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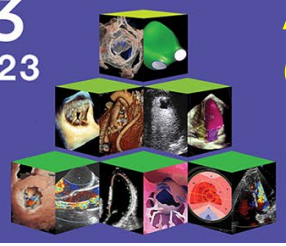

Aficamten is Associated with Improvements in Cardiac Mechanics in Obstructive Hypertrophic Cardiomyopathy: Results from the FOREST-HCM trial

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INTRODUCTION

Progressively abnormal global longitudinal strain (GLS) is associated with worse outcomes in hypertrophic cardiomyopathy[1,2]. Aficamten is a next-in-class, selective cardiac myosin inhibitor (CMI) that reduces left ventricular outflow tract gradients (LVOTg) in obstructive hypertrophic cardiomyopathy (oHCM)[3]. The impact of CMIs on myocardial mechanics as measured by GLS is unknown.

AIM

To assess the association between aficamten therapy and change in GLS in individuals with oHCM.

METHOD

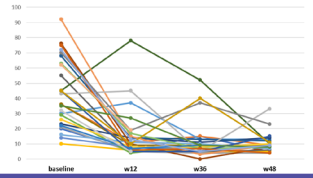
- FOREST-HCM, is an ongoing open-label extension study (NCT04848506) for eligible patients with HCM who completed a parent study of aficamten. Here we report echocardiographic (GE E-95® ultrasound machines) parameters (LVOTg and GLS) obtained from baseline up to week 48 from patients in 2 high-enrolling sites (n=27; table)
- GLS was calculated using a vendor-neutral analysis package (TOMTEC® Imaging Systems) at baseline, week12 and week 36-48.

Figure 1: Resting and Valsalva LVOTG

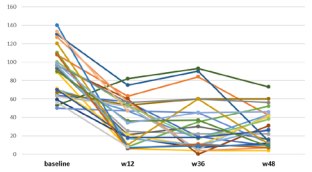
	Baseline N=27	W12 N=27	W36 N=25	W48 N=25
LVOTG, Rest(mmHg)	43	15.4	12.12	10.28

	Baseline N=27	W12 N=27	W36 N=25	W48 N=25
LVOTG, Valsalva (mmHg)	90.8	36.4	31.64	28.4

Serial LVOT-PG, Resting



Serial LVOT-PG, Valsalva



RESULTS

From baseline to 36-48 weeks, aficamten reduced LVOTg at rest (43 mmHg vs. 10.3 mmHg) and with Valsalva (91 vs. 28.4 mmHg; Figure 1). Compared with baseline, strain analysis revealed similar GLS at week 12 but a **significant improvement at week 36-48** (Figure 2). These improvements were more pronounced in those with optimal hemodynamic response (patients who achieved resting LVOTg <30 mmHg and Valsalva LVOTg<50 mmHg at week 36-48; n = 21; Figure 3 & 4). Improvement of GLS > 1% occurred in 56 % of patients at week 36-48 (Figure 5).

Table: Baseline clinical and echocardiographic data

Clinical data	N =27
Age, years (mean ± SD)	**60.3** ± 12.9
Female, n(%)	13 (48%)
Medical history, n(%)	
Family history of HCM	4 (15%)
Atrial fibrillation	6 (22%)
Hypertension	16 (59%)
Background HCM therapy, n(%)	
β blocker	21(78%)
Calcium channel blocker	7 (26%)
Disopyramide	3 (11%)
ICD implantation, n(%)	6 (22%)
NYHA Functional class II, n(%)	11 (41%)
NYHA Functional class III, n(%)	15 (56%)
Baseline Echo parameters	**(mean ± SD)**
LVEF, %	71.3 ± 7.4
Maximum left ventricular wall thickness, cm	**1.9 ± 0.4**
LVOT gradient, rest, mm Hg	**54.0 ± 29.7**
LVOT gradient, Valsalva, mm Hg	**97.3 ± 35.0**
LVOT gradient, post-exercise, mm Hg	**114.0 ± 52.4**
Left atrial volume index, mL/m²	44.9 ± 15.0
E/A	1.2 ± 0.6
Average E/e'	15.2 ± 7.4
Peak pulmonary artery pressure, mmHg	31.3 ± 12.3

