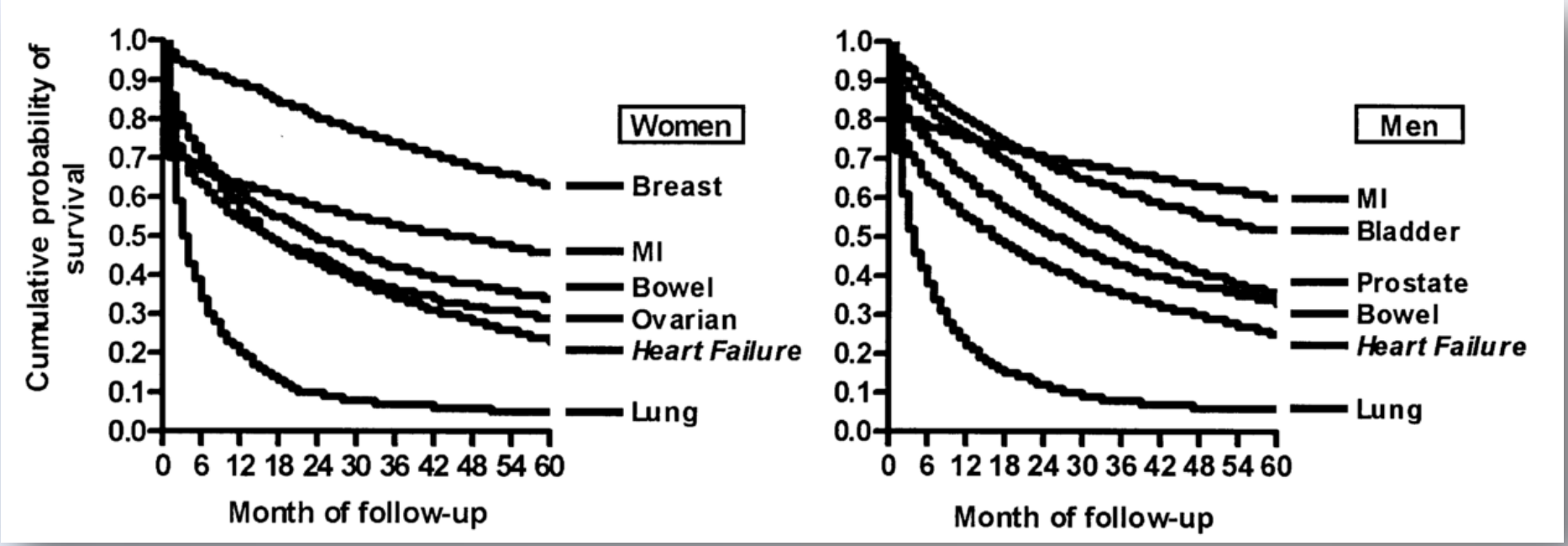
CRT:
jak minimalizovat riziko chybění odpovědi?

Kamil Sedláček

Klinika kardiologie IKEM
Praha

Prognóza HF v roce 1991
bez komplexní současné EBM



Stewart S, MacIntyre K, Hole DJ, Capewell S and McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. *European journal of heart failure. 2001;3:315-22.*

Typický začátek článku o CRT

CRT je účinnou léčbou pro pacienty se srdečním selháním a dysynchronií stahu levé komory.

Zlepšuje symptomy, výkonnost a vede k reverzní remodelaci.

Dále snižuje morbiditu a mortalitu srdečního selhání.

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Přesto asi 30 % pacientů léčených CRT neodpovídá na tuto terapii podle očekávání.

EBM - CRT

Trial (ref)	No.	Design	NYHA	LVEF	QRS	Primary endpoints	Secondary endpoints	Main findings
MUSTIC-SR[52]	58	Single-blinded, crossover, randomized CRT vs. OMT, 6 months	III	<35%	≥150	6MWD	NYHA class, QoL, peak VO_2 LV volumes, MR hospitalizations, mortality	CRT-P improved 6MWD, NYHA class, QoL, peak VO_2, reduced LV volumes and MR and reduced hospitalizations
PATH-CHF[51]	41	Single-blinded, crossover, randomized RV vs. LV vs. BiV, 12 months	III–IV	NA	≥150	Peak VO_2, 6MWD	NYHA class, QoL hospitalizations	CRT-P improved NYHA class, QoL and 6MWD and reduced hospitalizations
MIRACLE[49]	453	Double-blinded, randomized CRT vs. OMT, 6 months	III–IV	≤35%	≥130	NYHA class, 6MWD , QoL	Peak VO_2 LVEDD, LVEF, MR clinical composite response	CRT-P improved NYHA class, QoL and 6MWD and reduced LVEDD, MR and increased LVEF
MIRACLE-ICD[54]	369	Double-blinded, randomized CRT-D vs. ICD, 6 months	III–IV	≤35%	≥130	NYHA class, 6MWD , QoL	Peak VO_2 LVEDD, LVEF, MR clinical composite response	CRT-D improved NYHA class, QoL, peak VO_2
CONTAK-CD[53]	490	Double-blinded randomized CRT-D vs. ICD, 6 months	II–III–IV	≤35%	≥120	NYHA class, 6MWD , QoL	LV volume, LVEF composite of mortality, VT/VF, hospitalizations	CRT-D improved 6MWD, NYHA class, QoL, reduced LV volume and increased LVEF
MIRACLE-ICD II[60]	186	Double-blinded, randomized CRT-D vs. ICD, 6 months	II	≤35%	≥130	Peak VO_2	VE/VCO_2, NYHA, QoL, 6MWD, LV volumes and EF, composite clinical endpoint	CRT-D improved NYHA, VE/CO_2 and reduced LV volumes and improved LVEF
COMPANION[55]	1520	Double-blinded randomized OMT vs. CRT-P / or vs. CRT-D, 15 months	III–IV	≤35%	≥120	All-cause mortality or hospitalization	All-cause mortality, cardiac mortality	CRT-P and CRT-D reduced all-cause mortality or hospitalization
CARE-HF[56]	813	Double-blinded randomized OMT vs. CRT-P 29.4 months	III–IV	≤35%	≥120	All-cause mortality or hospitalization	All-cause mortality, NYHA class, QoL	CRT-P reduced all-cause mortality and hospitalization and improved NYHA class and QoL
REVERSE[61]	610	Double-blinded, randomized CRT-ON vs. CRT-OFF, 12 months	I–II	≤40%	≥120	% worsened by clinical composite endpoint	LVESV index, heart failure hospitalizations and all-cause mortality	CRT-P/CRT-D did not change the primary endpoint and did not reduce all-cause mortality but reduced LVESV index and heart failure hospitalizations.
MADIT-CRT[50]	1820	Single-blinded, randomized CRT-D vs. ICD, 12 months	I–II	≤30%	≥130	All-cause mortality or heart failure hospitalizations	All-cause mortality and LVESV	CRT-D reduced the endpoint heart failure hospitalizations or all-cause mortality and LVESV. CRT-D did not reduced all-cause mortality
RAFT[62]	1798	Double-blinded, randomized CRT-D vs. ICD 40 months	II–III	≤30%	≥120	All-cause mortality or heart failure hospitalizations	All-cause mortality and cardiovascular death	CRT-D reduced the endpoint all-cause mortality or heart failure hospitalizations. In NYHA III, CRT-D only reduced significantly all-cause mortality

Brignole M et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy *Eur Heart J. 2013;34:2281-329.*

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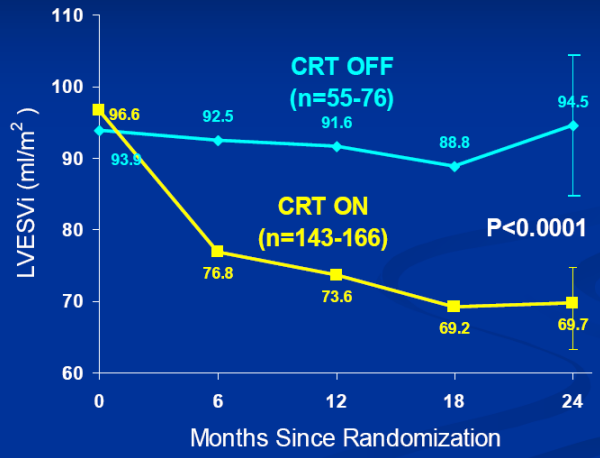
REVERSE Clinical Trial

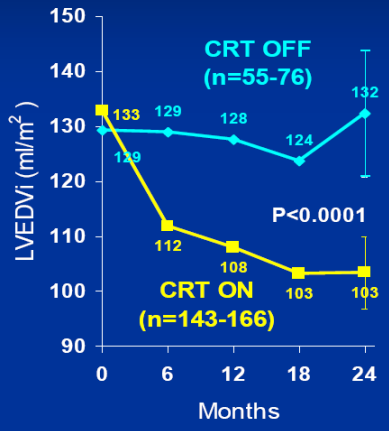
Powered Secondary End Point: LVESVi

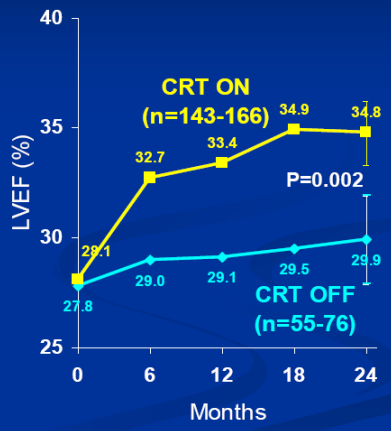


P-value compares 24-month changes. All patients with data are included at each time point.

