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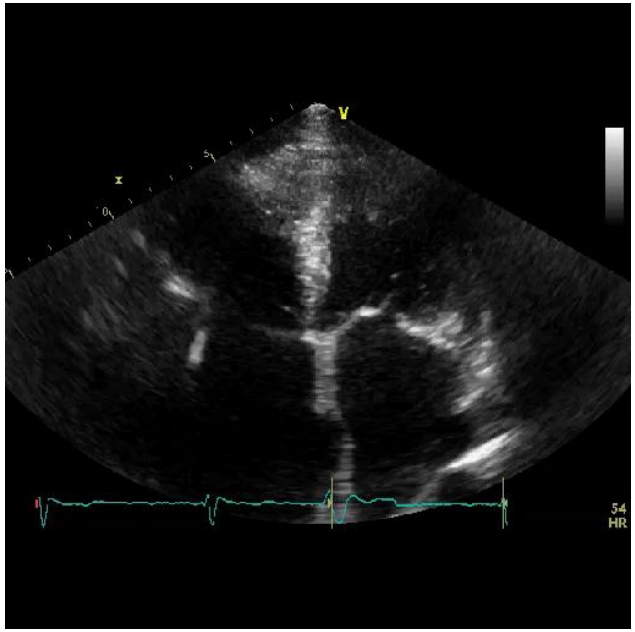
Léčba restriktivní kardiomyopatie

Jan Krejčí

I. interní kardioangiologická klinika FNUSA a LF MU v Brně

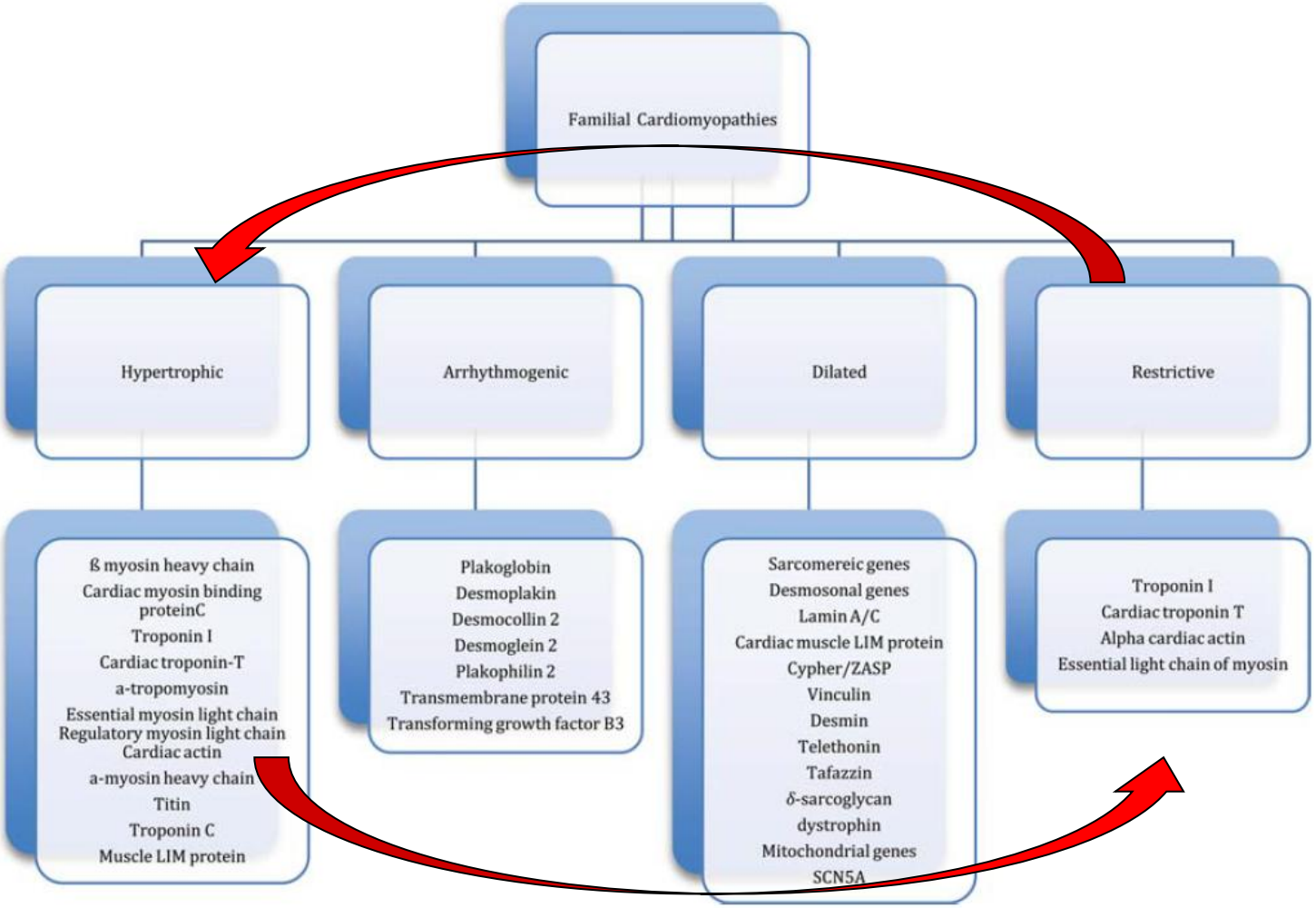
RKMP

- Nejméně častá kardiomyopatie
- Typický zástupce srdečního selhání se středně sníženou (HFmrEF) či se zachovanou ejekční frakcí levé komory (HFpEF)
- Terminální fenotyp některých jiných typů KMP
- Genotypový překryv



Genetics of inherited cardiomyopathy

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



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

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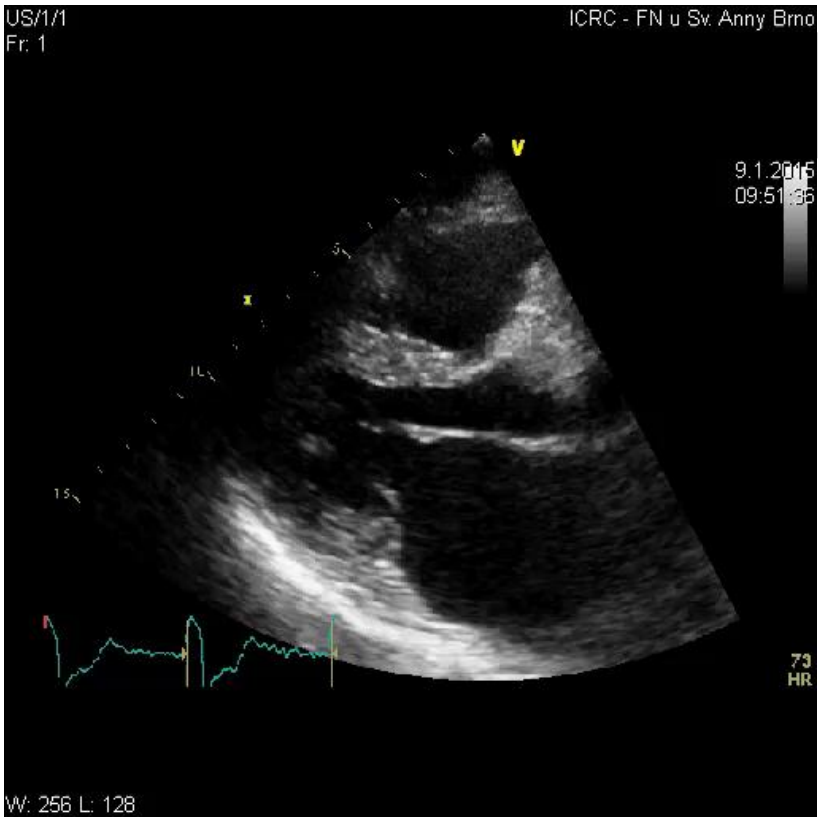
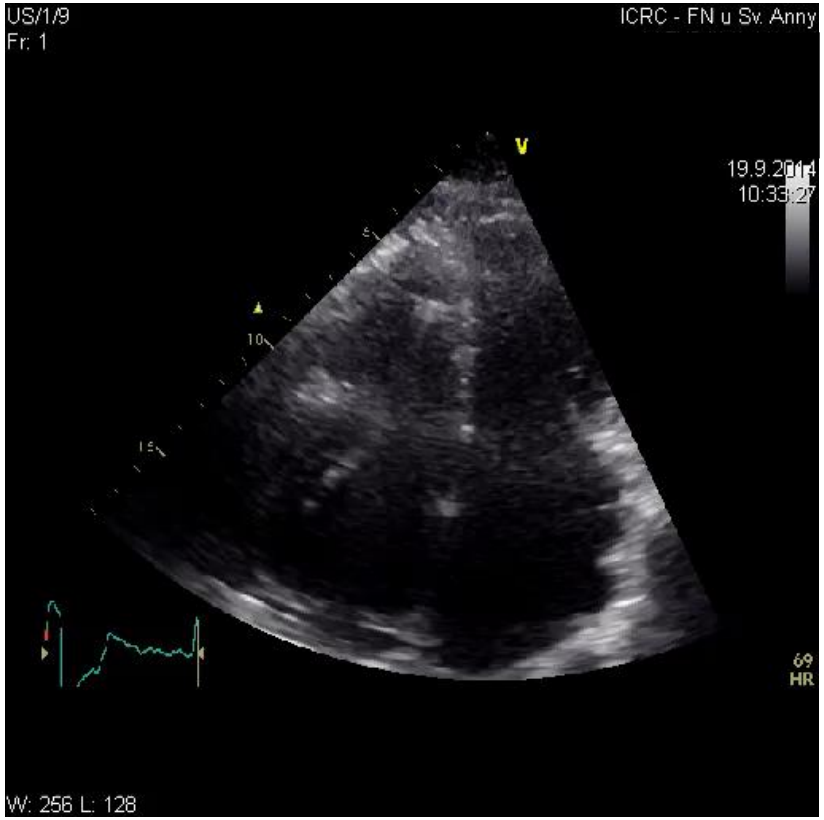
Cardiomyopathy

