Léčebné možnosti HCM

J. Krejčí

REVIEW ARTICLE

New perspectives in the pharmacological treatment of hypertrophic cardiomyopathy☆

Abstract Hypertrophic cardiomyopathy is an inherited cardiac disease and a major cause of heart failure and sudden death. Although it was first described more than 50 years ago, sarcomeric hypertrophic cardiomyopathy still lacks a disease-specific treatment: the drugs routinely used alleviate symptoms but do not prevent or revert the phenotype. With recent advances in knowledge of the genetics and pathophysiology of hypertrophic cardiomyopathy, new genetic and pharmacological approaches have recently been identified and studied that, by influencing different pathways involved in this disease, have the potential to function as disease-modifying therapies. These promising new pharmacological and genetic therapies will be the focus of this review.

Rev Port Cardiol. 2020;**39(2)**:99–109

REVIEW ARTICLE

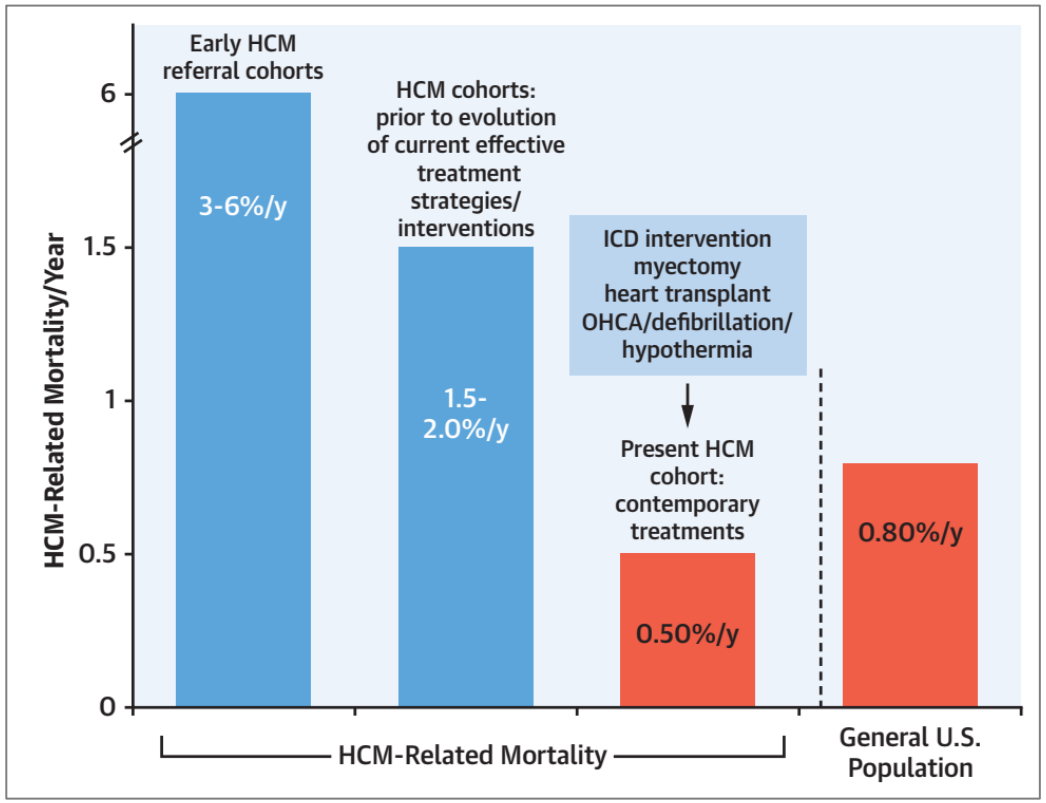
New perspectives in the pharmacological treatment of hypertrophic cardiomyopathy☆

Although HCM was first described more than 50 years ago, evidence-based therapies are scarce and there have been few clinical trials, with small numbers of patients, evaluating the efficacy of pharmacological treatments for this disease.[7,8,12–14] In recent decades, advances in the understanding of HCM have led to the discovery of new approaches which may influence its complex pathophysiology, alter its natural history and act as disease-modifying therapies.[7,8,12–14]

Rev Port Cardiol. 2020;39(2):99–109

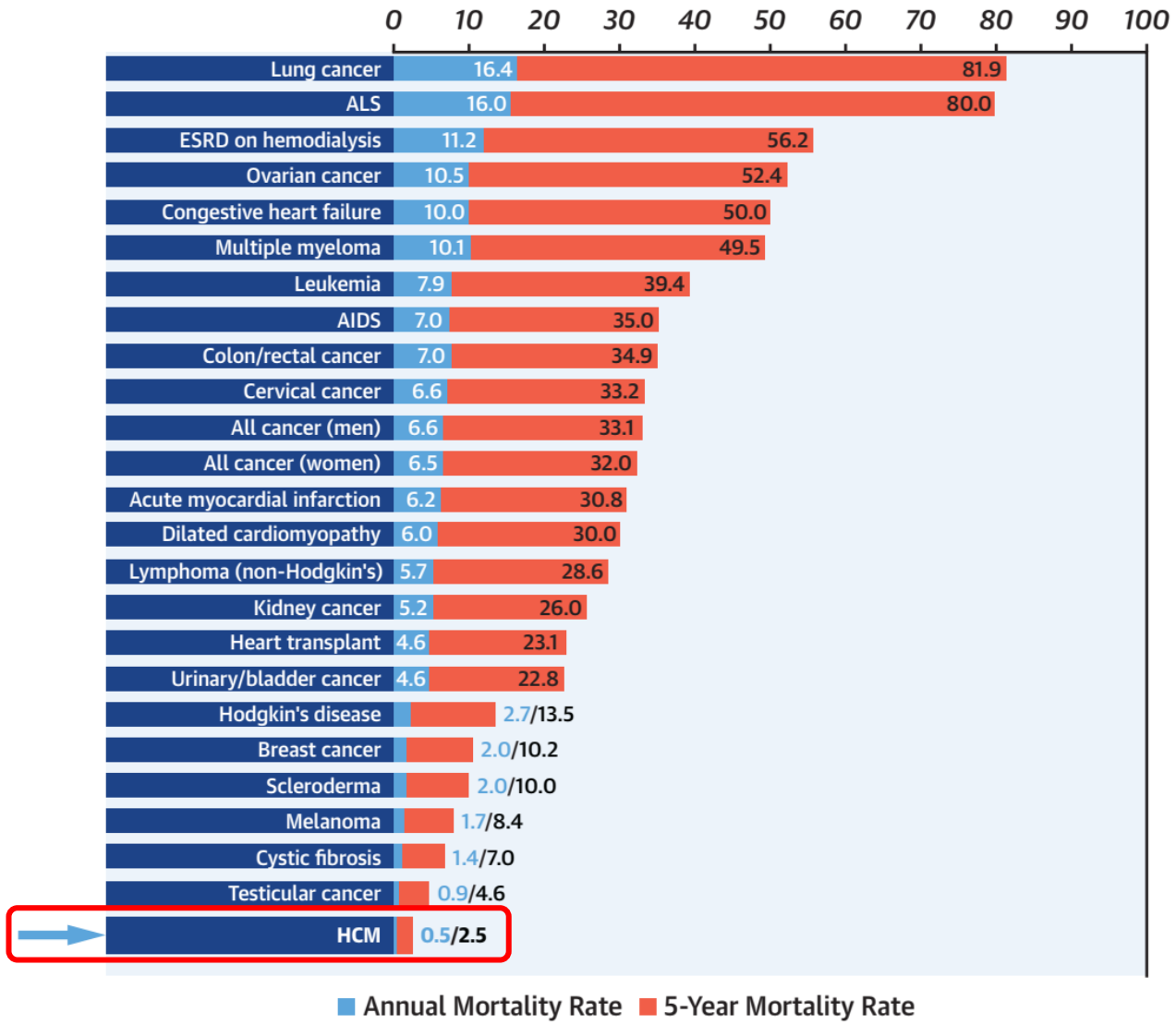
Management of Hypertrophic Cardiomyopathy

JACC State-of-the-Art Review



Hypertrophic cardiomyopathy (HCM) is now recognized as a relatively common contemporary and treatable disease, not inevitably progressive, with potential for low mortality, and compatible with normal or extended life expectancy.

Maron, B.J. et al. J Am Coll Cardiol. 2022;79(4):390–414.



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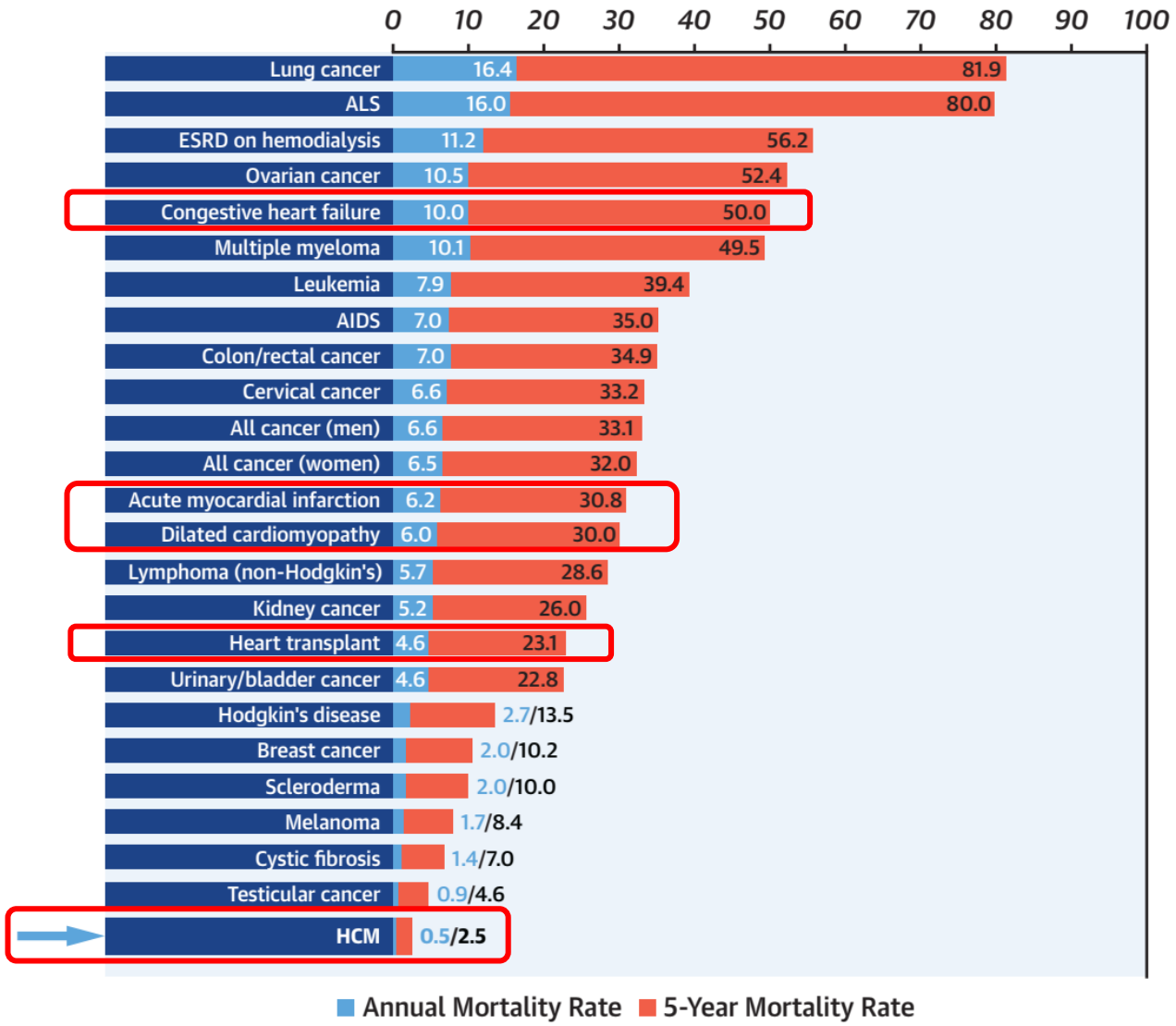

Management of Hypertrophic Cardiomyopathy

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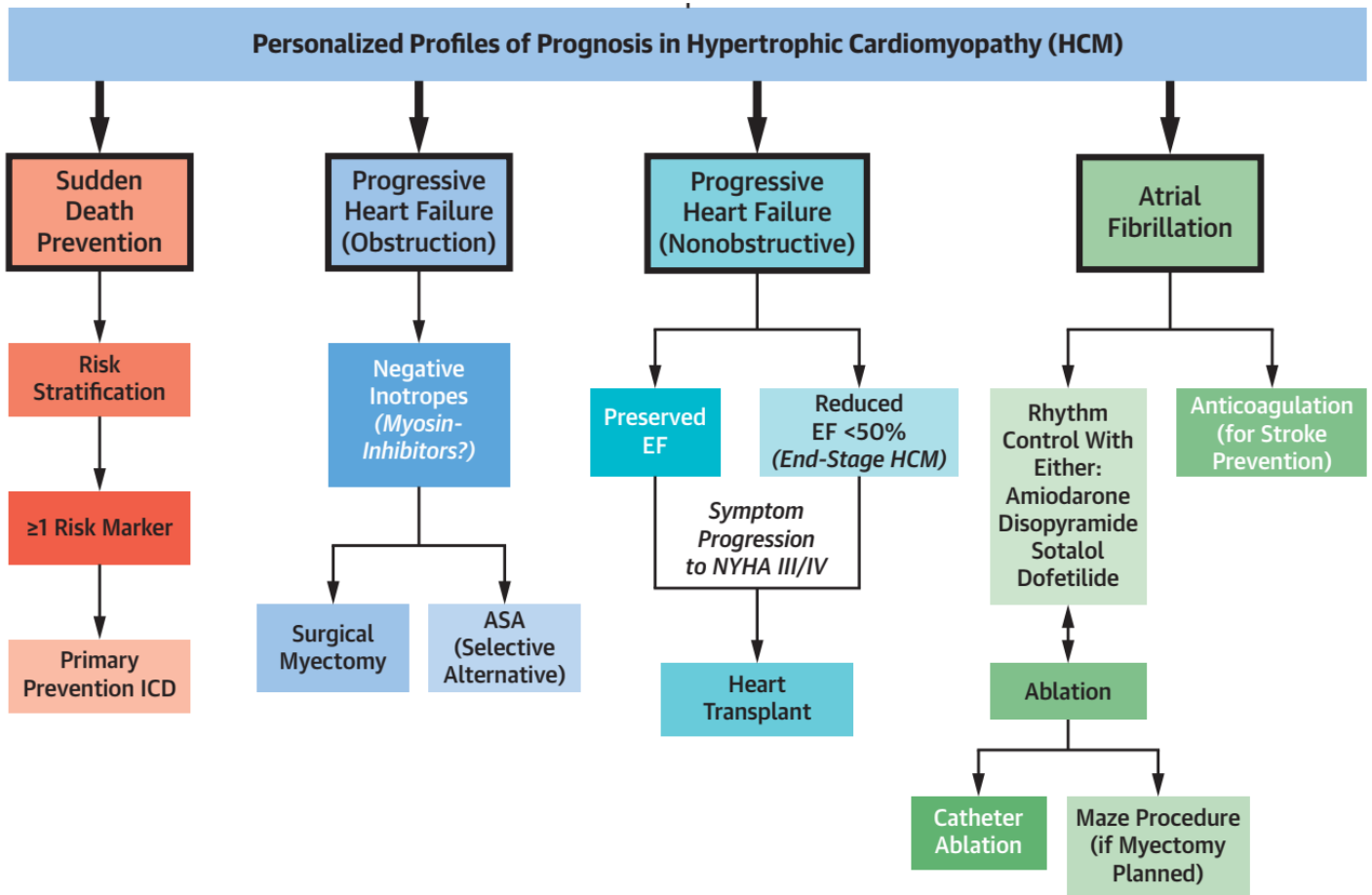

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Management of Hypertrophic Cardiomyopathy