REVERSE Clinical Trial

LVEDVi and LVEF

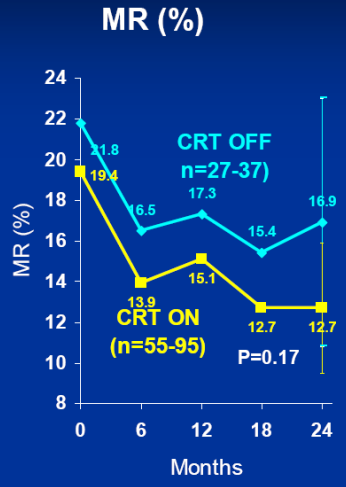


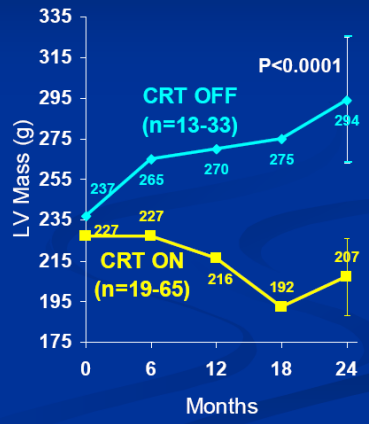


P-values compare 24-month changes.

REVERSE Clinical Trial

MR and LV mass

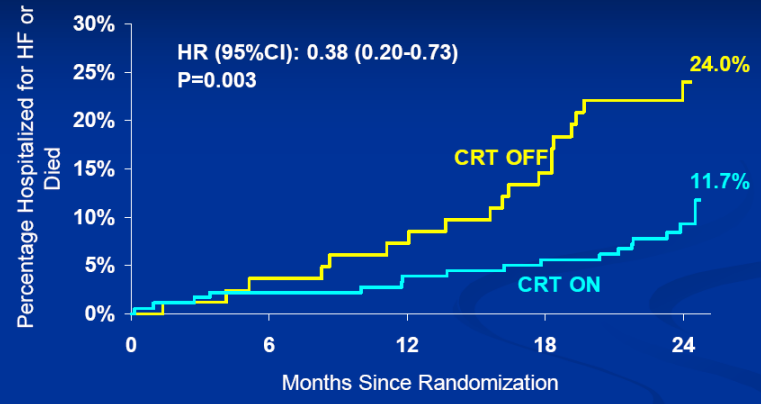




P-values compare 24-month changes.

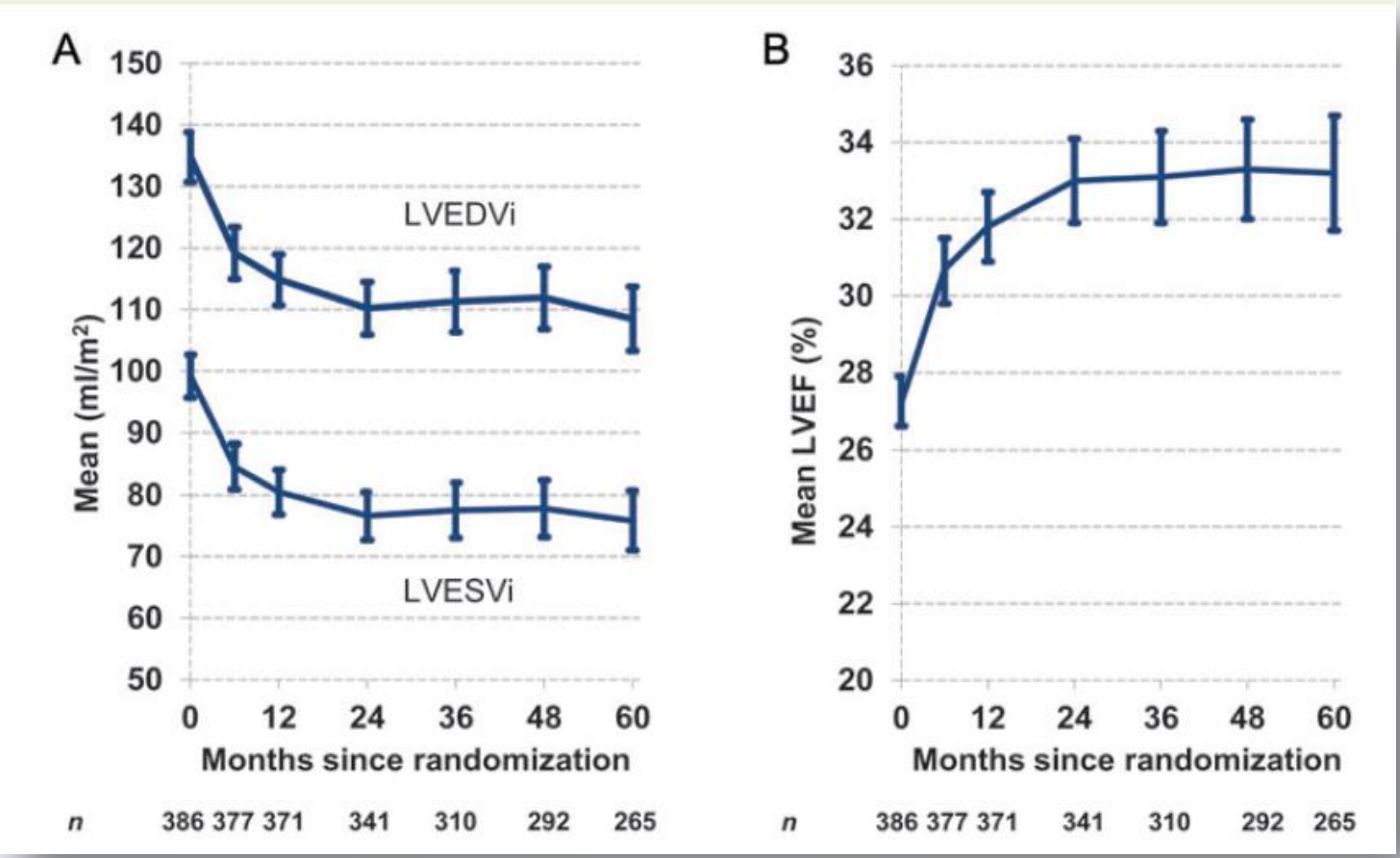
REVERSE Clinical Trial

Time to First HF Hospitalization or Death



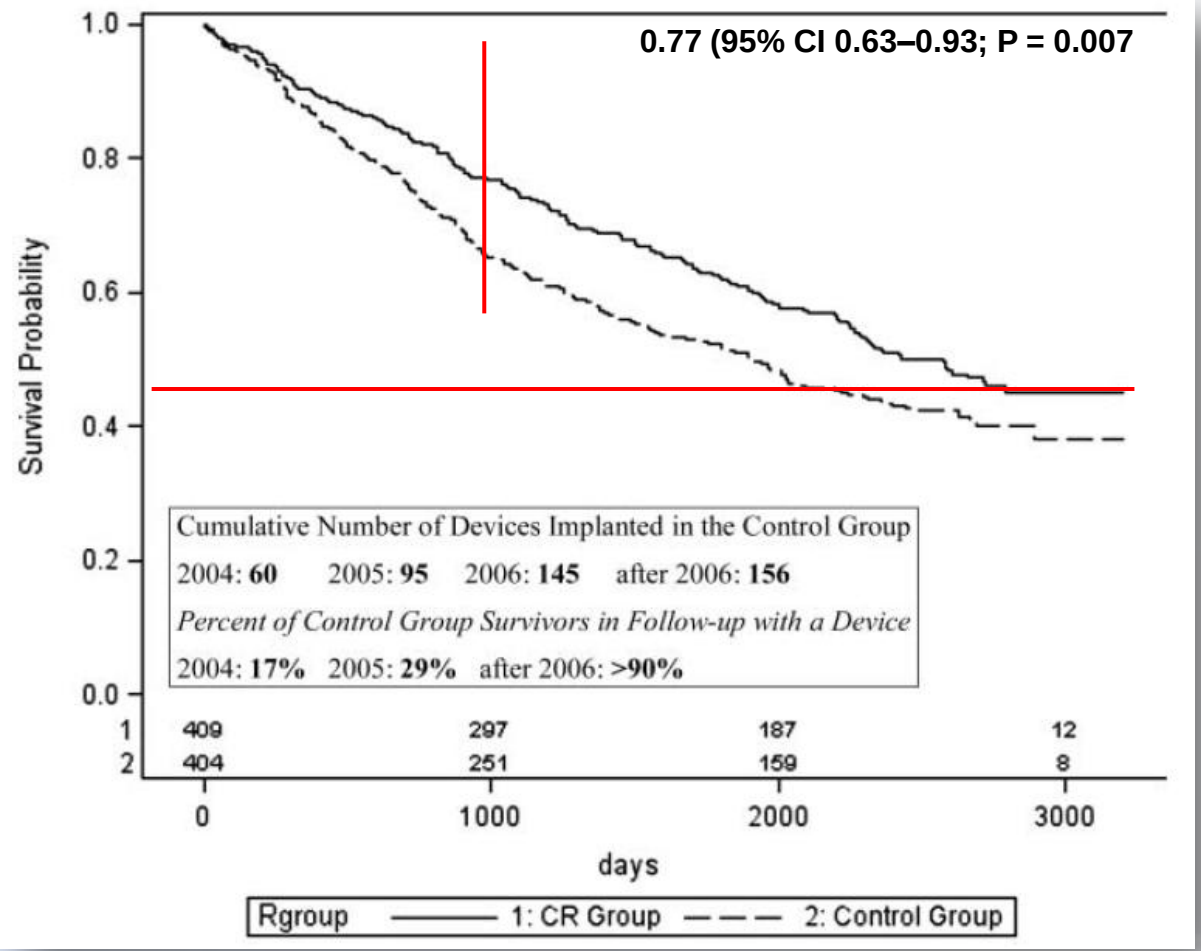
Number at Risk					
CRT OFF	82	79	76	70	39
CRT ON	180	176	173	168	77