Prevalence, Clinical Significance, and Genetic Basis of Hypertrophic Cardiomyopathy With Restrictive Phenotype

Toru Kubo, MD,*† Juan R. Gimeno, MD,* Ajay Bahl, MD,* Ulla Steffensen,* Morten Steffensen,* Eyman Osman, BSc,* Rajesh Thaman, MD,* Jens Mogensen, MD, PhD,*‡ Perry M. Elliott, MD, FACC,* Yoshinori Doi, MD, FACC,† William J. McKenna, MD, FACC*





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Léčba HFmrEF/HFpEF ...tedy RKMP

Doporučení pro... | Guidelines

Souhrn Doporučených postupů ESC pro diagnostiku a léčbu akutního a chronického srdečního selhání z roku 2016.

Připraven Českou kardiologickou společností

EUROPEAN SOCIETY OF CARDIOLOGY

ČESKÁ KARDIOLOGICKÁ SPOLEČNOST
THE CZECH SOCIETY OF CARDIOLOGY

(Summary of the 2016 ESC Guidelines on the diagnosis and treatment of acute and chronic heart failure. Prepared by the Czech Society of Cardiology)

Jindřich Špinar[a], Jaromír Hradec[b], Lenka Špinarová[c], Jiří Vítovec[c]

Doporučení pro léčbu pacientů se srdečním selháním se zachovanou ejekční frakcí (HFpEF) a pacientů se srdečním selháním s ejekční frakcí ve středním pásmu (HFmrEF)

Doporučení	Třída[a]	Úroveň[b]
Doporučuje se screening pacientů s HFpEF nebo HFmrEF z hlediska jak kardiovaskulárních, tak nekardiovaskulárních přidružených onemocnění; pokud jsou přítomna, je nutno je léčit za předpokladu, že existují bezpečné a účinné postupy/intervence ke zmírnění symptomů, zlepšení pocitu pohody a/nebo prognózy.	I	C
U pacientů s městnáním a s HFpEF nebo HFmrEF se ke zmírnění symptomů a známek doporučuje podání diuretik.	I	B

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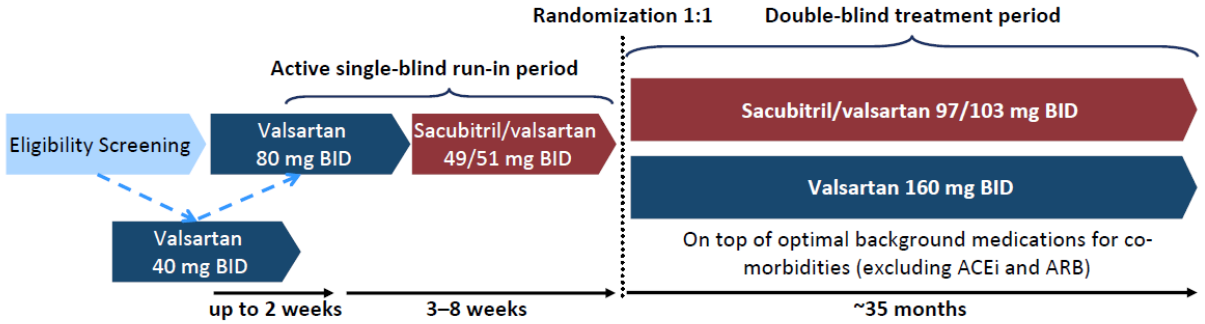
Novinky v léčbě HFmrEF/HFpEF

PARAGON-HF study design

Randomized, double-blind, active comparator trial testing the hypothesis that sacubitril/valsartan, compared with valsartan, would reduce the composite outcome of total HF hospitalizations and CV death



Primary Endpoint
Composite of total (first and recurrent) HF hospitalizations and CV death

Secondary Endpoints:
- Improvement in NYHA functional classification at 8 months
- Changes in KCCQ clinical summary score at 8 months
- Time to first occurrence of worsening renal function
- Time to all-cause mortality

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Solomon SD, *et al. JACC-Heart Fail* 2017; 5(7):471-482.

PARAGONHF

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Zařazovací kritéria studie PARAGON

Key inclusion & exclusion criteria

Key inclusion criteria

- ≥ 50 years of age and LVEF ≥ 45%
- Heart failure signs/symptoms (NYHA Class II–IV) requiring treatment with diuretic(s) for at least 30 days prior to enrollment
- Structural heart disease (LAE or LVH by echocardiography)
- Elevation in natriuretic peptides
  - NT-proBNP 200 pg/ml if hospitalized for HF within 9 months, and 300 pg/ml if not hospitalized; 3-fold increase for patients in AF at enrollment

HFmrEF	HFpEF
Symptomy ± známky[a]	Symptomy ± známky[a]
EFLK 40–49 %	EFLK ≥ 50 %
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)

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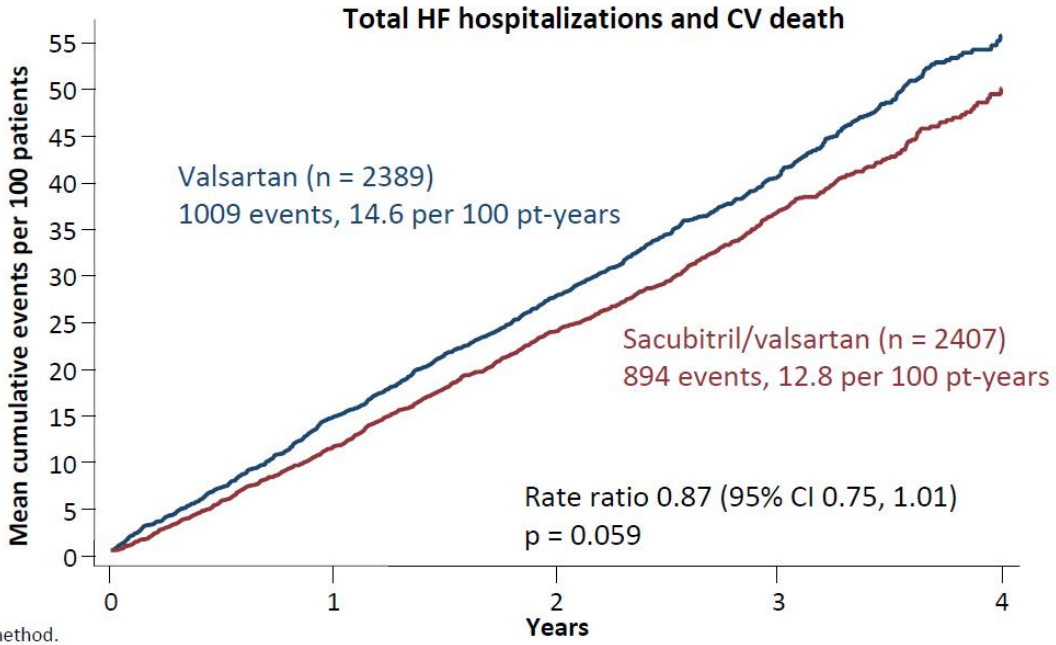
Solomon SD, *et al. JACC-Heart Fail* 2017

PARAGONHF

Novinky v léčbě HFmrEF/HFpEF

PARAGON-HF primary results

Recurrent event analysis of total HF hospitalizations and CV death*



*Semiparametric LWYY method.