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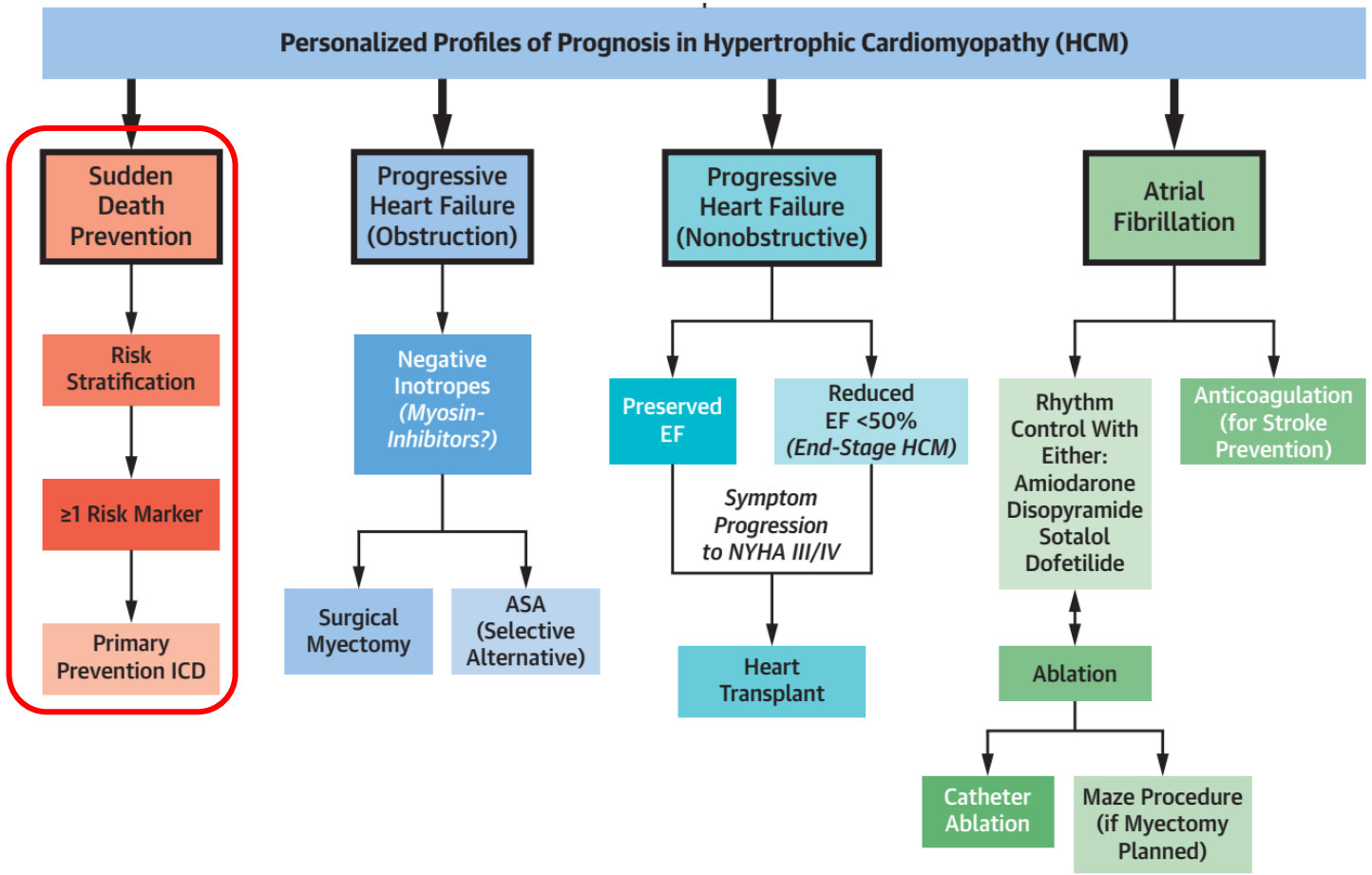

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Prevence SCD – US pohled

TABLE 7 Established Clinical Risk Factors for HCM Sudden Death Risk Stratification

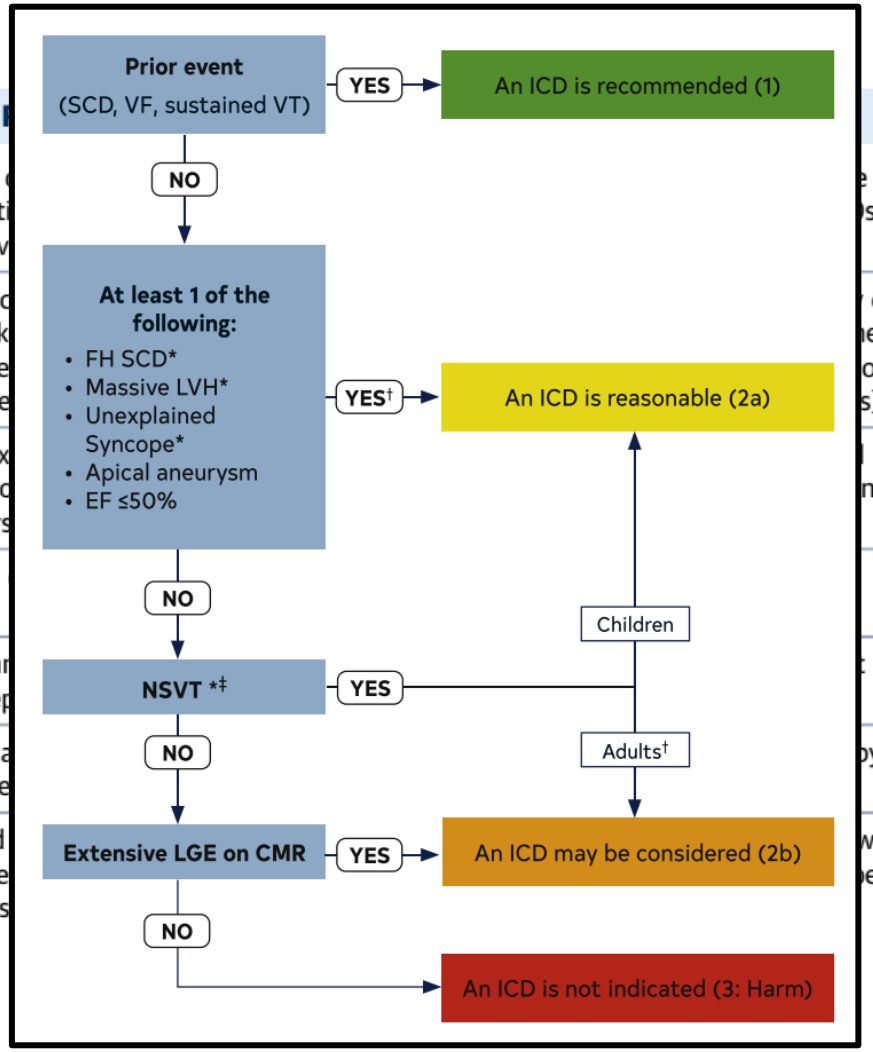
Family history of sudden death from HCM	Sudden death judged definitively or likely attributable to HCM in ≥1 first-degree or close relatives who are ≤50 years of age. Close relatives would generally be second-degree relatives; however, multiple SCDs in tertiary relatives should also be considered relevant.
Massive LVH	Wall thickness ≥30 mm in any segment within the chamber by echocardiography or CMR imaging; consideration for this morphologic marker is also given to borderline values of ≥28 mm in individual patients at the discretion of the treating cardiologist. For pediatric patients with HCM, an absolute or z-score threshold for wall thickness has not been established; however, a maximal wall that corresponds to a z-score ≥20 (and >10 in conjunction with other risk factors) appears reasonable.
Unexplained syncope	≥1 Unexplained episodes involving acute transient loss of consciousness, judged by history unlikely to be of neurocardiogenic (vasovagal) etiology, nor attributable to LVOTO, and especially when occurring within 6 months of evaluation (events beyond 5 years in the past do not appear to have relevance).
HCM with LV systolic dysfunction	Systolic dysfunction with EF <50% by echocardiography or CMR imaging.
LV apical aneurysm	Apical aneurysm defined as a discrete thin-walled dyskinetic or akinetic segment of the most distal portion of the LV chamber; independent of size.
Extensive LGE on CMR imaging	Diffuse and extensive LGE, representing fibrosis, either quantified or estimated by visual inspection, comprising ≥15% of LV mass (extent of LGE conferring risk has not been established in children).
NSVT on ambulatory monitor	It would seem most appropriate to place greater weight on NSVT as a risk marker when runs are frequent (≥3), longer (≥10 beats), and faster (≥200 bpm) occurring usually over 24 to 48 hours of monitoring. For pediatric patients, a VT rate that exceeds the baseline sinus rate by >20% is considered significant.

Circulation. 2020;142:e558–e631.

Prevence SCD – US pohled

TABLE 7 Established Clinical

Family history of sudden death from HCM	Sudden relati relev
Massive LVH	Wall thic mark patie corre
Unexplained syncope	≥1 Unex (vasc years
HCM with LV systolic dysfunction	Systolic
LV apical aneurysm	Apical ar indep
Extensive LGE on CMR imaging	Diffuse a (exte
NSVT on ambulatory monitor	It would faste sinus



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	by history unlikely to be of neurocardiogenic ng within 6 months of evaluation (events beyond 5
	of the most distal portion of the LV chamber;
	by visual inspection, comprising ≥15% of LV mass
	when runs are frequent (≥3), longer (≥10 beats), and ediatric patients, a VT rate that exceeds the baseline

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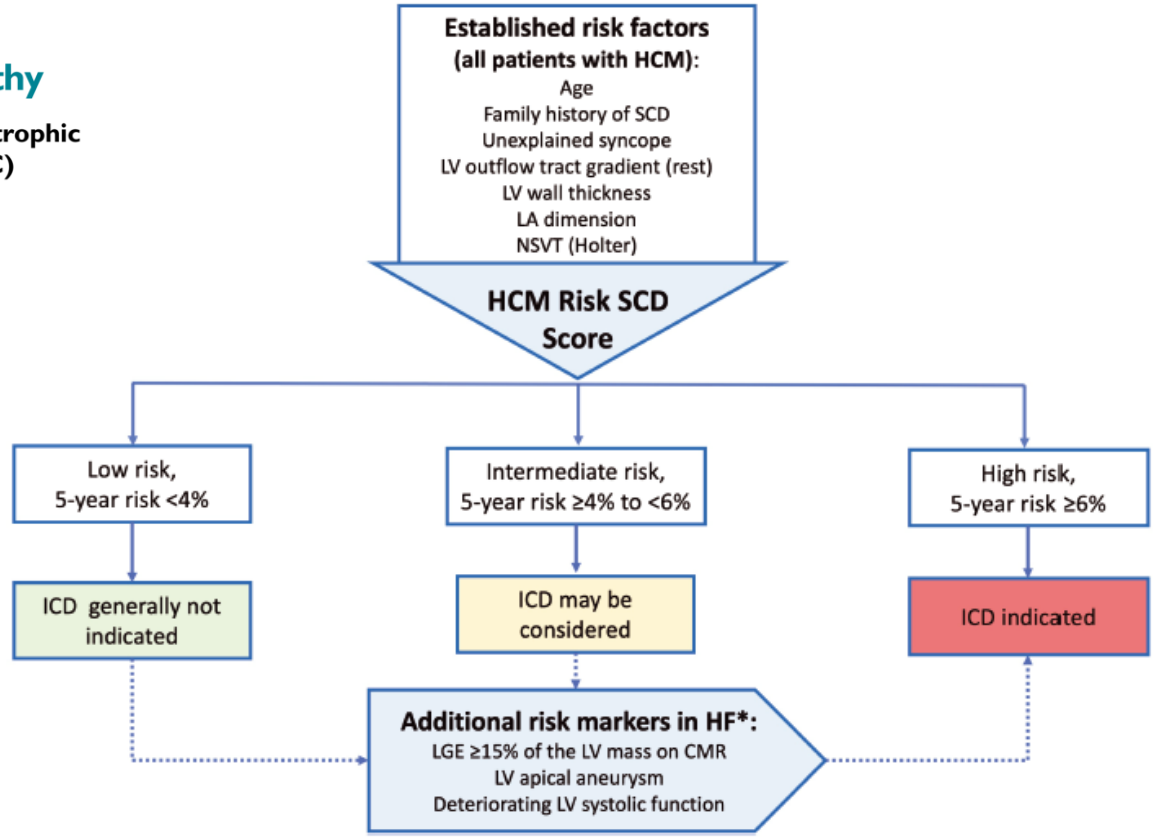
Prevence SCD – EU pohled

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

Prevence SCD – EU pohled

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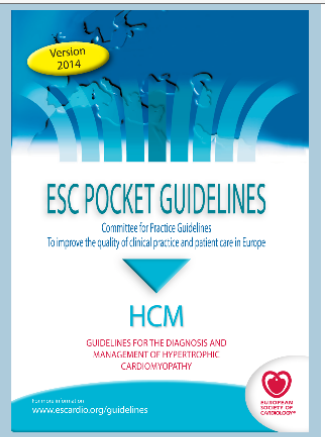
EUROPEAN SOCIETY OF CARDIOLOGY®

HCM Risk-SCD Calculator

Age	**Years**	*Age at evaluation*
Maximum LV wall thickness	**mm**	*Transthoracic Echocardiographic measurement*
Left atrial size	**mm**	*Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation*
Max LVOT gradient	**mmHg**	*The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three and five chamber views. Peak outflow tract gradients should be determined using the modified Bernouilli equation: Gradient= $4V^2$, where V is the peak aortic outflow velocity*
Family History of SCD	○ No ○ Yes	*History of sudden cardiac death in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post or ante-mortem diagnosis).*
Non-sustained VT	○ No ○ Yes	*3 consecutive ventricular beats at a rate of 120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation.*
Unexplained syncope	○ No ○ Yes	*History of unexplained syncope at or prior to evaluation.*

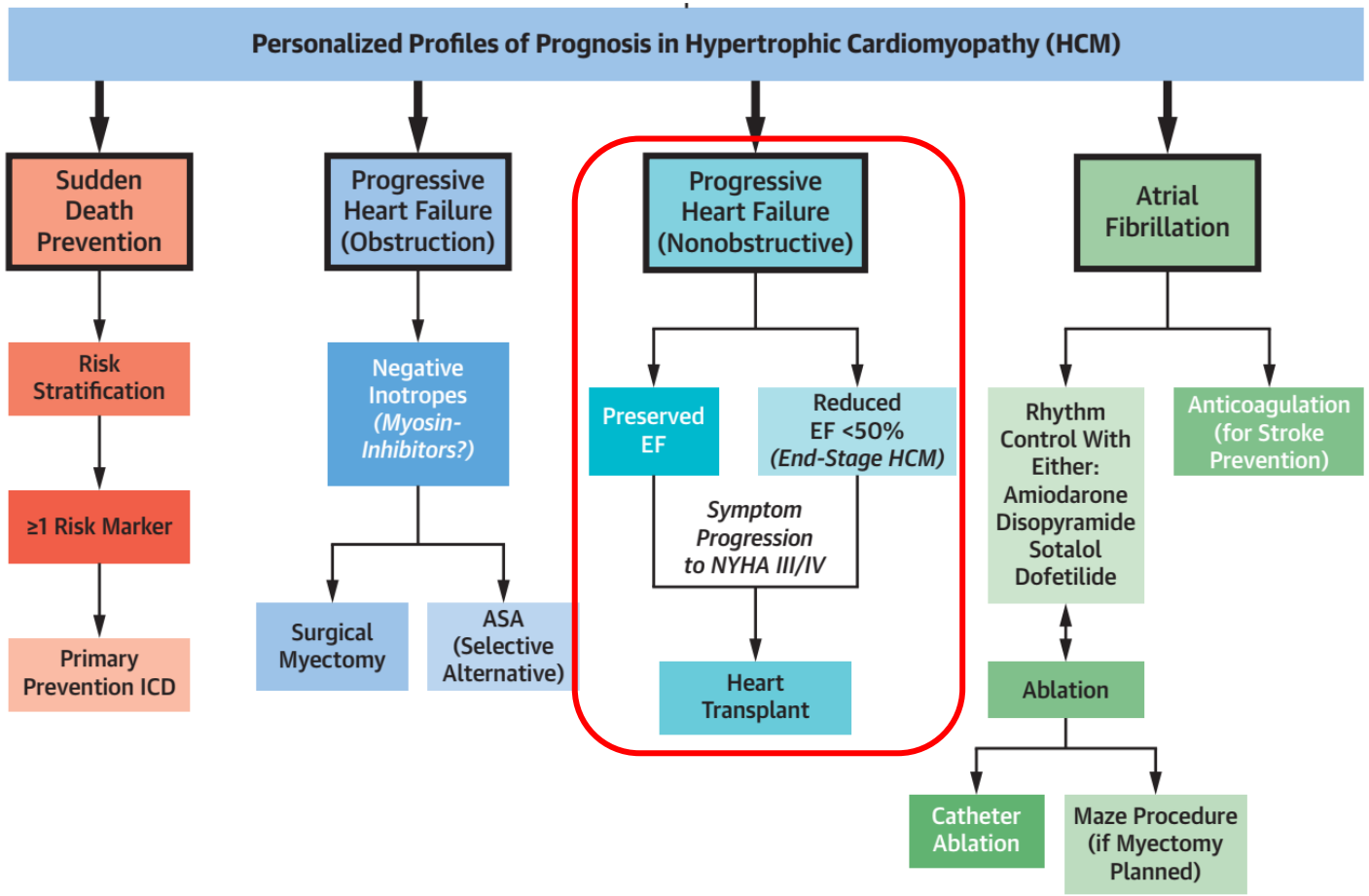
Risk of SCD at 5 years (%):	
ESC recommendation:	



https://www.doc2do.com/hcm/webHCM.html

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

HCM bez obstrukce



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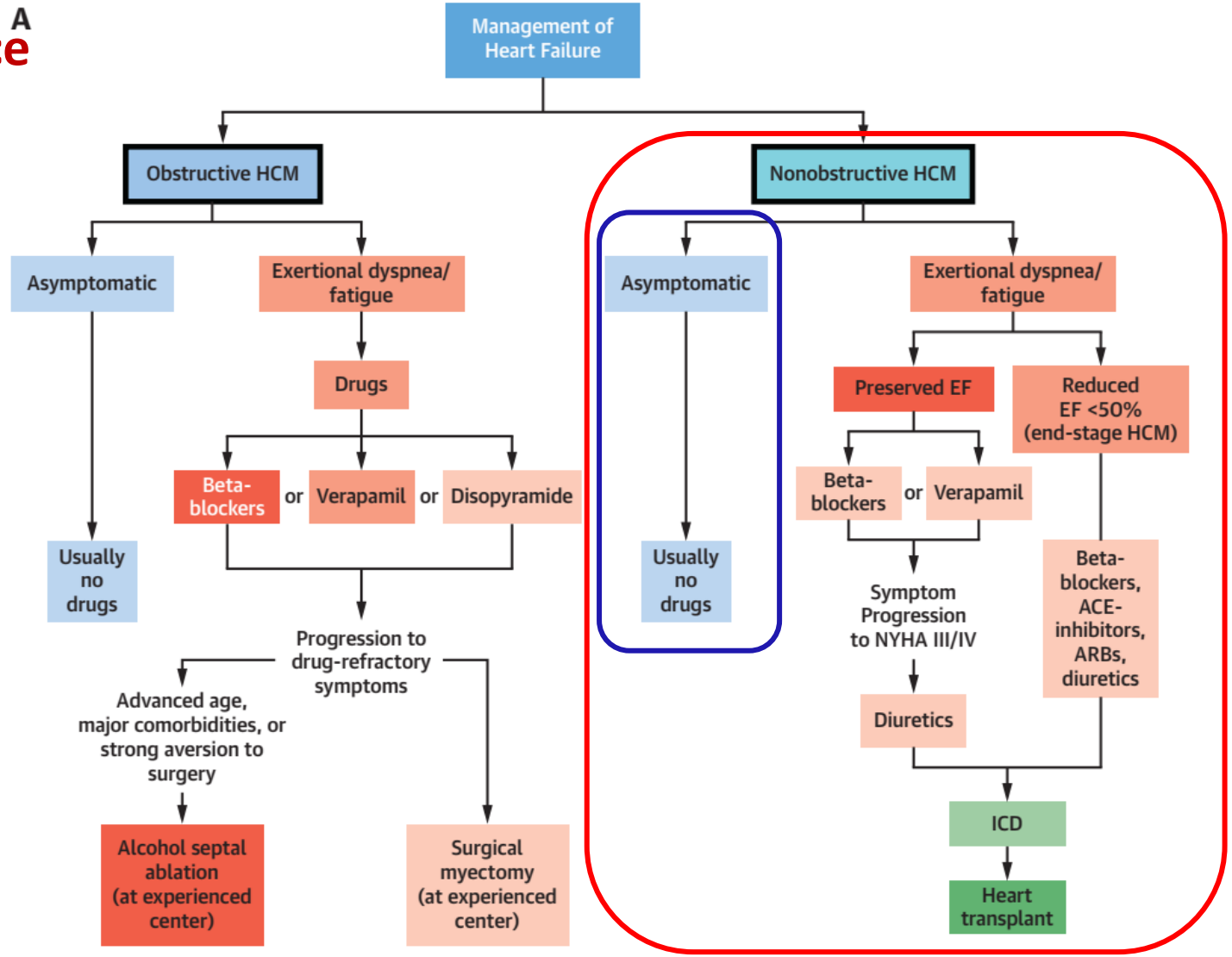