Dlouhodobý (5-letý) efekt CRT REVERSE



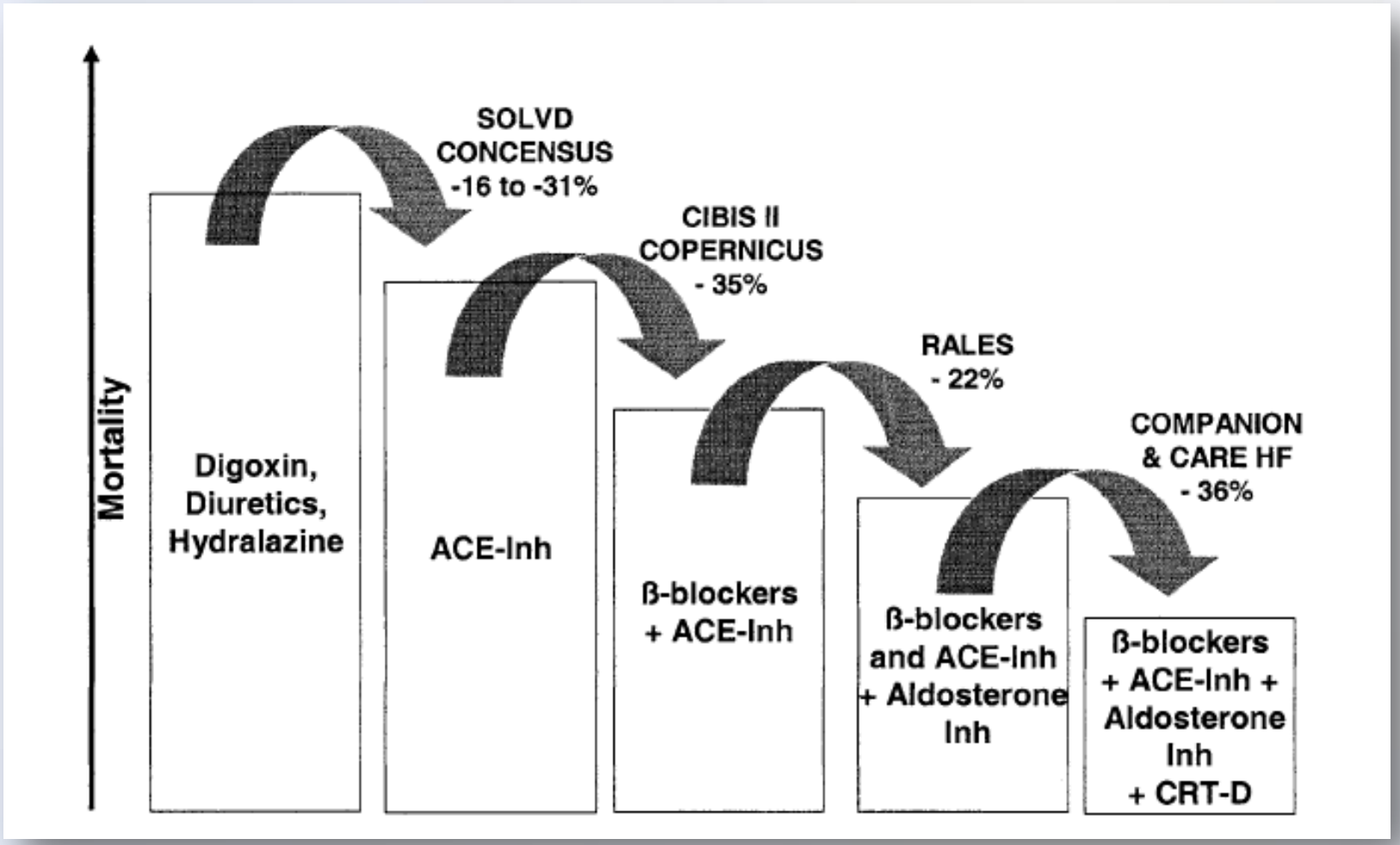
Linde C et al. Long-term impact of cardiac resynchronization therapy in mild heart failure: 5-year results from the REVERSE study. *European heart journal. 2013;34:2592-9.*

Dlouhodobý (9-letý) mortalitní efekt CRT CARE-HF

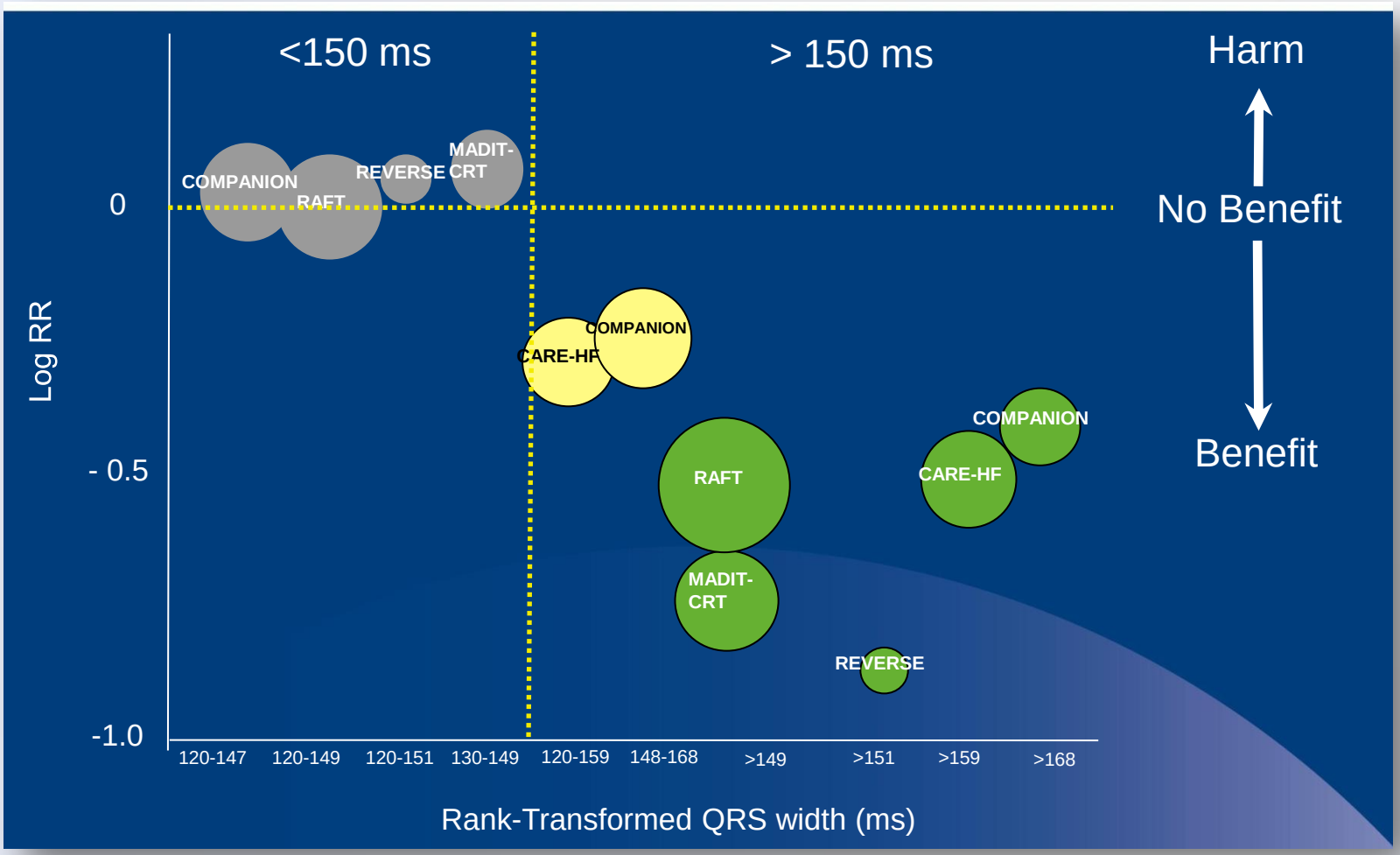


Cleland JG et al. Long-term mortality in the CARE-HF trial. *European journal of heart failure. 2012;14:628-34.*

