KOMPLEXNÍ KARDIO VASKULÁRNÍ CENTRUM VFN Praha

SEQUOIA-HCM

(Safety, Efficacy, and Quantitative Understanding of Obstruction Impact of *Aficamten* in HCM)

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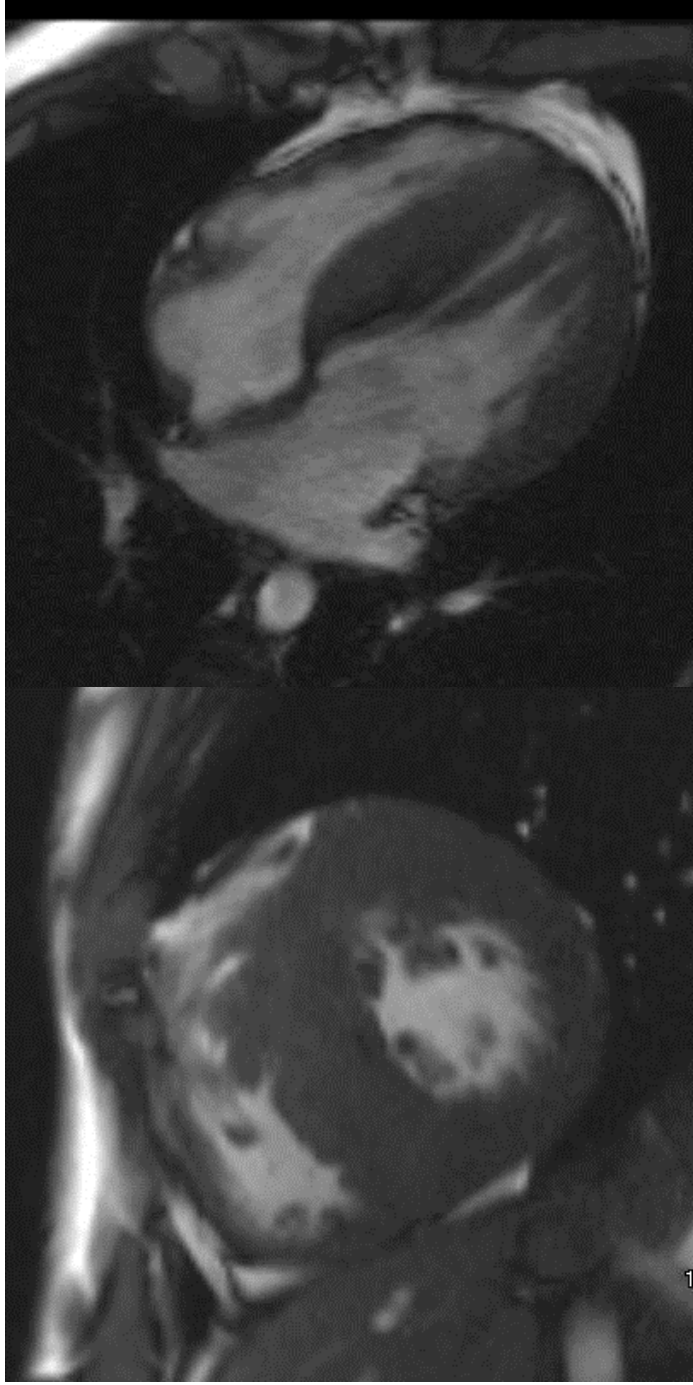
VŠEOBECNÁ FAKULTNÍ NEMOCNICE V PRAZE

Hypertrofická kardiomyopatie

- **HCM je definována jeho ztluštění stěny levé komory (≥ 15 mm) s/bez hypertrofie pravé komory**, které nemůže být vysvětleno hemodynamickými podmínkami (změnou preloadu a afterloadu)
- Nejčastější kardiomyopatií (prevalence 0,2 %)
- Pacienti jsou ohroženi rizikem náhlé srdeční smrti a také mohou být limitováni námahovou dušností, případně anginou
- Obstrukce ve výtokovém traktu levé komory (LVOTO) může být přítomná až u 70% pacientů



