MASARYKOVA UNIVERZITA
LÉKAŘSKÁ FAKULTA

FAKULTNÍ NEMOCNICE U SV. ANNY V BRNĚ

KARDIOMYOPATIE JAKO PŘÍČINA SRDEČNÍHO SELHÁNÍ

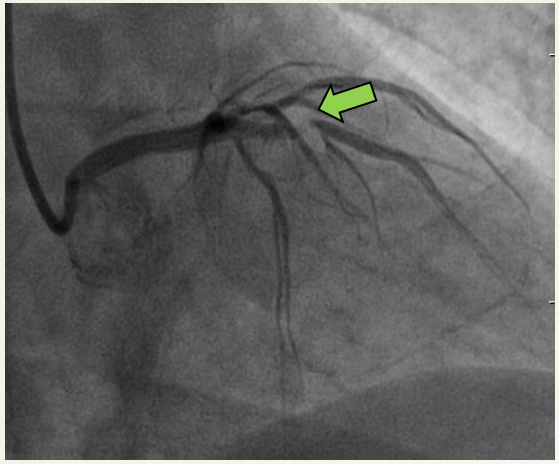
Jan Krejčí

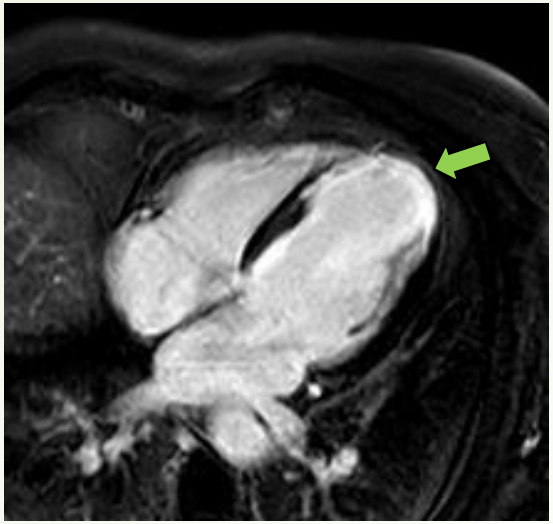
I. interní kardioangiologická klinika FNUSA v Brně

Etiologie srdečního selhání

- **Ischemická choroba srdeční**

  (HFrEF - populačně nejčastější příčina srd. selhání)





Etiologie srdečního selhání

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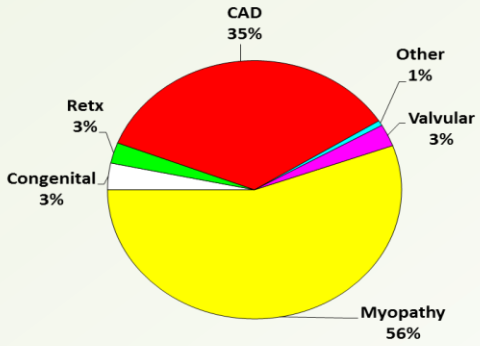
- **Kardiomyopatie**

  (HFrEF i HFpEF - nejčastější příčina srdeční transplantace)



ISHLT registry

Etiologie srdečního selhání

- **Ischemická choroba srdeční**

  (HFrEF - populačně nejčastější příčina srd. selhání)
- **Kardiomyopatie**

  (HFrEF i HFpEF - nejčastější příčina srdeční transplantace)
- **Hypertenze** (HFpEF)
- **Chlopenní vady (**HFrEF i HFpEF)

Etiologie srdečního selhání

- Ischemická choroba srdeční (HFrEF)
- **Kardiomyopatie** (HFrEF i HFpEF, ev. HFmrEF)
- Hypertenze (HFpEF)
- Chlopenní vady (HFrEF i HFpEF)

Tabulka 3.1 – Definice srdečního selhání se zachovanou ejekční frakcí (HFpEF), s ejekční frakcí ve středním pásmu (HFmrEF) a sníženou ejekční frakcí (HFrEF)

Typ srdečního selhání		HFrEF	HFmrEF	HFpEF
KRITÉRIA	1	Symptomy ± známky[a]	Symptomy ± známky[a]	Symptomy ± známky[a]
	2	EFLK < 40 %	EFLK 40–49 %	EFLK ≥ 50 %
	3	–	Zvýšené hodnoty natriuretických peptidů[b] Alespoň jedno další kritérium: • významné strukturální onemocnění srdce (HLK a/nebo LAE) • diastolická dysfunkce (detaily viz oddíl 4.3)	Zvýšené hodnoty natriuretických peptidů[b] Alespoň jedno další kritérium: • významné strukturální onemocnění srdce (HLK a/nebo LAE) • diastolická dysfunkce (detaily viz oddíl 4.3)

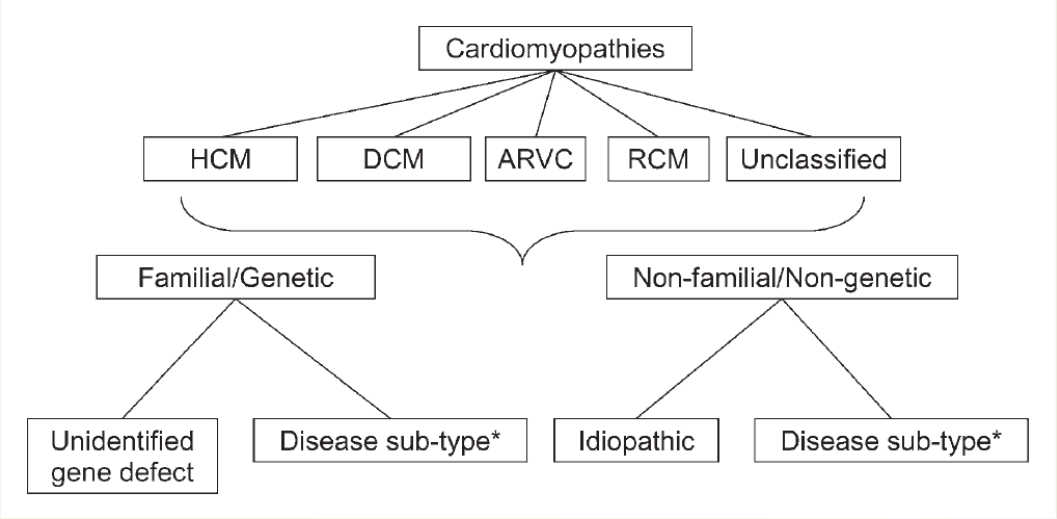
Špinar et al. Cor et Vasa 2016;58:e530-e568

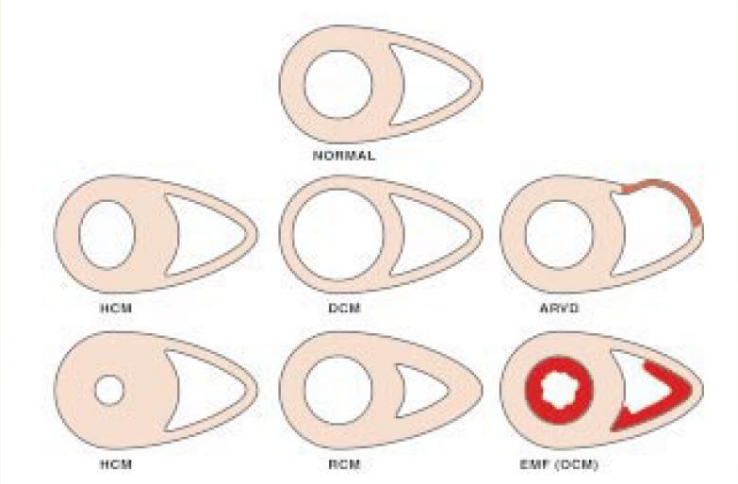
Kardiomyopatie

- strukturálně či funkčně abnormální myokard
- nepřítomnost ICHS, HN, chlopenní či vrozené srdeční vady, které by mohly způsobit tuto poruchu.

Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases

Perry Elliott, Bert Andersson, Eloisa Arbustini, Zofia Bilinska, Franco Cecchi, Philippe Charron, Olivier Dubourg, Uwe Kühl, Bernhard Maisch, William J. McKenna, Lorenzo Monserrat, Sabine Pankuweit, Claudio Rapezzi, Petar Seferovic, Luigi Tavazzi, and Andre Keren*





European Heart Journal (2008) **29**, 270–276

Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases

Table 1 Examples of different diseases that cause cardiomyopathies

	HCM	DCM	ARVC	RCM	Unclassified
Familial	Familial, unknown gene Sarcomeric protein mutations ß myosin heavy chain Cardiac myosin binding protein C Cardiac troponin I Troponin-T α-tropomyosin Essential myosin light chain Regulatory myosin light chain Cardiac actin α-myosin heavy chain Titin Troponin C Muscle LIM protein Glycogen storage disease (e.g. Pompe; PRKAG2, Forbes', Danon) Lysosomal storage diseases (e.g. Anderson–Fabry, Hurler's) Disorders of fatty acid metabolism Carnitine deficiency Phosphorylase B kinase deficiency Mitochondrial cytopathies Syndromic HCM Noonan's syndrome LEOPARD syndrome Friedreich's ataxia Beckwith–Wiedermann syndrome Swyer's syndrome Other Phospholamban promoter Familial amyloid	Familial, unknown gene Sarcomeric protein mutations (see HCM) Z-band Muscle LIM protein TCAP Cytoskeletal genes Dystrophin Desmin Metavinculin Sarcoglycan complex CRYAB Epicardin Nuclear membrane Lamin A/C Emerin Mildly dilated CM Intercalated disc protein mutations (see ARVC) Mitochondrial cytopathy	Familial, unknown gene Intercalated disc protein mutations Plakoglobin Desmoplakin Plakophilin 2 Desmoglein 2 Desmocollin 2 Cardiac ryanodine receptor (RyR2) Transforming growth factor-β3 (TGFβ3)	Familial, unknown gene Sarcomeric protein mutations Troponin I (RCM +/− HCM) Essential light chain of myosin Familial amyloidosis Transthyretin (RCM + neuropathy) Apolipoprotein (RCM + nephropathy) Desminopathy Pseuxanthoma elasticum Haemochromatosis Anderson–Fabry disease Glycogen storage disease	Left ventricular non-compaction Barth syndrome Lamin A/C ZASP α-dystrobrevin
Non-familial	Obesity Infants of diabetic mothers Athletic training Amyloid (AL/prealbumin)	Myocarditis (infective/toxic/immune) Kawasaki disease Eosinophilic (Churg Strauss syndrome) Viral persistence Drugs Pregnancy Endocrine Nutritional — thiamine, carnitine, selenium, hypophosphataemia, hypocalcaemia Alcohol Tachycardiomyopathy	Inflammation?	Amyloid (AL/prealbumin) Scleroderma Endomyocardial fibrosis Hypereosinophilic syndrome Idiopathic Chromosomal cause Drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan) Carcinoid heart disease Metastatic cancers Radiation Drugs (anthracyclines)	Tako Tsubo cardiomyopathy

