, 1137–1141

Digoxin je stále vzrušující téma…

Digoxin for patients with atrial fibrillation and heart failure: paradise lost or not?†

Dirk J. van Veldhuisen[1]*, Isabelle C. Van Gelder[1], Ali Ahmed[2], and Mihai Gheorghiade[3]

while in DIG no beta-blockers were used. Therefore, digoxin in patients with HF may still have a place, not as an inotropic drug, because for these drugs paradise is 'lost',[20] but as a neurohormonal modulator, when given in low doses. Indeed, low-dose digoxin may still be useful, but trials examining this question are urgently needed.

European Heart Journal (2013) **34**, 1468–1470

Něco na obranu digoxinu před prof. Linhartem…

Digoxin: beneficial or harmful?

Gianluigi Savarese* and Lars H. Lund

Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

ers. Thus, although alarming, the evidence of increased mortality associated with digitalis in observational and post-hoc studies cannot be used to decide whether digitalis may still have a place in HF or AF, but points out the urgency of randomized clinical trials to address this question.

European Heart Journal - Cardiovascular Pharmacotherapy (2017) **3**, 127–128

Why is the use of digitalis withering?
Another reason that we need medical heart failure specialists

Milton Packer*

Digitalis should always be prescribed under specialist supervision.

- **Zásadní je zohlednění lékových interakcí spojených se zvýšením SDC (bezpečné rozmezí je 0,5-0,9 ng/ml), resp. precipitujících faktorů zvýšeného rizika arytmií (např. hypokalemie)**
- **např. v post-hoc analýze studie AFFIRM (kde byl digoxin spojen s vyšším relativním rizikem mortality) bylo doporučeno udržovat SDC ≥ 1,0 ng/ml**

European Journal of Heart Failure (2017)
doi:10.1002/ejhf.1043

Závěry

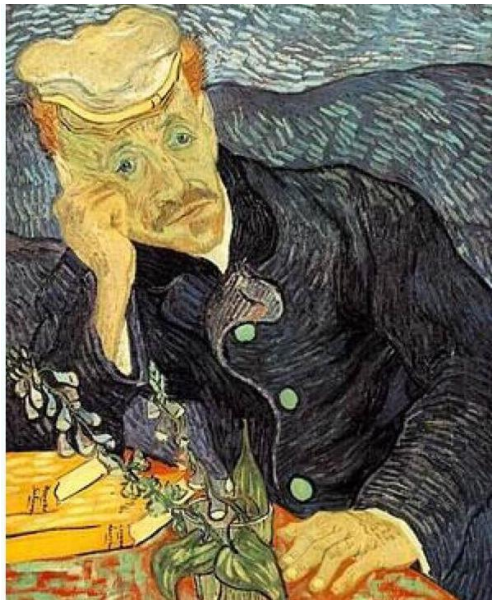
- Digoxin je velmi starý a obyčejný lék, jehož používání není vzhledem k jeho úzkému terapeutickému oknu úplně jednoduché.
- Nicméně pokud je využíván s rozvahou a poučeně, může i v nynější době přinést řadě nemocných významné benefity, zejména v situacích, kdy převládnou důvody pro redukci symptomů nad snahou o zlepšení prognózy.
- Základním handicapem pro posouzení jeho významu je skutečnost, že nemá data z prospektivních klinických studií v éře současné farmakologické i nefarmakologické léčby.

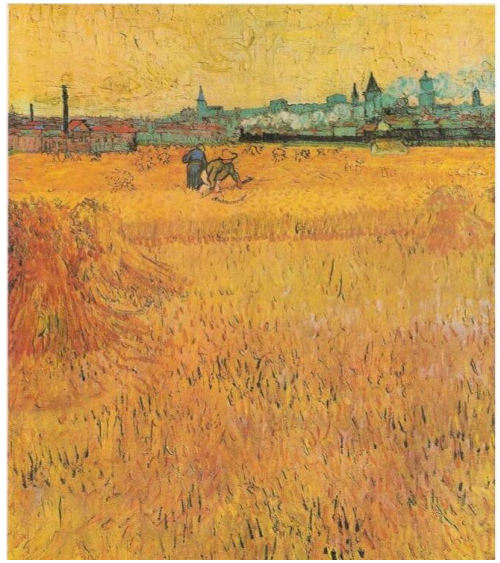
Závěry

- Retrospektivní hodnocení mohou trpět skutečností, že k digoxinu často sáhneme až v bezvýchodných stavech, kdy nám už nezbývají jiné terapeutické možnosti.

- Na vlastní oči jsem viděl desítky nemocných, jimž nasazení digoxinu pomohlo a další desítky těch, jimž jeho vysazení neprospělo.

- Digoxin není lékem pro všechny nemocné se srdečním selháním, ale nevylijme s vaničkou i dítě…





Děkuji za pozornost!