Left Ventricular Systolic Dysfunction in Long-Term Aficamten Therapy for Obstructive HCM: A FOREST-HCM Analysis

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Background

- Cardiac myosin inhibitors reduce myocardial hypercontractility and left ventricular outflow tract obstruction in HCM
- LVEF reduction is an expected effect of cardiac myosin inhibition, requiring echocardiographic monitoring
- The clinical significance and trajectory of transient reductions in LVEF during aficamten treatment remain unclear
- Objective: To characterize the incidence, severity, reversibility, and clinical correlates of LV systolic dysfunction during long-term aficamten therapy in FOREST-HCM

Methods

- FOREST-HCM analysis of adults with symptomatic oHCM who completed REDWOOD-HCM, SEQUOIA-HCM, or MAPLE-HCM
- Aficamten initiated at 5 mg once daily and individually titrated to a maximum of 20 mg using site-read echocardiography
- Dose optimization targeted Valsalva LVOT-G <30 mmHg while maintaining LVEF ≥50%
- Analysis groups:
  - Any LVEF <50% vs LVEF always ≥50%
  - Prespecified subgroup with any LVEF ≥50% to <55%
- Outcomes: LVEF trajectory, dose adjustment, HF events, AF, mortality, LVOT gradients, NYHA class, KCCQ-CSS, NT-proBNP, and hs-cTnI

Results: LVEF ≥50% to <55%

47 (11.5%) patients with LVEF 50-55%

8.8 events per 100 patient-years

4/47 (8.5%) subsequently developed LVEF <50%

52.4% mean LVEF at detection

56.5% mean LVEF at next visit

No dose adjustment

Clinical Benefits Remained

Results

Baseline Characteristic	LVEF <50% (n=12)	LVEF ≥50% (n=398)
LVEF (%)	63.8	68.3
Valsalva LVOT-G, mmHg	70.8	93.3
QRS duration, ms	128.7	105.7

Other baseline characteristics were broadly similar between groups

410 Patients with oHCM

582 patient-years exposure

3,764 post-baseline echocardiograms

12 (2.9%) patients with LVEF <50%

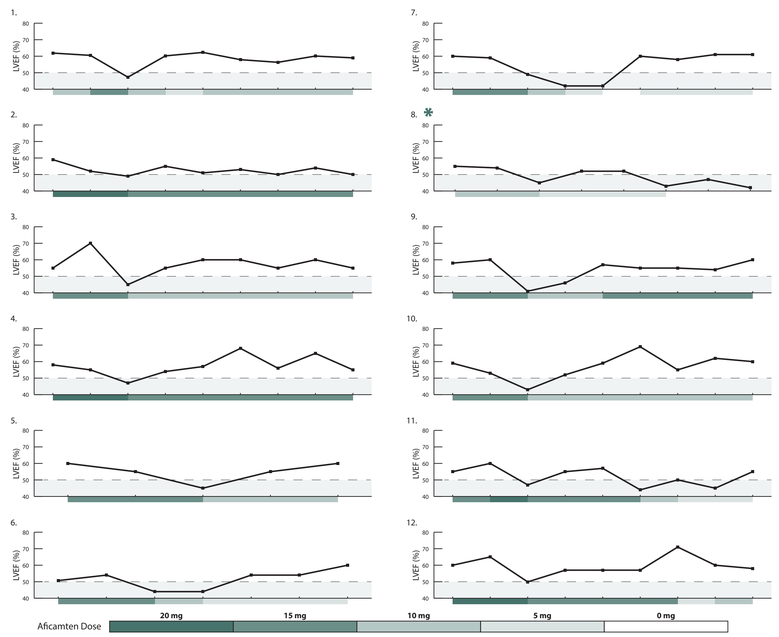
2.1 events per 100 patient-years

21 LVEF <50% episodes

0 patients with LVEF <40%

***Only 0.6% of post-baseline echocardiograms demonstrated LVEF <50%**

LVEF Trajectory & Recovery

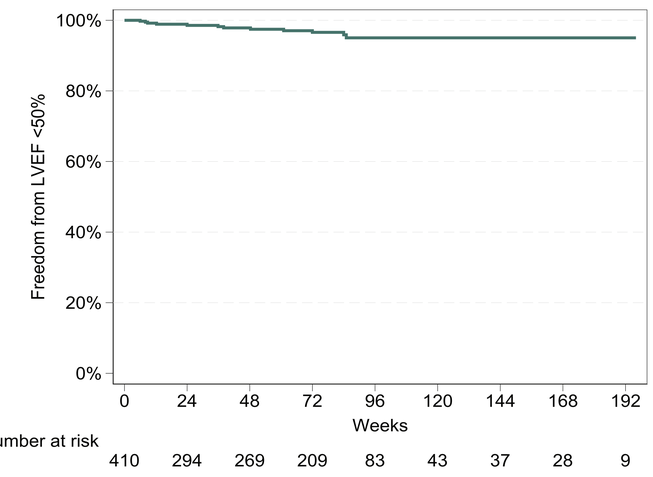


11 out of 12 patients recovered LVEF >50%*
10 out of 12 with dose reduction alone

* **Patient #8 continued to have LVEF <50% and discontinued aficamten. This patient also had LVEF <50% during the parent study while on placebo.**

Results

Freedom from LVEF <50%



Clinical Benefit Maintained

Measure	Baseline	At LVSD	Follow-up
LVEF (%)	63.8	45.1	51.7
Resting LVOT-G, mmHg	47.8	8.7	14.6
Valsalva LVOT-G, mmHg	70.8	27.6	39.1
NT-proBNP, ng/L	716.5	131.5	451

LVOT gradients and NT-proBNP improved compared to baseline at the time of LVSD

Conclusions

- LV systolic dysfunction was uncommon
  - LVEF <50% occurred in 2.9% of patients during long-term aficamten therapy
- Reductions in LVEF were mild and rapidly reversible following dose reduction
- No patient developed LVEF <40%
- No HF hospitalization or death was associated with LVSD
- Hemodynamic, biomarker, and symptomatic benefits were maintained despite transient reductions in LVEF
- LVEF ≥50% to <55% appeared clinically benign and was infrequently associated with subsequent LVEF <50%