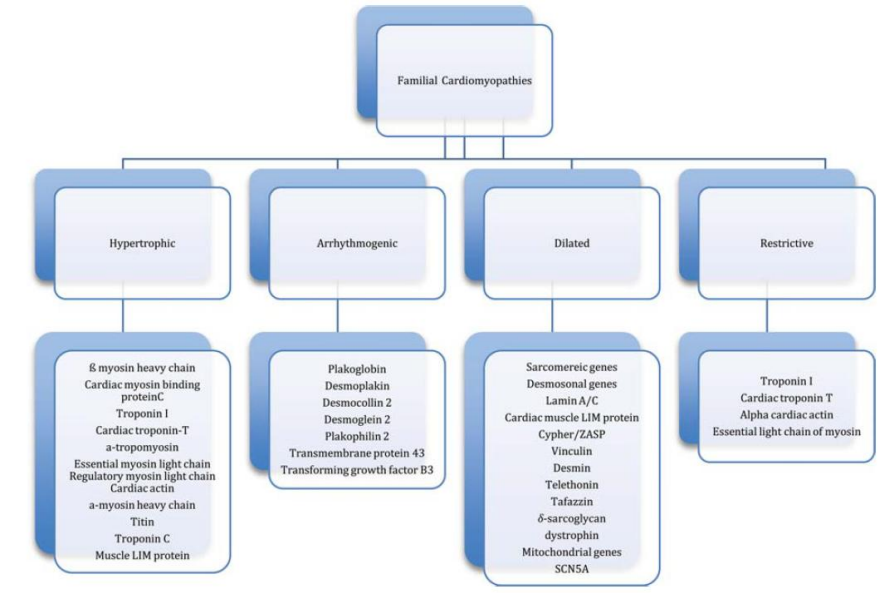
European Heart Journal (2008) **29**, 270–276

Diagnostika kardiomyopatií

- EKG, Holterovo monit. EKG, ergometrie, SKG, PK, CT…
- **ECHOkg, MRI…**
- **EMB**, EFV…
- genetická diagnostika

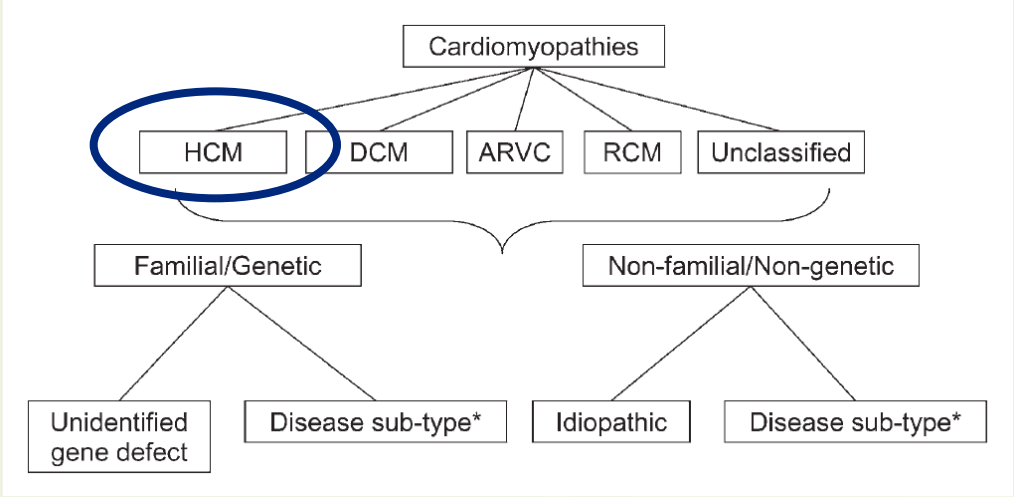
Genetics of inherited cardiomyopathy

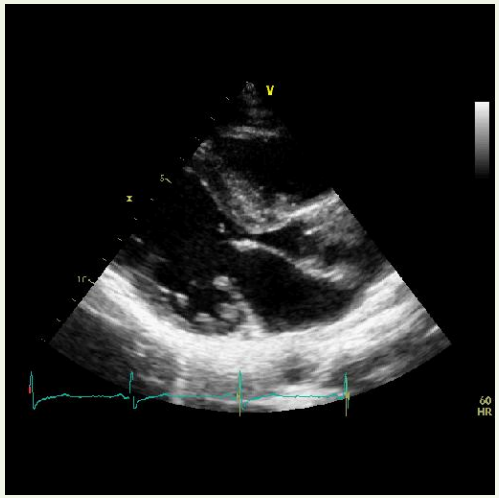
Daniel Jacoby[1] and William J. McKenna[2]*

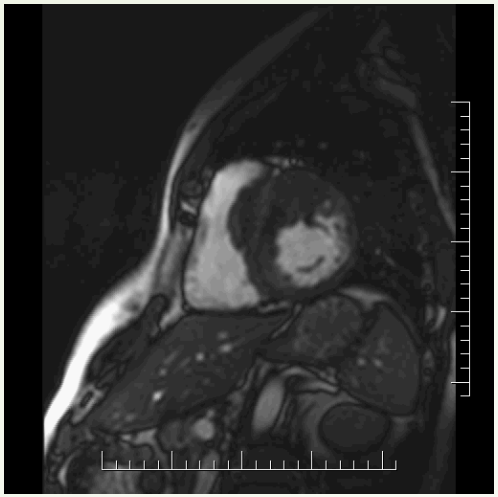


European Heart Journal (2012) **33**, 296–304

Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases







	HCM
Familial	Familial, unknown gene
	Sarcomeric protein mutations
	ß myosin heavy chain
	Cardiac myosin binding protein C
	Cardiac troponin I
	Troponin-T
	α-tropomyosin
	Essential myosin light chain
	Regulatory myosin light chain
	Cardiac actin
	α-myosin heavy chain
	Titin
	Troponin C
	Muscle LIM protein
	Glycogen storage disease (e.g. Pompe; PRKAG2, Forbes', Danon)
	Lysosomal storage diseases (e.g. Anderson–Fabry, Hurler's)
	Disorders of fatty acid metabolism
	Carnitine deficiency
	Phosphorylase B kinase deficiency
	Mitochondrial cytopathies
	Syndromic HCM
	Noonan's syndrome
	LEOPARD syndrome
	Friedreich's ataxia
	Beckwith–Wiedermann syndrome
	Swyer's syndrome
	Other
	Phospholamban promoter
	Familial amyloid
Non-familial	Obesity
	Infants of diabetic mothers
	Athletic training
	Amyloid (AL/prealbumin)

Hypertrofická KMP jako příčina HFpEF

- HKMP je definována přítomností zesílení stěn jednoho či více segmentů levé komory ≥ 15mm na některé ze zobrazovacích metod (ECHOkg, MRI, CT), které není vysvětlitelné hemodynamickými důvody.

- Nejčastější geneticky vázané onemocnění v kardiologii
- Nejčastější kardiomyopatie v populaci s prevalencí 1:500 obyvatel
- > 1500 mutací v až 80 genech…
- Mutace nejčastěji postihují geny pro sarkomerické proteiny („sarkomerická kardiomyopatie“)

- Je příkladem onemocnění vedoucího k HFpEF

Elliot et al. EHJ 2008;29:270-276.

Léčba HFpEF

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Recommendations for treatment of patients with heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction

Recommendations	Class [a]	Level [b]	Ref [c]
it is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.	I	C	
Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.	I	B	178, 179

www.escardio.org/guidelines

In HFmrER and HFpEF no recommendations for therapies improving mortality & morbidity

EUROPEAN SOCIETY OF CARDIOLOGY

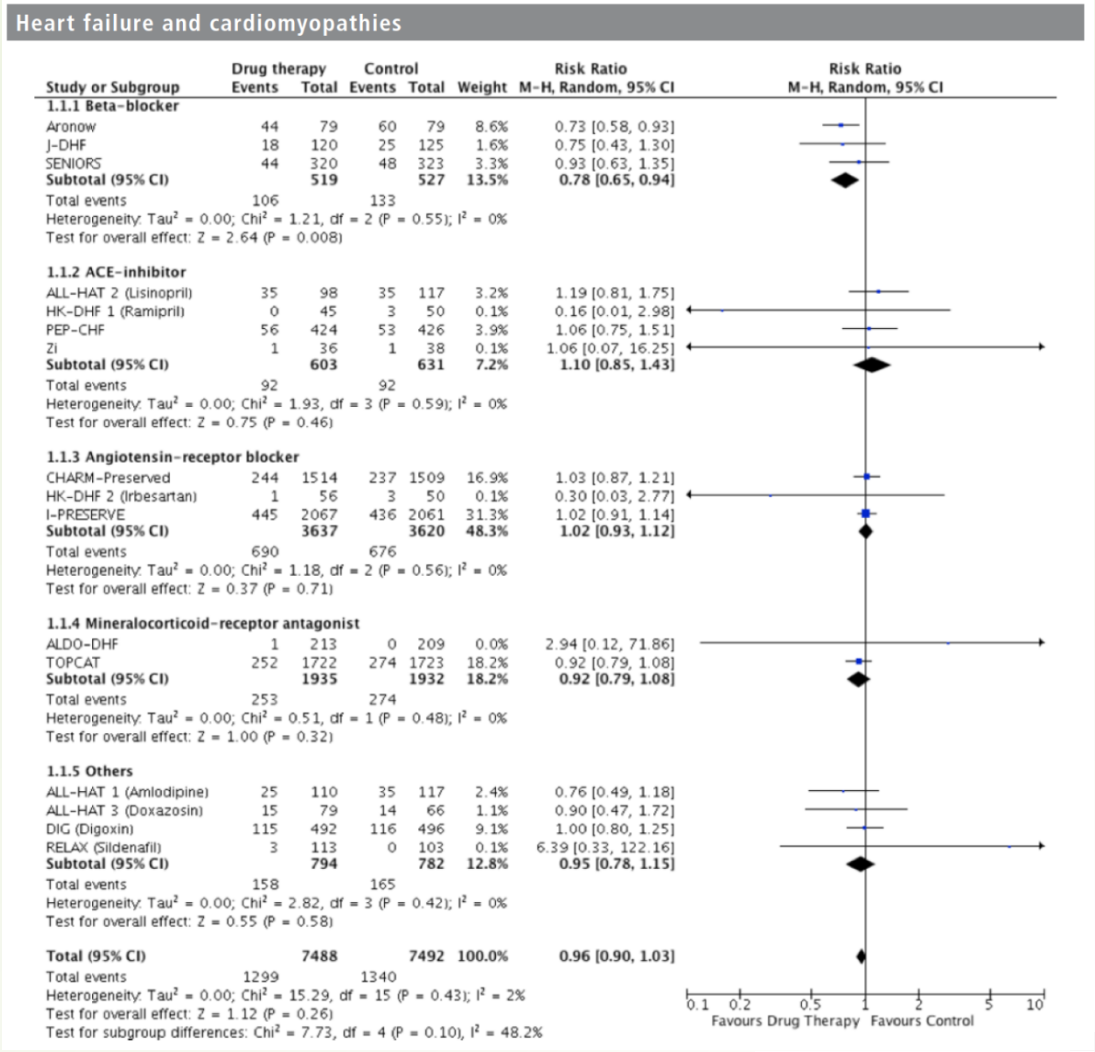
Eur J Heart Fail. 2016 Aug;18(8):891-975

Léčba HFpEF

Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis

Sean Lee Zheng,[1,2,3] Fiona T Chan,[3] Adam A Nabeebaccus,[1,2] Ajay M Shah,[1,2] Theresa McDonagh,[1,2] Darlington O Okonko,[1,2] Salma Ayis[4]

- BB snižovaly – na rozdíl od ACEI, ARB či MRA – celkovou i KV mortalitu
- Blokáda RAAS (dohromady, nikoliv individuálně) – na rozdíl od BB – snižovala hospitalizace pro HF