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HCM bez obstrukce

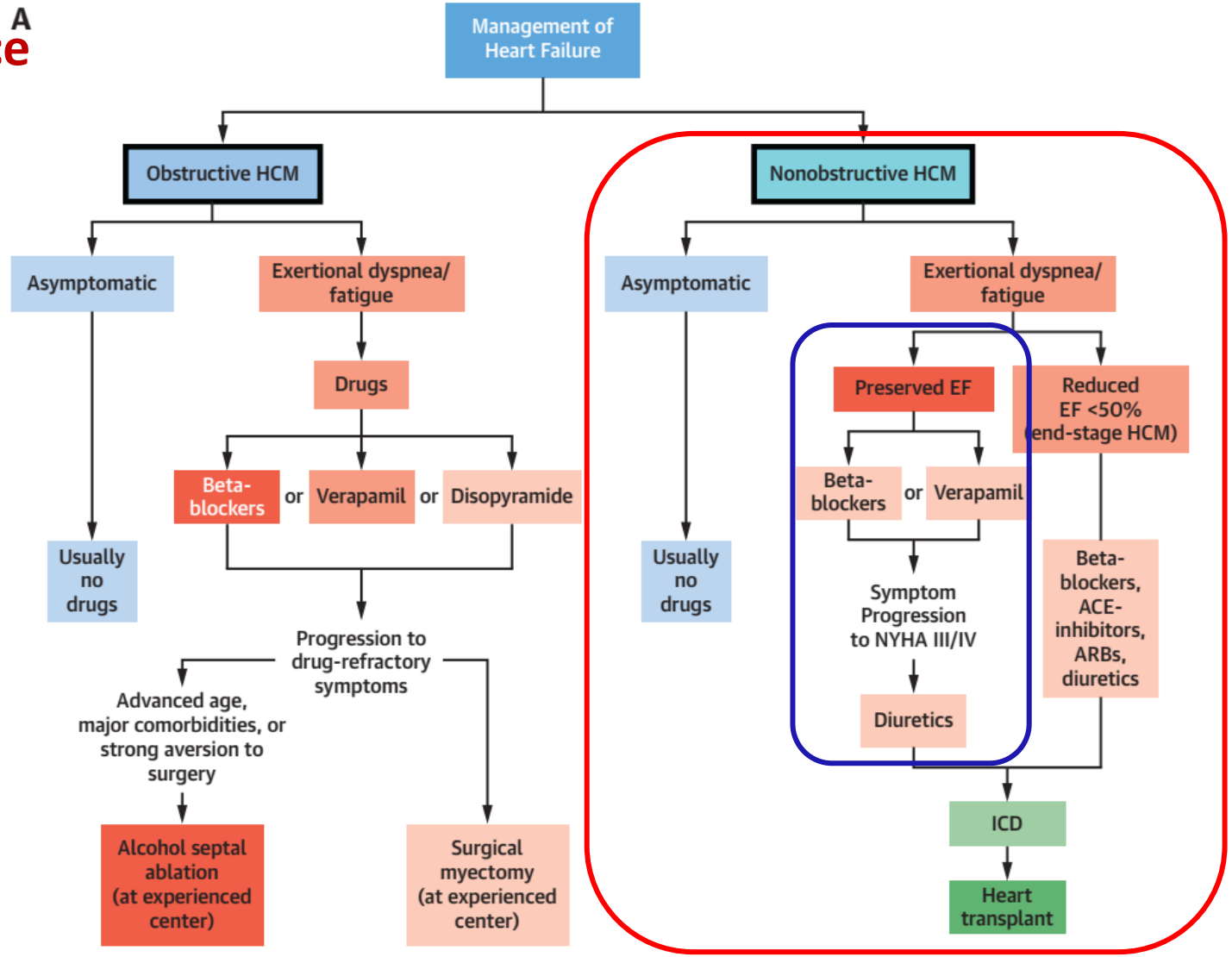
2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy

Recommendations for Management of Patients With Nonobstructive HCM With Preserved EF
Referenced studies that support the recommendations are summarized in Online Data Supplement 15.

COR	LOE	RECOMMENDATIONS
1	C-LD	1. In patients with nonobstructive HCM with preserved EF and symptoms of exertional angina or dyspnea, beta-blockers or non-dihydropyridine calcium channel blockers are recommended (1-10).
2a	C-EO	2. In patients with nonobstructive HCM with preserved EF, it is reasonable to add oral diuretics when exertional dyspnea persists despite the use of beta-blockers or non-dihydropyridine calcium channel blockers.
2b	C-LD	3. In patients with nonobstructive HCM with preserved EF, the usefulness of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in the treatment of symptoms (angina and dyspnea) is not well established (11).
2b	C-LD	4. In highly selected patients with apical HCM with severe dyspnea or angina (NYHA class III or class IV) despite maximal medical therapy, and with preserved EF and small LV cavity size (LV end-diastolic volume <50 mL/m^2 and LV stroke volume <30 mL/m^2), apical myectomy by experienced surgeons at comprehensive centers may be considered to reduce symptoms (12).
2b	C-EO	5. In asymptomatic patients with nonobstructive HCM, the benefit of beta-blockers or calcium channel blockers is not well established.

Circulation. 2020;142:e558–e631.

HCM bez obstrukce



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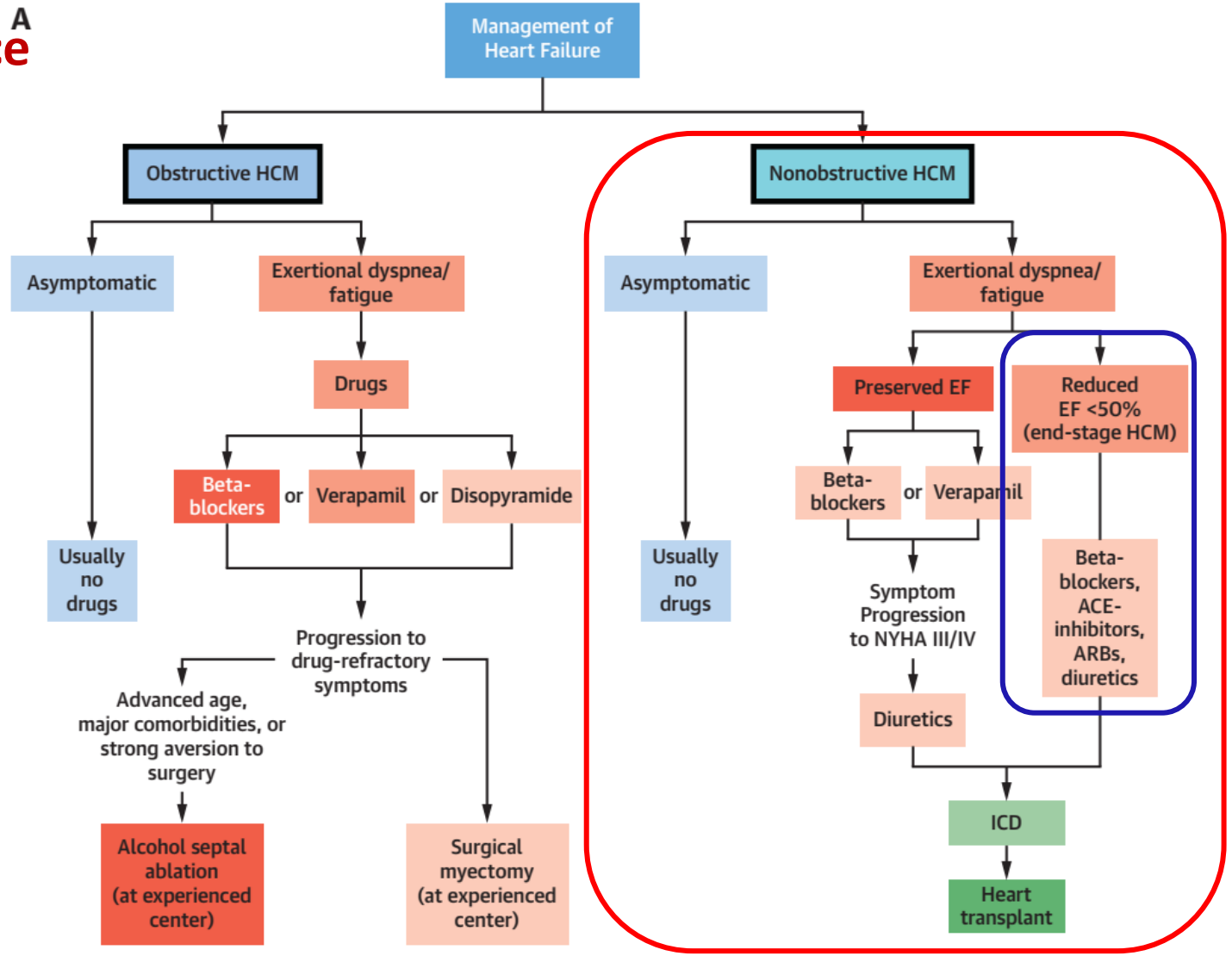
HCM bez obstrukce



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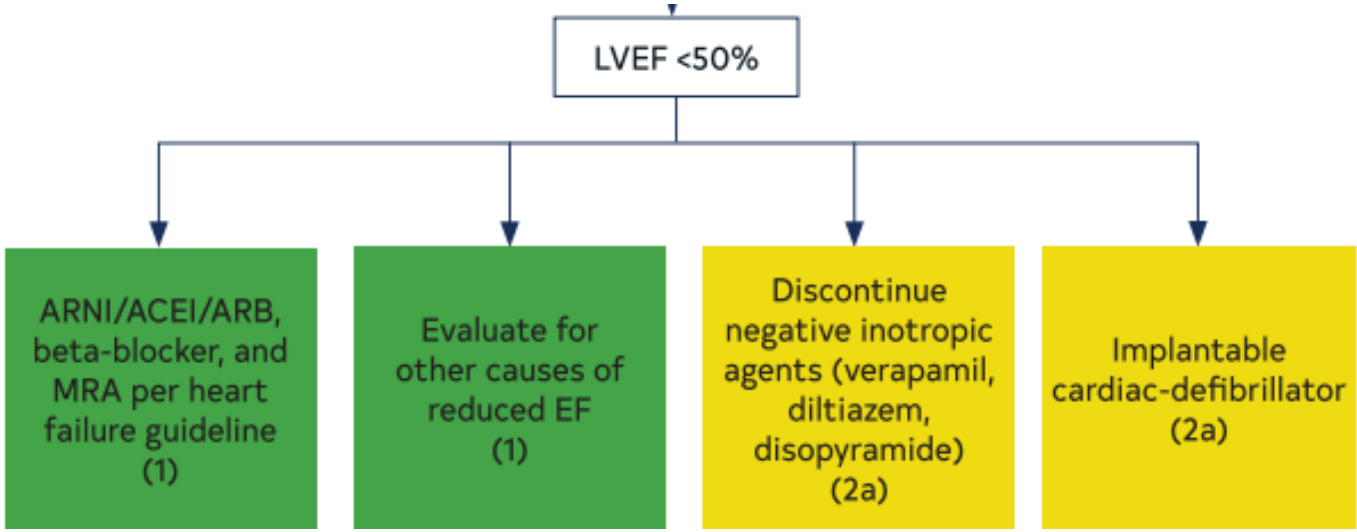
HCM bez obstrukce s rozvojem systolické dysfunkce LK



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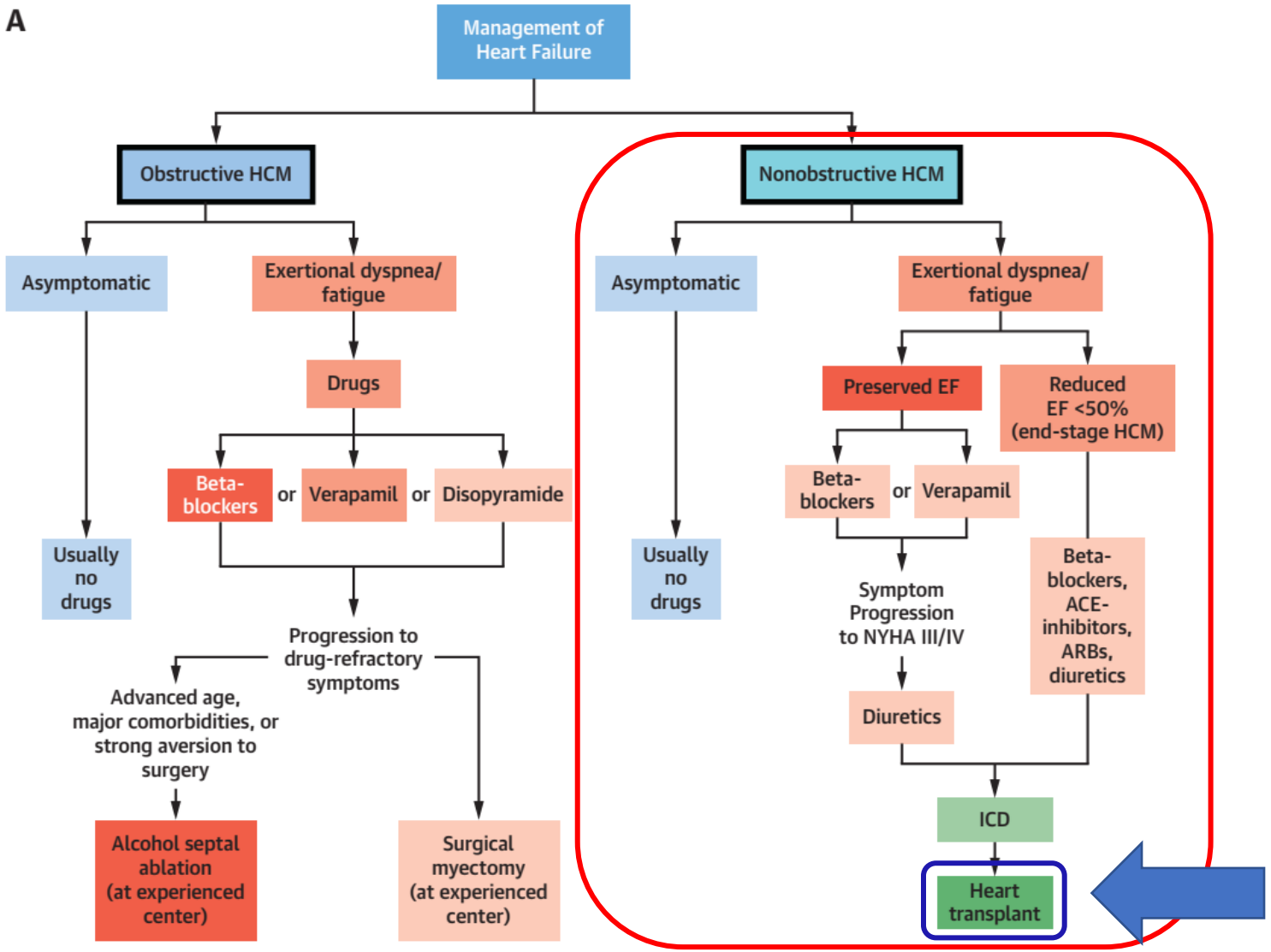