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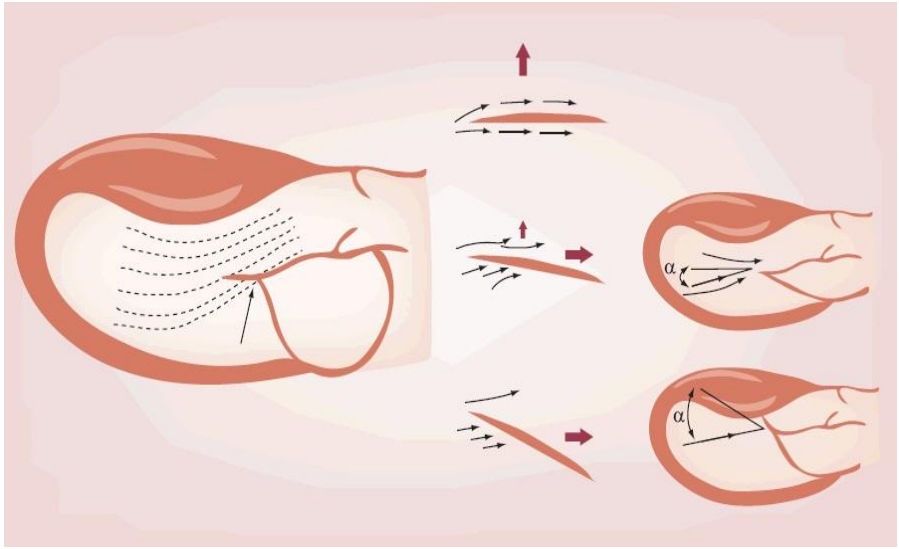
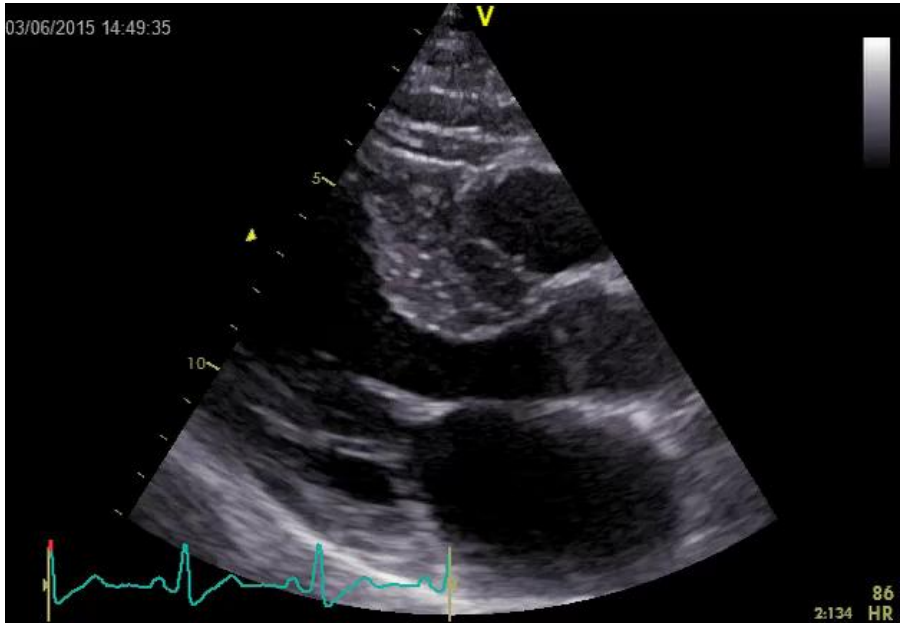
Obstrukce ve výtokovém traktu

- Obstrukce ve výtokovém traktu (LVOT) je jedním z častých a charakteristických nálezů u hypertrofické kardiomyopatie (HCM)
- Představuje rizikový faktorem náhlé srdeční smrti