Heart 2018;**104**:407–415

Léčba HFpEF

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 10, 2014 VOL. 370 NO. 15

Spironolactone for Heart Failure with Preserved Ejection Fraction

Bertram Pitt, M.D., Marc A. Pfeffer, M.D., Ph.D., Susan F. Assmann, Ph.D., Robin Boineau, M.D., Inder S. Anand, M.D., Brian Claggett, Ph.D., Nadine Clausell, M.D., Ph.D., Akshay S. Desai, M.D., M.P.H., Rafael Diaz, M.D., Jerome L. Fleg, M.D., Ivan Gordeev, M.D., Ph.D., Brian Harty, M.A., John F. Heitner, M.D., Christopher T. Kenwood, M.S., Eldrin F. Lewis, M.D., M.P.H., Eileen O'Meara, M.D., Jeffrey L. Probstfield, M.D., Tamaz Shaburishvili, M.D., Ph.D., Sanjiv J. Shah, M.D., Scott D. Solomon, M.D., Nancy K. Sweitzer, M.D., Ph.D., Song Yang, Ph.D., and Sonja M. McKinlay, Ph.D., for the TOPCAT Investigators*

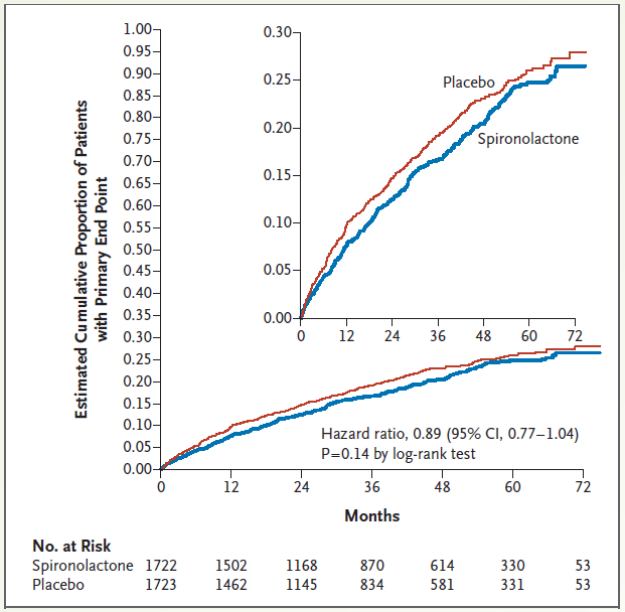


Table 2. Incidence Rates of the Primary Composite Outcome, Its Components, and Additional Secondary Outcomes.*

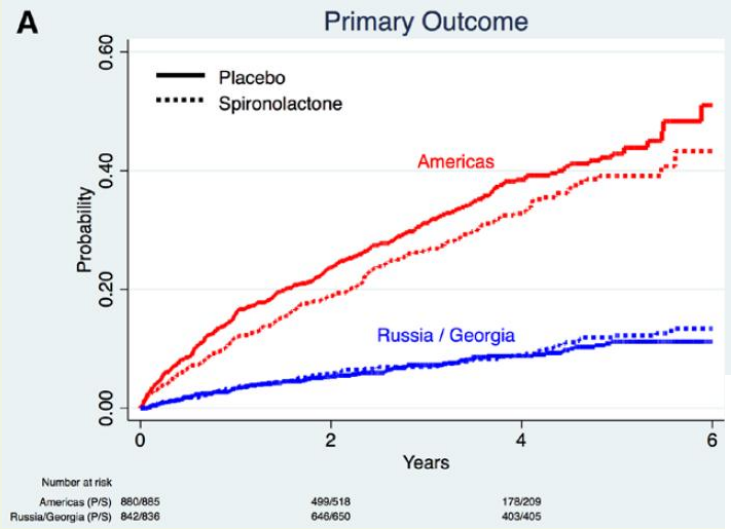
Outcome	Spironolactone (N=1722)		Placebo (N=1723)		Hazard Ratio with Spironolactone (95% CI)†	P Value
	Participants with Event	Incidence Rate	Participants with Event	Incidence Rate		
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary outcome	320 (18.6)	5.9	351 (20.4)	6.6	0.89 (0.77–1.04)	0.14
Components of the primary outcome						
Death from cardiovascular causes	160 (9.3)	2.8	176 (10.2)	3.1	0.90 (0.73–1.12)	0.35
Aborted cardiac arrest	3 (0.2)	0.05	5 (0.3)	0.09	0.60 (0.14–2.50)	0.48
Hospitalization for heart failure	206 (12.0)	3.8	245 (14.2)	4.6	0.83 (0.69–0.99)	0.04
Additional secondary outcomes						
Death from any cause	252 (14.6)	4.2	274 (15.9)	4.6	0.91 (0.77–1.08)	0.29
Hospitalization for any reason	766 (44.5)	18.8	792 (46.0)	20.0	0.94 (0.85–1.04)	0.25
Myocardial infarction	65 (3.8)	1.2	64 (3.7)	1.1	1.00 (0.71–1.42)	0.98
Stroke	57 (3.3)	1.0	60 (3.5)	1.1	0.94 (0.65–1.35)	0.73

Závěr:

Žádný benefit z podávání MRA na mortalitu, méně hospitalizací

N Engl J Med 2014;370:1383-92.

Léčba HFpEF



Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial

Marc A. Pfeffer, MD, PhD; Brian Claggett, PhD; Susan F. Assmann, PhD; Robin Boineau, MD; Inder S. Anand, MD; Nadine Clausell, MD, PhD; Akshay S. Desai, MD, MPH; Rafael Diaz, MD; Jerome L. Fleg, MD; Ivan Gordeev, MD; John F. Heitner, MD; Eldrin F. Lewis, MD, MPH; Eileen O'Meara, MD; Jean-Lucien Rouleau, MD; Jeffrey L. Probstfield, MD; Tamaz Shaburishvili, MD, PhD; Sanjiv J. Shah, MD; Scott D. Solomon, MD; Nancy K. Sweitzer, MD, PhD; Sonja M. McKinlay, PhD; Bertram Pitt, MD

Table 4. Summary of Trial Outcomes by Treatment Arm and Region

	Americas (n=1767) No. (%) With Event [Incidence Rate per 100 patient-y]			Russia/Georgia (n=1678) No. (%) With Event [Incidence Rate per 100 patient-y]			
Outcome	Spironolactone (n=886)	Placebo (n=881)	HR (95% CI) *P* Value	Spironolactone (N=836)	Placebo (N=842)	HR (95% CI) *P* Value	*P*, Regional Difference*
Primary outcome	242 (27.3) [10.4]	280 (31.8) [12.6]	0.82 (0.69–0.98) 0.026	78 (9.3) [2.5]	71 (8.4) [2.3]	1.10 (0.79–1.51) 0.58	<0.001
Cardiovascular mortality	96 (10.8) [3.6]	127 (14.4) [4.9]	0.74 (0.57–0.97) 0.027	64 (7.7) [2.0]	49 (5.8) [1.6]	1.31 (0.91–1.90) 0.15	<0.001
Aborted cardiac arrest	2 (0.2) [0.08]	4 (0.5) [0.16]	N/A	1 (0.1) [0.03]	1 (0.1) [0.03]	N/A	N/A
Hospitalization for heart failure	184 (20.8) [7.9]	216 (24.5) [9.7]	0.82 (0.67–0.99) 0.042	22 (2.6) [0.72]	29 (3.4) [0.95]	0.76 (0.44–1.32) 0.327	<0.001
Recurrent heart failure	361 events [13.7]	438 events [17.0]	IRR=0.75 (0.58–0.96) 0.024	33 events [1.1]	37 events [1.2]	IRR=0.83 (0.42–1.62) 0.58	<0.001
All-cause mortality	178 (20.1) [6.5]	207 (23.5) [7.7]	0.83 (0.68–1.02) 0.08	74 (8.9) [2.3]	67 (8.0) [2.0]	1.12 (0.80–1.55) 0.51	<0.001

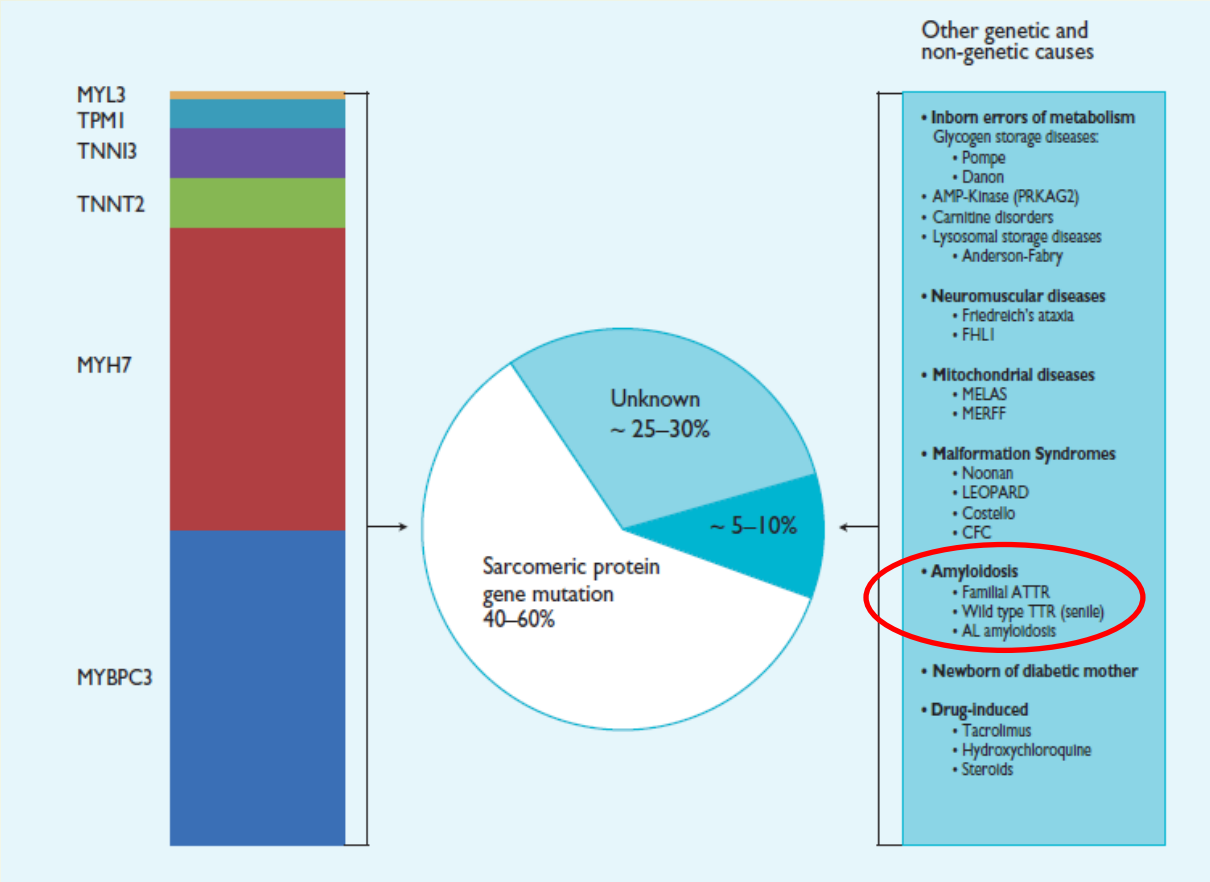
- **Americká větev – benefit z podání MRA**
- **Ru/Gru větev žádný benefit**

(*Circulation*. 2015;131:34-42. DOI: 10.1161/CIRCULATIONAHA.114.013255.)