Additive principle of EB CV therapy

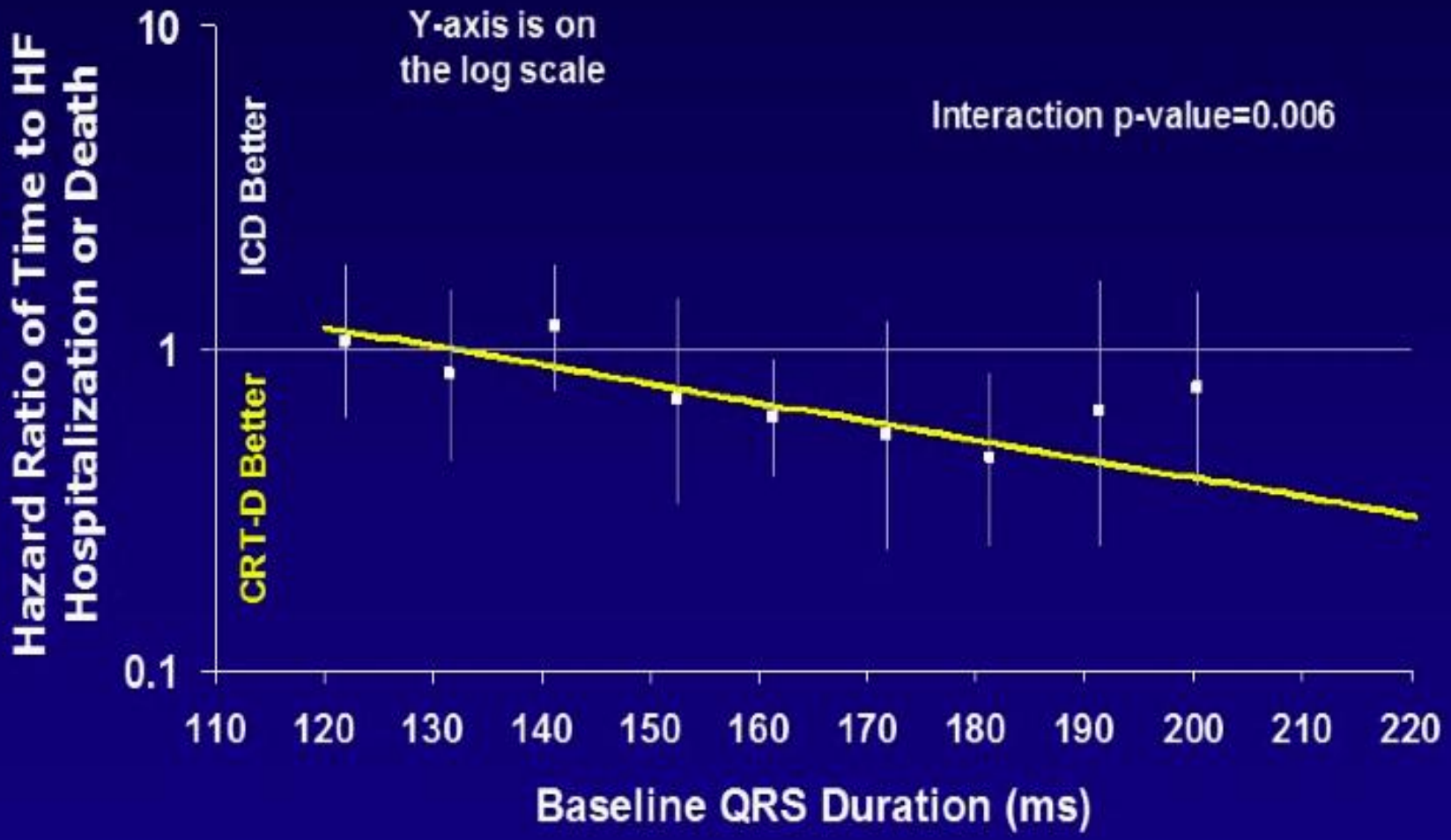


Šíře QRS je důležitá



Sipahi I, et al. *Arch Intern Med,* June 2011

RAFT NYHA Class II: CRT Beneficial Across QRS Durations for HF Hospitalization or All-cause Death

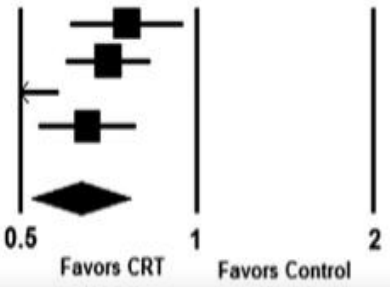


Proportional odds model: QRS duration as a continuous variable

Efekt CRT podle typu blokády

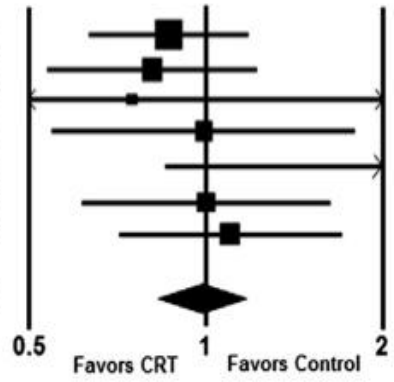
LBBB

Study name	Risk Ratio	Lower Limit	Upper limit	Z-Value	p-Value
COMPANION[10] - LBBB	0.76	0.61	0.95	-2.43	0.016
CARE-HF[11,32] - LBBB	0.70	0.60	0.83	-4.21	<0.0001
MADIT-CRT[12,13,15] - LBBB	0.45	0.35	0.58	-6.20	<0.00001
RAFT[14] - LBBB	0.65	0.54	0.79	-4.44	0.00001
Meta Analysis	**0.64**	**0.52**	**0.77**	**-4.55**	**0.00001**



IVCD and RBBB

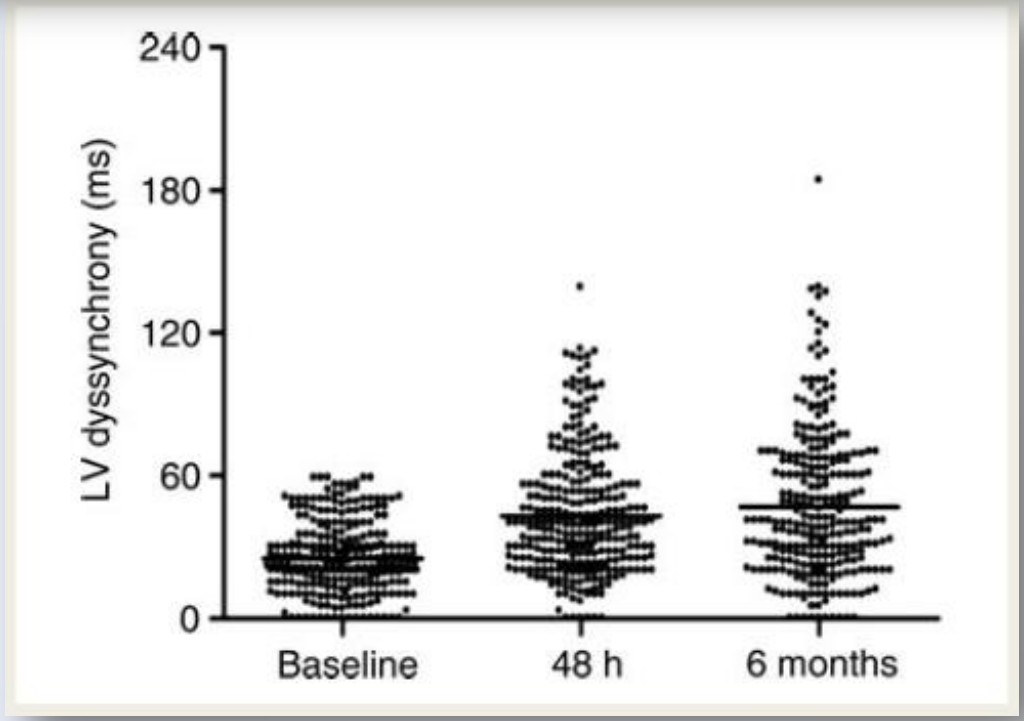
Study name	Risk Ratio	Lower Limit	Upper Limit	Z-Value	p-Value
COMPANION[10] - Non-LBBB	0.86	0.63	1.17	-0.96	0.34
CARE-HF[11,32] - RBBB	0.81	0.54	1.22	-0.99	0.32
CARE-HF[11,32] - IVCD	0.75	0.24	2.33	-0.50	0.62
MADIT-CRT[12,13,15] - RBBB	0.99	0.55	1.79	-0.03	0.97
MADIT-CRT[12,13,15] - IVCD	1.44	0.88	2.36	1.45	0.15
RAFT[14] - RBBB	1.00	0.62	1.62	0.00	1.00
RAFT[14] – IVCD	1.10	0.71	1.69	0.43	0.67
Meta Analysis	**0.97**	**0.82**	**1.15**	**-0.32**	**0.75**



Sipahi I, et al. *Am Heart J* 2012;163:260-267.e3.)

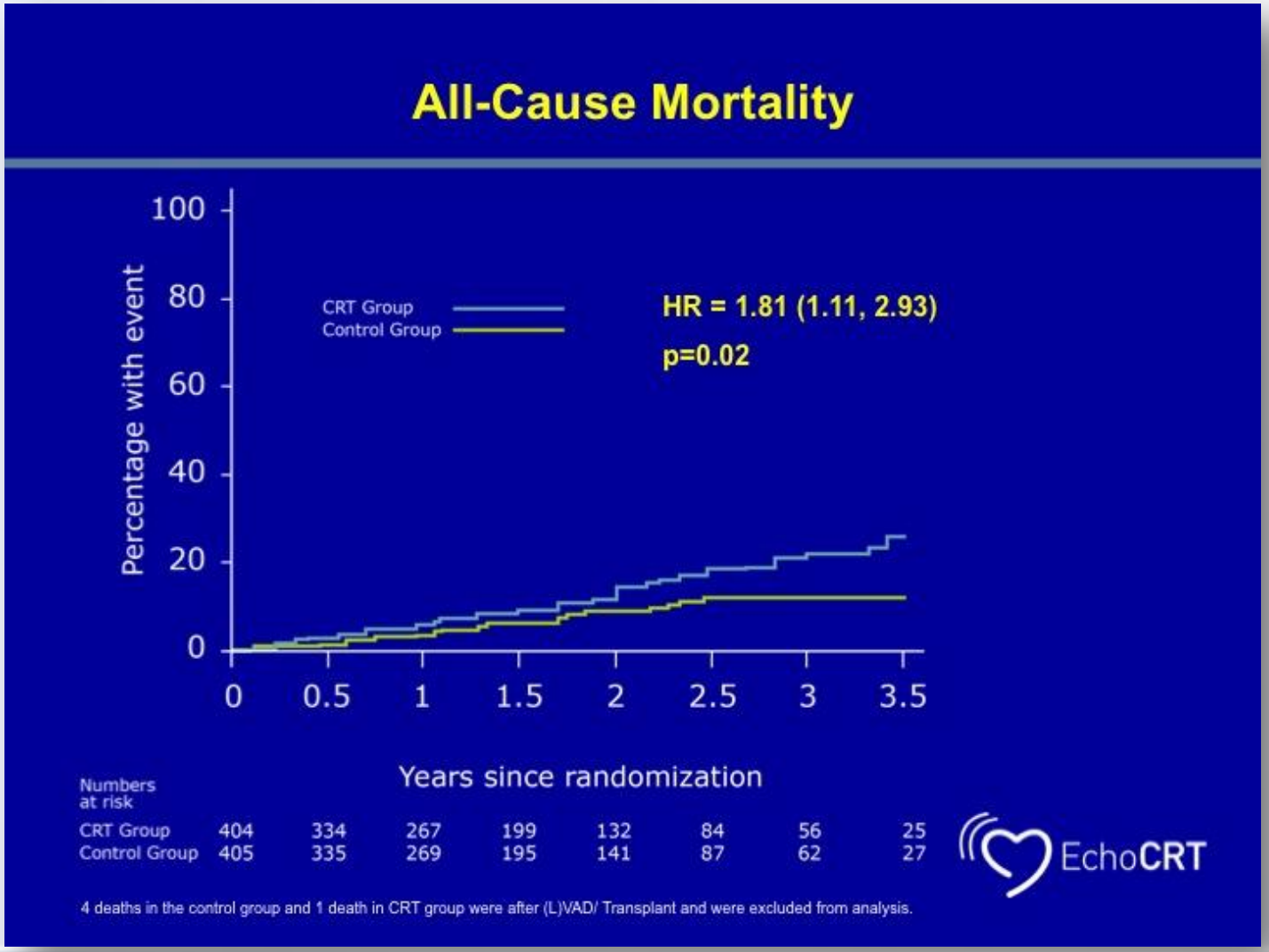
Effect of cardiac resynchronization therapy in patients without left intraventricular dyssynchrony