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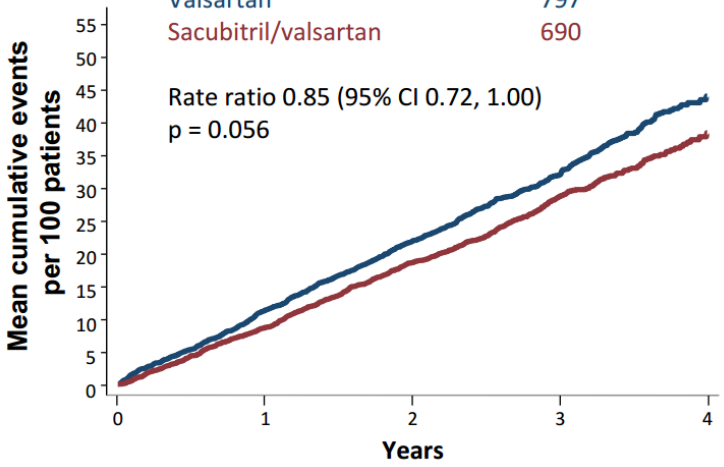
Novinky v léčbě HFmrEF/HFpEF

HF hospitalizations and CV death

HF hospitalizations*

	Events
Valsartan	797
Sacubitril/valsartan	690

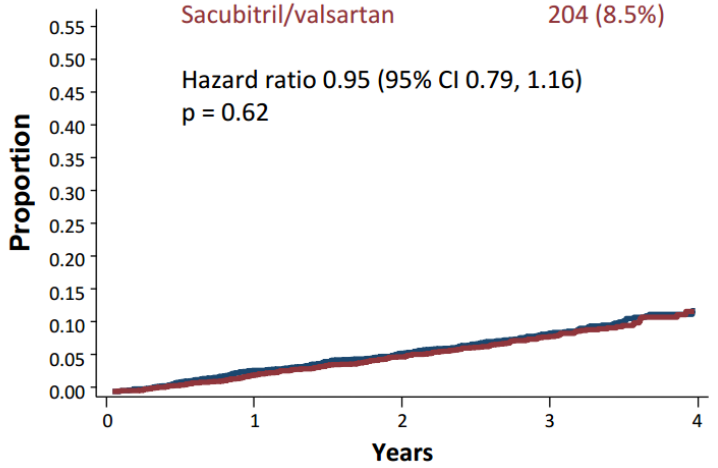
Rate ratio 0.85 (95% CI 0.72, 1.00)
p = 0.056



CV death*

	Patients
Valsartan	212 (8.9%)
Sacubitril/valsartan	204 (8.5%)

Hazard ratio 0.95 (95% CI 0.79, 1.16)
p = 0.62



*Semiparametric LWYY method

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Novinky v léčbě HFmrEF/HFpEF

Conclusions

In patients with HFpEF, when comparing sacubitril/valsartan to valsartan, we observed a modest non-significant ~13% reduction in the primary outcome overall, which was driven mainly by a reduction in first and recurrent HF hospitalizations

Several sensitivity analyses and secondary analyses, including improvement in various measures of symptoms, quality of life, and renal function, suggested benefits with sacubitril/valsartan compared with valsartan

The use of an angiotensin receptor blocker as an active comparator, which we felt necessary because of the large number of patients with HFpEF already on RAS inhibitors, may have attenuated our overall treatment effect

Our data suggest heterogeneity in the treatment response, with suggestion of greater benefit in women and in individuals with lower LVEF

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*

Table I 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

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.

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

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Co nového je tedy v léčbě HFmrEF/HFpEF…tedy RKMP?

ESC European Society of Cardiology
European Journal of Heart Failure (2019)
doi:10.1002/ejhf.1531

CONSENSUS DOCUMENT

Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology

Petar M. Seferovic[1], Piotr Ponikowski[2], Stefan D. Anker[3]*, Johann Bauersachs[4], Ovidiu Chioncel[5], John G.F. Cleland[6], Rudolf A. de Boer[7], Heinz Drexel[8], Tuvia Ben Gal[9], Loreena Hill[10], Tiny Jaarsma[11], Ewa A. Jankowska[2], Markus S. Anker[12], Mitja Lainscak[13], Basil S. Lewis[14], Theresa McDonagh[15], Marco Metra[16], Davor Milicic[17], Wilfried Mullens[18], Massimo F. Piepoli[19], Giuseppe Rosano[20], Frank Ruschitzka[21], Maurizio Volterrani[22], Adriaan A. Voors[7], Gerasimos Filippatos[23], and Andrew J.S. Coats[24]*

ESC European Society of Cardiology
European Journal of Heart Failure (2019) 21, 553–576
doi:10.1002/ejhf.1461

POSITION PAPER

Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology

Petar M. Seferović[1,2]*, Marija Polovina[1,3], Johann Bauersachs[4], Michael Arad[5], Tuvia Ben Gal[6], Lars H. Lund[7], Stephan B. Felix[8], Eloisa Arbustini[9], Alida L.P. Caforio[10], Dimitrios Farmakis[11], Gerasimos S. Filippatos[11], Elias Gialafos[12], Vladimir Kanjuh[2], Gordana Krljanac[1,3], Giuseppe Limongelli[13], Aleš Linhart[14], Alexander R. Lyon[15], Ružica Maksimović[1,16], Davor Miličić[17], Ivan Milinković[3], Michel Noutsias[18], Ali Oto[19], Öztekin Oto[20], Siniša U. Pavlović[1,21], Massimo F. Piepoli[22], Arsen D. Ristić[1,3], Giuseppe M.C. Rosano[23], Hubert Seggewiss[24], Milika Ašanin[1,3], Jelena P. Seferović[25,26], Frank Ruschitzka[27], Jelena Čelutkiene[28,29], Tiny Jaarsma[30], Christian Mueller[31], Brenda Moura[32], Loreena Hill[33], Maurizio Volterrani[34], Yuri Lopatin[35], Marco Metra[36], Johannes Backs[37,38], Wilfried Mullens[39,40], Ovidiu Chioncel[41,42], Rudolf A. de Boer[43], Stefan Anker[44,45,46], Claudio Rapezzi[47], Andrew J.S. Coats[48,49], and Carsten Tschöpe[50]

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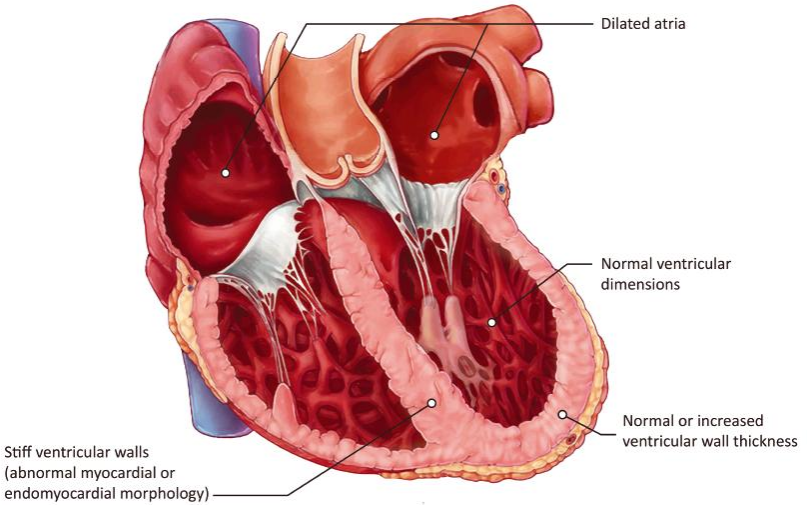