Léčba HFpEF – dif. dg. HKMP

2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy

The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC)

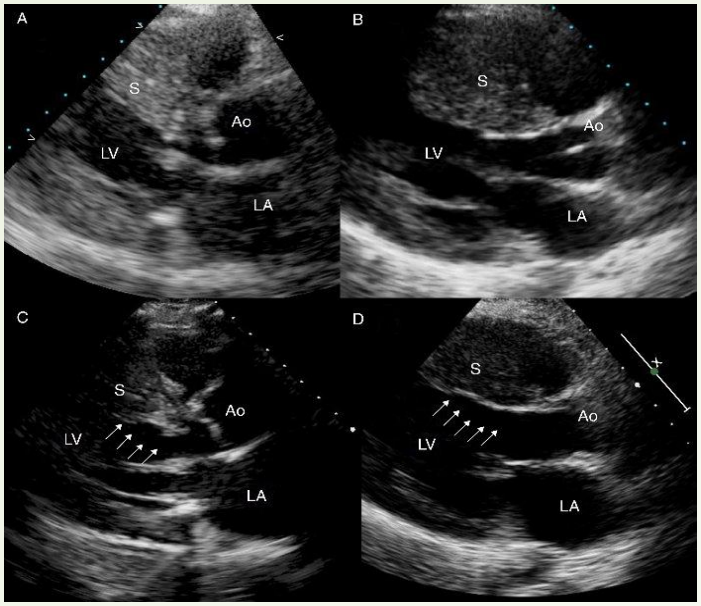


European Heart Journal (2014) **35**, 2733–2779

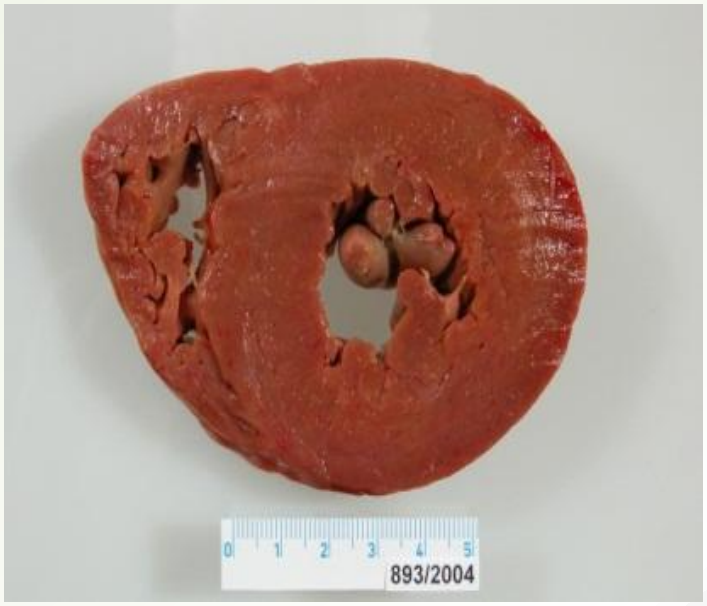
Diferenciální dg. HKMP

Jde o sekundární postižení myokardu nebo primární KMP?

sarkomerická HKMP



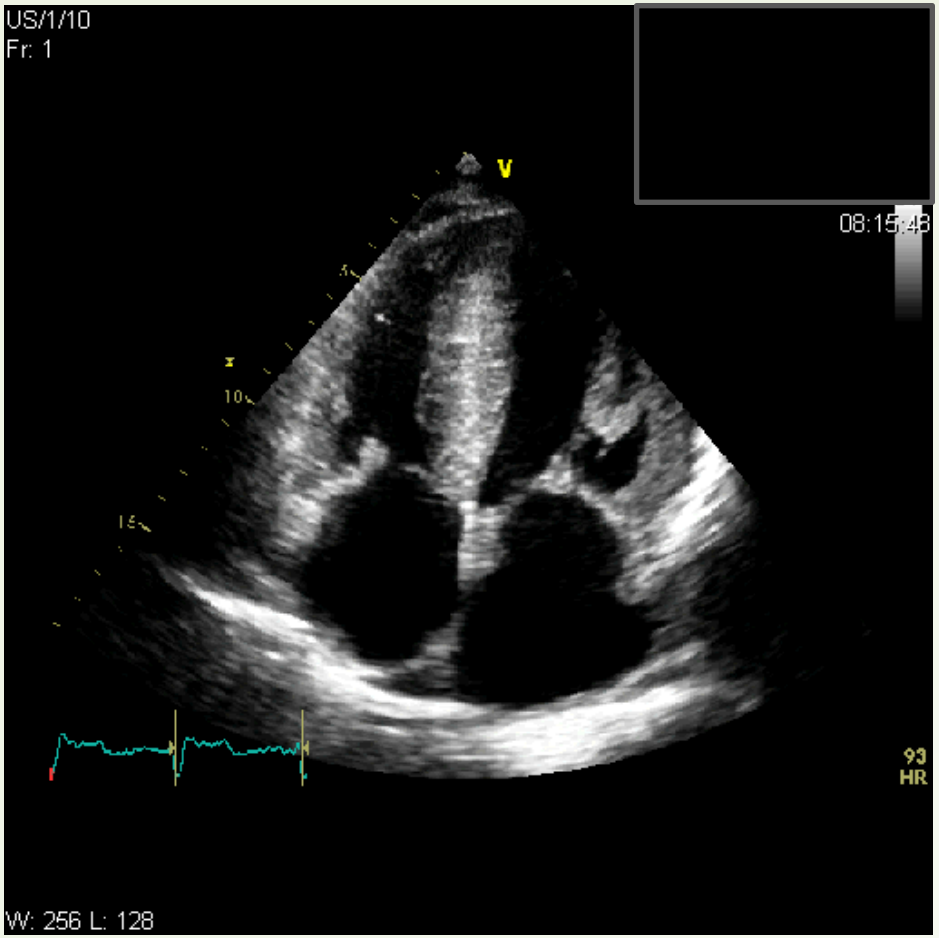
srdeční amyloidóza



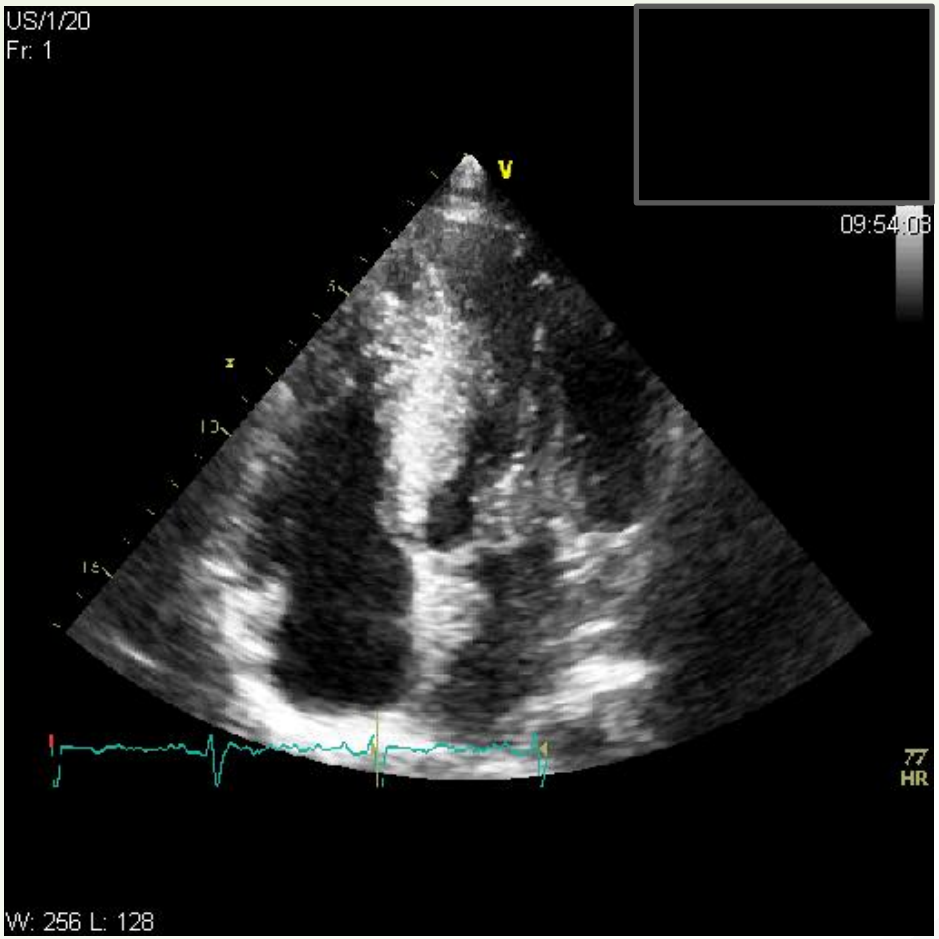
zdroj: archiv autora

Diferenciální dg. HKMP

srdeční amyloidóza



sarkomerická HKMP



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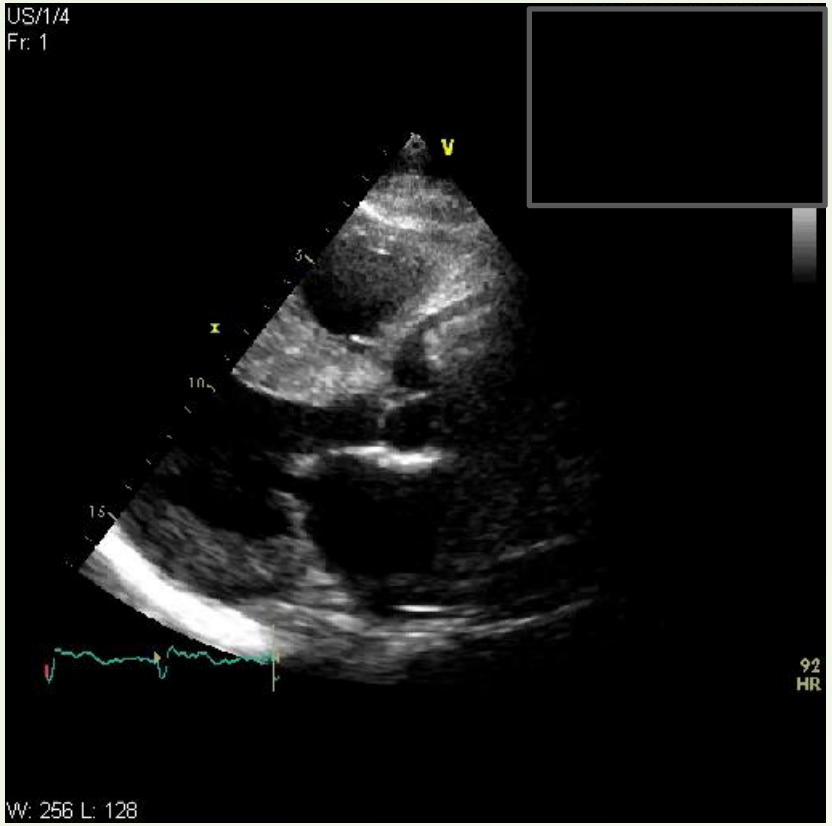
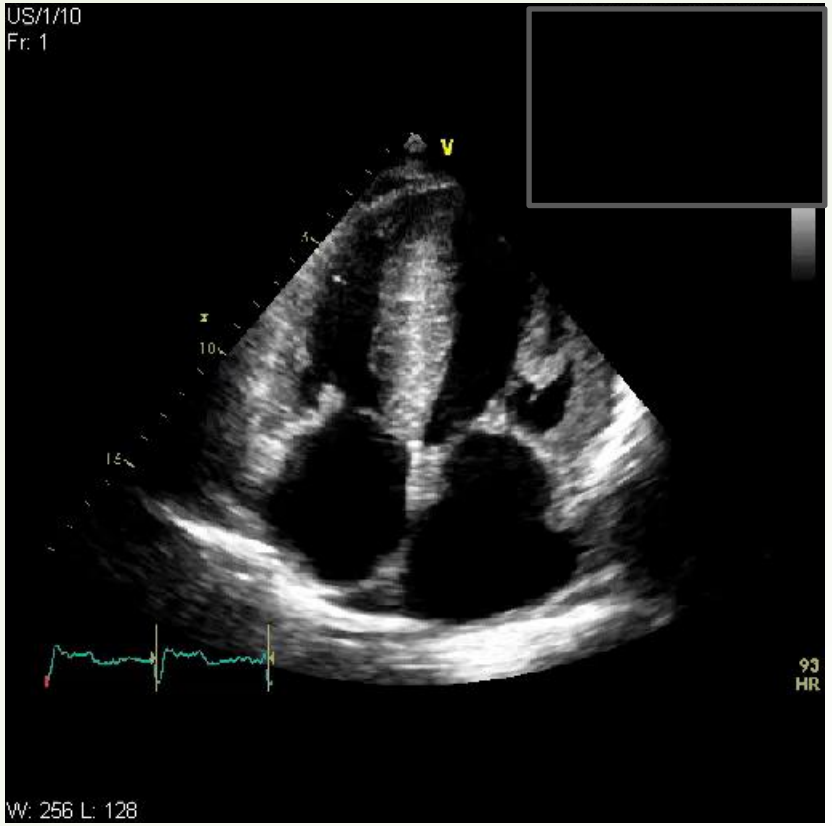
ECHOkg u srdeční amyloidózy