Dominique Auger [1,2], Gabe B. Bleeker [1], Matteo Bertini [1], See H. Ewe [1], Rutger J. van Bommel [1], Tomasz G. Witkowski [1], Arnold C.T. Ng [1], Lieselot van Erven [1], Martin J. Schalij [1], Jeroen J. Bax [1], and Victoria Delgado [1*]



Auger et al. European Heart Journal (2012) 33, 913–920

Echo-CRT


All-Cause Mortality
Percentage with event
100
80
60
40
20
0
CRT Group
Control Group
HR = 1.81 (1.11, 2.93)
p=0.02
0
0.5
1
1.5
2
2.5
3
3.5
Years since randomization
Numbers at risk
CRT Group 404 334 267 199 132 84 56 25
Control Group 405 335 269 195 141 87 62 27
EchoCRT
4 deaths in the control group and 1 death in CRT group were after (L)VAD/ Transplant and were excluded from analysis.

Evaluation of Early Complications Related to De Novo Cardioverter Defibrillator Implantation

Insights From the Ontario ICD Database

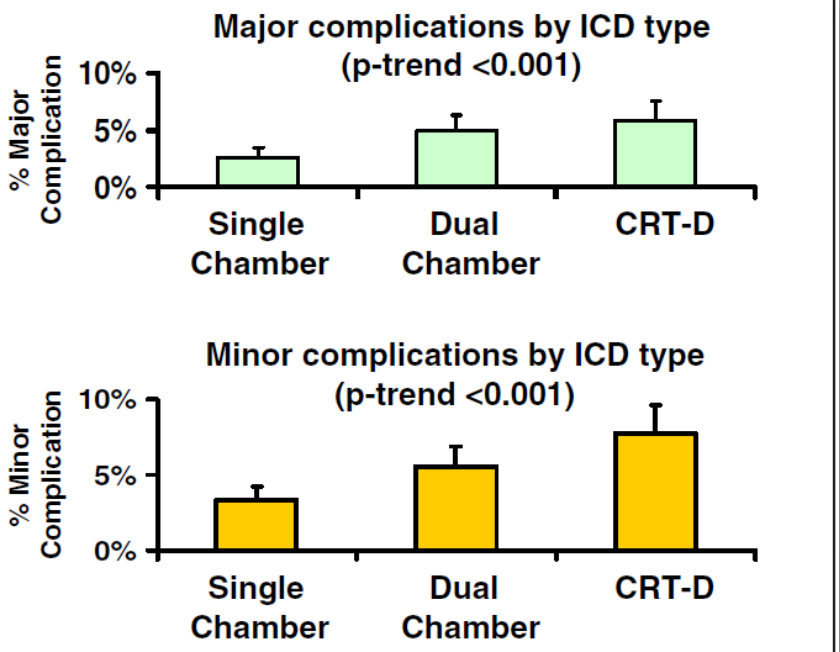


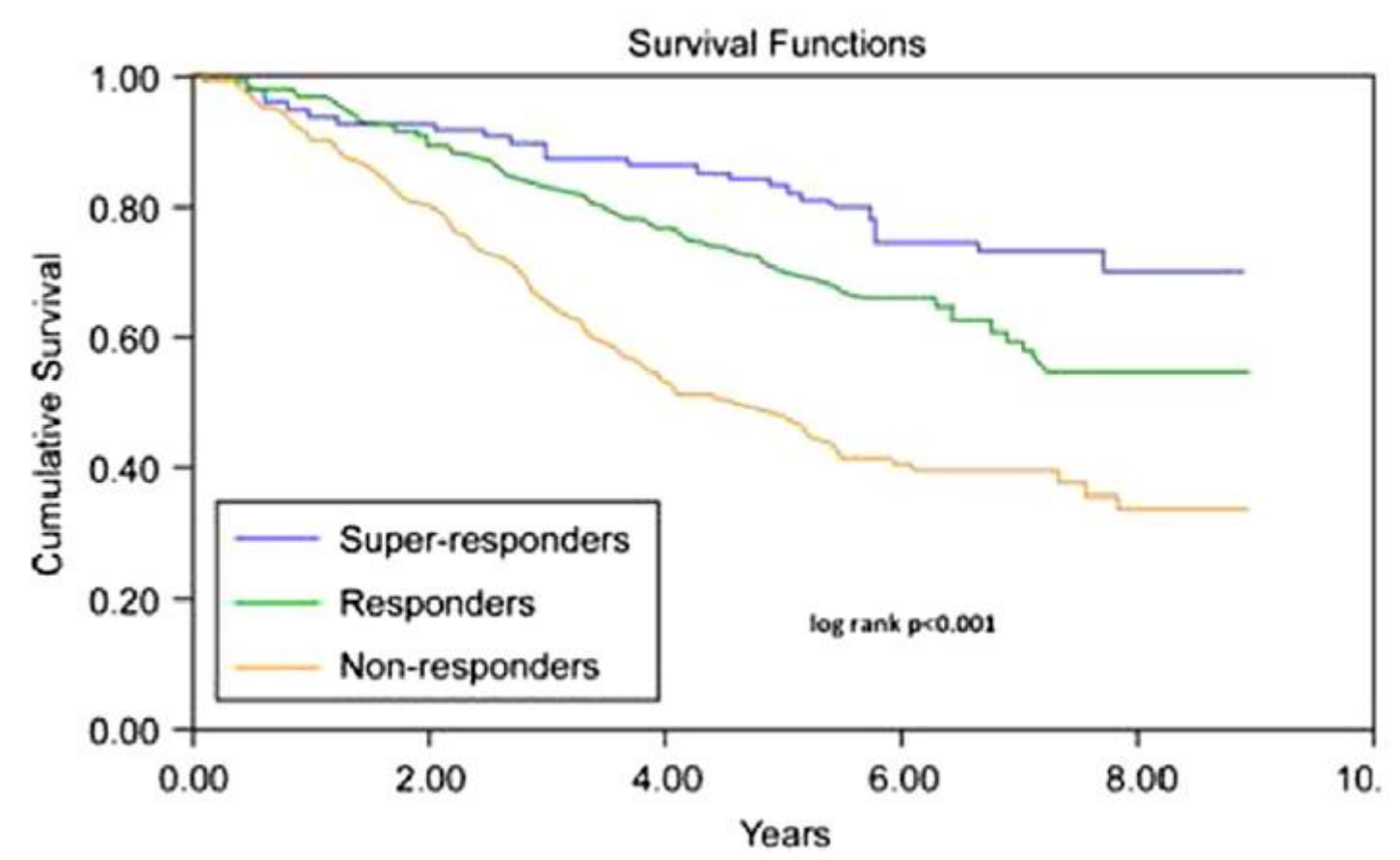
Figure 1 Rates of 45-Day Complications by Defibrillator Type

Table 6 Adjusted Hazard Ratios for Mortality According to Presence of a Major Nondeath Complication Within 45 Days

	Hazard Ratio	95% CI	p Value
Any major complication excluding death			
Adjusted for age and sex	3.79	1.69–8.51	0.001
Adjusted for age, sex, and ICD type	3.70	1.64–8.33	0.002
Minor complication			
Adjusted for age and sex	1.12	0.35–3.62	0.85
Adjusted for age, sex, and ICD type	1.08	0.33–3.50	0.90

1 Lee et al. JACC 2010

Vliv odpovědi na přežití



Rickard J et al. Durability of the survival effect of CRT by level of left ventricular functional improvement: fate of "nonresponders". *Heart rhythm : the official journal of the Heart Rhythm Society. 2014;11:412-6.*

Definice response u CRT

- Klinické zlepšení
- Funkční změny (NYHA, 6MWT …)
- Echo: EF, LVEDV, LVESV, parametry dysynchronie
- Biomarkery

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- Biomarkery

- Non-progrese????

Minimalizace / eliminace non-response

- Co očekáváme, případně co očekávající administrátoři zdravotnictví – 100 %?