Figure 2: GLS in TOTAL COHORT

	Baseline N=27	W12 N=27	Baseline v.s W12 p-value	W36 N=25	Baseline v.s W36~48 p-value
GLS (%, mean±SD)	-13.9 ± 3.2	-14.3 ± 3.0	0.32	-14.9 ± 2.7	0.012*

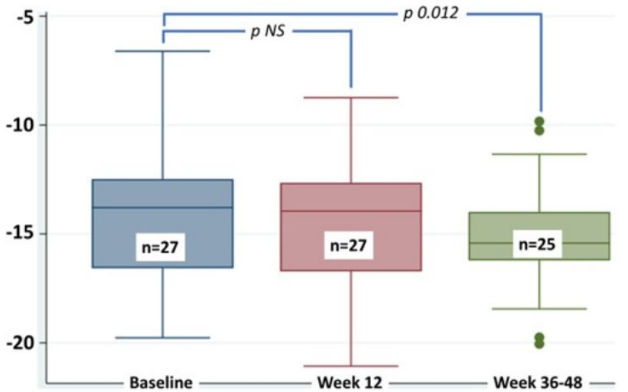


Figure 3: GLS in patients who achieved resting LVOTG < 30 mmHg (N=21)

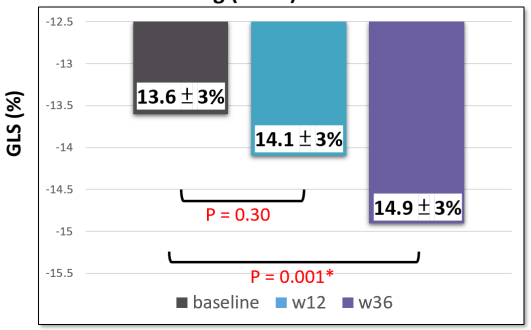


Figure 4: GLS in patients who achieved Valsalva LVOTG < 50 mmHg (N=21)

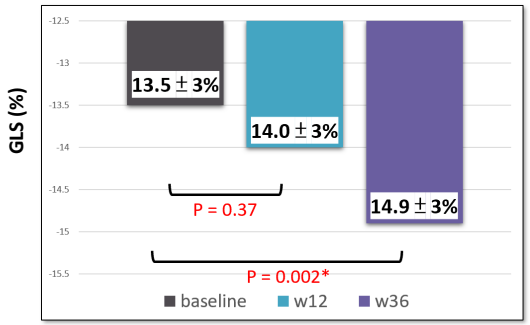
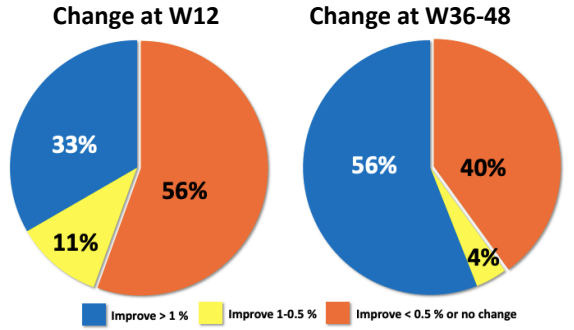


Figure 5: Temporal Trajectories of GLS



CONCLUSIONS

- Aficamten therapy favorably impacts myocardial mechanics after longer term treatment and these changes appear more pronounced in those with optimal hemodynamic response.
- Despite the expected modest reduction in LVEF after receiving aficamten usage, global myocardial deformation actually improved over time. This may reflect the totality of the effect of relieving afterload (LVOT obstruction) and normalization of hypercontractility".
- Potential underlying mechanisms may include long-term afterload reduction secondary to decrease of the LVOTg resulting in other pathophysiologic changes since the strain improvements occur several weeks after gradient reduction. These data support a strategy to dose CMIs towards an optimal LVOTg threshold.

REFERENCES

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