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Hlavní typy srdečních amyloidóz

Systemic Cardiac Amyloidoses

Disease Profiles and Clinical Courses of the 3 Main Types

Claudio Rapezzi, MD; Giampaolo Merlini, MD; Candida C. Quarta, MD; Letizia Riva, MD;

AL amyloidóza - lehké řetězce IgG

- nejčastěji lambda, abnormální poměr FLC λ/κ 3:1

Familiární amyloidóza - mutovaný transthyretin (mATTR)

- často spojena senzorimotorickou neuropatií

Senilní systémová amyloidóza - „normální“ transthyretin (wtATTR)

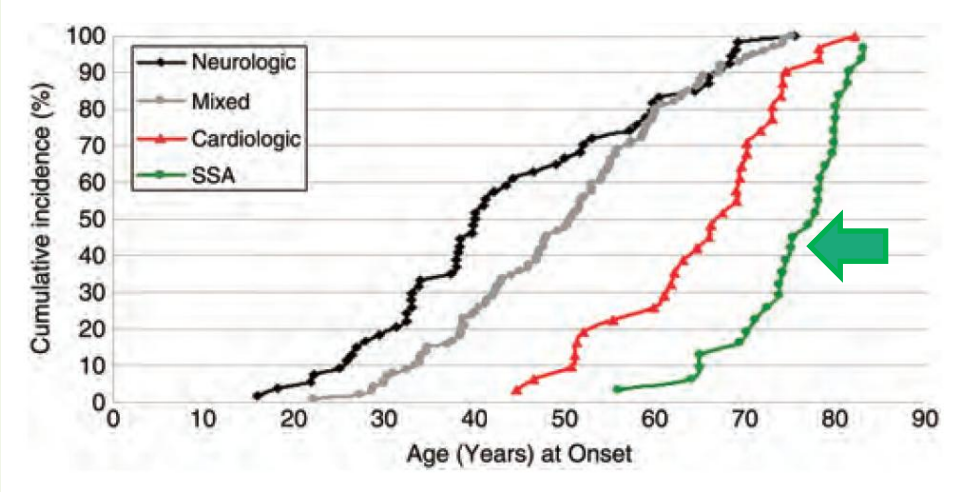
- postihuje ale prakticky výhradně myokard (+ sy karpálního tunelu)

Circulation 2009;120:1203-1212

Transthyretinové amyloidózy

- **nemutovaný transthyretin wtATTR (senilní A)**

  - starší nemocní (> 65 let), muži, izolované kardiální postižení



- **Se stárnutím populace a zlepšením diagnostiky (MRI) narůstá výskyt ATTR !**

- **Je již kauzální léčba na obzoru?**

Co by nás mohlo čekat v léčbě ATTR?

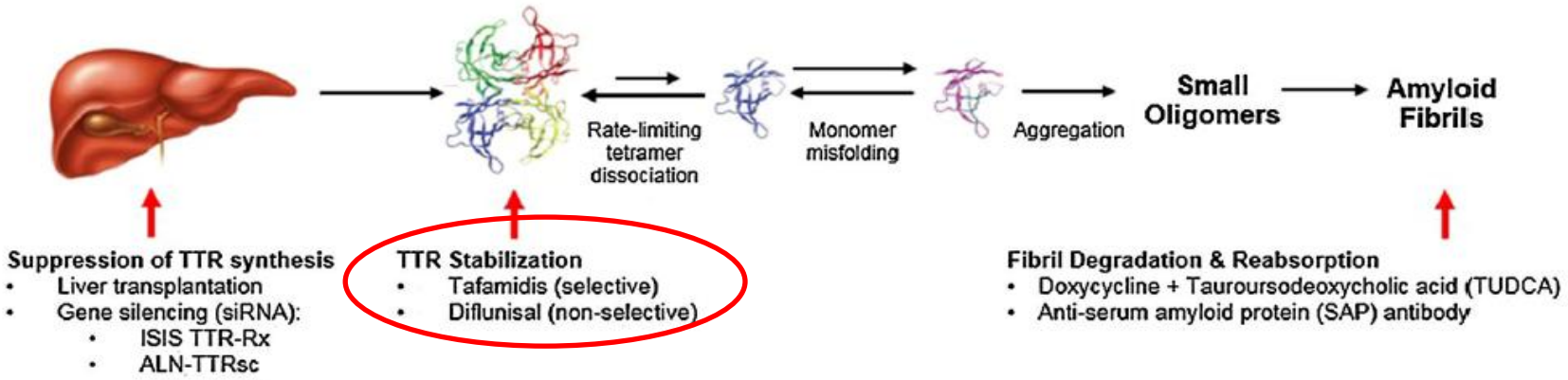
- Tafamidis se osvědčil v léčbě TTR neuropatie
- stabilizuje tetramerickou strukturu transthyretinu, čímž zabraňuje tvorbě amyloidních fibril

B3461028

ATTR-ACT

TRANSTHERETIN AMYLOID CARDIOMYOPATHY
TAFAMIDIS STUDY

Heart Fail Rev (2015) 20:163–178



Co by nás mohlo čekat v léčbě ATTR?

B3461028

ATTR-ACT

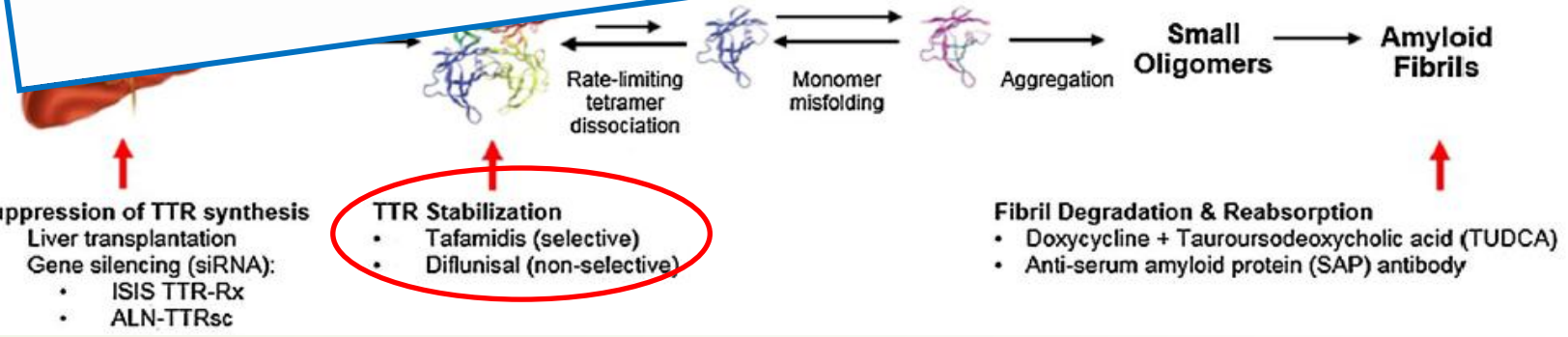
TRANSTHERETIN AMYLOID CA

Pfizer Announces Positive Topline Results from Phase 3 ATTR-ACT Study of Tafamidis in Patients with Transthyretin Cardiomyopathy

—Tafamidis demonstrated a statistically significant reduction in the combination of all-cause mortality and frequency of cardiovascular-related hospitalizations in global trial—

—Currently, there are no approved pharmacological medications specifically indicated for treating transthyretin cardiomyopathy—

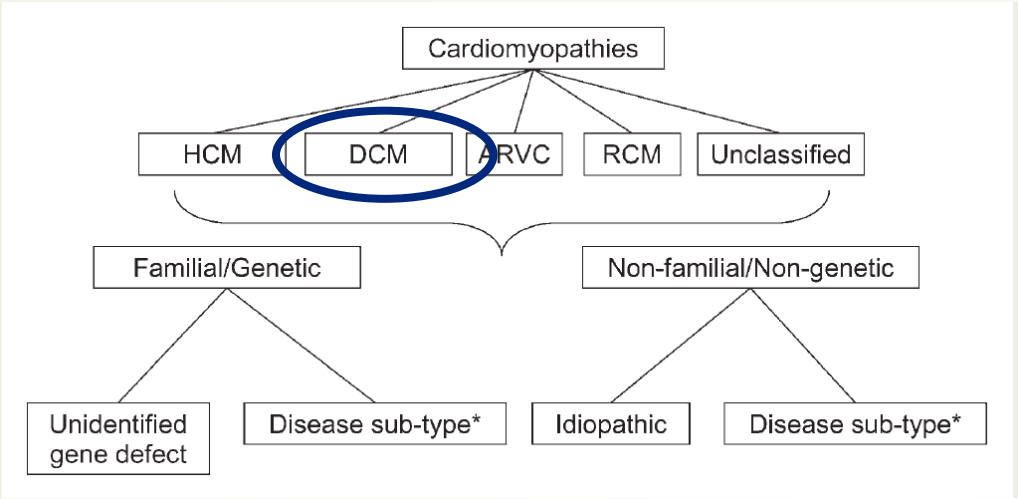
Heart Fail



Dilatační kardiomyopatie (DKMP) jako příklad HFrEF

- druhá nejčastější kardiomyopatie s prevalencí 1:2500
- definována dilatací LK (či obou komor) a její systolickou dysfunkcí v nepřítomnosti zjevné příčiny (ICHS, HN, chlopenní vada)

Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases

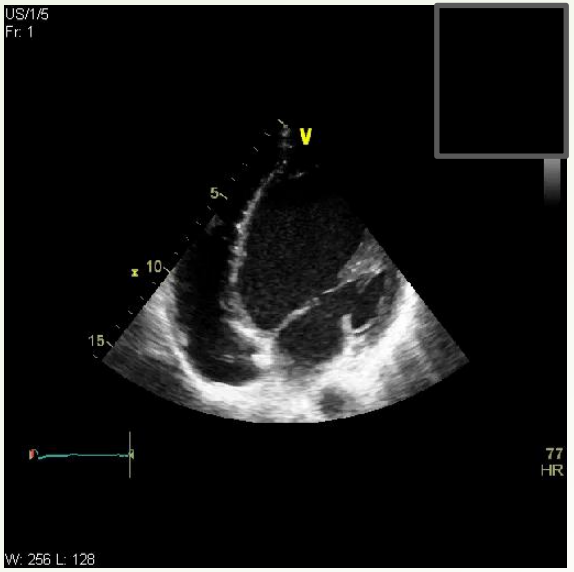


Eur Heart J 2008;29(2):270-276

Diferenciální dg. DKMP

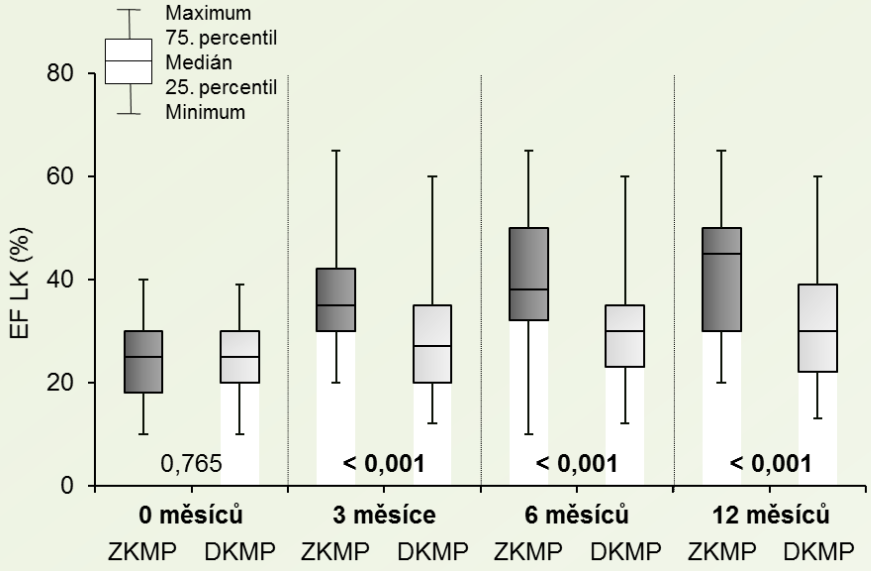
Jde o specifické onemocnění myokardu nebo familiární KMP?

- Familiární DKMP
- Zánětlivá KMP
- Posttachykardická KMP
- Endokrinně podmíněná KMP
- Toxická KMP



- Pátrání po potenciálně reverzibilní příčině dysfunkce LK
- Specifická cílená léčba dle vyvolávající příčiny

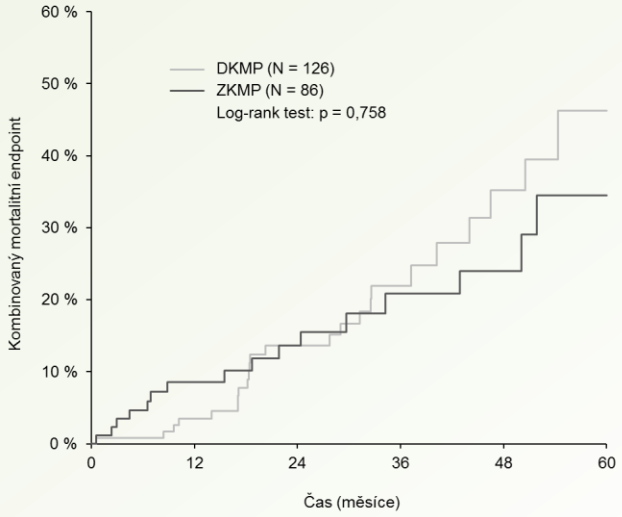
Průkaz myokarditidy, vývoj EF LK a prognóza



Přítomnost myokarditidy znamená větší šanci na zlepšení funkce LK…

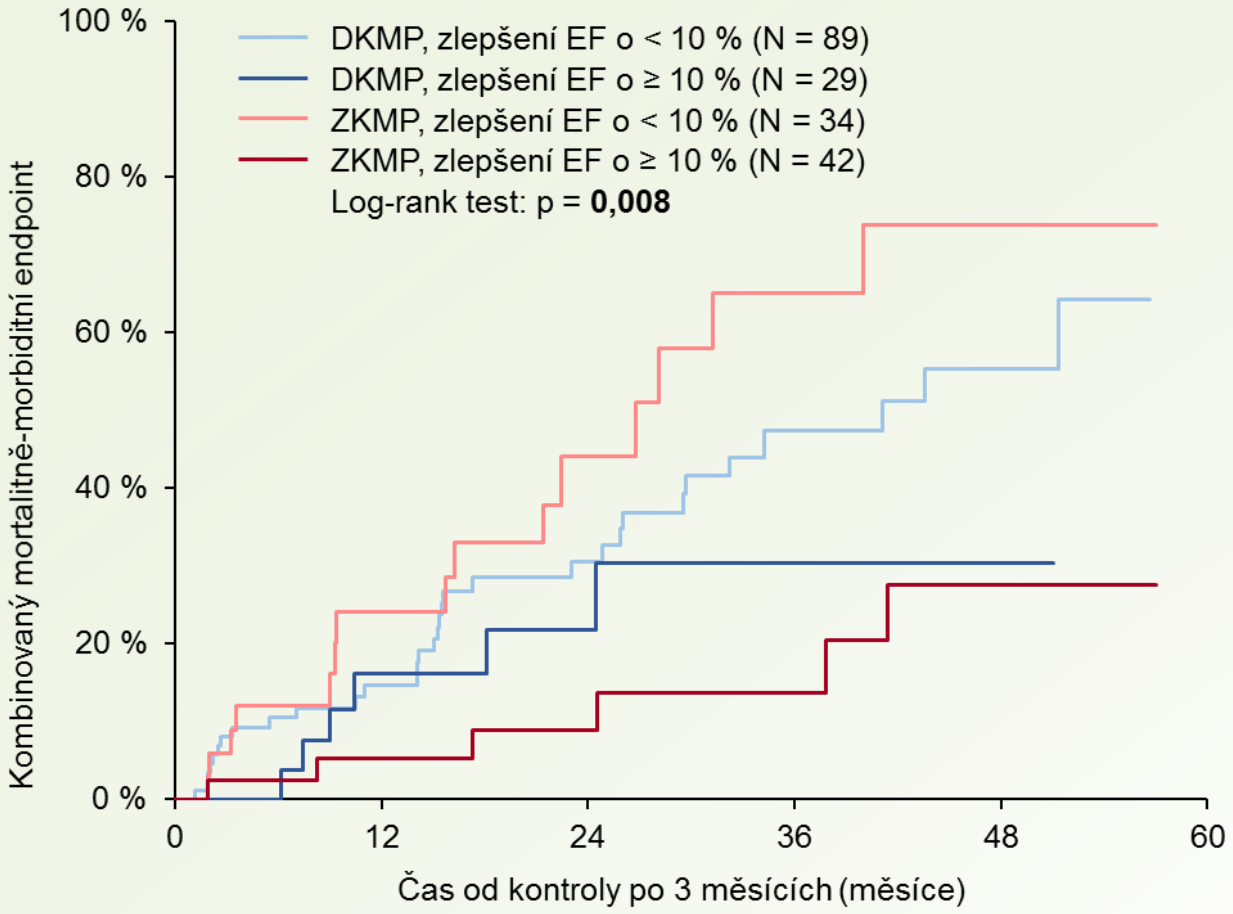
…ale prognóza není významně ovlivněna

Krejčí J, 2017, zatím nepublikováno



Výskyt kombinovaného mortalitního endpointu (95% IS)	
DKMP	**(N = 126)**
6 měsíců	0,8% (0,0%; 2,3%)
1 rok	3,5% (0,1%; 6,8%)
2 roky	13,6% (6,6%; 20,5%)
3 roky	21,9% (12,5%; 31,3%)
4 roky	35,2% (20,9%; 49,4%)
5 let	46,2% (27,6%; 64,9%)
ZKMP	**(N = 86)**
6 měsíců	4,7% (0,2%; 9,1%)
1 rok	8,5% (2,5%; 14,6%)
2 roky	13,6% (5,6%; 21,6%)
3 roky	20,8% (10,0%; 31,6%)
4 roky	24,0% (12,0%; 36,0%)
5 let	34,5% (17,5%; 51,6%)

Vliv přítomnosti zánětu a změny EF LK na prognózu



Krejčí J, 2017, zatím nepublikováno

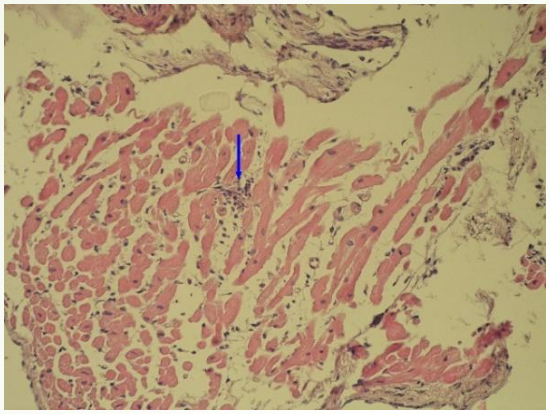
Léčba myokarditid / ZKMP

Recommendations

21. Immunosuppression should be started only after ruling out active infection on EMB by PCR.
22. Based on experience with non-cardiac autoimmune disease, the task group recommends consideration of immunosuppression in proven autoimmune (e.g. infection-negative) forms of myocarditis, with no contraindications to immunosuppression, including giant cell myocarditis, cardiac sarcoidosis, and myocarditis associated with known extra-cardiac autoimmune disease.[10,99]
23. Steroid therapy is indicated in cardiac sarcoidosis in the presence of ventricular dysfunction and/or arrhythmia and in some forms of infection-negative eosinophilic or toxic myocarditis with heart failure and/or arrhythmia.
24. Immunosuppression may be considered, on an individual basis, in infection-negative lymphocytic myocarditis refractory to standard therapy in patients with no contraindications to immunosuppression.

Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

Caforio et al. Eur Heart J. 2013; 34(33):2636-48.



Jaký přínos má imunosupresivní léčba u ZKMP?