The New England
Journal of Medicine

Volume 325 AUGUST 1, 1991 Number 5

EFFECT OF ENALAPRIL ON SURVIVAL IN PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTIONS AND CONGESTIVE HEART FAILURE

THE SOLVD INVESTIGATORS*

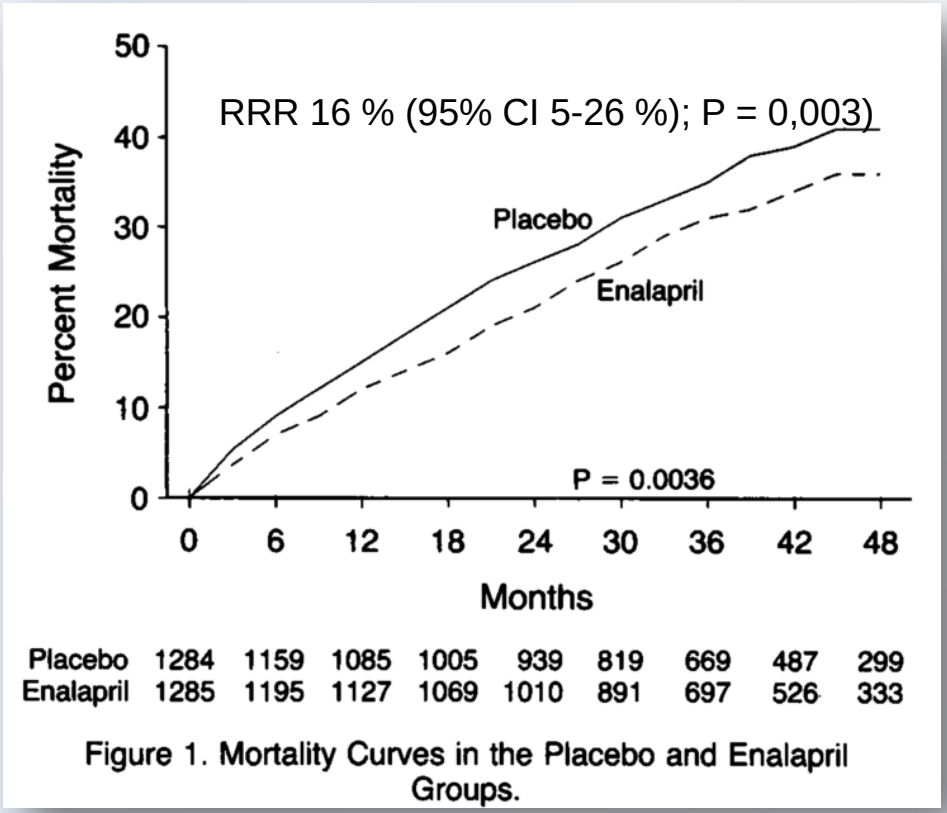
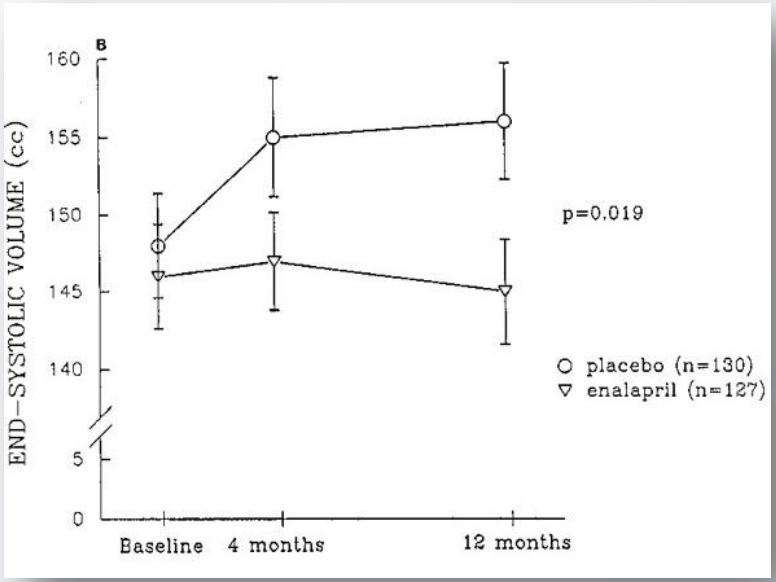


Figure 1. Mortality Curves in the Placebo and Enalapril Groups.



Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med. 1991;325:293-302.*

Greenberg B et al. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Results of the SOLVD echocardiography substudy. Circulation. 1995;91:2573-81.

Prediktory

chybění odpovědi

- BPRT, nespecifická porucha vedení
- iKMP
- NYHA IV
- CHRI
- Diabetes
- Vysoké hladiny BNP
- Těžká mitrální regurgitace
- Vysoký věk

dobré odpovědi

- BLRT
- QRS > 150 ms
- NIDCM a absence jizev
- Ženské pohlaví
- Méně dilatovaná LK
- Malá levá síň a MR
- Echokardiografie (?)

Saxon LA et al. Predictors of sudden cardiac death and appropriate shock in the COMPANION Trial. Circulation 2006;114(25):2766-72

Bilchick KC et al. Bundle-branch block morphology and other predictors of outcome after cardiac resynchronization therapy in Medicare patients. Circulation. 2010;122(20):2022-30

Richardson M et al.; CARE-HF Study Steering Committee and Investigators. Predictors and treatment response with cardiac resynchronization therapy in patients with heart failure characterized by dyssynchrony: a pre-defined analysis from the CARE-HF trial. Eur Heart J 2007;28(15):1827-34

Cappola TP et al. Predictors of remodeling in the CRT era: influence of mitral regurgitation, BNP, and gender. J Card Fail 2006;12(3):182-8.

Xu YZ et al. Cardiac resynchronization therapy: do women benefit more thanmen? J Cardiovasc Electrophysiol 2012;23(2):172-8

Hsing JM et al. Paced left ventricular QRS width and ECG parameters predictoutcomes after cardiac resynchronization therapy: PROSPECT-ECG substudy. Circ Arrhythm Electrophysiol 2011;4(6):851-7

Goldenberg I et al.; MADIT-CRT Executive Committee. Predictors of response to cardiac resynchronization therapy in the MADIT-CRT. Circulation 2011;124(14):1527-36

Prediktory super-response

Reprodukovatelné	Hůře reprodukovatelné
Ženy	Malá MR
Malá levá síň	Žádná TR
NIDCM	Výrazná redukce šíře QRS
Typický LBBB	Šíře QRS

Stefan L, Sedlácek K et al. Small left atrium and mild mitral regurgitation predict super-response to cardiac resynchronization therapy. Europace. 2012 Apr 4

Pokud máte cíl 100 % odpovědi implantujte:

Pouze ženy s neischemickou kardiomyopatií v časných fázích rozvoje (bez dilatace srdce, bez MR, bez dilatace LA) a s typickou LBBB (> 150 ms), nejlépe ve stadiu NYHA I (max. NYHA II).

Nemusíte se obtěžovat se CRTD, vystačíte si CRTP a váš administrátor vás bude chválit, jak šetříte veřejné zdroje

Pokud jste rozumní a rozumíte, že 100 % response není ani u anginy, natož u maligního onemocnění ....

Můžete optimalizovat CRT s cílem dát všem vašim pacientům maximální prospěch z této terapie

Můžete rozumět, že response je kontinuum od super-response až po škodlivý efekt CRT a snažit tento eliminovat

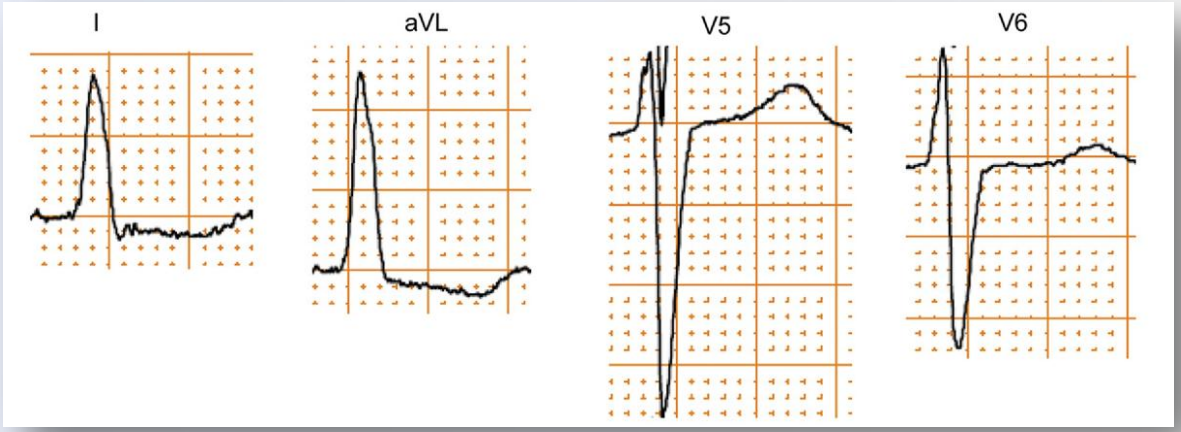
Praktický integrativní přístup

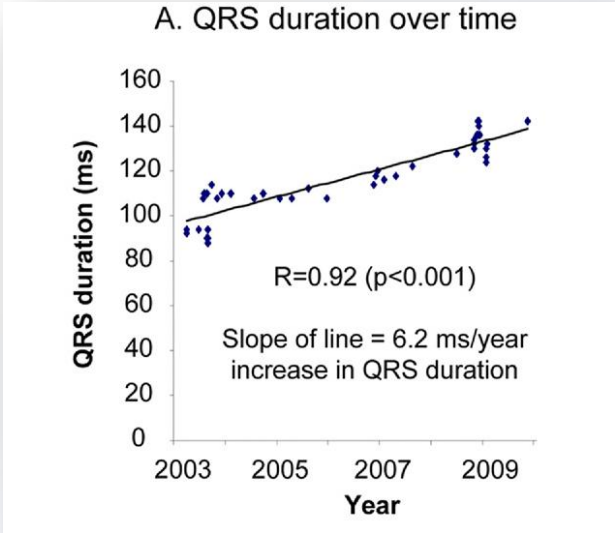
Správný výběr pacientů – zvážit indikaci či aktivaci u těch, kde hrozí zhoršení
- EKG
- Zobrazovací metody: echo, CMR