- Obstrukce v LVOT se podílí na symptomech pacientů s HCM, ale na druhé straně ji můžeme léčit

  → máme po ní aktivně pátrat
- V případě, že není v klidu přítomná, tak bychom měli provést zátěžový test



Geske JB et al. Interventional Cardiology 2014



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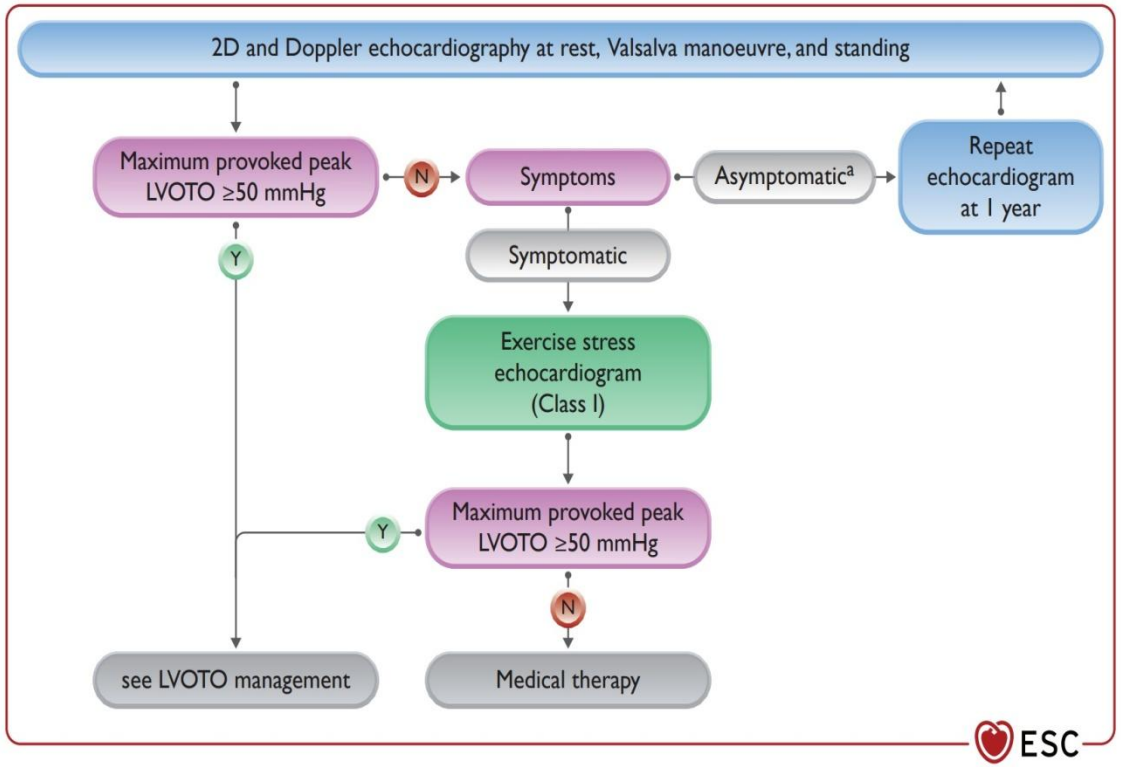
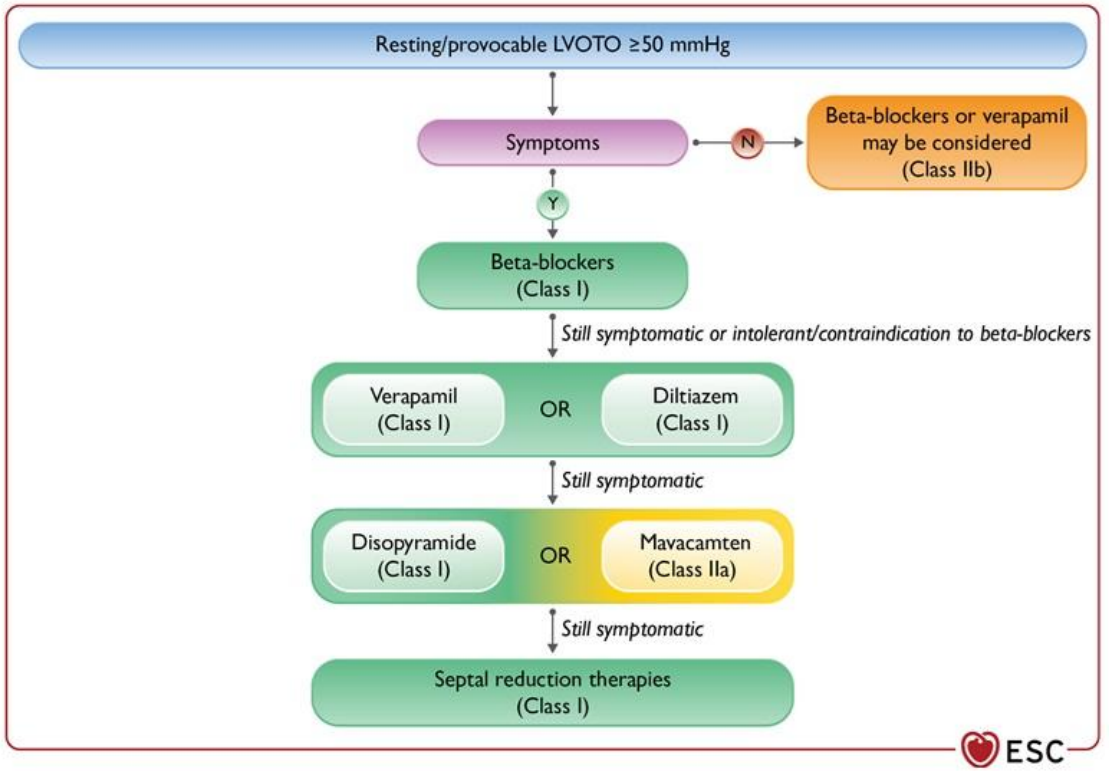
Hypertrofická kardiomyopatie - léčba