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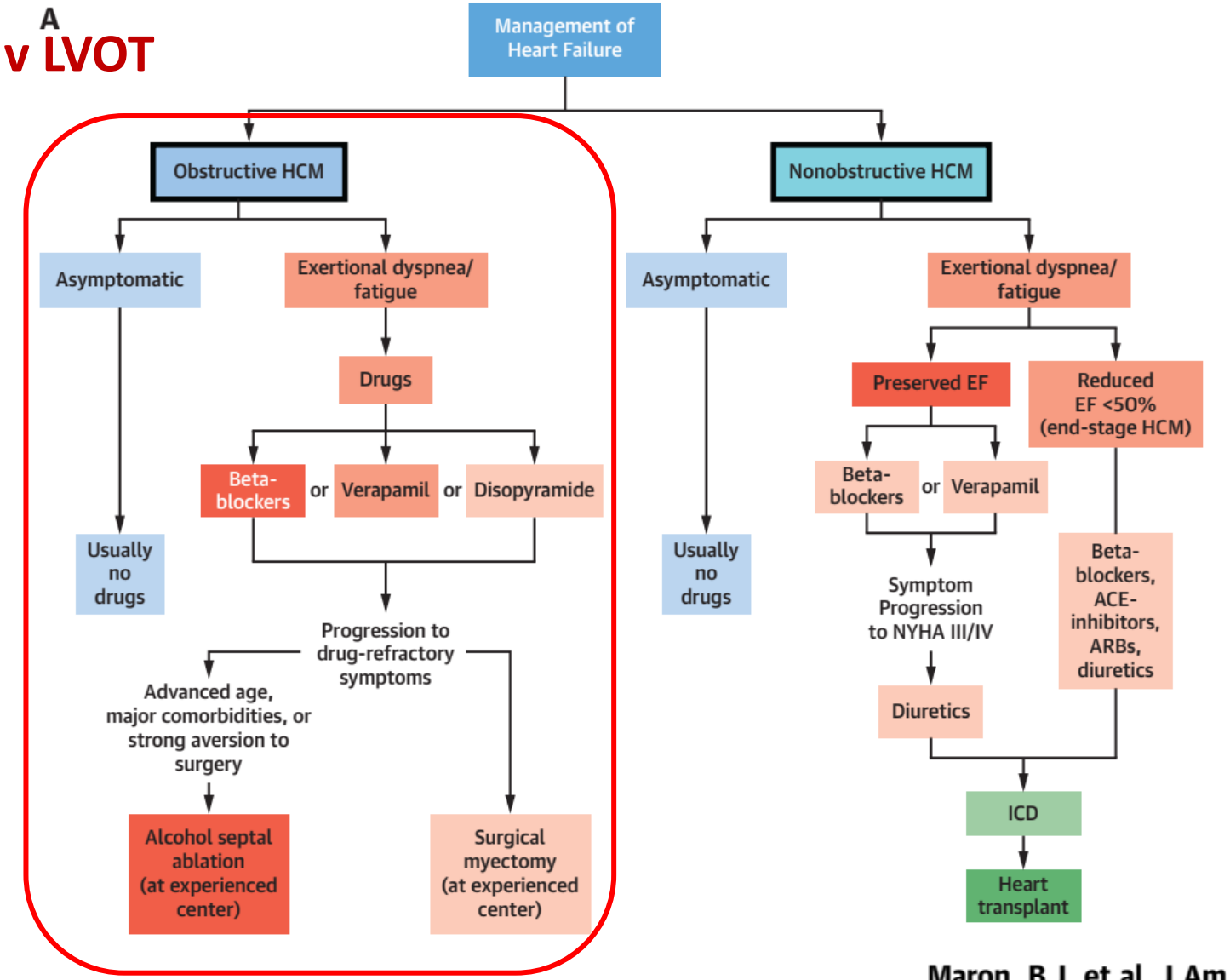
HCM s obstrukcí v LVOT



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HCM s obstrukcí v LVOT

2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy

Recommendations for Pharmacologic Management of Patients With Obstructive HCM
Referenced studies that support the recommendations are summarized in Online Data Supplement 14.

COR	LOE	RECOMMENDATIONS
1	B-NR	1. In patients with obstructive HCM and symptoms* attributable to LVOTO, nonvasodilating beta-blockers, titrated to effectiveness or maximally tolerated doses, are recommended (1–3).
1	Verapamil B-NR Diltiazem C-LD	2. In patients with obstructive HCM and symptoms* attributable to LVOTO, for whom beta-blockers are ineffective or not tolerated, substitution with non-dihydropyridine calcium channel blockers (e.g., verapamil, diltiazem) is recommended (4–6).
1	B-NR	3. For patients with obstructive HCM who have persistent severe symptoms* attributable to LVOTO despite beta-blockers or non-dihydropyridine calcium channel blockers, either adding disopyramide in combination with 1 of the other drugs, or SRT performed at experienced centers,† is recommended (7–12).

HCM s obstrukcí v LVOT - SRT

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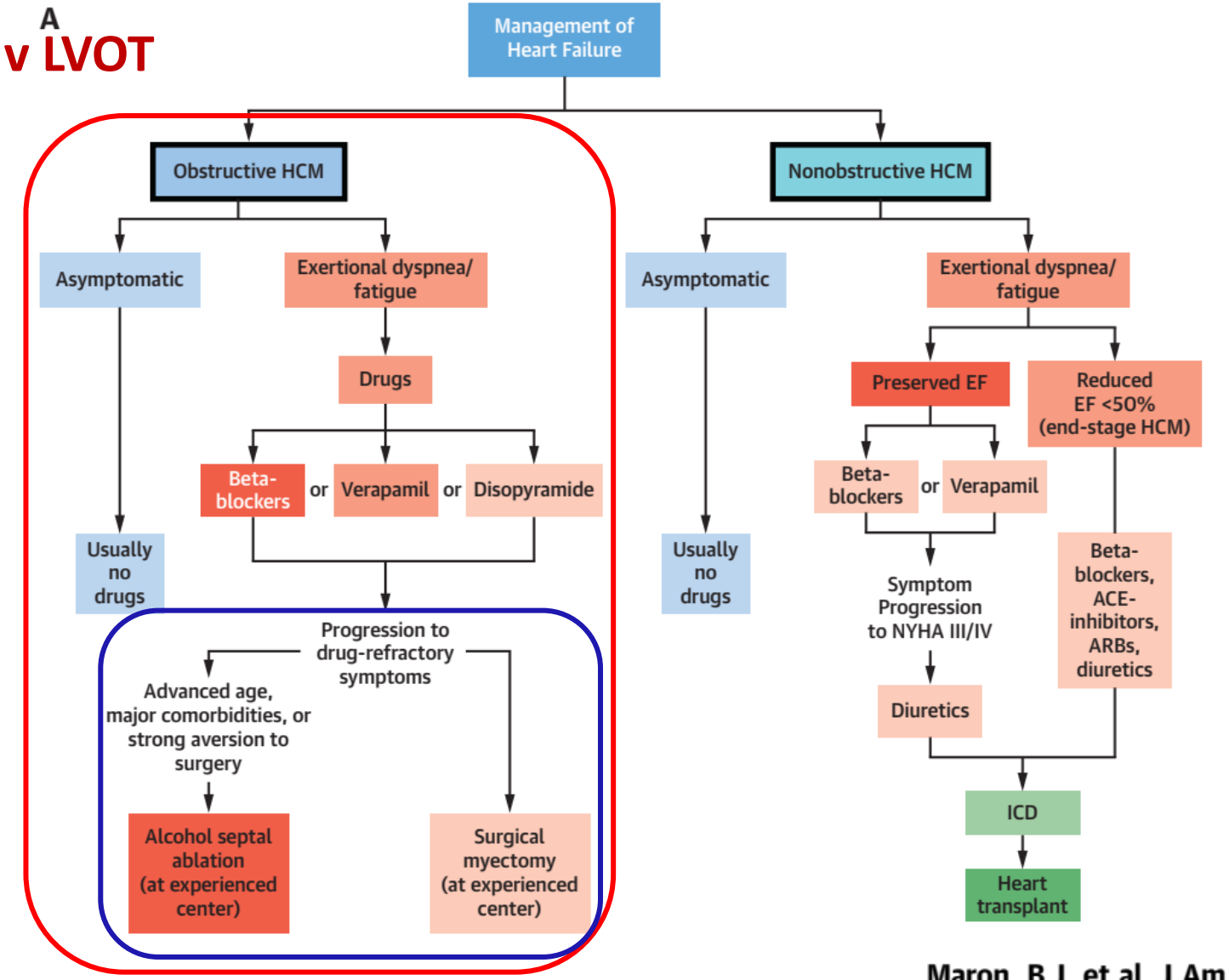
Recommendations on septal reduction therapy

Recommendations	Class[a]	Level[b]
It is recommended that septal reduction therapies be performed by experienced operators, working as part of a multidisciplinary team expert in the management of HCM.	I	C
Septal reduction therapy to improve symptoms is recommended in patients with a resting or maximum provoked LVOT gradient of ≥50 mm Hg, who are in NYHA functional Class III–IV, despite maximum tolerated medical therapy.	I	B
Septal reduction therapy should be considered in patients with recurrent exertional syncope caused by a resting or maximum provoked LVOTO gradient ≥50 mm Hg despite optimal medical therapy.	IIa	C

HCM s obstrukcí v LVOT

A



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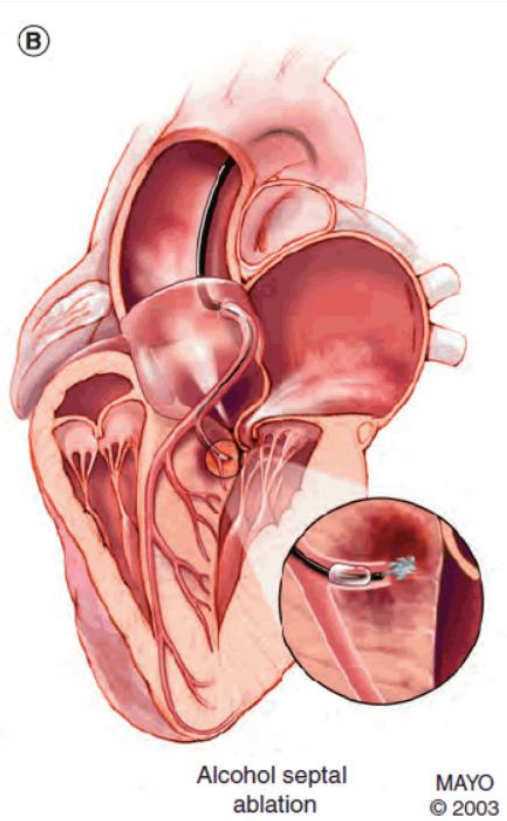
Septal reduction therapy

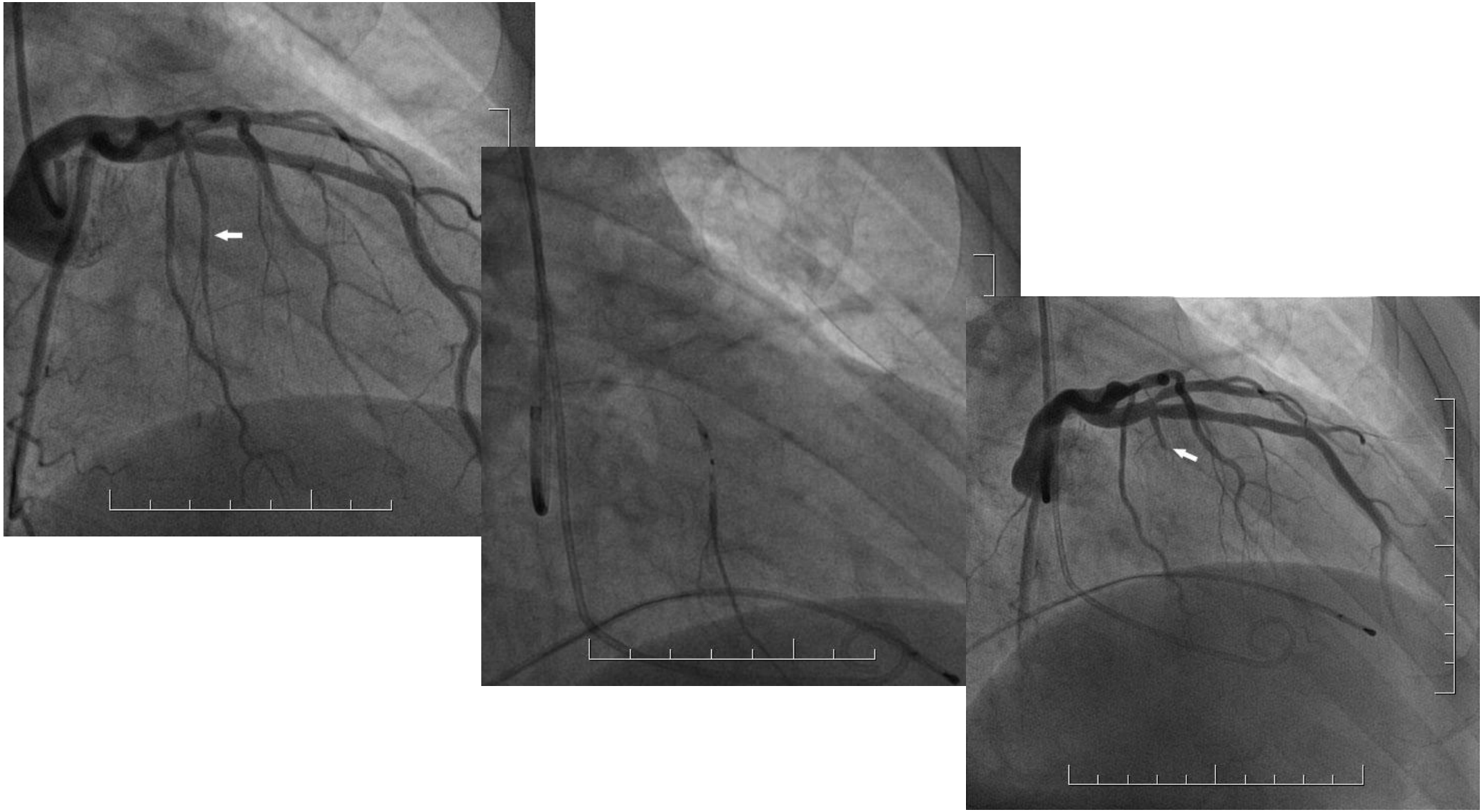
- **ASA (alkoholová septální ablace)**
- Ulrich Sigwart r. 1994 v Londýně
- Aplikace 96% alkoholu (1-3ml) do vhodné septální větve
  → nekróza → jizva se ztenčením IVS → rozšíření LVOT
  → ↓ LVOTG → zlepšení klinického stavu

- 10-15% suboptimální koronární řečiště → jiná metoda
- Mortalita cca 1%, srovnatelné přežívání se zdravou populací

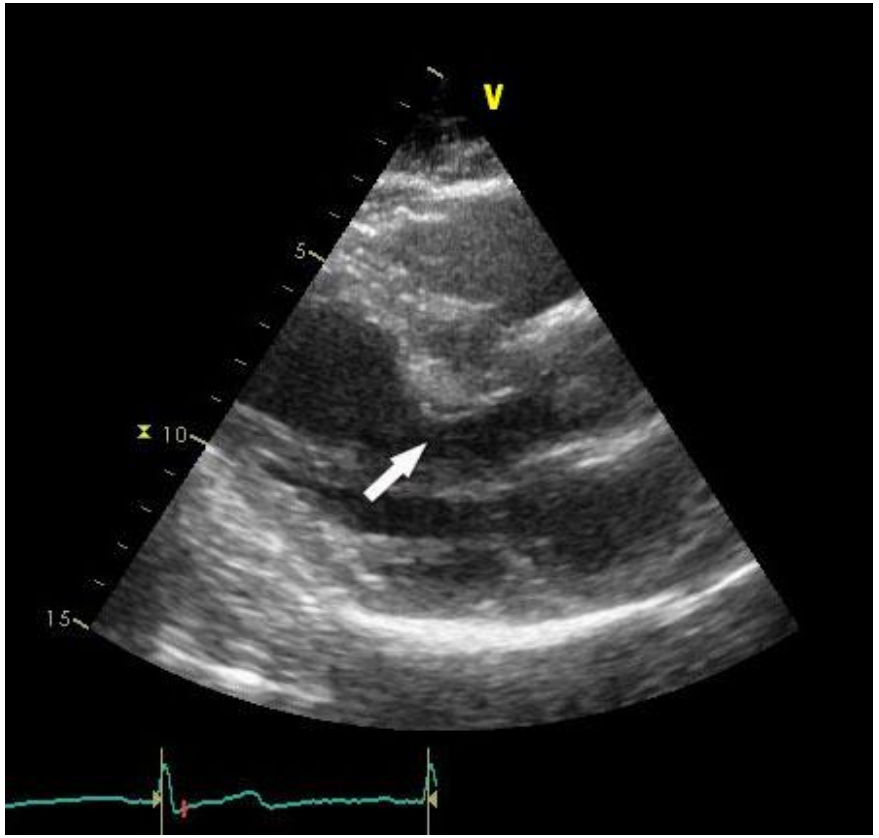
- Komplikace
  - AVB (až 20%) s nutností implantace PM, cave preexistující LBBB (50%)
  - Defekt komorového septa (hranice IVS pro ASA 15-16mm)
  - Ústřik alkoholu do periferie RIA s vytvořením „no-reflow“ fenoménu
  - Arytmie
  - Lokální v místě vpichu