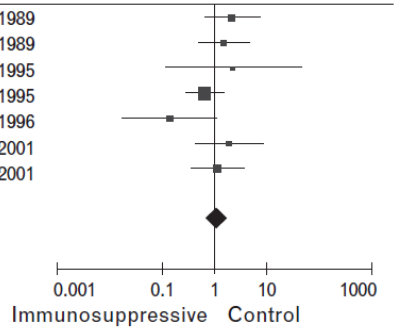
Immunosuppressive treatment for myocarditis: a meta-analysis of randomized controlled trials

Cong Lu[a], Fang Qin[a], Yafei Yan[a], Tong Liu[a], Jing Li[b] and Hang Chen[a]

- **imunosupresivní léčba nemá vliv na mortalitu či nutnost srdeční transplantace**
- **naopak má příznivý efekt na zlepšení systolické funkce a geometrii LK**

Study or subgroup	Immunosuppressive Events	Total	Control Events	Total	Weight	Odds ratio M-H, Fixed, 95% CI	Year	Odds ratio M-H, Fixed, 95% CI
Parrillo JE (1989)	9	49	5	52	11.1%	2.12 [0.66, 6.83]	1989	
Latham RD (1989)	11	23	11	29	14.2%	1.50 [0.49, 4.55]	1989	
Camargo PR (1995)	4	41	0	9	2.0%	2.28 [0.11, 46.13]	1995	
Mason JW (1995)	15	64	15	47	37.1%	0.65 [0.28, 1.52]	1995	
Mirić M (1996)	2	26	3	8	11.9%	0.14 [0.02, 1.06]	1996	
McNamara DM (2001)	6	33	3	29	7.3%	1.93 [0.44, 8.52]	2001	
Wojnicz R (2001)	8	35	8	39	16.4%	1.15 [0.38, 3.48]	2001	
Total (95% CI)		271		213	100.0%	1.08 [0.69, 1.71]		
Total events	55		45					

Heterogeneity: Chi^2 = 7.71, df = 6 (P = 0.26); I^2 = 22%
Test for overall effect: Z = 0.34 (P = 0.74)

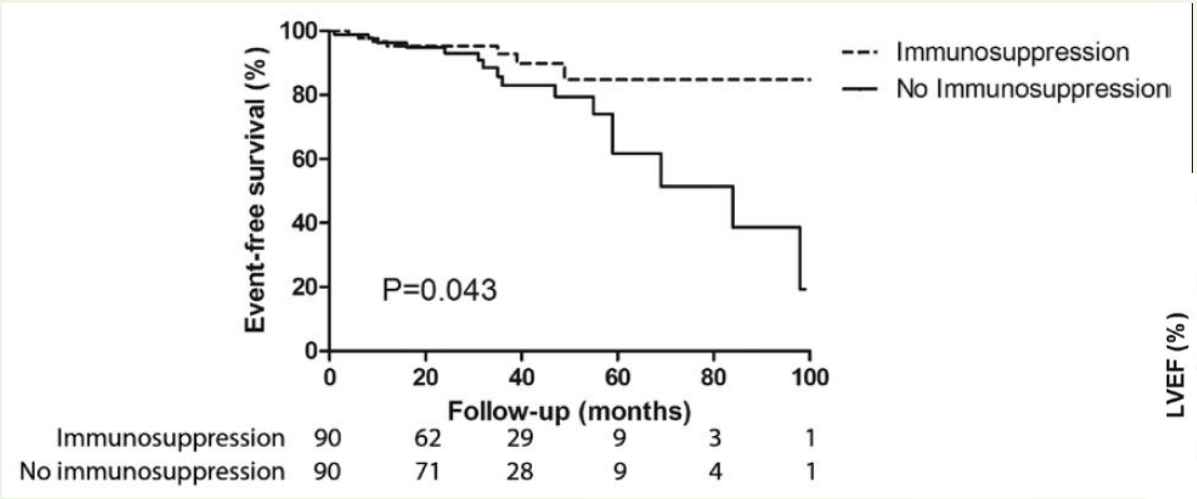


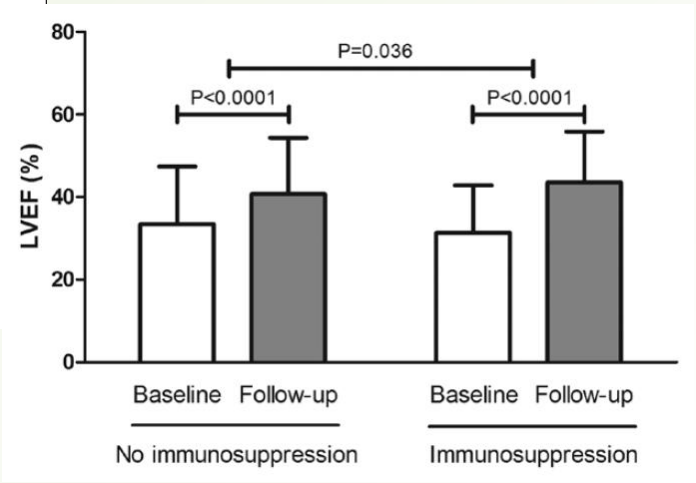
Immunosuppressive treatment versus conventional treatment on the outcome of rate of death or transplantation. Size of squares corresponds to th

Journal of Cardiovascular Medicine 2016;17:631-637

Jaký přínos má imunosupresivní léčba u ZKMP?

Immunosuppressive Therapy Improves Both Short- and Long-Term Prognosis in Patients With Virus-Negative Nonfulminant Inflammatory Cardiomyopathy





Merken et al. *Circ Heart Fail.* 2018;11:e004228. DOI: 10.1161/CIRCHEARTFAILURE.117.004228

Léčba myokarditid / ZKMP

Recommendations

14. Patients with a life-threatening presentation should be sent to specialized units with capability for haemodynamic monitoring, cardiac catheterization, and expertise in EMB.
15. In patients with haemodynamic instability, a mechanical cardio-pulmonary assist device may be needed as a bridge to recovery or to heart transplantation.
16. Cardiac transplantation should be deferred in the acute phase, because recovery may occur, but can be considered for haemodynamically unstable myocarditis patients, including those with giant cell myocarditis, if optimal pharmacological support and mechanical assistance cannot stabilize the patient.

Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

Caforio et al. Eur Heart J. 2013; 34(33):2636-48.

17. Management of ventricular dysfunction should be in line with current ESC guidelines on heart failure.

18. ICD implantation should be deferred until resolution of the acute episode.
19. Arrhythmia management outside the acute phase should be in line with current ESC guidelines on arrhythmia and device implantation.

Jaký je tedy terapeutické přístup ke kardiomyopatiím se sníženou systol. funkcí LK?

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

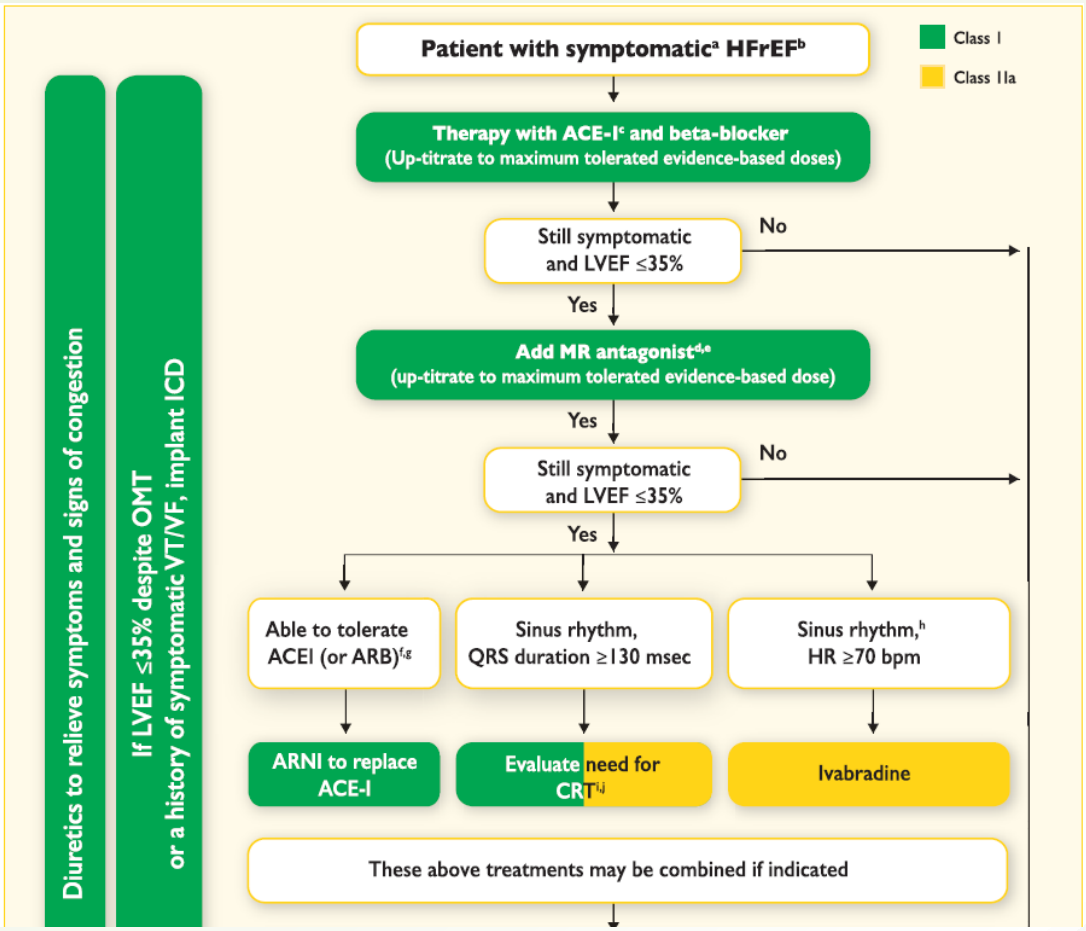
The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Ponikowski et al. Eur Heart J. 2016; 37:2129–2200

z hlediska farmakologické léčby shodný bez ohledu na výsledek EMB

přidání specifické léčby dle výsledku EMB



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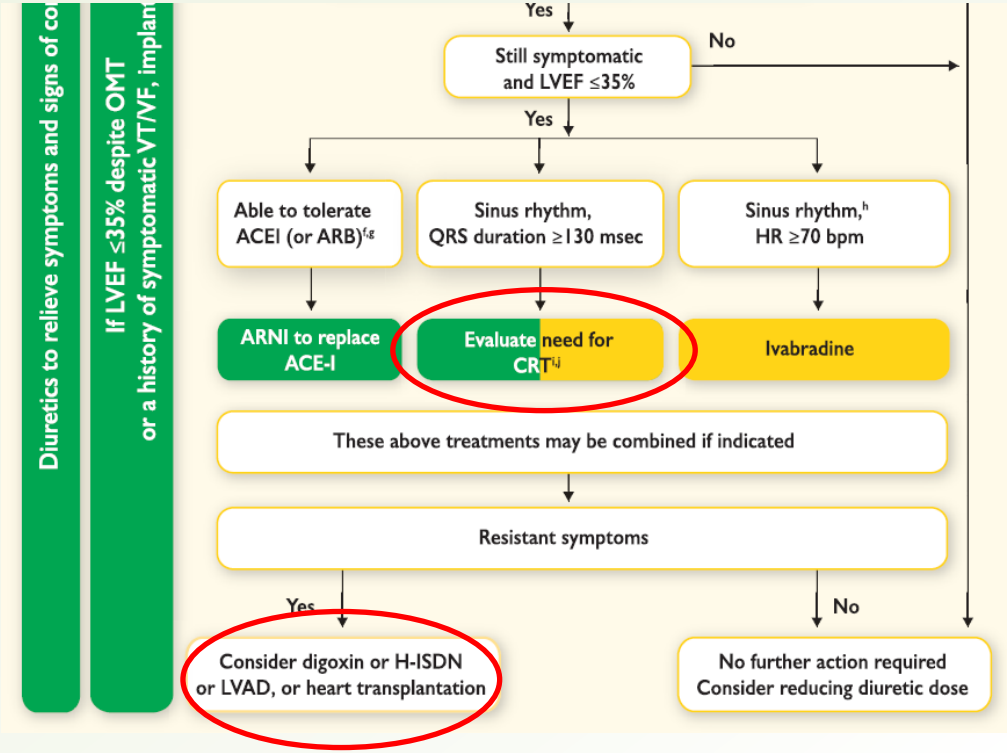
Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Ponikowski et al. Eur Heart J. 2016; 37:2129–2200