Schéma léčby LVOTO



Algoritmus léčby LVOTO

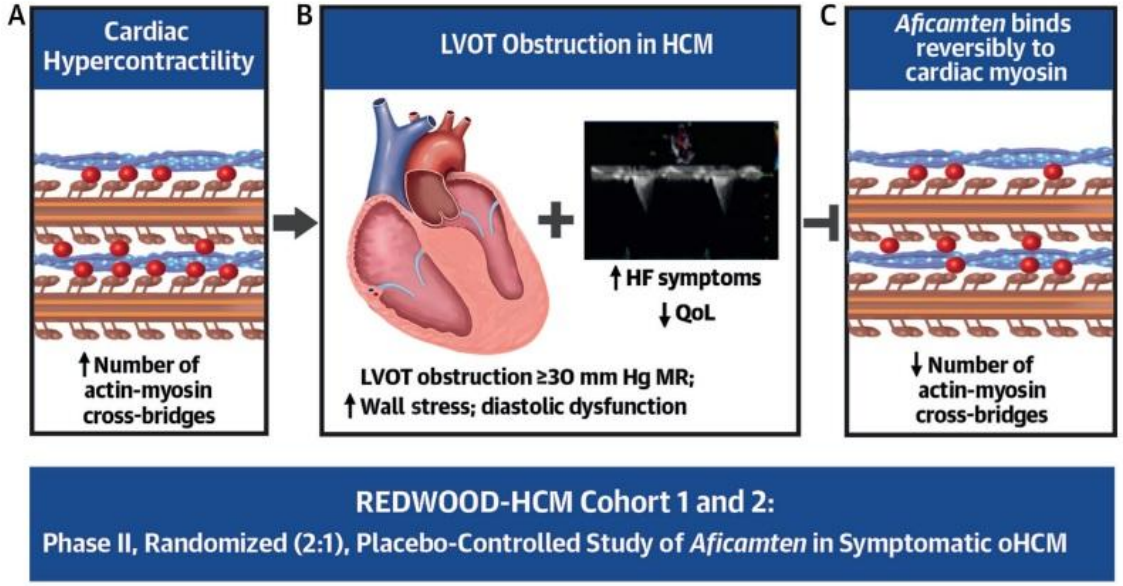


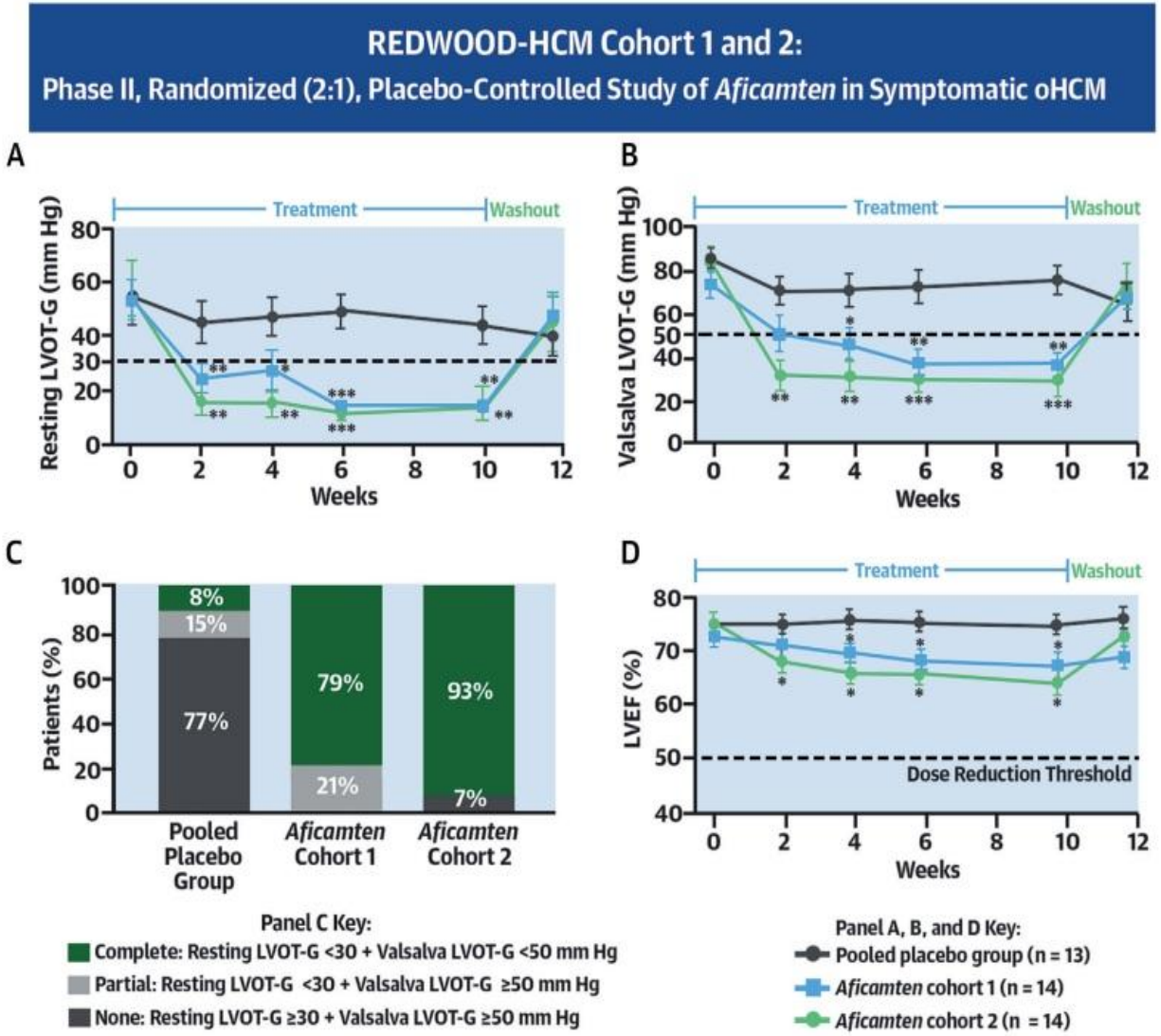
2023 ESC Guidelines for the management of cardiomyopathies

Aficamten

Aficamten patří do skupiny inhibitorů myozinu, kteří fungují tak, že redukují nadbyteční počet aktino-myozinových můstků

- Pilotní studie REDWOOD-HCM





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SEQUOIA-HCM

- multicentrická randomizovaná placebem kontrolovaná studie (USA, Evropa, Čína)
- fáze 3
- srovnání léčby **aficamtenem s placebem** u pacientů se symptomatickou obstrukční hypertrofickou kardiomyopatií **(NYHA II.-III.st.)**
- 282 pacientů (1:1)
- 24-týdnů
- **Obstrukce v LVOT** (≥ 30 v klidu a ≥ 50 mmHg u Valsalvova manévru)
- Primární cíl – **změna vrcholové spotřeby kyslíku při spiroergometrii** (VO2max.)

BACKGROUND

One of the major determinants of exercise intolerance and limiting symptoms among patients with obstructive hypertrophic cardiomyopathy (HCM) is an elevated intracardiac pressure resulting from left ventricular outflow tract obstruction. Aficamten is an oral selective cardiac myosin inhibitor that reduces left ventricular outflow tract gradients by mitigating cardiac hypercontractility.

METHODS

In this phase 3, double-blind trial, we randomly assigned adults with symptomatic obstructive HCM to receive aficamten (starting dose, 5 mg; maximum dose, 20 mg) or placebo for 24 weeks, with dose adjustment based on echocardiography results. The primary end point was the change from baseline to week 24 in the peak oxygen uptake as assessed by cardiopulmonary exercise testing. The 10 prespecified secondary end points (tested hierarchically) were change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), improvement in the New York Heart Association (NYHA) functional class, change in the pressure gradient after the Valsalva maneuver, occurrence of a gradient of less than 30 mm Hg after the Valsalva maneuver, and duration of eligibility for septal reduction therapy (all assessed at week 24); change in the KCCQ-CSS, improvement in the NYHA functional class, change in the pressure gradient after the Valsalva maneuver, and occurrence of a gradient of less than 30 mm Hg after the Valsalva maneuver (all assessed at week 12); and change in the total workload as assessed by cardiopulmonary exercise testing at week 24.

RESULTS

A total of 282 patients underwent randomization: 142 to the aficamten group and 140 to the placebo group. The mean age was 59.1 years, 59.2% were men, the baseline mean resting left ventricular outflow tract gradient was 55.1 mm Hg, and the baseline mean left ventricular ejection fraction was 74.8%. At 24 weeks, the mean change in the peak oxygen uptake was 1.8 ml per kilogram per minute (95% confidence interval [CI], 1.2 to 2.3) in the aficamten group and 0.0 ml per kilogram per minute (95% CI, −0.5 to 0.5) in the placebo group (least-squares mean between-group difference, 1.7 ml per kilogram per minute; 95% CI, 1.0 to 2.4; P<0.001). The results for all 10 secondary end points were significantly improved with aficamten as compared with placebo. The incidence of adverse events appeared to be similar in the two groups.