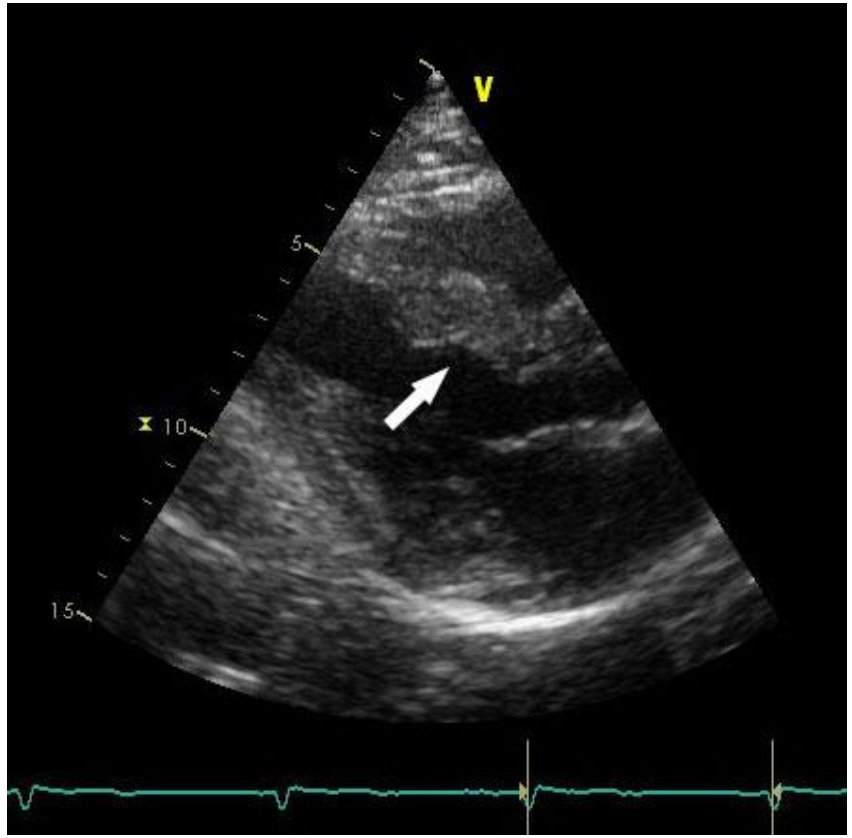


ASA



ECHO před a po provedení ASA





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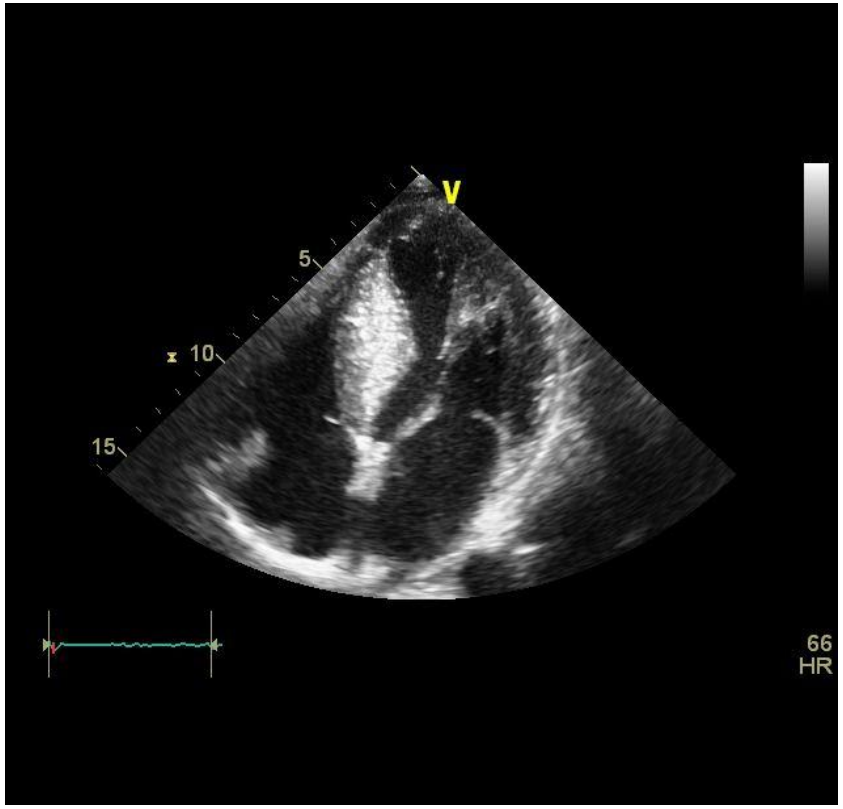
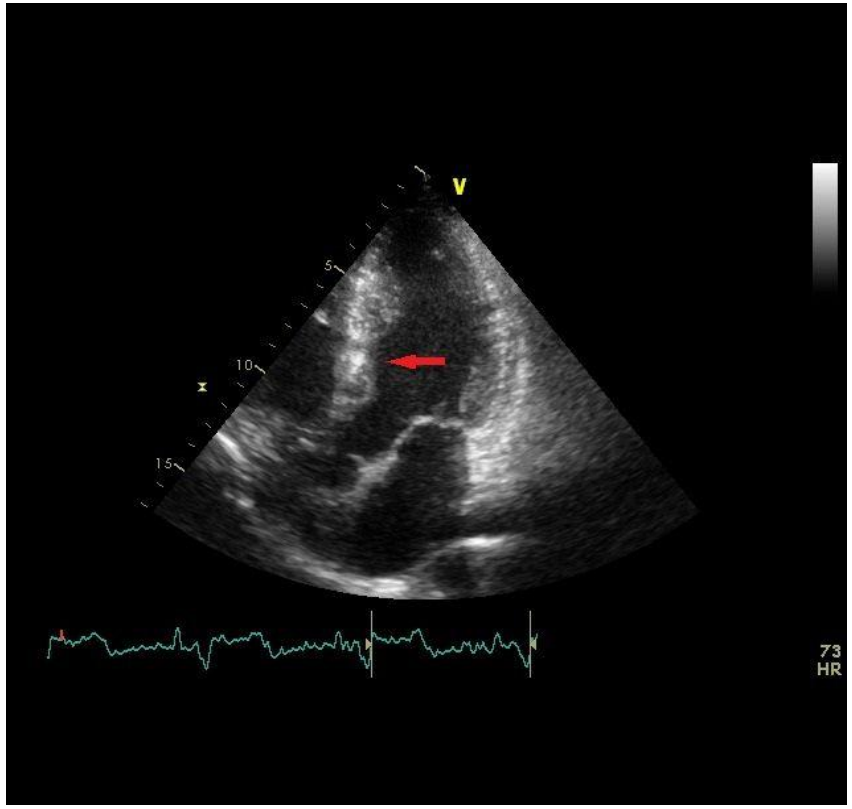
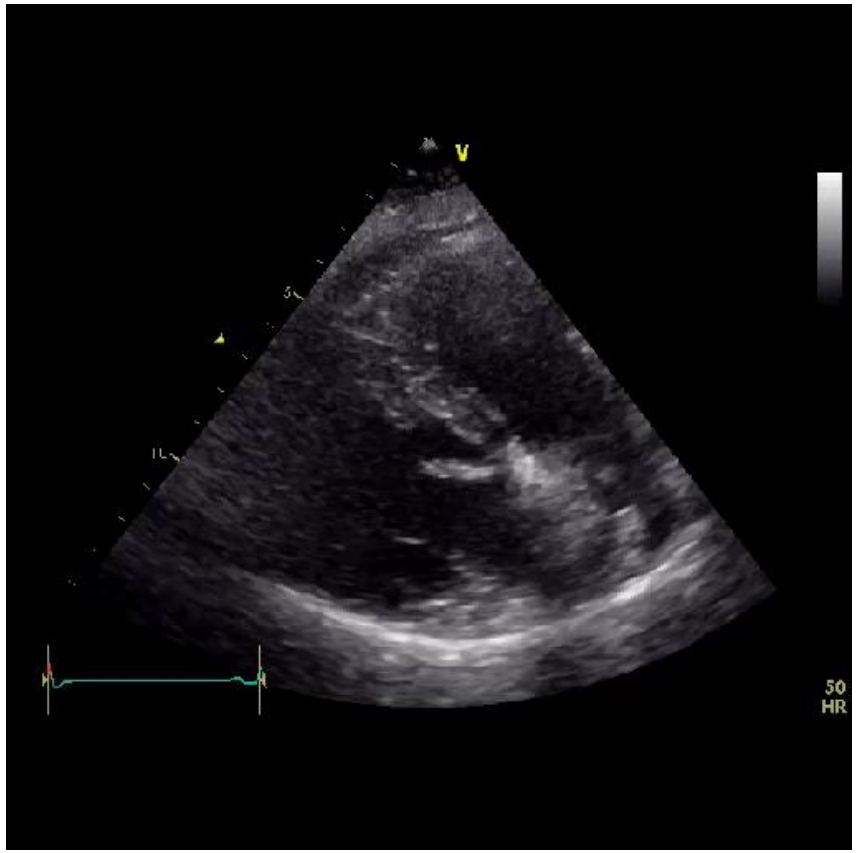
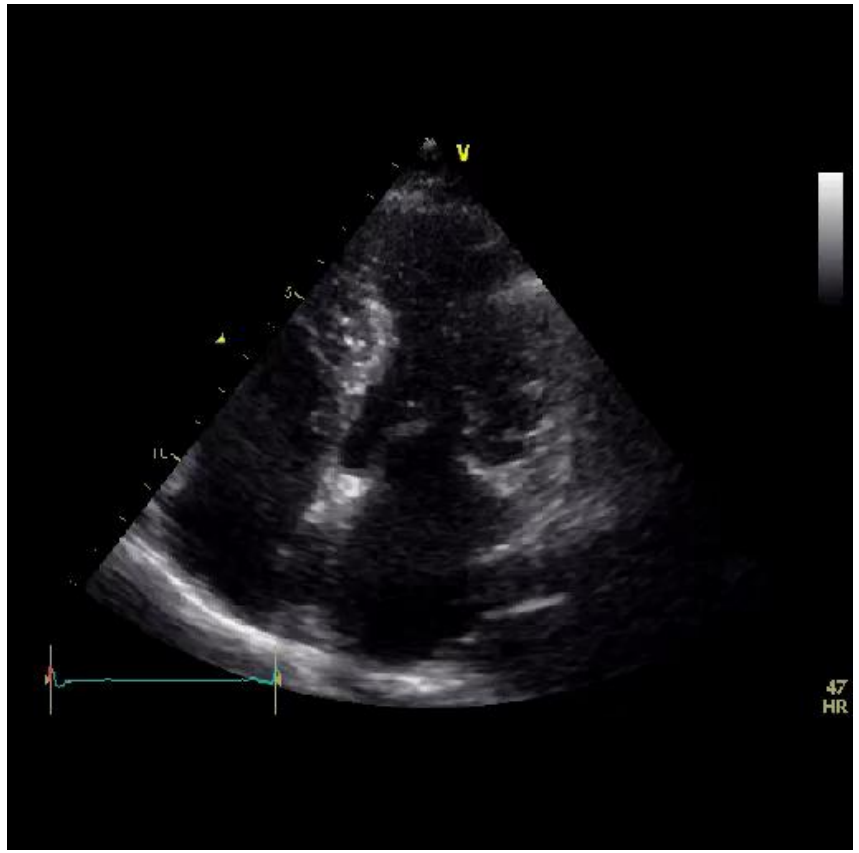




Úspěšná ASA s redukcí bazálního septa, LVOTG a třídy NYHA klasifikace



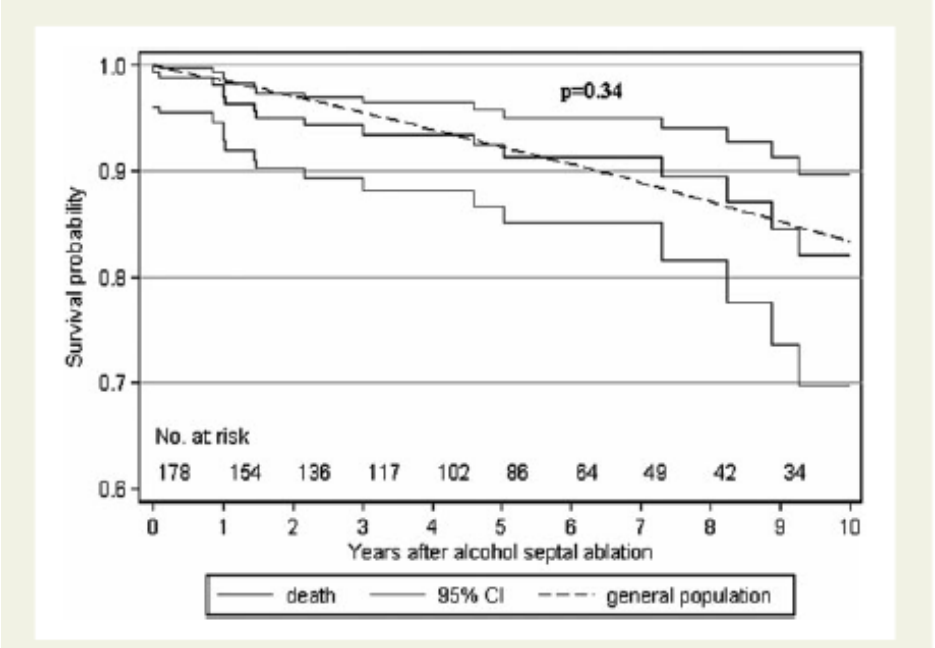


Pokles LVOTG a prognóza

Long-term survival after alcohol septal ablation for hypertrophic obstructive cardiomyopathy: a comparison with general population

Josef Veselka[1]*, Jan Krejčí[2], Pavol Tomašov[1], and David Zemánek[1]

[1]Department of Cardiology, 2nd Medical School, Charles University, University Hospital Motol, Prague, Czech Republic; and [2]1st Department of Internal Medicine/Cardioangiology, International Clinical Research Center, St Anne's University Hospital, Brno, Czech Republic



Eur Heart J. 2014 Aug 7;35(30):2040-5.

Survival After Alcohol Septal Ablation for Obstructive Hypertrophic Cardiomyopathy

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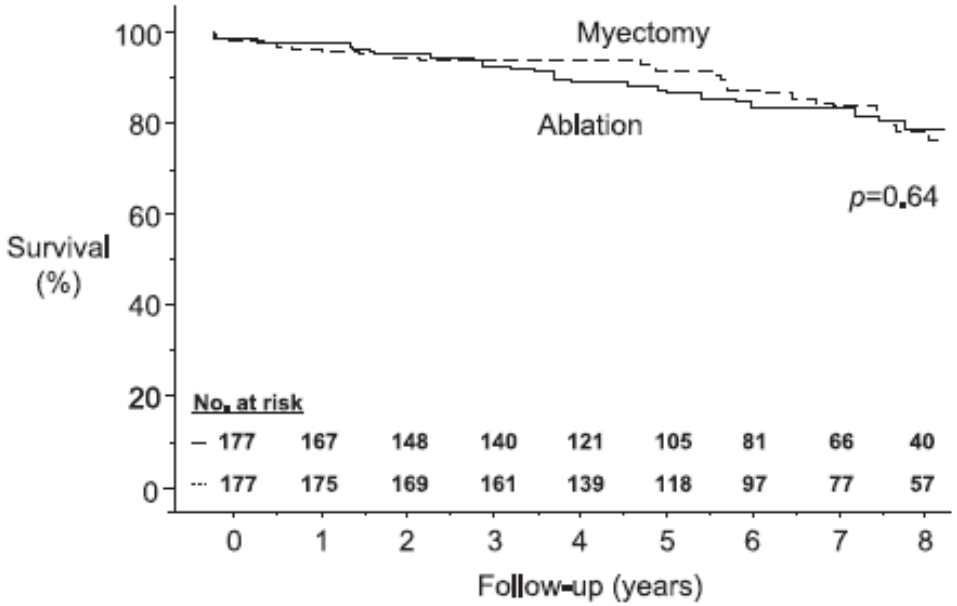

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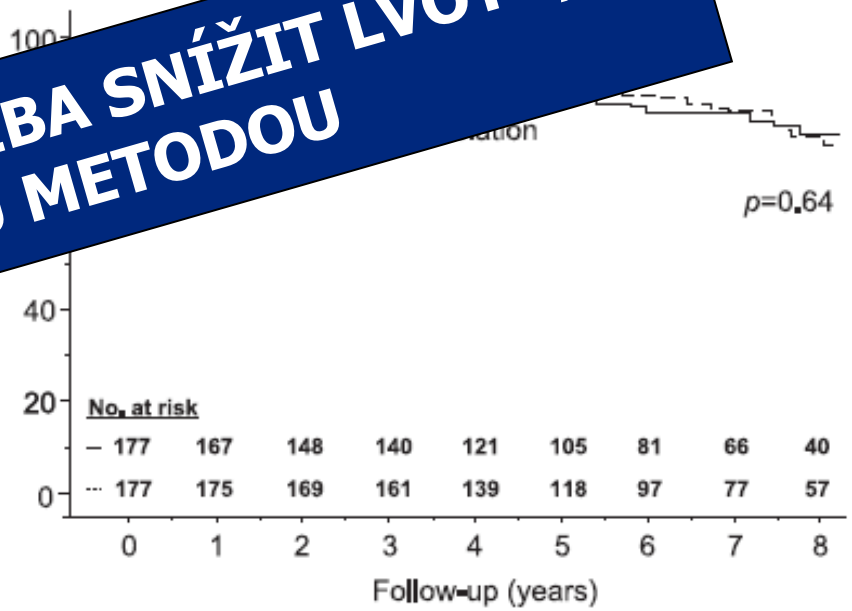
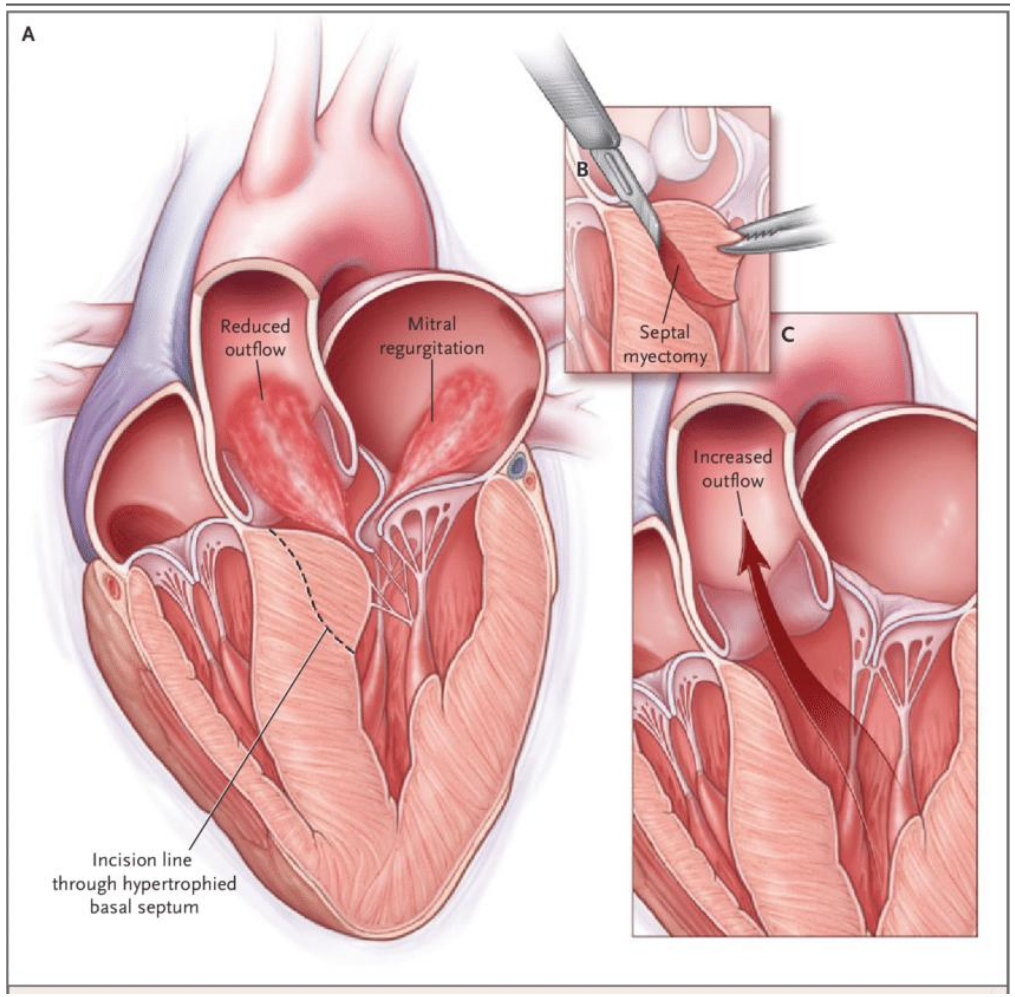


Circulation. 2012;126:2374-2380.)