Restrictive cardiomyopathy

Noninfiltrative disorders	Infiltrative disorders	Storage diseases	Endomyocardial disorders

• Idiopathic
• Hereditary (sarcomere protein disorders, myofibrillar myopathies, Werner syndrome)
• Systemic sclerosis
	• Amyloidosis:
	  ○ Immunoglobulin light chain (AL)
	  ○ Hereditary (ATTR-m)
	  ○ Wild-type (ATTR-wt)
	  ○ Other
	• Sarcoidosis
	• Hereditary hyperoxaluria
		• Anderson-Fabry disease
		• Danon disease
		• Pompe disease
		• Gaucher disease
		• Iron overload
		• Hereditary haemochromatosis
			• Carcinoid
			• Endomyocardial fibrosis (idiopathic, hypereosinophilic syndrome, drug-related)
			• Endocardial fibroelastosis
			• Metastatic tumor
			• Chemotherapy
			• Radiation therapy

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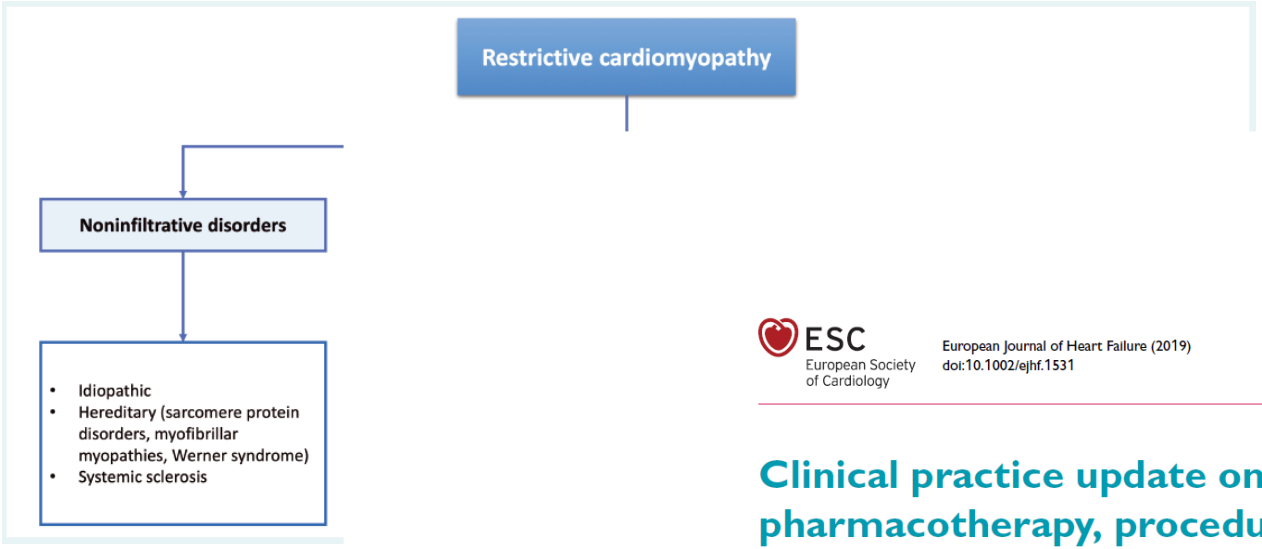

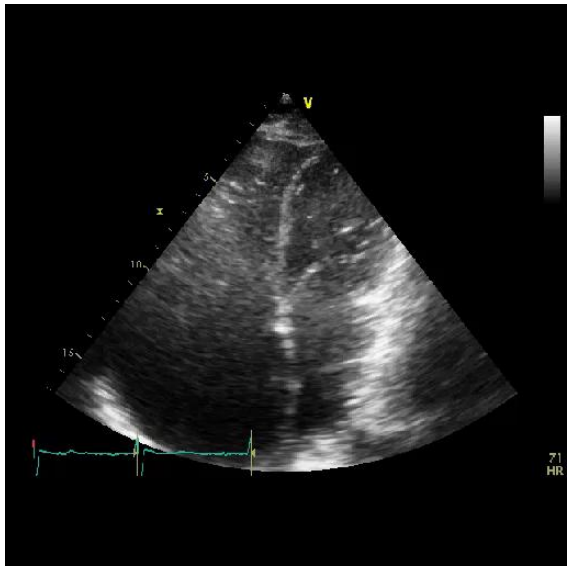

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Beta-blockers for heart failure with mid-range ejection fraction

Consensus recommendation

A beta-blocker *may be considered* for ambulatory patients with symptomatic HFmrEF in sinus rhythm in order to reduce the risk of all-cause and CV death.

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A beta-blocker *may be considered* symptomatic HFmrEF in sinus rhy of all-cause and CV death.

Candesartan for heart failure with mid-range ejection fraction

Consensus recommendation

Candesartan *may be considered* for ambulatory patients with symptomatic HFmrEF in order to reduce the risk of HF hospitalization and CV death.

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Candesartan for heart failure with mid-range ejection fraction

Consensus recommendation

Candesartan *may be conside* tomatic HFmrEF in order t and CV death.

Spironolactone for heart failure with mid-range ejection fraction

Consensus recommendation

Spironolactone *may be considered* for ambulatory patients with symptomatic HFmrEF without contraindications in order to reduce the risk of CV death and HF hospitalization.

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Consensus recommendation

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Spironolactone for heart failure with mid-range ejection fraction

Consensus recommendation

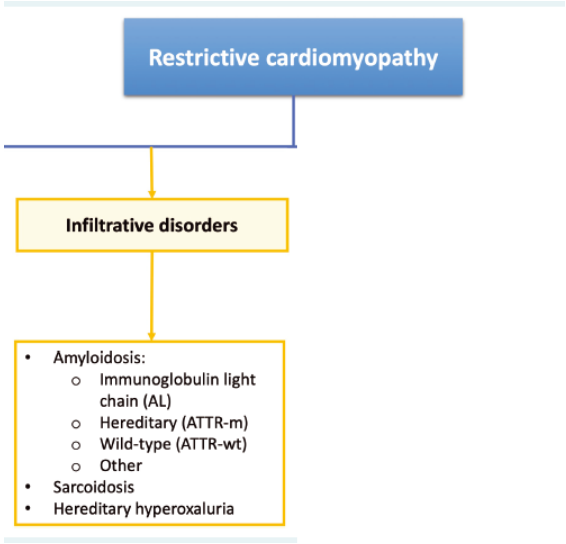
Spironolactone *may be considered* for ambulatory patients with in order to reduce

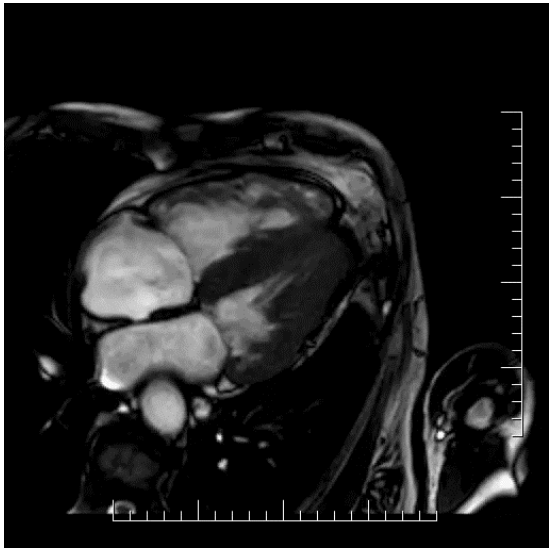
Cardiac contractility modulation

Consensus recommendation

Cardiac contractility modulation (CCM) *may be considered* in patients with HFrEF (LVEF 25–45%) and a narrow QRS complex (<130 ms) in order to improve exercise capacity, quality of life and alleviate HF symptoms.

Léčba RKMP





- **Srdeční amyloidóza není jedno onemocnění**
- **Zásadní význam diferenciální dg. jednotlivých typů srdečních amyloidóz**
- **Symptomatická léčba je obdobná, kazuální léčba je odlišná!**

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Symptomatická léčba

- **Městnavé srdeční selhání**
  diuretika (furosemid) + antagonisté aldosteronu

Curr Probl Cardiol. 2018 Jan;43(1):10-34. doi: 10.1016/j.cpcardiol.2017.04.003. Epub 2017 Apr 13.