CONCLUSIONS

Among patients with symptomatic obstructive HCM, treatment with aficamten resulted in a significantly greater improvement in peak oxygen uptake than placebo. (Funded by Cytokinetics; SEQUOIA-HCM ClinicalTrials.gov number, NCT05186818.)

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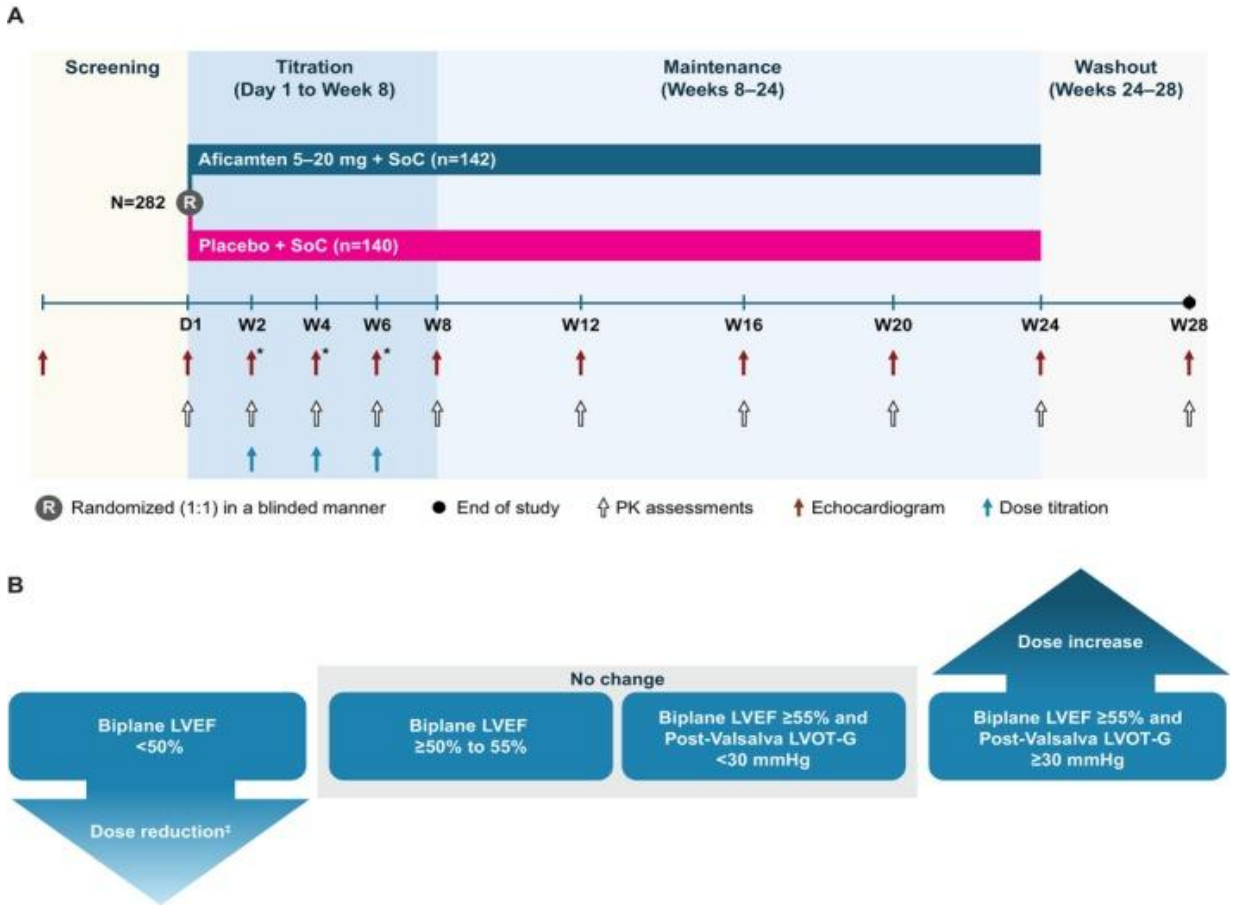

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Aficamten (N=142)	Placebo (N=140)
Age — yr	59.2±12.6	59.0±13.3
Female sex — no. (%)	56 (39.4)	59 (42.1)
Race — no. (%)†		
White	108 (76.1)	115 (82.1)
Asian	29 (20.4)	25 (17.9)
Black	3 (2.1)	0
Other	2 (1.4)	0
Geographic region — no. (%)		
North America	49 (34.5)	45 (32.1)
China	24 (16.9)	22 (15.7)
Europe or Israel	69 (48.6)	73 (52.1)
Medical history — no. (%)		
Hypertension	75 (52.8)	70 (50.0)
Family history of HCM or presence of known genetic mutation for HCM	47 (33.1)	44 (31.4)
Family history of HCM	41 (28.9)	34 (24.3)
Pathogenic sarcomere variant	24 (16.9)	25 (17.9)
Paroxysmal atrial fibrillation	21 (14.8)	20 (14.3)
Coronary artery disease	19 (13.4)	16 (11.4)
Diabetes	14 (9.9)	9 (6.4)
Permanent atrial fibrillation	2 (1.4)	1 (0.7)
Background HCM therapy — no. (%)		
Beta-blocker	86 (60.6)	87 (62.1)
Calcium-channel blocker	45 (31.7)	36 (25.7)
Disopyramide	16 (11.3)	20 (14.3)
None	19 (13.4)	22 (15.7)
Implantable cardioverter–defibrillator — no. (%)	22 (15.5)	17 (12.1)
KCCQ-CSS‡	76±18	74±18
NYHA functional class — no. (%)§		
II	108 (76.1)	106 (75.7)
III	34 (23.9)	33 (23.6)
IV	0	1 (0.7)
Median NT-proBNP (IQR) — pg/ml	818 (377–1630)	692 (335–1795)
Median high-sensitivity cardiac troponin I (IQR) — ng/liter	12.9 (7.6–33.6)	11.5 (7.7–25.0)
Echocardiographic variables		
Left ventricular outflow tract gradient after Valsalva maneuver — mm Hg	82.9±32	83.3±32.7
Resting left ventricular outflow tract gradient — mm Hg	54.8±27	55.3±32.1
Left ventricular ejection fraction — %	74.8±5.5	74.8±6.3
Maximal left ventricular wall thickness — mm	20.7±3.0	21.0±3.0