PRO ZLEPŠENÍ PROGNÓZY JE TŘEBA SNÍŽIT LVOTG, NENÍ DŮLEŽITÉ KTEROU METODOU

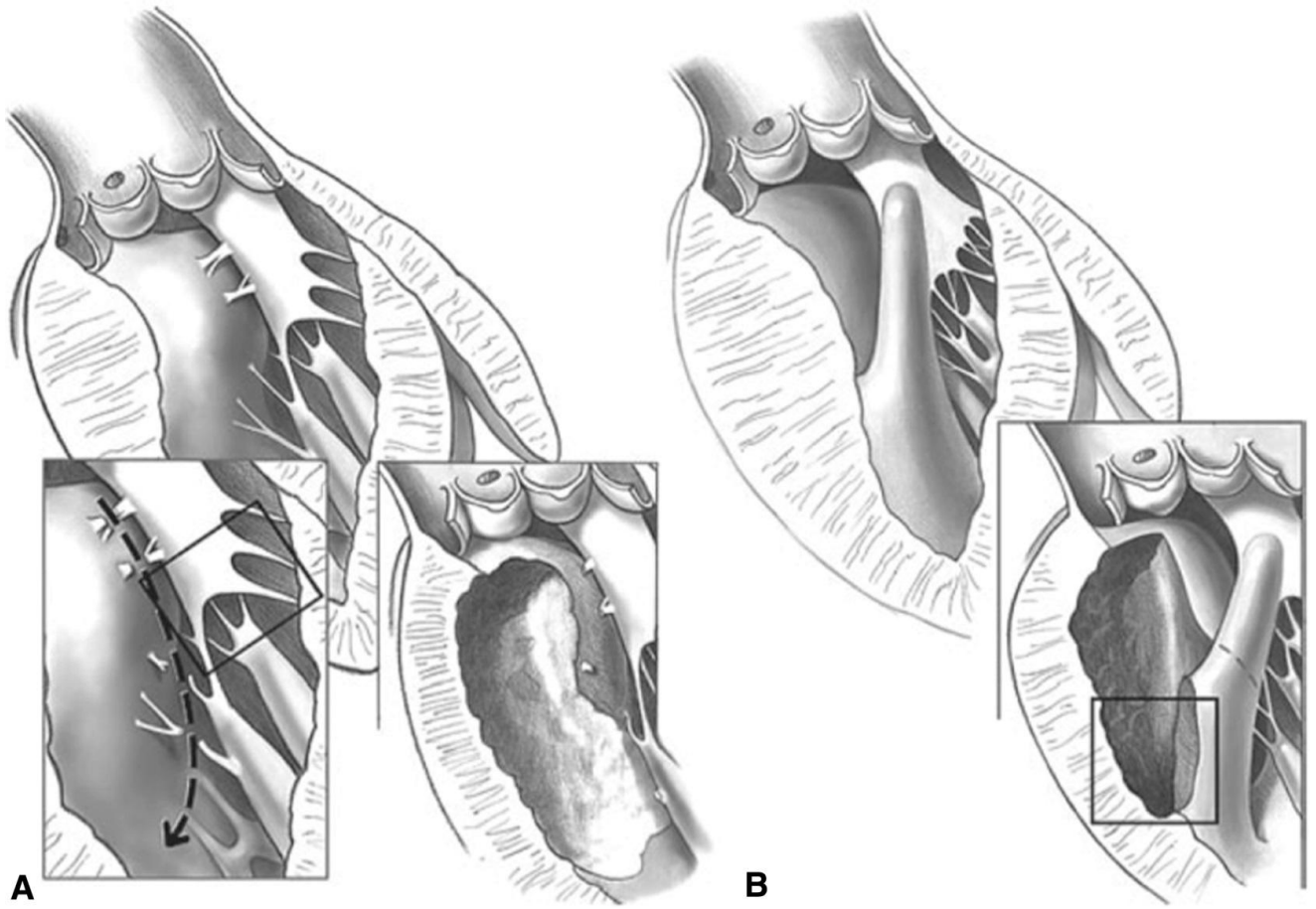
Septal reduction therapy

- **chirurgická myektomie**
  - 60. léta 20. století
  - tzv. rozšířená myektomie (resekce IVS až k bázi papilárních svalů s jejich částečnou resekcí, mobilizací a případně plikací zvětšeného předního cípu mitrální chlopně)
  - mortalita < 1%
  - rozvoj AVB cca 2%, defekt septa komor, Ao regurgitace



Septal reduction therapy

- **chirurgická myektomie**
  - 60. léta 20. století
  - tzv. rozšířená myektomie (resekce IVS až k bázi papilárních svalů s jejich částečnou resekcí, mobilizací a případně plikací zvětšeného předního cípu mitrální chlopně)
  - mortalita < 1%
  - rozvoj AVB cca 2%, defekt septa komor, Ao regurgitace



Pokles LVOTG a prognóza

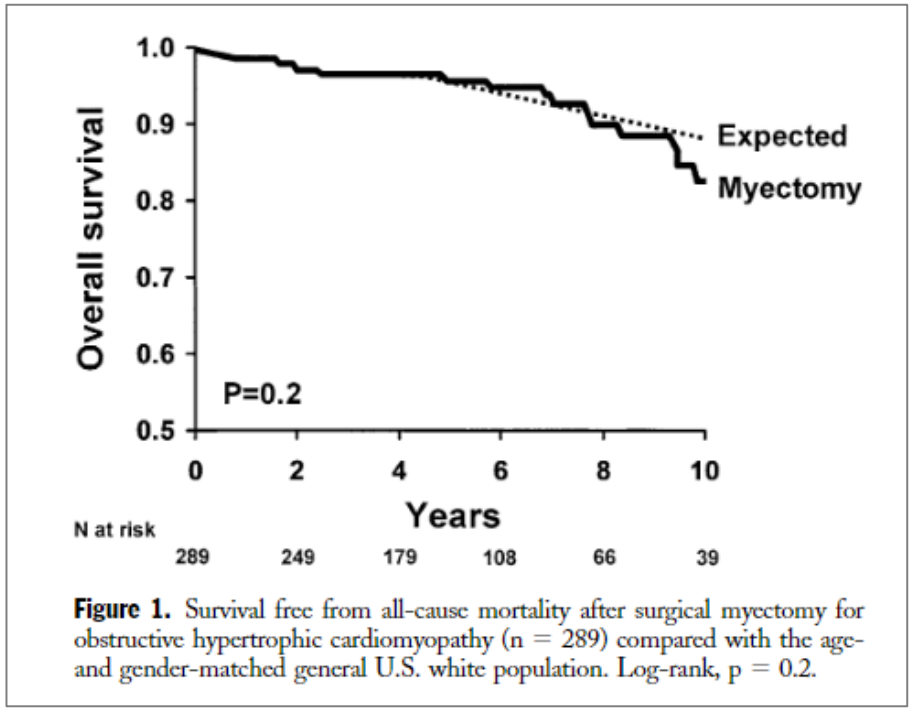


Figure 1. Survival free from all-cause mortality after surgical myectomy for obstructive hypertrophic cardiomyopathy (n = 289) compared with the age- and gender-matched general U.S. white population. Log-rank, p = 0.2.

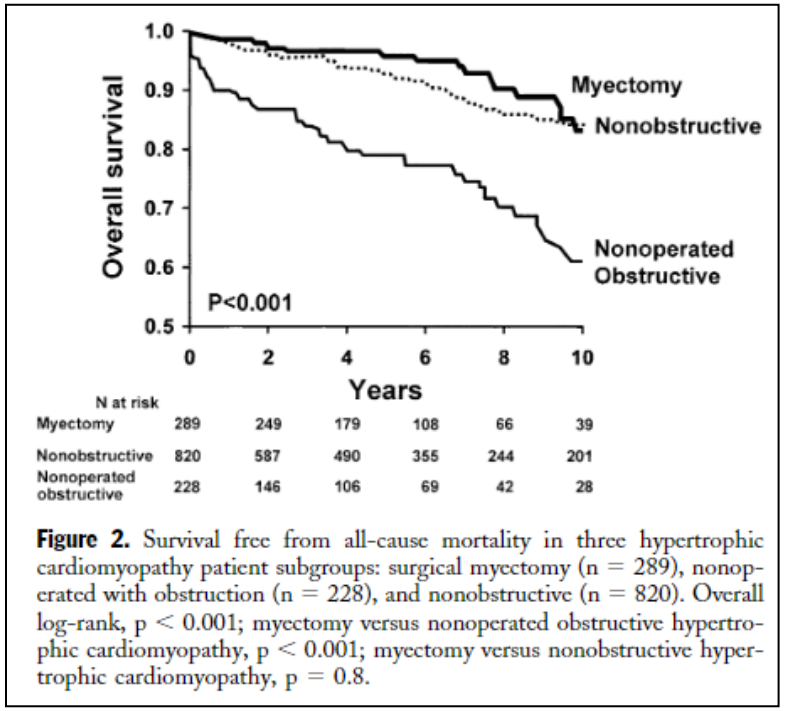
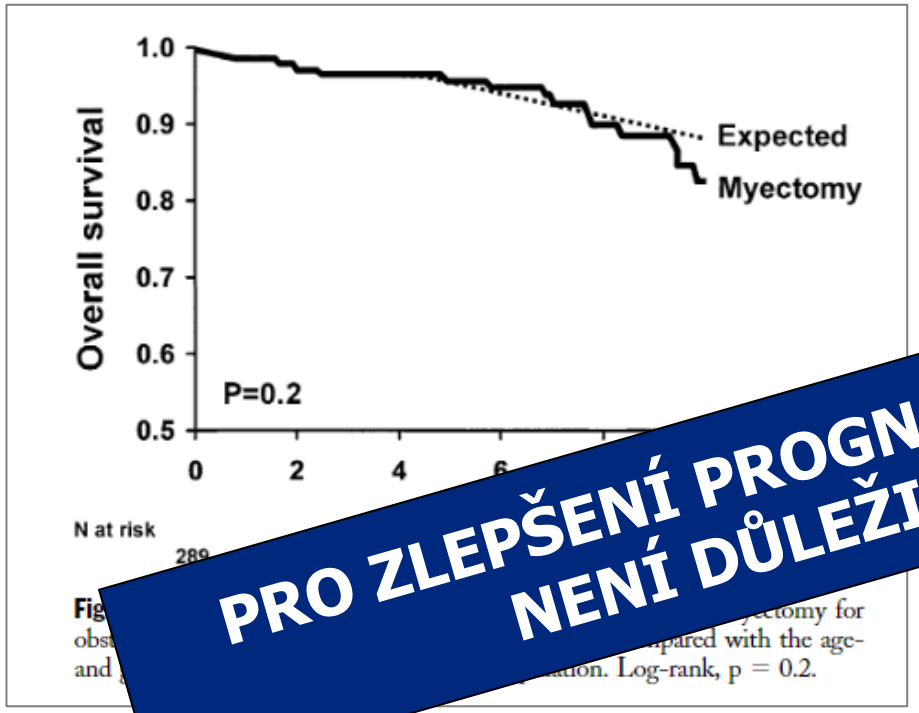


Figure 2. Survival free from all-cause mortality in three hypertrophic cardiomyopathy patient subgroups: surgical myectomy (n = 289), nonoperated with obstruction (n = 228), and nonobstructive (n = 820). Overall log-rank, p < 0.001; myectomy versus nonoperated obstructive hypertrophic cardiomyopathy, p < 0.001; myectomy versus nonobstructive hypertrophic cardiomyopathy, p = 0.8.

Ommen SR et al. J Am Coll Cardiol. 2005;46(3):470-476.

Pokles LVOTG a prognóza



PRO ZLEPŠENÍ PROGNÓZY JE TŘEBA SNÍŽIT LVOTG, NENÍ DŮLEŽITÉ KTEROU METODOU

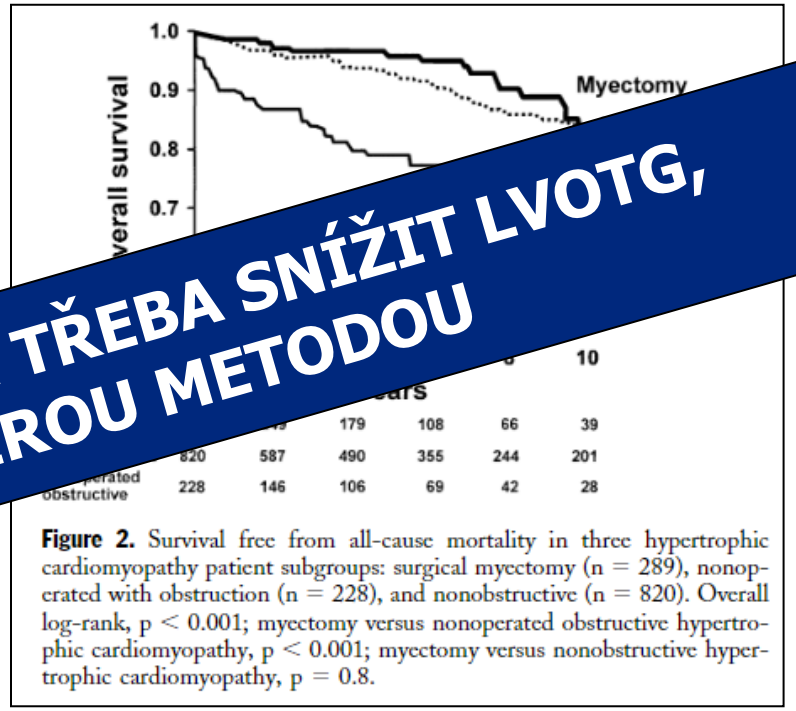


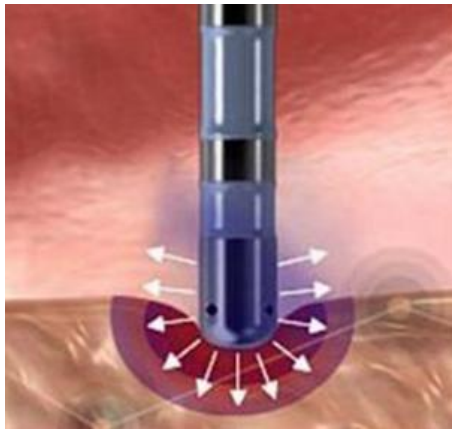
Figure 2. Survival free from all-cause mortality in three hypertrophic cardiomyopathy patient subgroups: surgical myectomy (n = 289), nonoperated with obstruction (n = 228), and nonobstructive (n = 820). Overall log-rank, p < 0.001; myectomy versus nonoperated obstructive hypertrophic cardiomyopathy, p < 0.001; myectomy versus nonobstructive hypertrophic cardiomyopathy, p = 0.8.