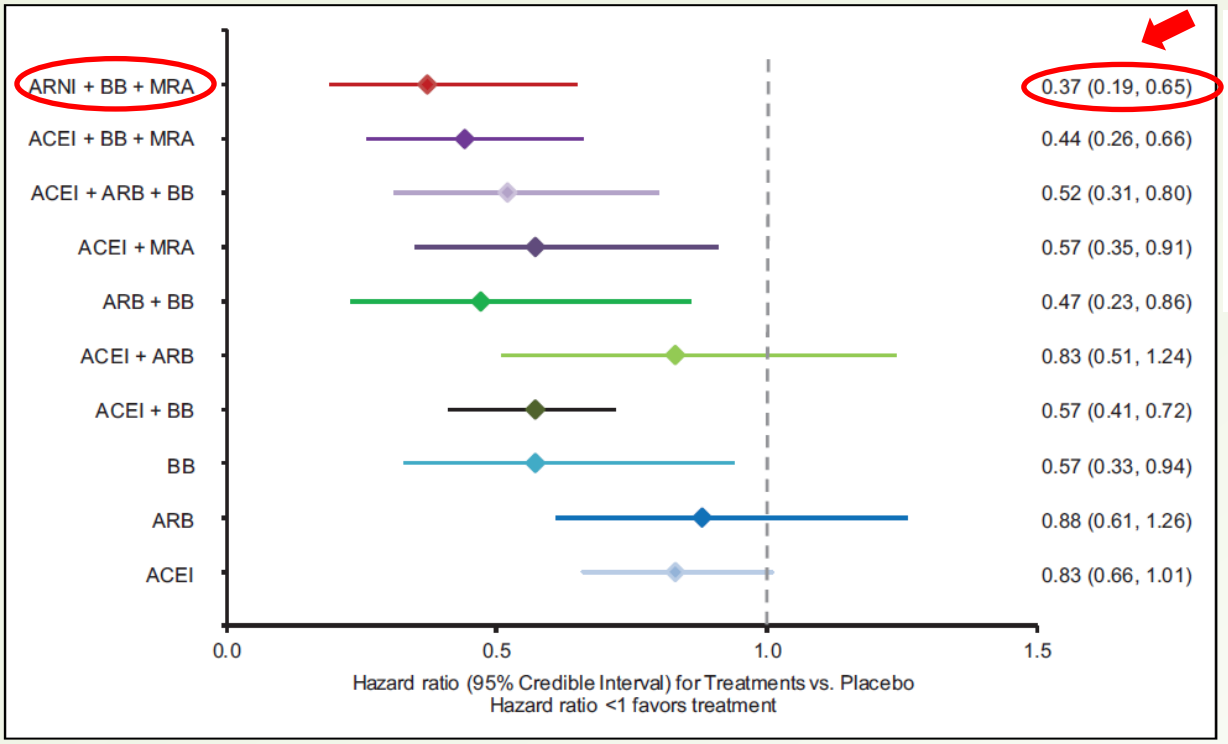
z hlediska nefarmakologické léčby odlišné načasování dle výsledku EMB



Kde jsme s léčbou HFrEF dnes?

Thirty Years of Evidence on the Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction
A Network Meta-Analysis

Heather Burnett, MSc; Amy Earley, BSc; Adriaan A. Voors, MD, PhD; Michele Senni, MD; John J.V. McMurray, MD; Celine Deschaseaux, MSc; Shannon Cope, MSc



63% redukce mortality při kombinaci ARNI + BB + MRA v porovnání s placebem!

Circ Heart Fail. 2017;10:e003529. DOI: 10.1161/CIRCHEARTFAILURE.116.003529.

Co by nás mohlo čekat zanedlouho…?

Cardiovascular & Hematological Agents in Medicinal Chemistry, 2017, *15*, 000-000

REVIEW ARTICLE

Entresto, a New Panacea for Heart Failure?

Peter Khalil[1,*], Ghazal Kabbach[1], Sarmad Said[2] and Debabrata Mukherjee[2]

Vedle rozšíření stávající indikace sacubitril/valsartanu bude důležité také zhodnocení dlouhodobé bezpečnosti vzhledem k dalším efektům inhibice neprilysinu

(snížená degradace amyloidu-β, vzestup endotelinu-1)

Table 1. Major ongoing trials on Entresto.

Trial	Study Description	Comments
PARADISE-MI Prospective ARNI vs ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI	A multi-center, randomized, double blinded, phase 3 trial that compares LCZ696 to Ramipril in patients following AMI. Patients in the LCZ696 arm receive the drug in titrated doses leveling from 1 up to 3 as following; 50, 100, and 200 mg BID. They also receive a Ramipril placebo pill twice daily. Patients in the Ramipril arm receive the drug in titrated doses leveling from 1 up to 3 as following; 1.25, 2.5, and 5 mg twice daily. They also receive LCZ696 placebo pill twice daily. The primary outcome measured is time to first confirmed endpoint; including cardiovascular death, heart failure hospitalization, or outpatient heart failure.	Study started April 2016 Estimated completion date is July 2019 The study is currently active and recruiting new patients.
PARAGON - HF Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction	A multi-center, randomized, double blinded, phase 3 trial that compares LCZ696 to Valsartan in patients with HFpEF. Patients in both arms (LCZ696 and Valsartan arms) went through a single blind run-in period for 3-8 weeks. They first received Valsartan 80 mg BID for 1-2 weeks followed by a safety and tolerability check. Then they received LCZ696 100 mg BID for 2-4 weeks, which was followed by another safety and tolerability check to ensure meeting the safety criteria before the double-blinded randomization for long term (up to 57 months). In the double blinded randomization, the LCZ696 arm patients receive a target dose of 200 mg BID, and patients in the Valsartan arm receive a target dose of 160 mg BID. The primary outcome measured in this study is the cumulative number of hospitalizations secondary to heart failure and events of cardiovascular death.	Study started in July 2014 Estimated completion date is March 2019 The study is currently active, but not recruiting any new patients.
PIONEER-HF ComParIson Of Sacubitril/valsartaN Versus Enalapril on Effect on ntpRobnp in Patients Stabilized From an Acute Heart Failure Episode	A multi-center, randomized, double blinded, phase 4 trial that evaluate the effect of LCZ696 on NT-proBNP levels when started in-hospital after stabilization of HFrEF patients with an acute decompensated heart failure (ADHF) attack, compared to Enalapril. Patients in the LCZ696 arm take two tablets twice daily (one being the LCZ696 and the other pill is an Enalapril matching placebo tablet) with the dose determined and titrated to target dose of 200 mg BID (sacubitril/valsartan 97/103 mg) based on the blood pressure. Patients in the Enalapril arm take two tablets twice daily (one being the Enalapril and the other pill is a LCZ696 matching placebo tablet) with the dose determined and titrated to a target dose of 10 mg BID based on the blood pressure.	Study started in April 2016 Estimated completion date is April 2018 The study is currently active and recruiting new patients.
HFN-LIFE Entresto (LCZ696) In Advanced Heart Failure (LIFE Study)	A single center, randomized, triple blinded, phase 4 trial comparing LCZ696 head to head with Valsartan in HFrEF patients with NYHA class IV symptomatic, advanced heart failure to determine whether treatment with LCZ696 for 24 weeks will improve Pro-B-type Natriuretic Peptide (NT-proBNP) levels. Patients in the LCZ696 arm receive 2 pills twice daily; LCZ696 pill with doses of 50 mg, 100 mg, or 200 mg orally twice daily for 24 weeks, plus a valsartan placebo (to match 40 mg, 80 mg, or 160 mg) orally twice daily for 24 weeks Patients in the Valsartan arm receive 2 pills twice daily; Valsartan pill with doses of 40 mg, 80 mg, or 160 mg orally twice daily for 24 weeks, plus LCZ696 placebo (to match 50 mg, 100 mg, or 200 mg) orally twice daily for 24 weeks	Study started March 2017. Estimated completion date is March 2019. The study is currently active and recruiting new patients.
PARALLAX A Randomized, Double-blind Controlled Study Comparing LCZ696 to Medical Therapy for Comorbidities in HFpEF Patients	A Multi-center, Randomized, Double-blind, phase 3 trial evaluating the effect of LCZ696 on NT-proBNP, symptoms, and exercise in patients with HFpEF. The study goal is to prove superiority of LCZ696 when compared to other medical therapies. The investigators will measure the mean change in NT-proBNP after 12 weeks of treatment and the mean change from baseline in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS) after 24 weeks of treatment. Patients are stratified before randomization into 3 strata based on prior medical therapy; ACEI, ARB, or no RASi (No renin angiotensin system inhibitors). Patients in the ACEI strata receive either LCZ696 or Enalapril plus a placebo pill twice daily	Study started September 2017 Estimated completion date is September 2019 The study is currently active and recruiting new patients.
	Patients in the ARB strata receive either LCZ696 or Valsartan plus a placebo pill twice daily Patients in the no RASi strata receive either LCZ696 or a placebo pill. LCZ696 is given in 3 different doses of 50 mg, 100 mg and 200 mg twice daily orally. Enalapril is given in doses; 2.5 mg, 5 mg and 10 mg twice daily. While Valsartan is given in the following doses; 40 mg, 80 mg and 160 mg twice daily.	
OUTSTEP-HF randOmized stUdy Using accelerometeRy to Compare Sacubitril/valsarTan and Enalapril in Patients With Heart Failure	A Multi-center, Randomized, Double-blind, phase 3 trial to evaluate the effect of LCZ696 vs. Enalapril on daily physical activity using an accelerometer device worn by HFrEF patients. Patients in the LCZ696 arm receive LCZ696 and a placebo pill twice daily. LCZ696 is initiated at a starting dose of 50 mg twice daily and titrated up to 100 mg twice daily after 2 weeks, then to a target dose of 200 mg twice daily after another 2 weeks, provided that patient has no safety or tolerability concerns. Patients in the Enalapril group receive Enalapril and a placebo pill twice daily. Enalapril is initiated at a starting dose of 2.5 mg twice daily and titrated up to 5 mg twice daily after 2 weeks, then to a target dose of 10 mg twice daily after another 2 weeks, provided that patient has no safety or tolerability concerns.	Study started December 2016 Estimated completion date is January 2018 The study is currently active and recruiting new patients.

Závěry

- Srdeční selhání je obvykle jedním ze základních symptomů kardiomyopatií
- Problematika kardiomyopatií je široká, komplikovaná…a často nejasná
- Léčba se odvíjí od doporučení pro léčbu srdečního selhání
- Narůstající výskyt srdečních amyloidóz u nemocných manifestujících se jako HKMP či RKMP (tzn. HFpEF) - nová léčba na obzoru!
- Častý výskyt myokarditid u nemocných manifestujících se jako DKMP (tzn. HFrEF) - cílená léčba pro vybrané nemocné!
- Důležitost jejich správné dif. dg. s ohledem na možnosti jejich cílené léčby

Děkuji za pozornost!