Cardiac Amyloidosis: An Updated Review With Emphasis on Diagnosis and Future Directions.

Bhogal S, Ladia V, Sitwala P, Cook E, Bajaj K, Ramu V, Lavie CJ, Paul TK.

Nedoporučeno:

Digoxin zvýšená toxicita vazbou na amyloidní fibrily

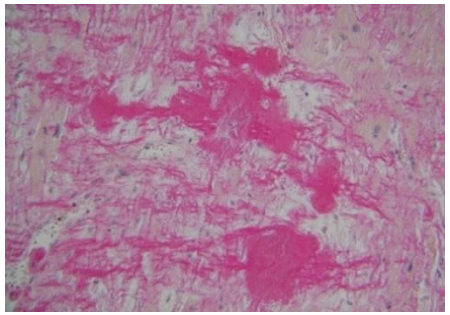
ACEI/ARB hypotenze, zhoršení renální insuficience

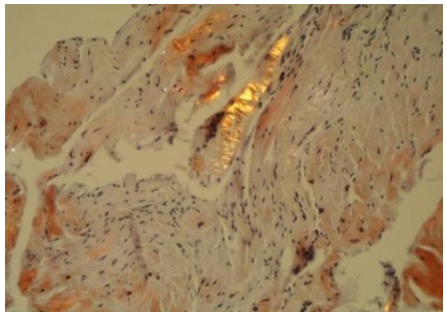
BB + CaA hypotenze, zhoršení systolické funkce LK

Kauzální léčba – obecné zásady

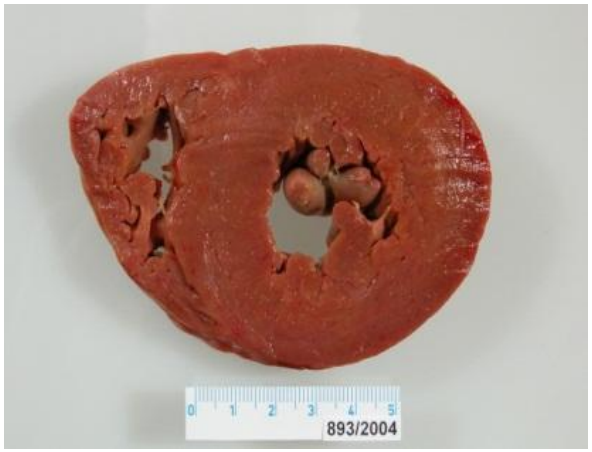
- **Liší se u jednotlivých typů srdečních amyloidóz**

- **Zabránit produkci amyloidogenních bílkovin**
- **Zabránit tvorbě amyloidních hmot**
- **Indukovat degradaci již vytvořeného amyloidu v orgánech a tkáních**





Z archivu MUDr. Žampachové

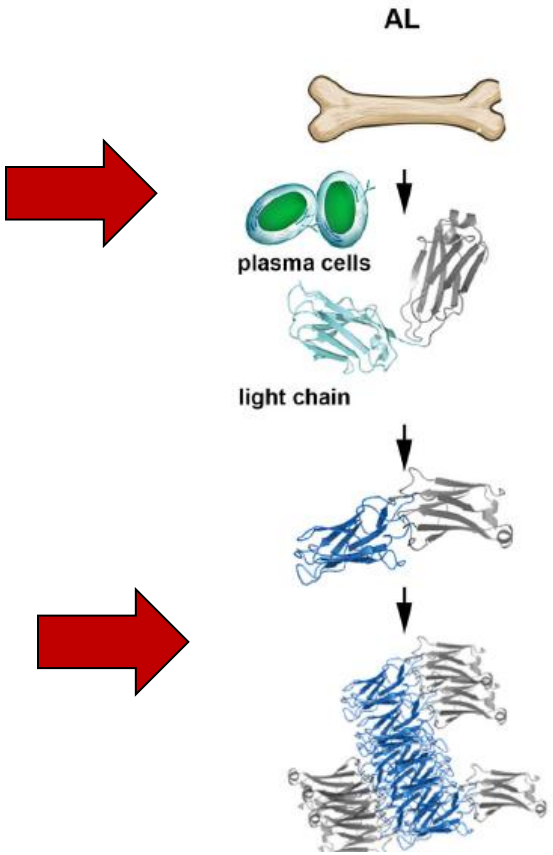


Z archivu prof. Šteinera

Kauzální léčba – light chain amyloidosis

- **Zabránit produkci amyloidogenních bílkovin**

- **Indukovat degradaci již vytvořeného amyloidu v orgánech a tkáních**



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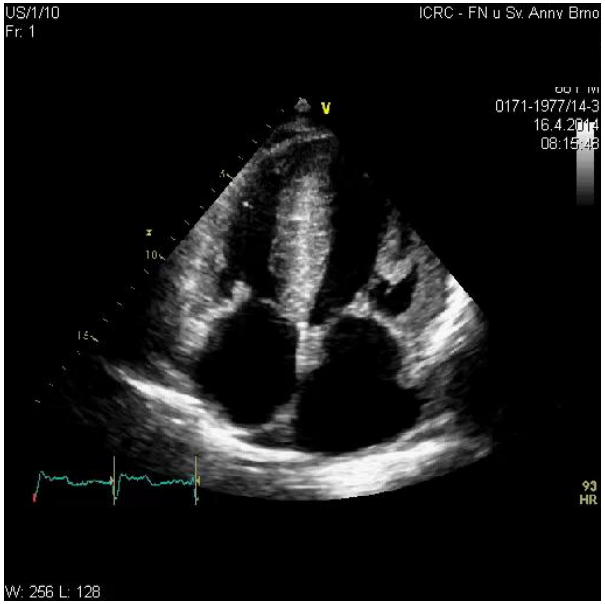
Kauzální léčba – light chain amyloidosis

- postižení plazmatických bb kostní dřeně
- hematologická léčba (ASCT, Mel + Dex, bortezomib, thalidomid, lenalidomid)

- Ale v případě:
  - ✓ EF LK pod 45%
  - ✓ NYHA III-IV
  - ✓ sTK pod 100mmHg
  - ✓ NTproBNP nad 8500 ng/l

  je ASCT kontraindikována!