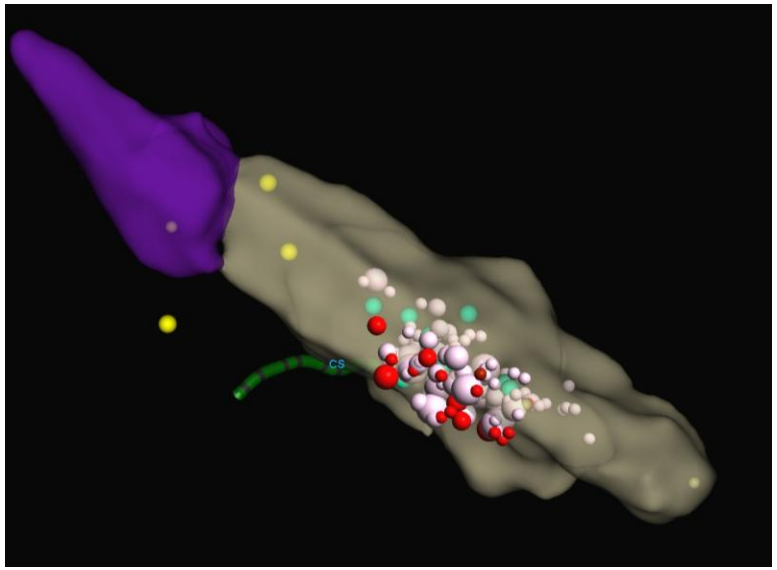
Ommen SR et al. J Am Coll Cardiol. 2005;46(3):470-476.

Septal reduction therapy

Katetrová RFA interventrikulárního septa (ERASH)

- Cílená RFA s podporou 3D elektroanatomických mapovacích systémů a ICE (intrakardiální ultrazvuk) s minimem komplikací
- RFA vytváří relativně ohraničenou koagulační nekrozu takto ošetřené tkáně s následným omezením kontraktility (ztlušťování) hypertrofické tkáně a následným jizvením
- Zatím v literatuře jen jednotlivá kazuistická sdělení a menší soubory pacientů (dosud desítky pacientů), chybí srovnání oproti zavedeným metodám





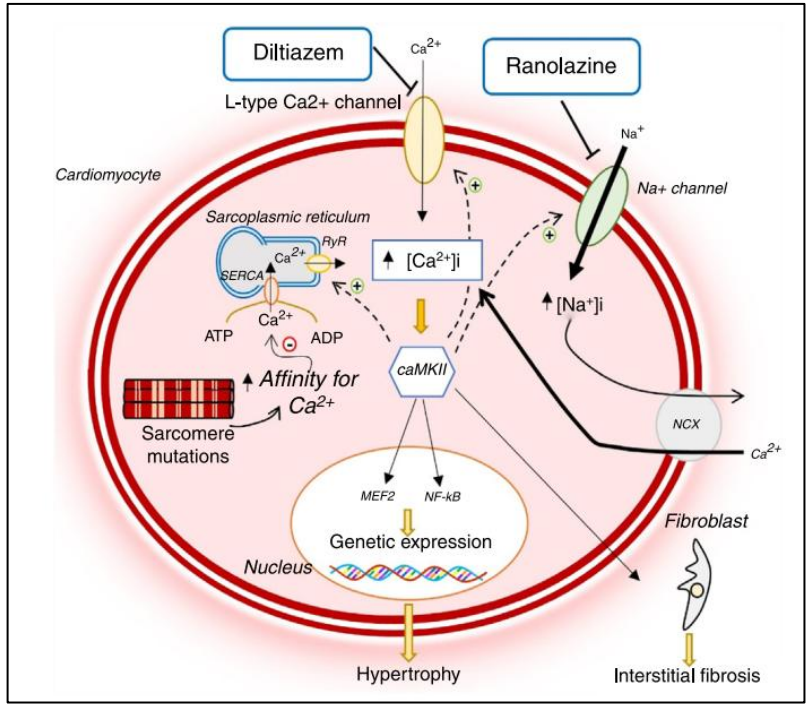
Lawrenz M.T., Kuhn M.H. Endocardial radiofrequency ablation of septal hypertrophy: a new catheter-based modality of gradient reduction in hypertrophic obstructive cardiomyopathy. Z Kardiol. 2004;93:493–499.

Lawrenz T, Borchert B, Leuner C, Bartelsmeier M, Reinhardt J, Strunk-Mueller C et al. Endocardial radiofrequency ablation for hypertrophic obstructive cardiomyopathy: acute results and 6 months' follow-up in 19 patients.J Am Coll Cardio.2011.57;572

V co všechno byly vkládány naděje?

New perspectives in the pharmacological treatment of hypertrophic cardiomyopathy☆

Blokátory pozdního sodíkového kanálu



Cardiomyopathy (RESTYLE-HCM) trial, which assessed the beneficial effects of ranolazine on the functional capacity of HCM patients.[22] In this double-blind, randomized, placebo-controlled trial in a sample of 80 symptomatic patients, although ranolazine reduced the risk of arrhythmia, it did not significantly improve LV diastolic function, exercise tolerance, quality of life or plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) levels.[22]

The Effect of Eleclazine (GS-6615) on Exercise Capacity in Subjects With Symptomatic Hypertrophic Cardiomyopathy (LIBERTY-HCM) trial assessed the effect of a more potent INaL inhibitor, eleclazine, on improving exercise tolerance in HCM.[23] This trial was ended prematurely due to the adverse effects the drug presented in parallel trials in patients with other heart disease.[23]

Rev Port Cardiol. 2020;39(2):99–109

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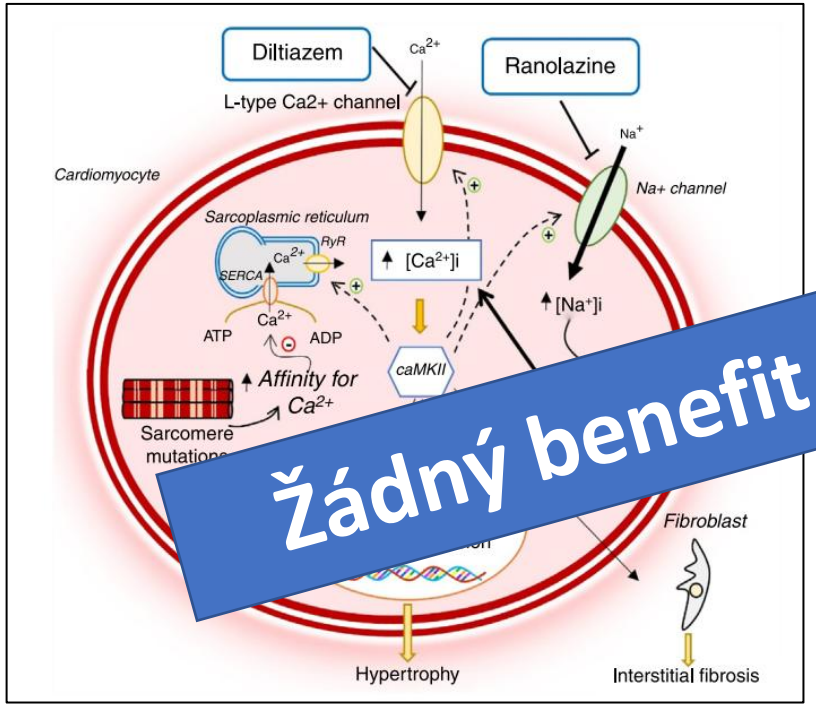

Žádný benefit, nežádoucí účinky ☹

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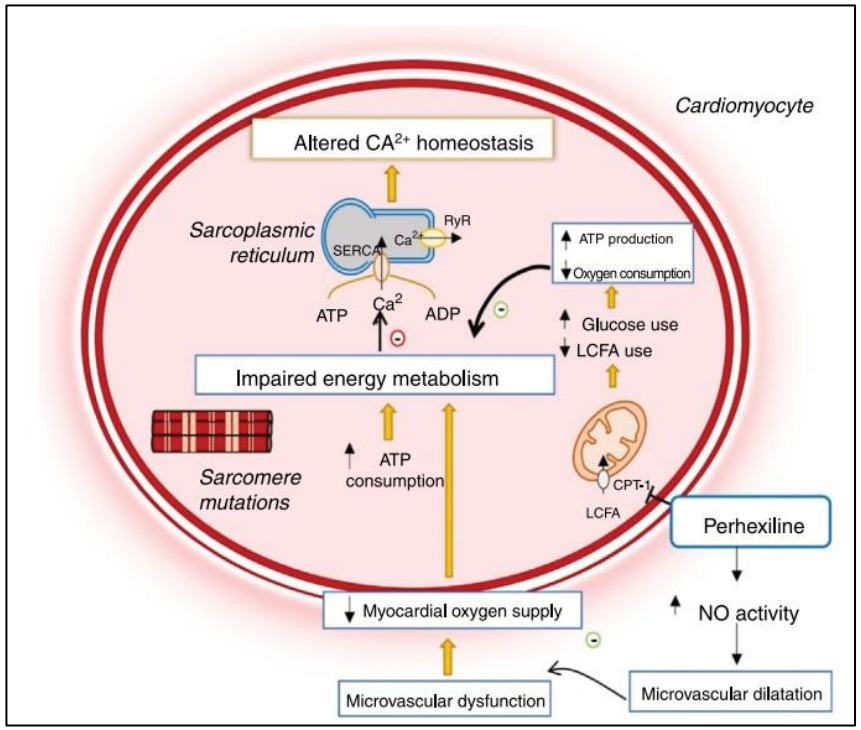
V co všechno byly vkládány naděje?

New perspectives in the pharmacological treatment of hypertrophic cardiomyopathy☆

Metabolické modulátory



Despite these promising initial results, a recent clinical trial in 35 patients with obstructive HCM was discontinued prematurely as perhexiline showed no demonstrable efficacy in symptom improvement and oxygen consumption in HCM patients (ClinicalTrials.gov identifier NCT02862600).

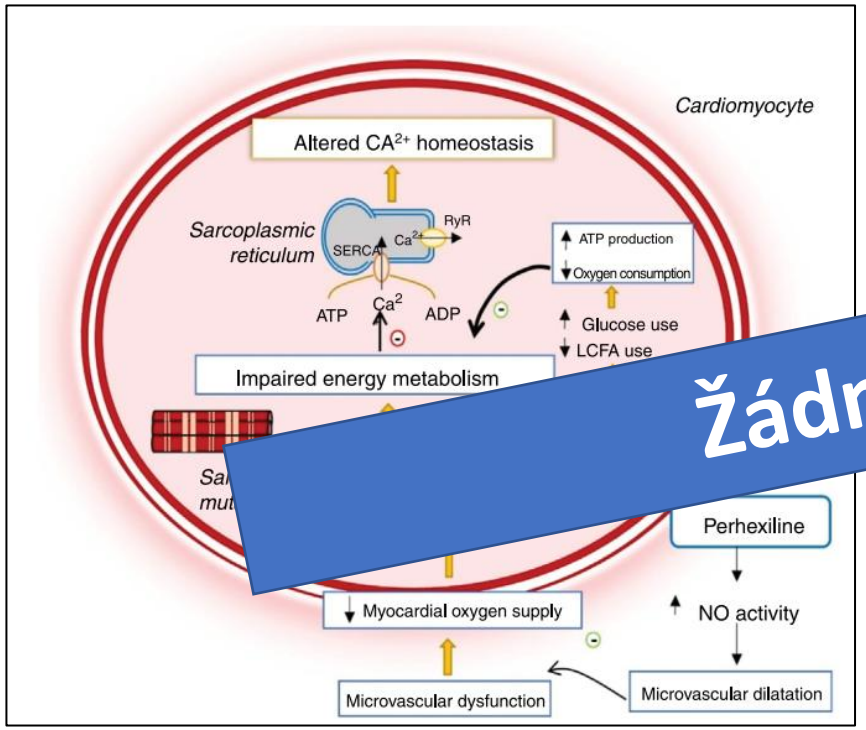
However, in a recent double-blind, randomized, placebo-controlled clinical trial, trimetazidine did not improve peak oxygen consumption or six-minute walk test distance in patients with symptomatic non-obstructive HCM.[30]

Rev Port Cardiol. 2020;**39(2)**:99–109

V co všechno byly vkládány naděje?

New perspectives in the pharmacological treatment of hypertrophic cardiomyopathy☆

Metabolické modulátory



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Žádný benefit ☹

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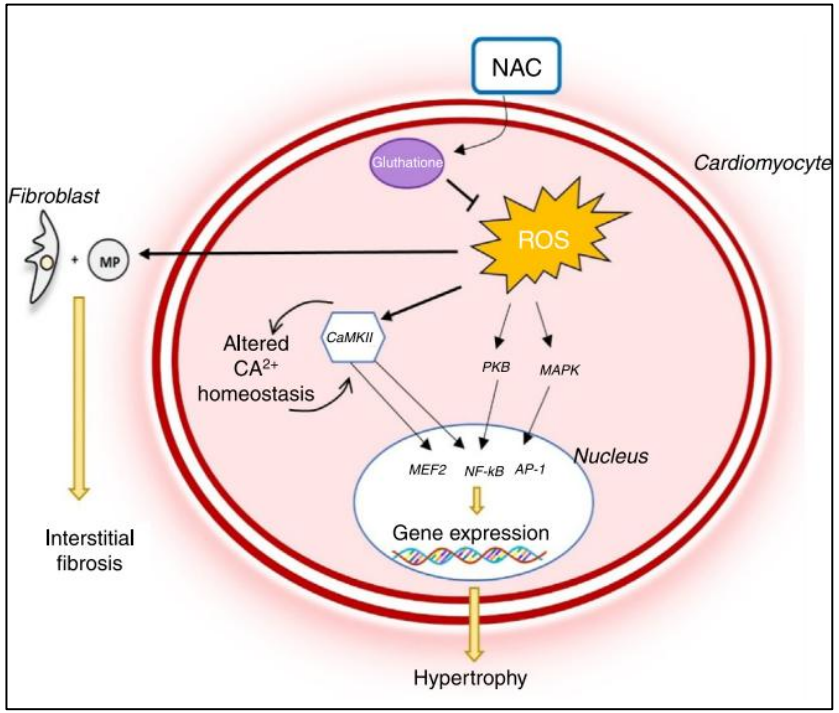
V co všechno byly vkládány naděje?

New perspectives in the pharmacological treatment of hypertrophic cardiomyopathy☆

N-acetylcystein



These promising results formed the basis for the Hypertrophy Regression With N-Acetylcysteine in Hypertrophic Cardiomyopathy (HALT-HCM) trial, a recent double-blind, randomized, placebo-controlled pilot trial to assess the effect of NAC on reversing LVH and interstitial fibrosis in HCM.[36] In this study, the benefit of treatment with NAC on LVH and myocardial fibrosis was disappointingly small.[36] The

Rev Port Cardiol. 2020;39(2):99–109

V co všechno byly vkládány naděje?

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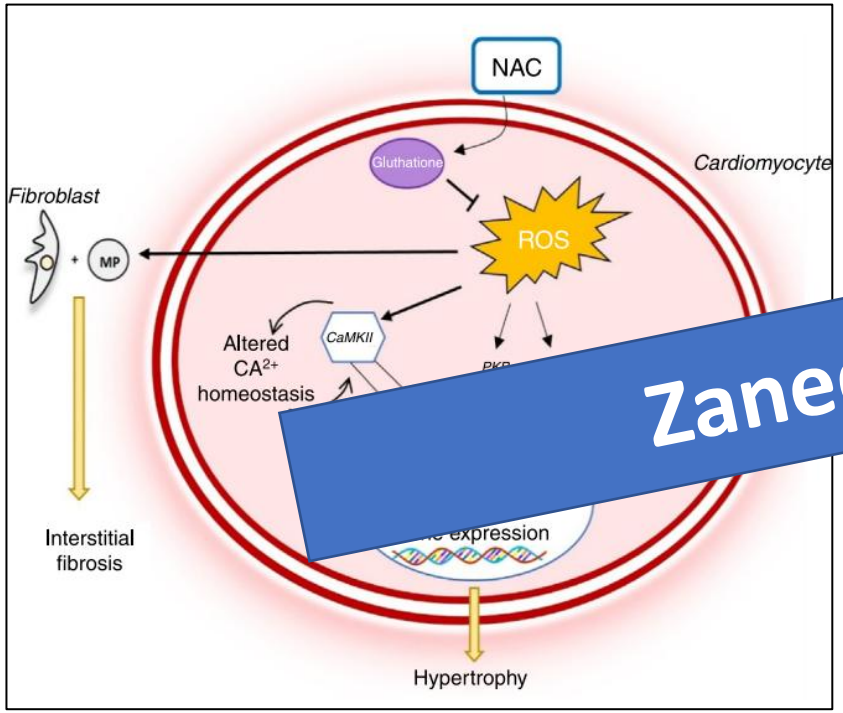

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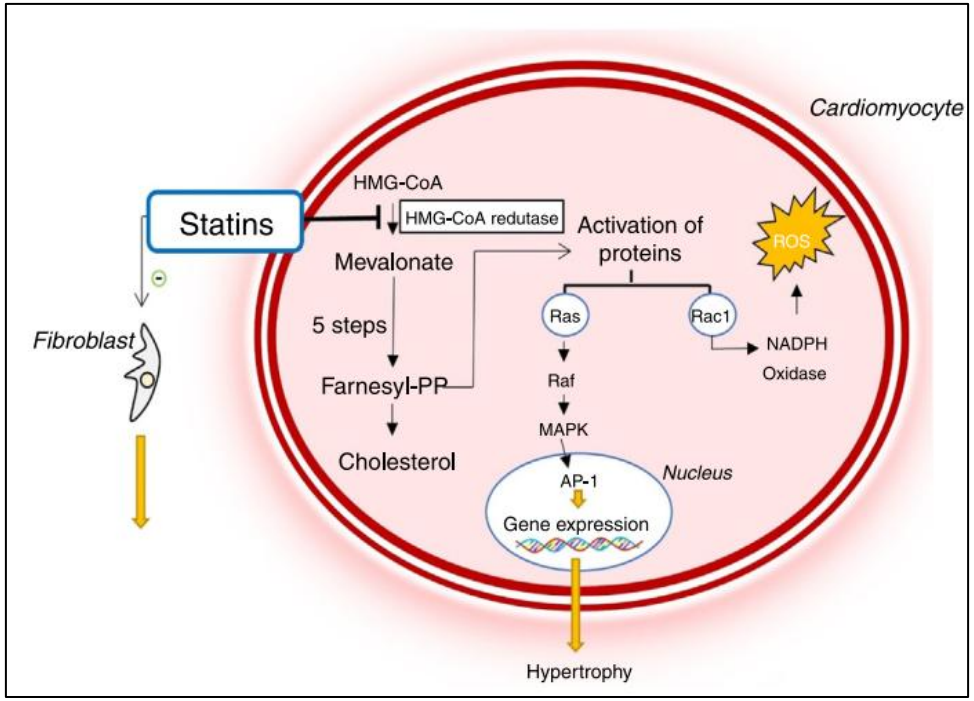
Zanedbatelný efekt ☹

Rev Port Cardiol. 2020;39(2):99–109

V co všechno byly vkládány naděje?