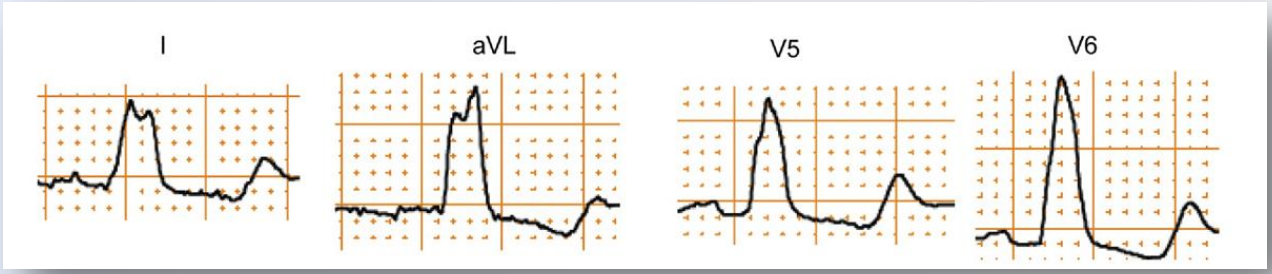
Optimalizace během implantace
- Zobrazení anatomie CS
- Shoda polohy elektrody a informací ze zobrazovacích metod
- Elektrické mapování - QLV
- Poloha RV elektrody
- Správná programace

Po implantaci
- Pečlivý follow-up
- Optimalizace terapie, event. zvážení deaktivace CRT při známkách škodlivosti
- RFA AVN při nedostatečné biventrikulární stimulaci a FiS
- Remote monitoring
- Redukce komplikací, především infekcí

Nespecifická porucha vedení vs. LBBB







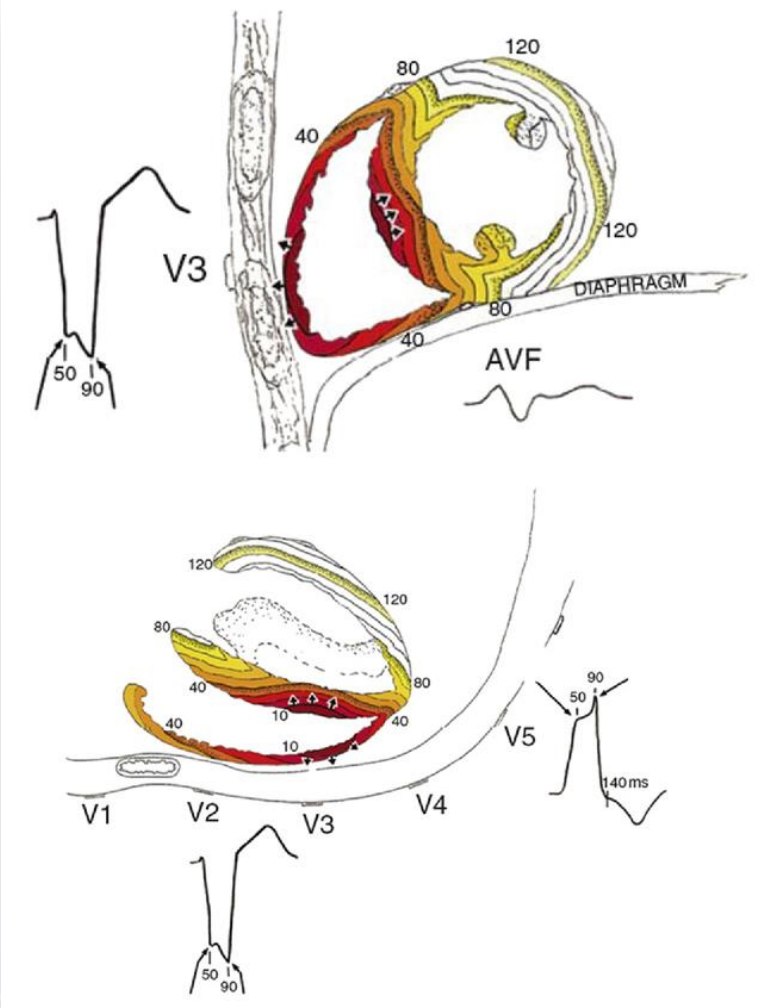
Strauss DG et al. Defining LBBB end the era of CRT. Am J Cardiol. 2011

Nová definice LBBB?

- QRS > 140 ms muži)
- 130 ms (ženy)

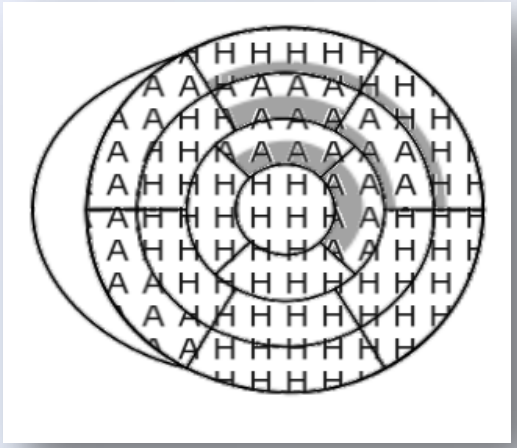
- QS nebo rS V1, V2

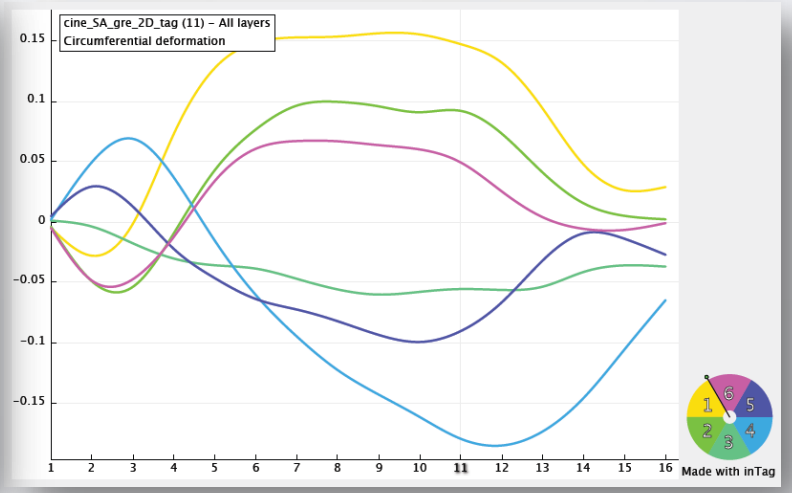
- Zalomení QRS (50 – 90 ms)



Strauss DG et al. Defining LBBB end the era of CRT. Am J Cardiol. 2011

Patient case - CMR



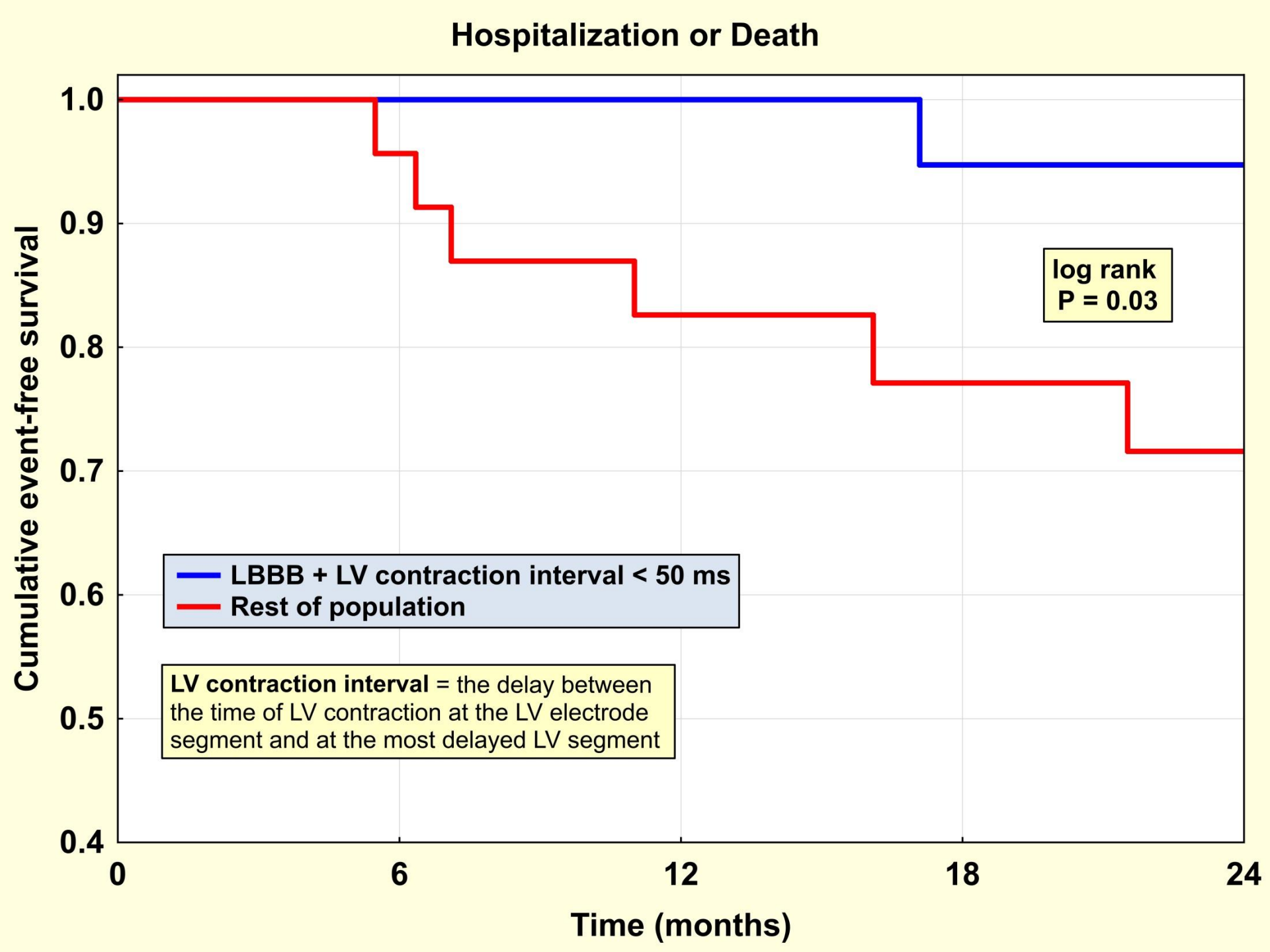


Max. dyssynchrony: **mid inferolateral, basal anterolateral, mid anterolateral**

Latest segment:

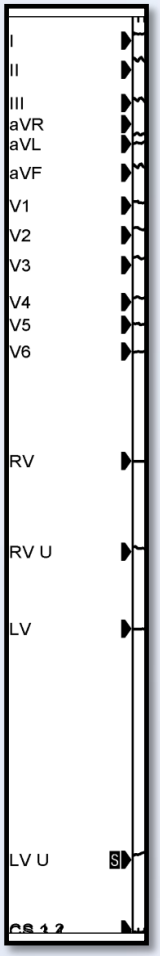
basal and mid-anterolateral: 478 ms after R

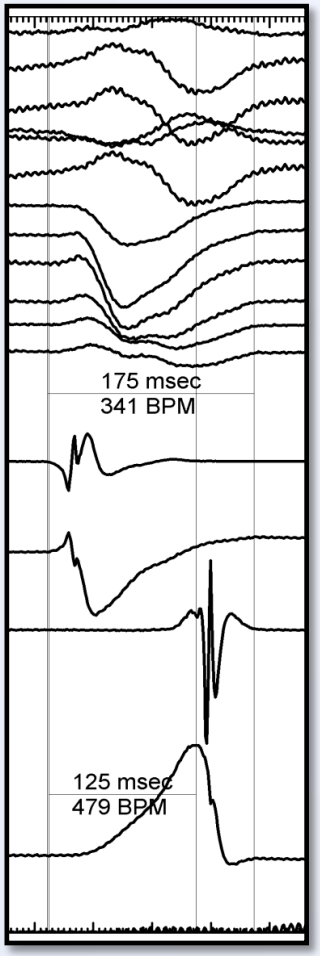
Mid-inferolateral 478 ms after R without scar


Hospitalization or Death
1.0
0.9
0.8
0.7
0.6
0.5
0.4
Cumulative event-free survival
0
6
12
18
24
Time (months)
log rank
P = 0.03
LBBB + LV contraction interval < 50 ms
Rest of population
LV contraction interval = the delay between the time of LV contraction at the LV electrode segment and at the most delayed LV segment

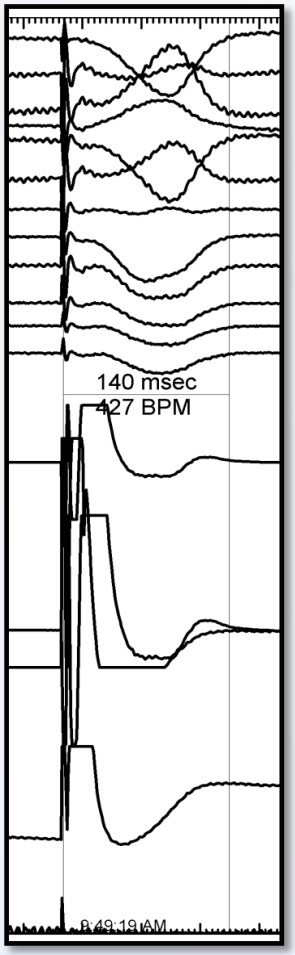
LK elektroda - QLV

QRS and QLV





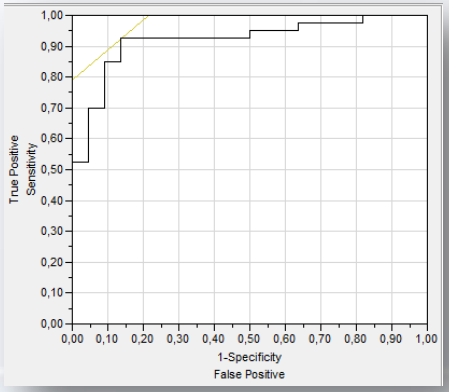
Biv sim. pace



Term	ChiSquare	Prob>ChiSq
Q-LV	8,3	0,004
MR b	5,1	0,024
TAPSE b	4,1	0,043
E	5,6	0,018
Creatinine	4,5	0,034

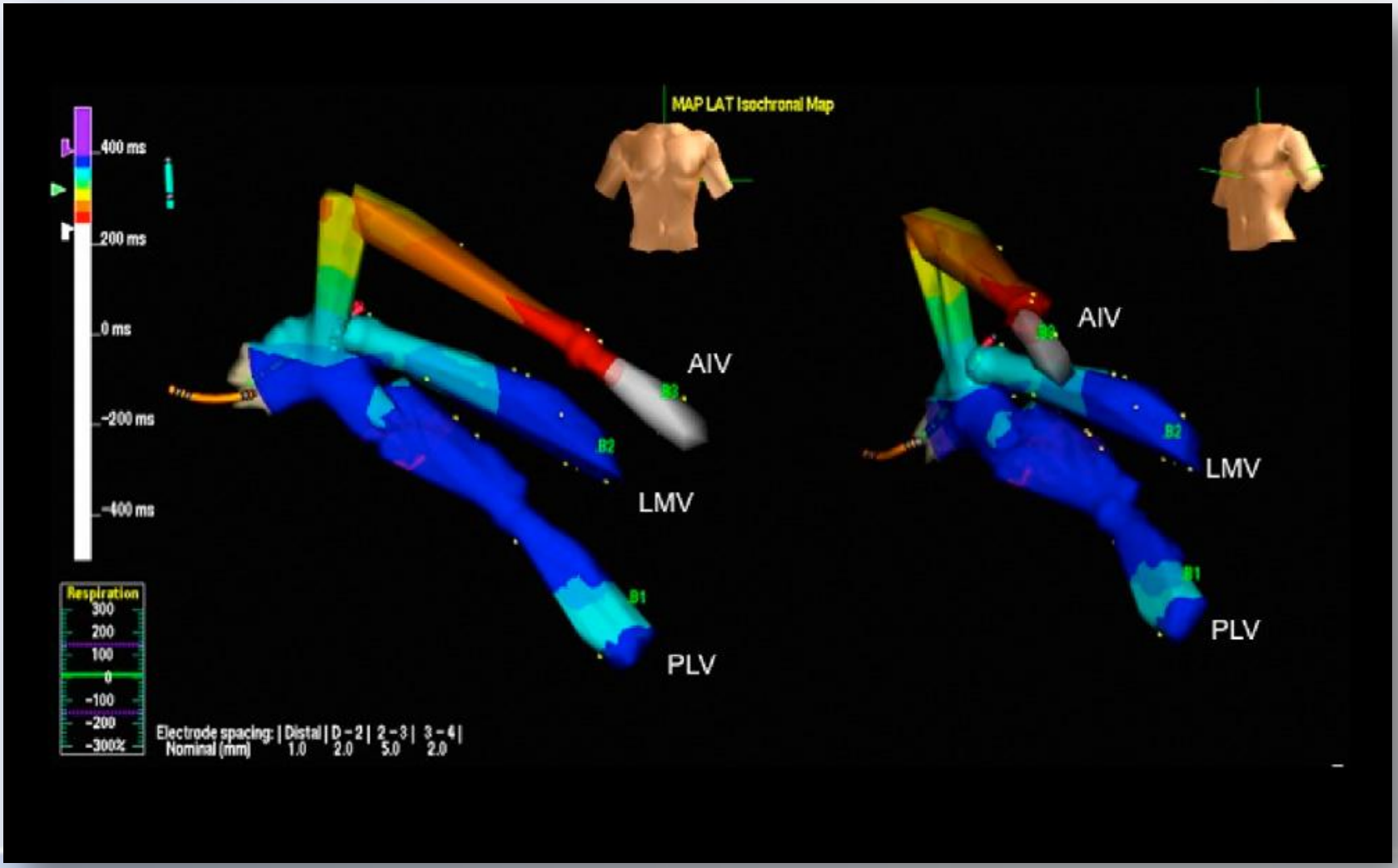
X^2 = 38; P< 0.0001

AUC (whole multivariate model) = 0.91



Polasek et al. BMC Cardiovascular Disorders 2012, 12:34
Gold MR et al. HeartRhythm2013;10:988–993
Sedlacek K …

Pozdně aktivovaná oblast LK - NavX



Závěr

Non-response je přirozený a nevyhnutelný jev u každé terapie a neznamená, že terapie sama o sobě je špatná

Response je kontinuum od super-response až po zhoršení stavu či komplikace ohrožující život

Minimalizace non-response spočívá v optimalizaci aplikace CRT u individuálních pacientů od správné indikace přes informovanou implantační strategii až po správný a pečlivý follow-up