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Primární cíl – změna VO2max. při spiroergometrii na začátku a po 24 týdnech léčby

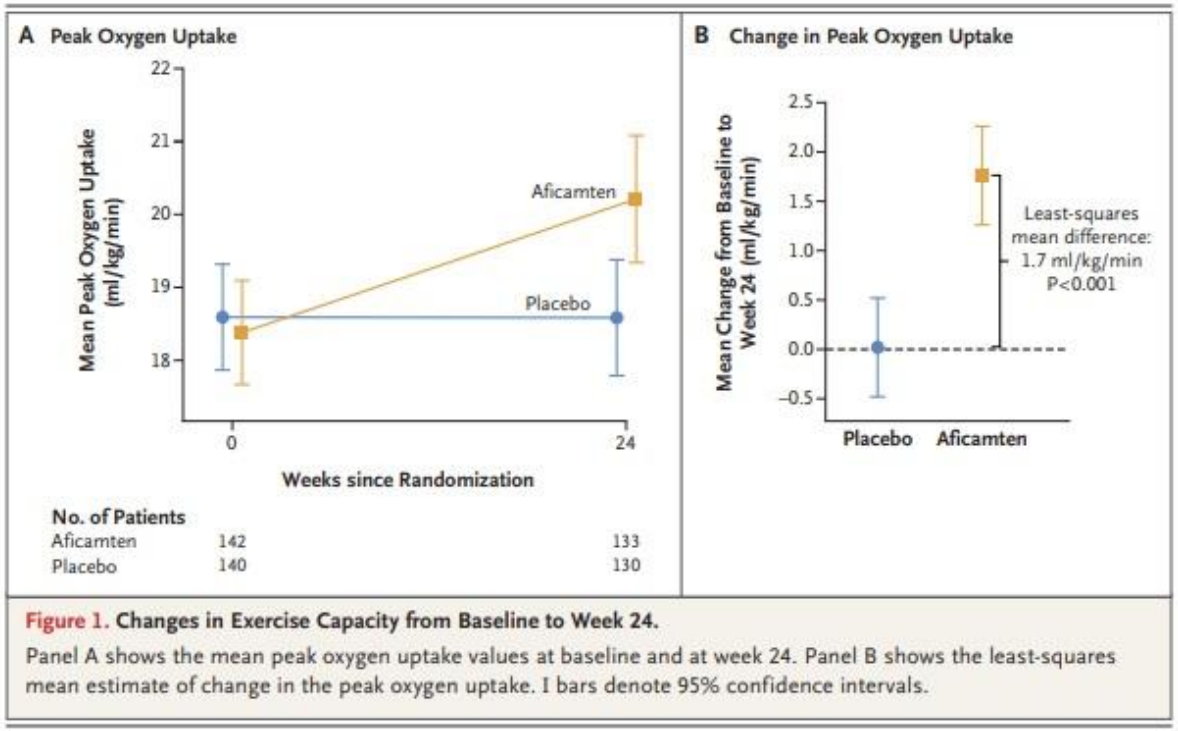

Figure 1. Changes in Exercise Capacity from Baseline to Week 24.

Panel A shows the mean peak oxygen uptake values at baseline and at week 24. Panel B shows the least-squares mean estimate of change in the peak oxygen uptake. I bars denote 95% confidence intervals.

Subgroup	Placebo	Aficamten	Least-Squares Mean Difference in Peak Oxygen Uptake (95% CI)
	no. of patients		*ml/kg/min*
Overall	140	142	1.7 (1.0–2.4)
Sex			
Male	81	86	1.8 (0.9–2.7)
Female	59	56	1.4 (0.4–2.5)
Age			
<65 yr	84	85	2.0 (1.1–2.8)
≥65 yr	56	57	1.4 (0.3–2.5)
Body-mass index			
<30	94	97	1.8 (1.0–2.7)
≥30	46	45	1.6 (0.3–2.8)
NYHA functional class			
II	106	108	1.7 (0.9–2.5)
III or IV	34	34	1.9 (0.5–3.3)
Left ventricular ejection fraction			
≤75.6%	68	73	1.8 (0.8–2.8)
>75.6%	72	69	1.6 (0.6–2.6)
NT-proBNP			
≤788 pg/ml	73	66	1.7 (0.7–2.7)
>788 pg/ml	65	73	2.0 (1.0–2.9)
Method of cardiopulmonary exercise testing			
Cycle ergometer	63	64	1.0 (0.0–2.1)
Treadmill	77	78	2.3 (1.4–3.2)
Peak oxygen uptake			
≤18.4 ml/kg/min	67	74	1.6 (0.6–2.5)
>18.4 ml/kg/min	73	68	1.9 (1.0–2.9)
Beta-blocker use			
Yes	87	86	1.6 (0.7–2.5)
No	53	56	1.9 (0.8–3.1)
Resting left ventricular outflow tract gradient			
≤51.1 mm Hg	69	72	1.3 (0.3–2.3)
>51.1 mm Hg	71	70	2.1 (1.2–3.1)
KCCQ-CSS			
≤78.1	75	67	1.8 (0.8–2.8)
>78.1	65	75	1.7 (0.7–2.6)
Genetic testing result			
Pathogenic or probably pathogenic	22	20	2.6 (0.9–4.2)
Variant of uncertain significance or negative	70	71	1.4 (0.5–2.3)