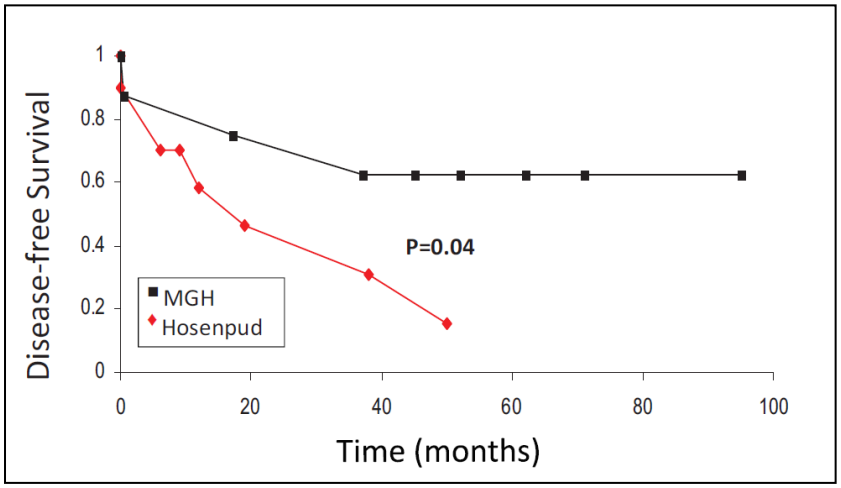
Blood. 2013;121(26):5124-5130

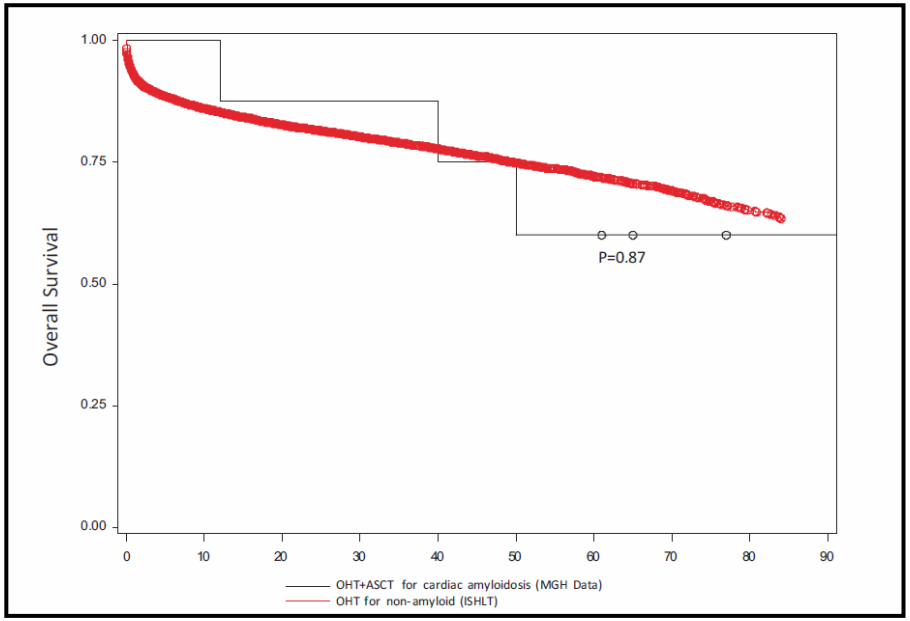
Kauzální léčba – AL
HTx + ASCT

- **transplantace srdce umožní následnou kurativní léčbou AL (tedy ASCT) u nemocných s izolovaně (dominantně) kardiálním postižením**
- **prognózu určuje úspěch hematologické léčby**

Cardiac Transplantation Followed by Dose-Intensive Melphalan and Autologous Stem-Cell Transplantation for Light Chain Amyloidosis and Heart Failure

Bimalangshu R. Dey,[1] Stephen S. Chung,[1] Thomas R. Spitzer,[1] Hui Zheng,[2] Thomas E. MacGillivray,[3] David C. Seldin,[4] Steven McAfee,[1] Karen Ballen,[1] Eyal Attar,[1] Thomas Wang,[5] Jordan Shin,[5] Christopher Newton-Cheh,[5] Stephanie Moore,[5] Vaishali Sanchorawala,[4] Martha Skinner,[4] Joren C. Madsen,[3] and Marc J. Semigran[5,6]





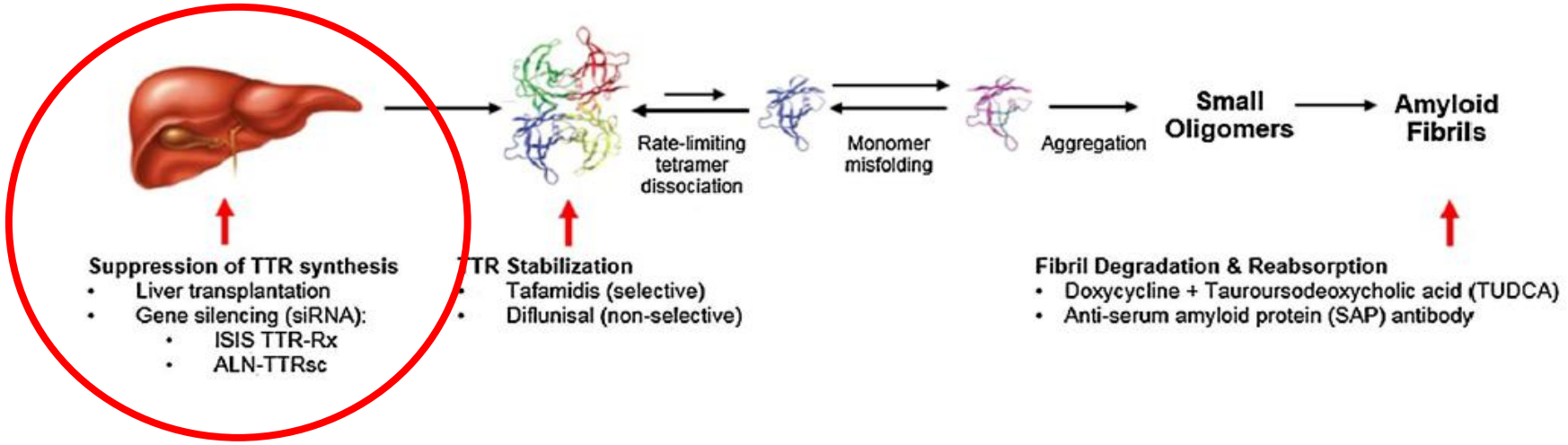
Transplantation 2010;90: 905–911

Kauzální léčba – ATTR-CMP

Natural history and therapy of TTR-cardiac amyloidosis: emerging disease-modifying therapies from organ transplantation to stabilizer and silencer drugs

Adam Castaño · Brian M. Drachman · Daniel Judge · Mathew S. Maurer

Heart Fail Rev (2015) 20:163–178

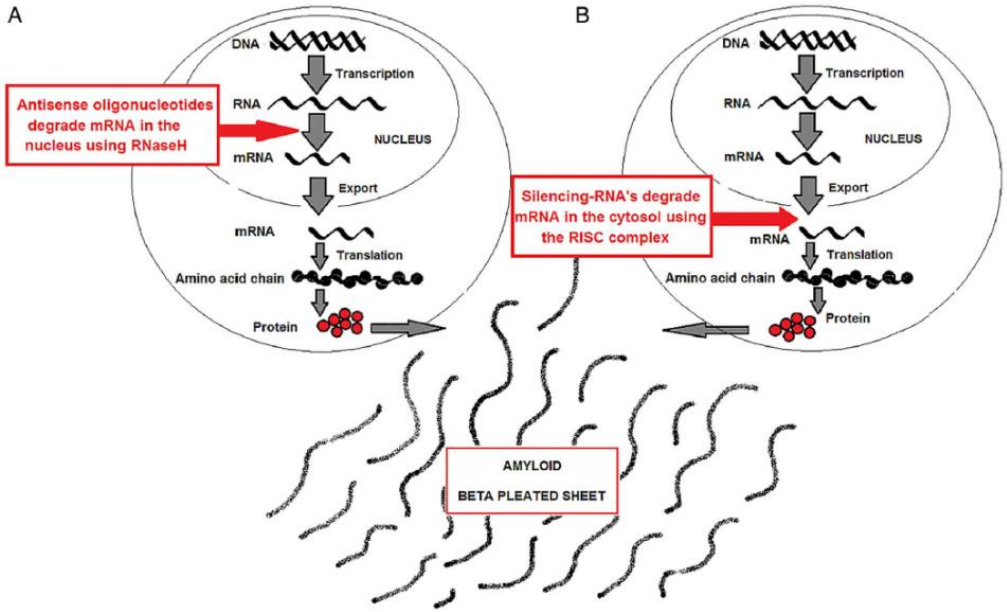


Kauzální léčba - ATTR

The transthyretin amyloidoses: advances in therapy

Simon Dubrey,[1] Elizabeth Ackermann,[2] Julian Gillmore[3]

- **ASO a siRNA (patisiran)**
- **Vazbou na mRNA vedou k její degradaci**
- **Brání transkripci mRNA, a tím produkci TTR**



Postgrad Med J 2015;**91**:439–448

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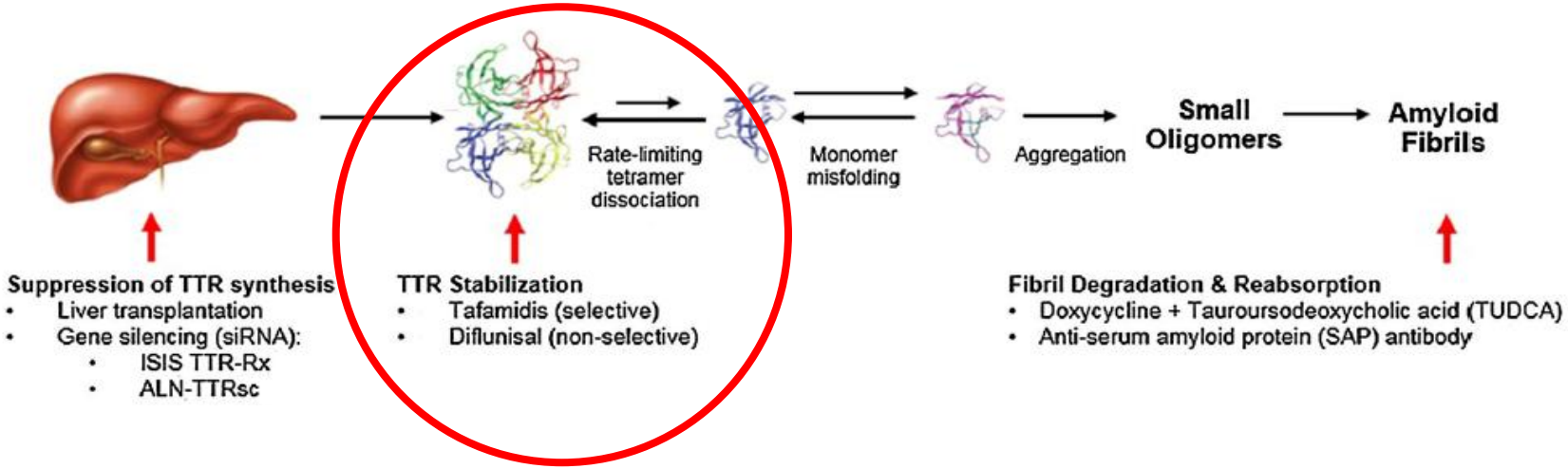