New perspectives in the pharmacological treatment of hypertrophic cardiomyopathy☆

Statiny



The Statin Induced Regression of Cardiomyopathy Trial (SIRCAT) also assessed atorvastatin's potential to reverse LVH in patients with HCM.[43] In this randomized, placebo-controlled clinical trial, atorvastatin was not shown to reduce LV mass compared with placebo.[43]

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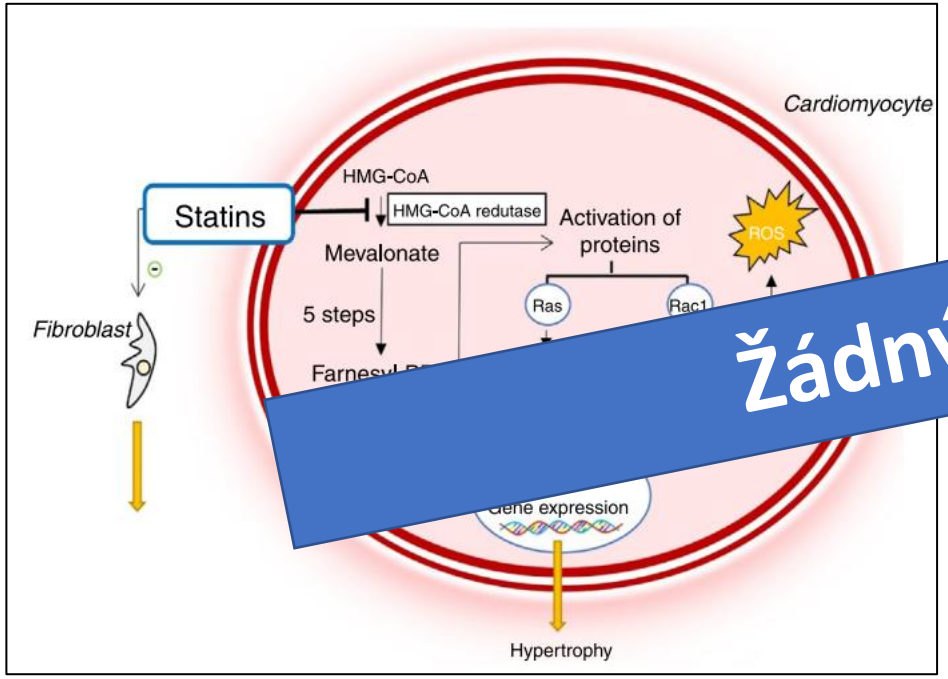

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Žádný benefit ☹

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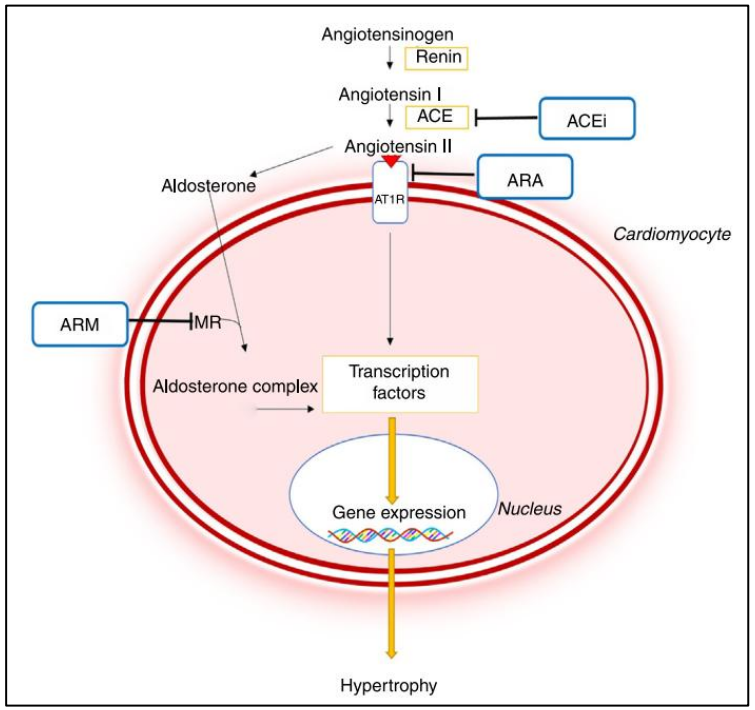
New perspectives in the pharmacological treatment of hypertrophic cardiomyopathy☆

RAAS inhibitory



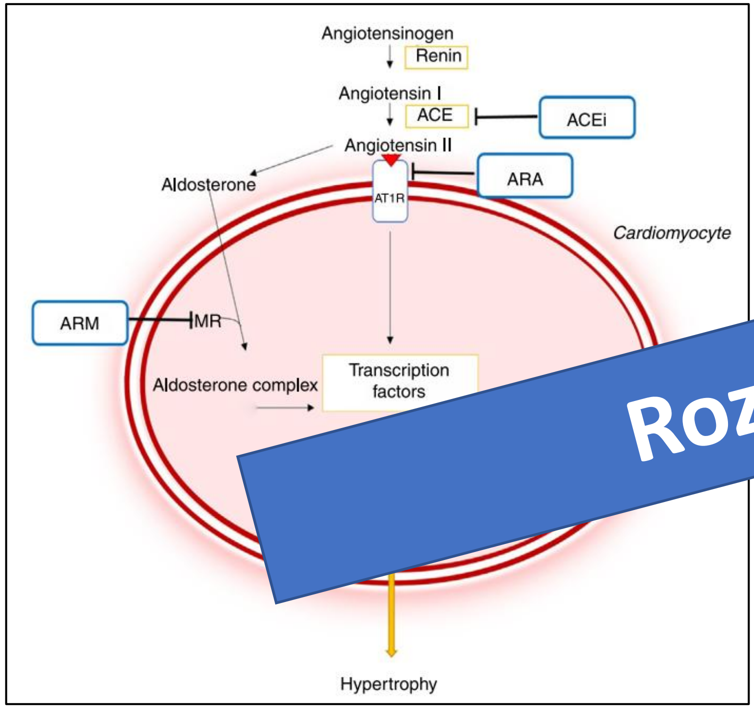
The Inhibition of the Renin Angiotensin System With Losartan in Patients With Hypertrophic Cardiomyopathy (INHERIT) trial was conducted to shed more light on the conflicting results of these clinical trials and to establish the efficacy of RAAS inhibitors in reversing LVH and interstitial fibrosis in HCM.[54] In this double-blind, placebo-controlled, randomized trial in 124 patients, treatment with losartan, although safe, did not significantly reduce LV mass or interstitial fibrosis.[54] This result does not support the hypothesis that this agent can change the HCM phenotype in individuals with established disease.[54]

Rev Port Cardiol. 2020;**39(2)**:99–109

V co všechno byly vkládány naděje?

New perspectives in the pharmacological treatment of hypertrophic cardiomyopathy☆

RAAS inhibitory



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Rozporuplná data :-/

Rev Port Cardiol. 2020;39(2):99–109

Záblesky naděje…?

Valsartan in early-stage hypertrophic cardiomyopathy: a randomized phase 2 trial

Carolyn Y. Ho[1]✉, Sharlene M. Day[2,22], Anna Axelsson[3], Mark W. Russell[2], Kenneth Zahka[4], Harry M. Lever[4], Alexandre C. Pereira[5], Steven D. Colan[6], Renee Margossian[6], Anne M. Murphy[7], Charles Canter[8], Richard G. Bach[8], Matthew T. Wheeler[9], Joseph W. Rossano[10], Anjali T. Owens[22], Henning Bundgaard[3,11], Lee Benson[12], Luisa Mestroni[13], Matthew R. G. Taylor[13], Amit R. Patel[14], Ivan Wilmot[15], Philip Thrush[16], Jose D. Vargas[17], Jonathan H. Soslow[18], Jason R. Becker[18,23], Christine E. Seidman[1,19], Neal K. Lakdawala[1], Allison L. Cirino[1], VANISH Investigators*, Kristin M. Burns[20], John J. V. McMurray[21], Calum A. MacRae[1], Scott D. Solomon[1], E. John Orav[1] and Eugene Braunwald[1]

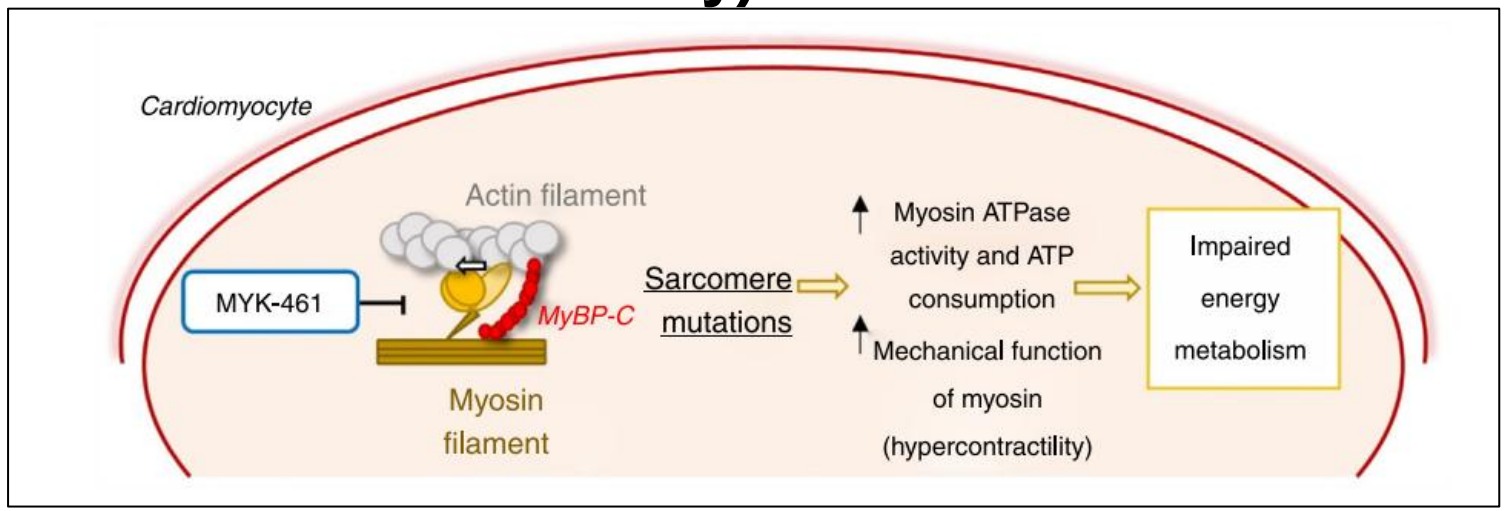
Valsartan ($n = 88$) improved cardiac structure and function compared to placebo ($n = 90$), as reflected by an increase in the composite *z*-score (between-group difference +0.231, 95% confidence interval (+0.098, +0.364); $P = 0.001$), which met the primary endpoint of the study. Treatment was well-tolerated. These results indicate a key opportunity to attenuate disease progression in early-stage sarcomeric HCM with an accessible and safe medication.

NATURE MEDICINE | VOL 27 | OCTOBER 2021 | 1818–1824 |

…co je naší velkou nadějí?

New perspectives in the pharmacological treatment of hypertrophic cardiomyopathy☆

Inhibitory myosinu (resp. myozinové ATPázy)



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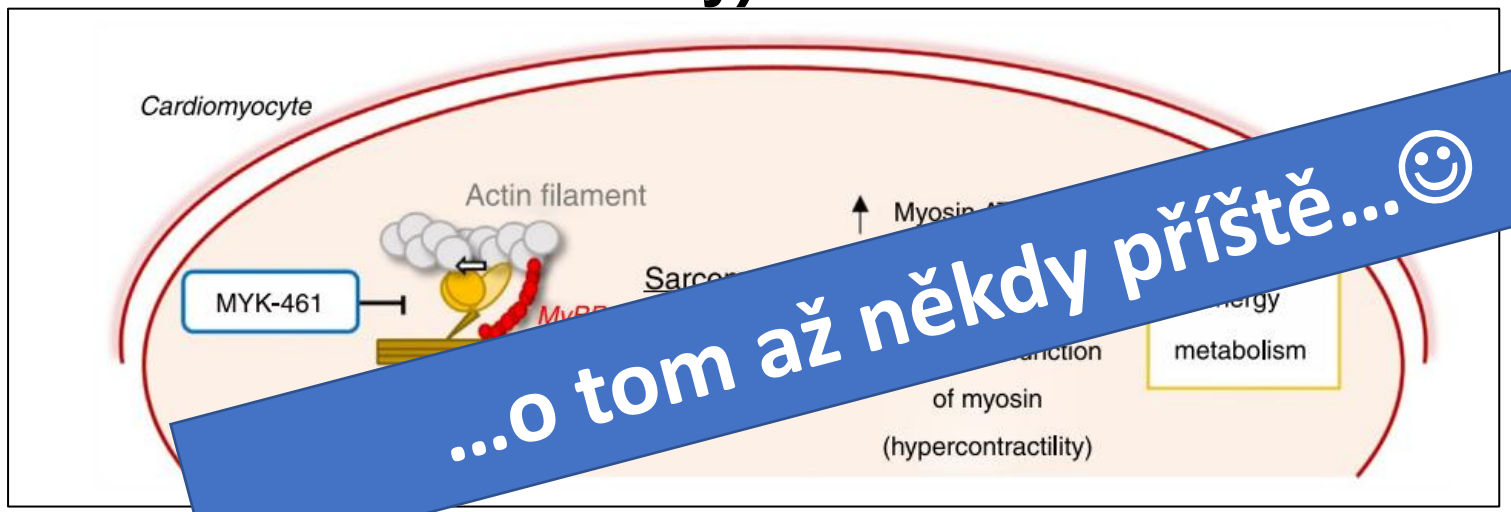


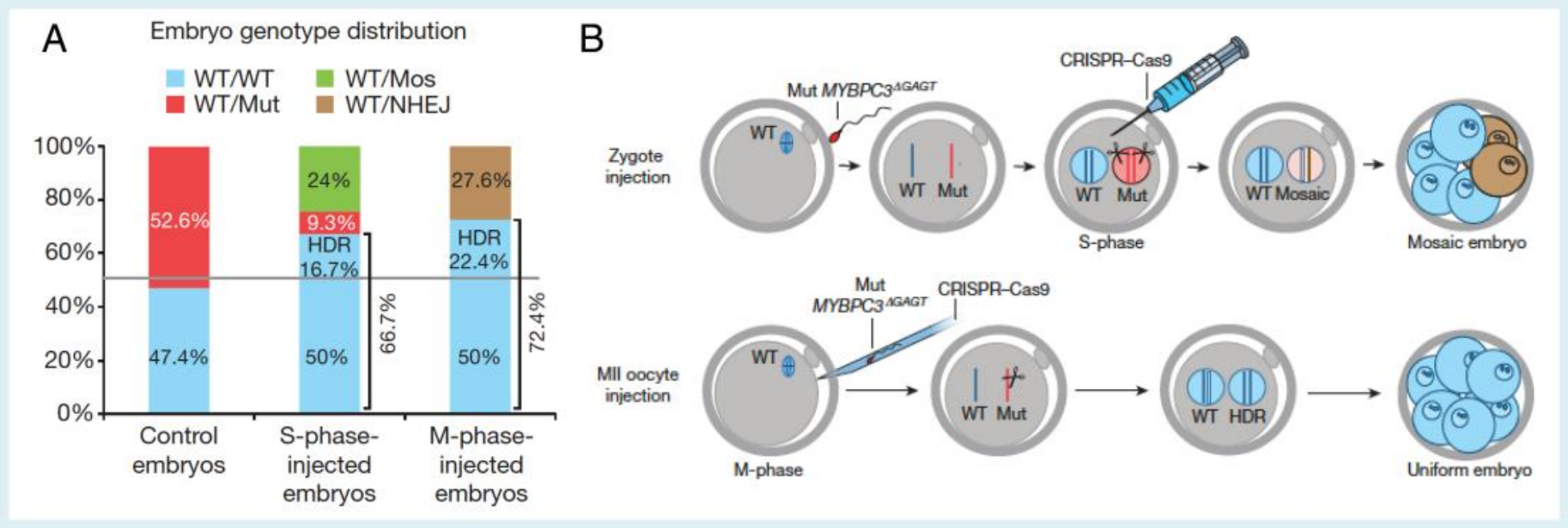
…o tom až někdy příště…☺

Rev Port Cardiol. 2020;39(2):99–109

…možná ne tak vzdálená budoucnost…

Hypertrophic cardiomyopathy: the future of treatment

Genome editing and gene silencing in hypertrophic cardiomyopathy



European Journal of Heart Failure (2020) **22**, 228–240

Závěry

- Léčba HCM je velmi komplexní záležitost
- Základním úkolem je prevence náhlé srdeční smrti
- Redukce příznaků srdečního selhání (farmakologické a nefarmakologické přístupy)
- Léčba fibrilace síní (a jejích komplikací)

- Budoucími cíli je zábrana rozvoje fenotypu u genotyp-pozitivních jedinců a zábrana produkce mutovaného proteinu, tedy odstranění samotné příčiny vzniku HCM.

Děkuji za pozornost!