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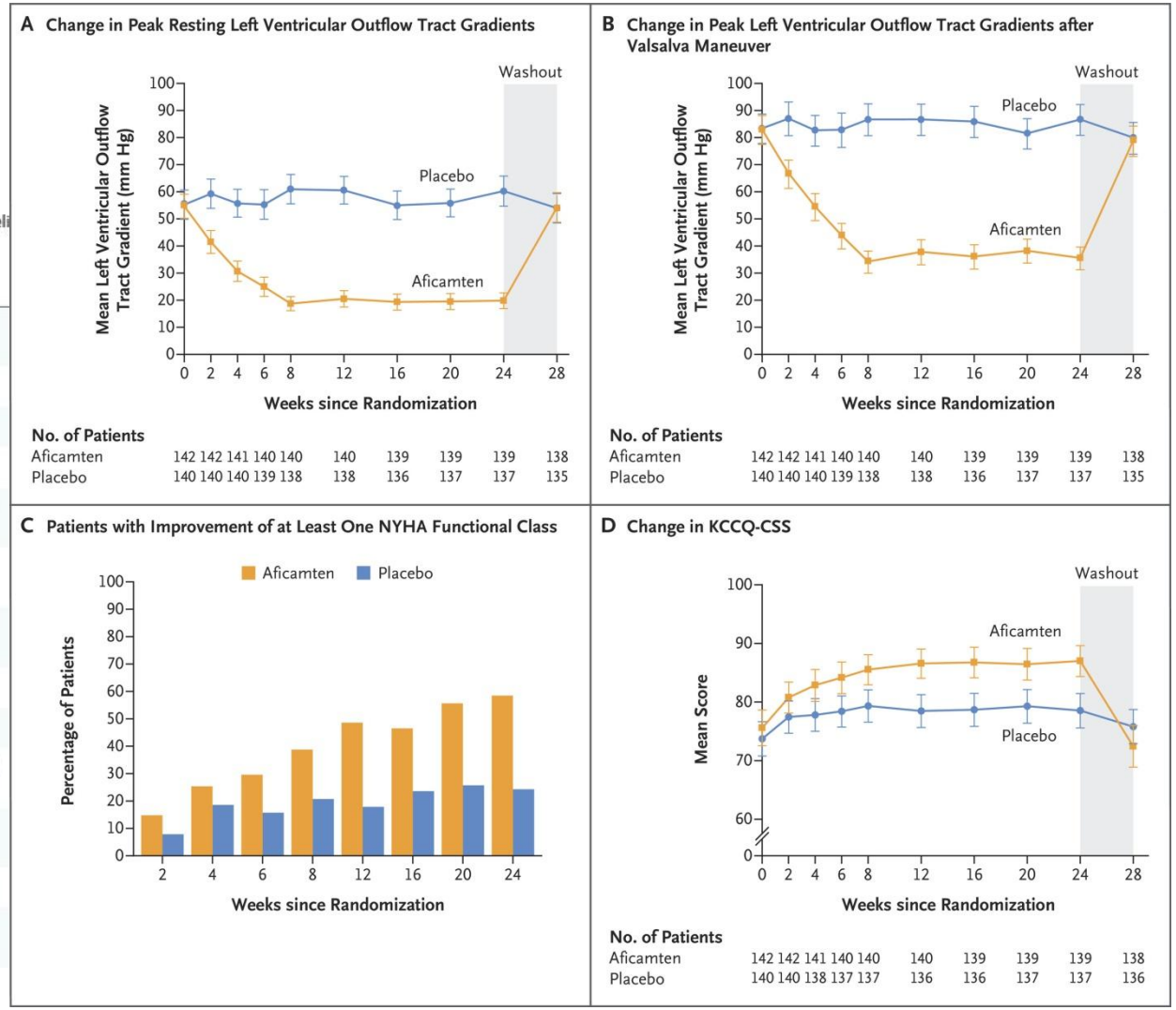
Sekundární cílové ukazatele

Variable	Aficamten (N=142)	
	Patients	Mean Change from Baseli (95% CI)
	no. (%)	
Primary end point: peak oxygen uptake by cardiopulmonary exercise testing at wk 24 — ml per kilogram per minute	133 (93.7)	1.8 (1.2 to 2.3)
Secondary end points		
KCCQ-CSS at wk 24	138 (97.2)	11 (9 to 14)
Improvement of ≥1 NYHA functional class at wk 24	83 (58.5)	NA
Left ventricular outflow tract gradient after the Valsalva maneuver at wk 24 — mm Hg	137 (96.5)	−47.6 (−54 to −41)
Left ventricular outflow tract gradient of <30 mm Hg after the Valsalva maneuver at wk 24	70 (49.3)	NA
Total duration of septal reduction therapy eligibility during treatment period — days‡	32 (22.5)	36.5 (27.0 to 46.1)
KCCQ-CSS at wk 12	140 (98.6)	11 (9 to 13)
Improvement of ≥1 NYHA functional class at wk 12	69 (48.6)	NA
Left ventricular outflow tract gradient after the Valsalva maneuver at wk 12 — mm Hg	139 (97.9)	−44.8 (−51 to −39)
Left ventricular outflow tract gradient of <30 mm Hg after the Valsalva maneuver at wk 12	74 (52.1)	NA
Total workload during cardiopulmonary exercise testing at wk 24 — watts	134 (94.4)	14.1 (9.5 to 18.6)
Exploratory end point: geometric mean proportional change in NT-proBNP at wk 24§	133 (93.7)	0.20 (0.17 to 0.22)