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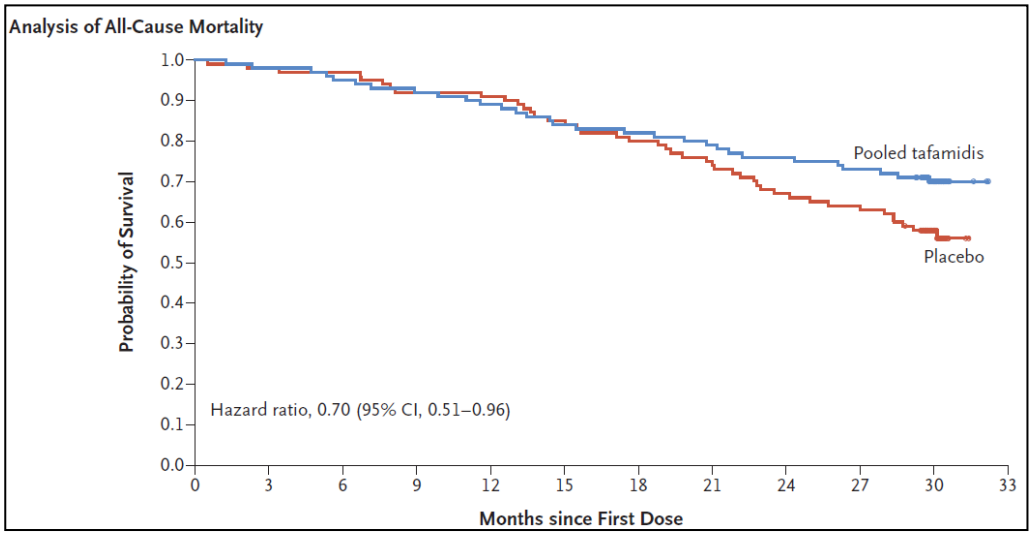
Kauzální léčba – ATTR-CMP

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D., Balarama Gundapaneni, M.S., Perry M. Elliott, M.D., Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D., Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D., Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D., Mazen Hanna, M.D., Daniel P. Judge, M.D., Alexandra I. Barsdorf, Ph.D., Peter Huber, R.Ph., Terrell A. Patterson, Ph.D., Steven Riley, Pharm.D., Ph.D., Jennifer Schumacher, Ph.D., Michelle Stewart, Ph.D., Marla B. Sultan, M.D., M.B.A., and Claudio Rapezzi, M.D., for the ATTR-ACT Study Investigators*

- **Studie ATTRACT fáze III**
- **441 pacientů**
- **30 měsíců follow-up**
- **tafamidis - stabilizace tetrameru TTR**



30% redukce mortality

C Frequency of Cardiovascular-Related Hospitalizations

	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations	Cardiovascular- Related Hospitalizations	Pooled Tafamidis vs. Placebo Treatment Difference
		total no. (%)	*no. per yr*	*relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	0.68 (0.56–0.81)
Placebo	177	107 (60.5)	0.70	

32% redukce KV hospitalizací

N Engl J Med 2018;379:1007-16.

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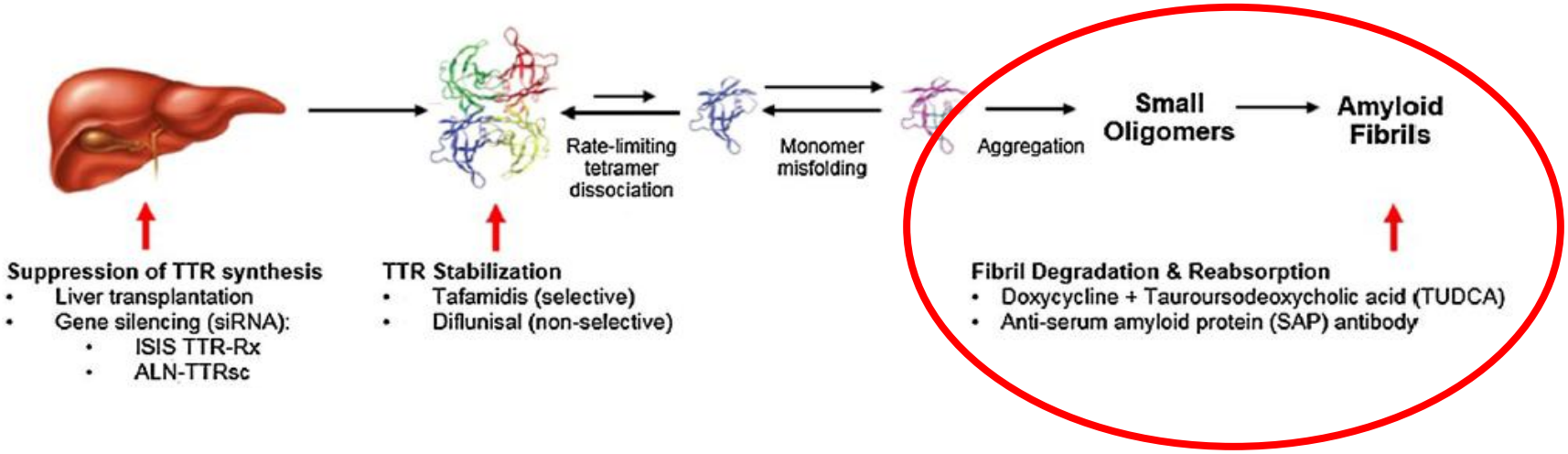

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Kauzální léčba - ATTR

- **regrese již vytvořených amyloidních depozit poškozujících cílové orgány**
- **sérum amyloid P component je součástí amyloidních depozit, protilátky proti SAP iniciují C3 indukovanou degradaci amyloidních hmot**

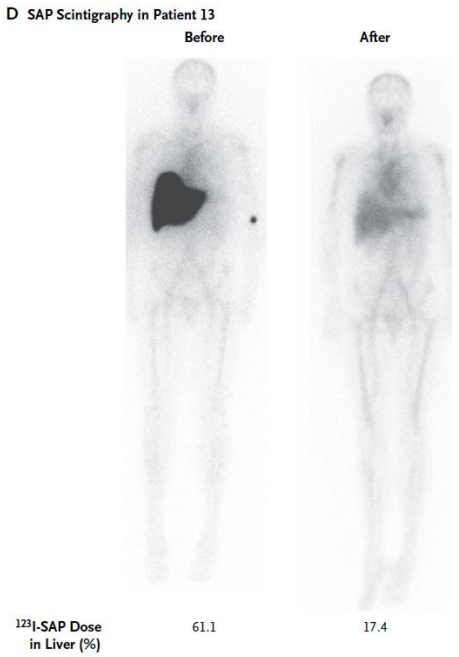
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component

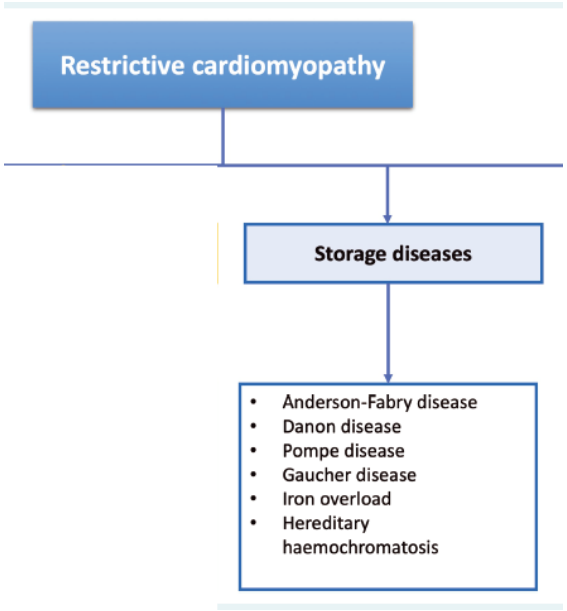
Duncan B. Richards, D.M., Louise M. Cookson, B.Sc., Alienor C. Berges, Pharm.D., Sharon V. Barton, M.Sc., Thirusha Lane, R.N., M.Sc., James M. Ritter, D.Phil., F.Med.Sci., Marianna Fontana, M.D., James C. Moon, M.D., Massimo Pinzani, M.D., Ph.D., Julian D. Gillmore, M.D., Ph.D., Philip N. Hawkins, Ph.D., F.Med.Sci., and Mark B. Pepys, Ph.D., F.R.S.