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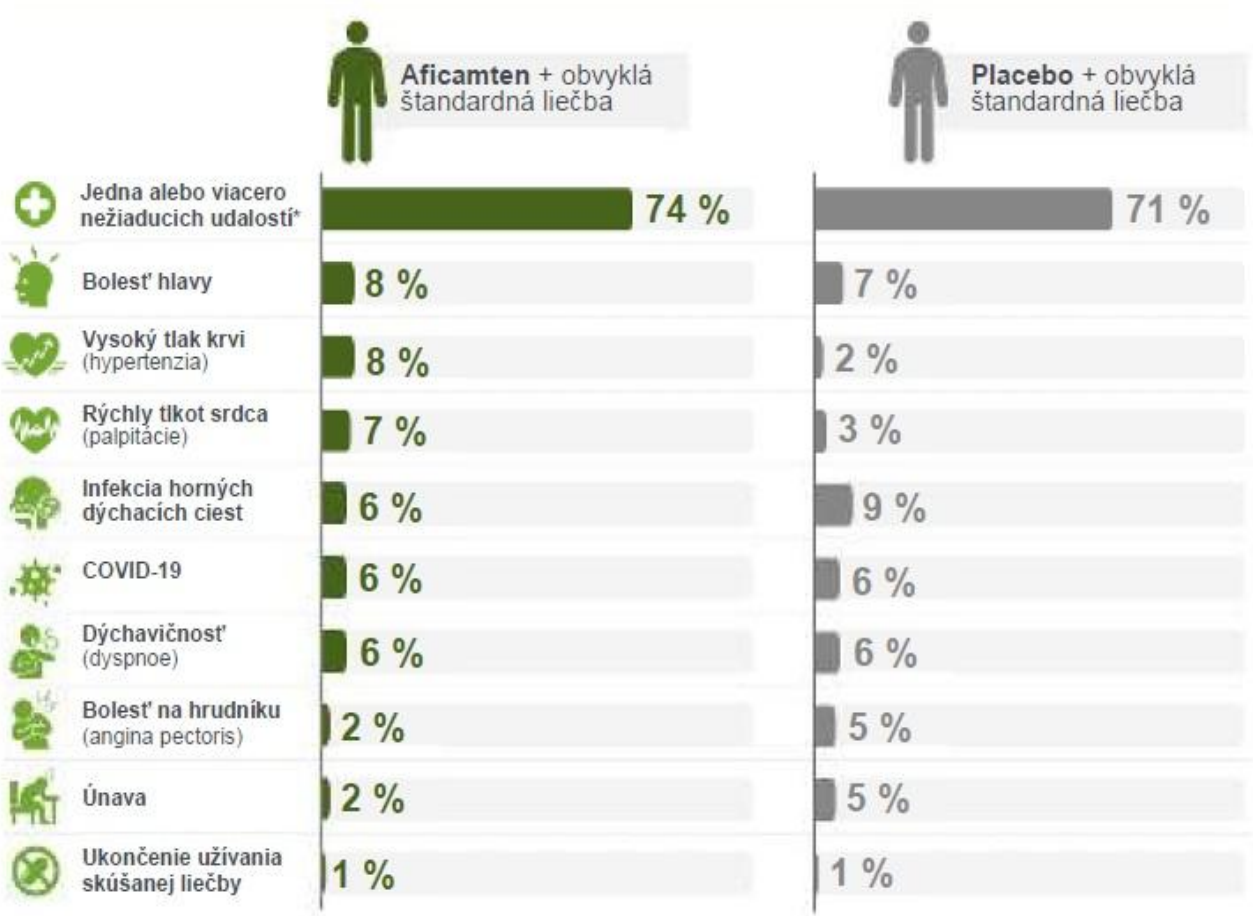
- Ve studii nebyl zaznamenán žádný zvýšený výskyt nežádoucích událostí
- Statisticky se také nelišilo množství pacientů, kteří přerušili nebo ukončili podávání medikace

Adverse events	
Any serious adverse event	8 (5.6)
Any serious adverse event that led to discontinuation of aficamten or placebo	0
Any serious adverse event that led to interruption of aficamten or placebo	1 (0.7)
Any adverse event	105 (73.9)
Any adverse event that led to discontinuation of aficamten or placebo	1 (0.7)
Any adverse event that led to interruption of aficamten or placebo	2 (1.4)



Poznámka: Tento obrázok ukazuje všetky nežiaduce udalosti, ktoré sa vyskytli u najmenej 5 zo 100 účastníkov (5 %) v oboch skupinách (účastníci, ktorí užívali aficamten, alebo účastníci, ktorí užívali placebo).
*Nežiaduca udalosť bola niečo (očakávané alebo neočakávané), čo účastníci zažili počas liečby aficamtenom alebo placebom
**Závažná nežiaduca udalosť bola nežiaduca udalosť, ktorá bola považovaná za život ohrozujúcu, vyžadovala nemocničnú starostlivosť alebo spôsobuje trvalé problémy

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zdroj Cytokinetics

Take home message:

- Aficamten se prokázal jako efektivní a bezpečný v léčbě obstrukce u pacientů s hypertrofickou kardiomyopatií ve srovnání s placebem
- Vedl k jednoznačnému klinickému zlepšení pacientů hodnocenému podle NYHA nebo dotazníku na kvalitu života
- Došlo k významné redukci gradientu ve výtokovém traktu levé komory v klidu i při provokaci Valsalvovým manévrem
- Nedošlo k žádnému zvýšenému výskytu nežádoucích událostí ve srovnání s placebem

DĚKUJI ZA POZORNOST!

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