15 pacientů
follow-up 6 týdnů



N Engl J Med 2015;373:1106-14

Léčba RKMP



JIMD
JOURNAL OF INHERITED METABOLIC DISEASE
SSIEM

Original Article

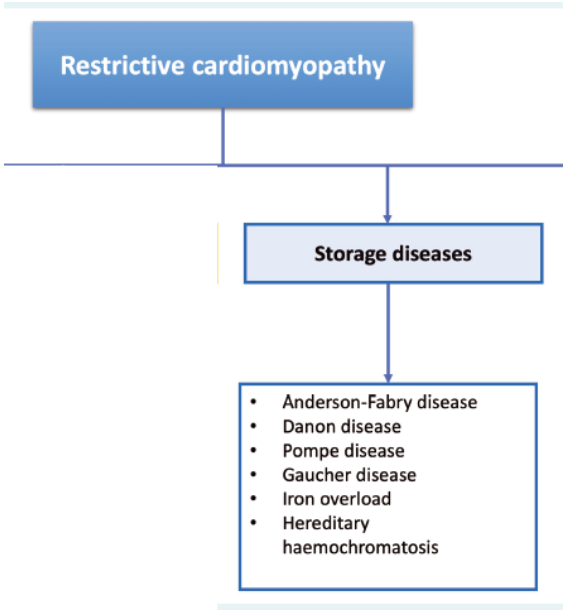
Prevalence of Fabry disease in male patients with unexplained left ventricular hypertrophy in primary cardiology practice: prospective Fabry cardiomyopathy screening study (FACSS)

Tomas Palecek, Jitka Honzikova, Helena Poupetova, Hana Vlaskova, Petr Kuchynka, Lubor Golan, Sudheera Magage, Ales Linhart

First published: 31 October 2013 | https://doi.org/10.1007/s10545-013-9659-2

- **Akumulace globotriaosylceramidu v lysozomech myocytů v důsledku mutace genu pro alfa-galaktosidázu A**
- **Léčebná substituce chybějící alfa-galaktosidázy A**

Léčba RKMP



Hemochromatosis heart disease: An unemphasized cause of potentially reversible restrictive cardiomyopathy

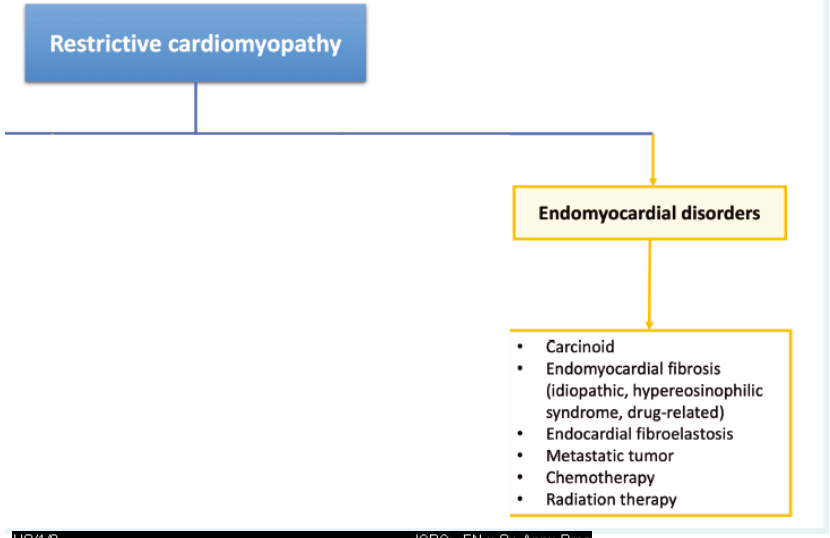
D. Joshua Cutler M.D. [a, b, c, d, *], Jeffrey M. Isner M.D. [a, b, c, d, †], Arthur W. Bracey M.D. [a, b, c, d], Charles A. Hufnagel M.D. [a, b, c, d], Peter W. Conrad M.D. [a, b, c, d], William C. Roberts M.D. [a, b, c, d], Donald M. Kerwin M.D. [a, b, c, d], Alan M. Weintraub M.D. [a, b, c, d]

Show more

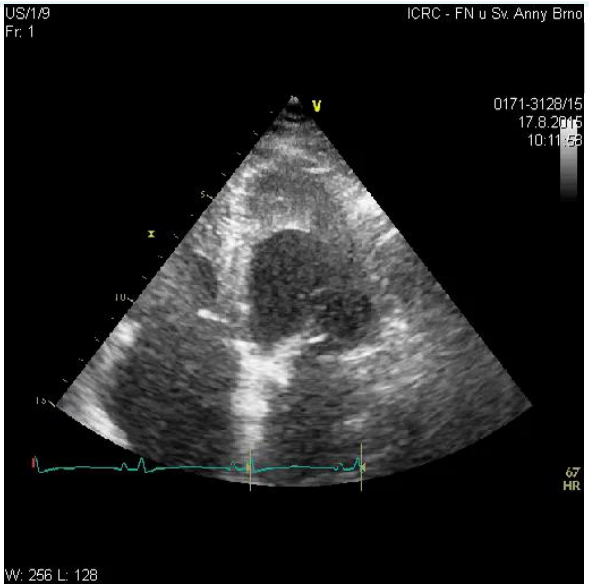
https://doi.org/10.1016/S0002-9343(80)80020-9

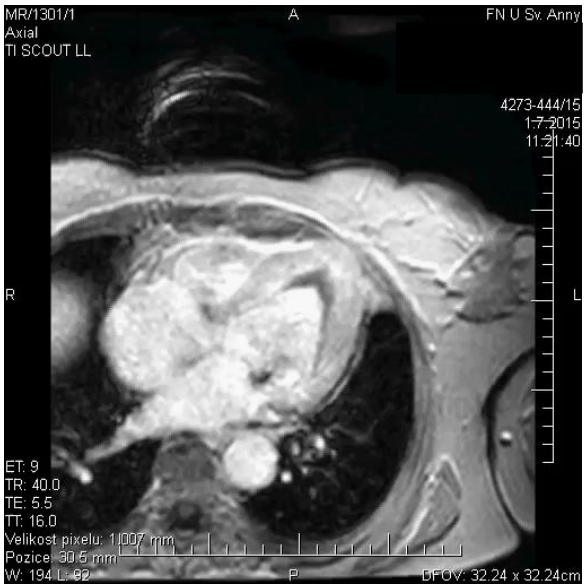
- **Terapeutická flebotomie, dietní opatření, podávání chelátů vázající železo…**

Léčba RKMP



- **Antikoagulace, kortikoidy u HES, chirurgická léčba**





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Závěry

- **RKMP je fenotypovou manifestací dlouhé řady zcela odlišných onemocnění.**
- **Je nutná pečlivá diferenciální diagnostika využívající řady zobrazovacích, laboratorních i bioptických metod.**
- **Terapie se odvíjí od konkrétní příčiny, univerzální léčba neexistuje!**

Zásadní je po záchytu fenotypu RKMP kontaktovat specializovaná centra disponující širokým armamentáriem diagnostických metod a zkušenostmi s léčbou nejen RKMP, ale i jejích jednotlivých příčin!

Děkuji za pozornost!