National Harbor, MD
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Withdrawal of Background Standard of Care Medical Therapy in Patients with Obstructive Hypertrophic Cardiomyopathy Treated with *Aficamten* in REDWOOD-HCM OLE

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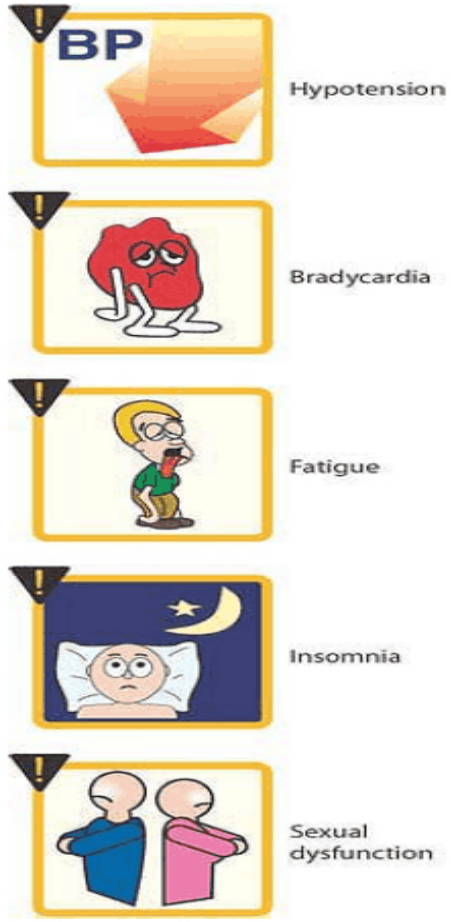
Background

- Standard of care (SoC) medications for the treatment of obstructive hypertrophic cardiomyopathy (oHCM) are currently recommended as first-line therapy.

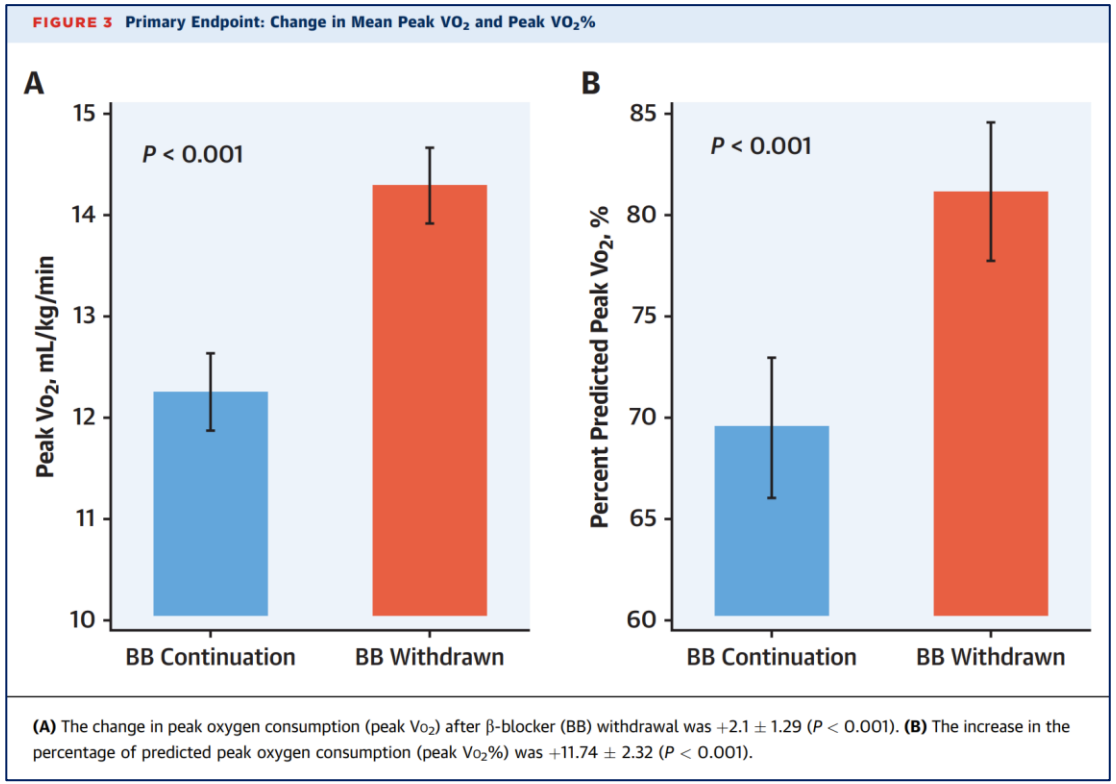
- There are off-target side-effects that often render them unappealing for patients.

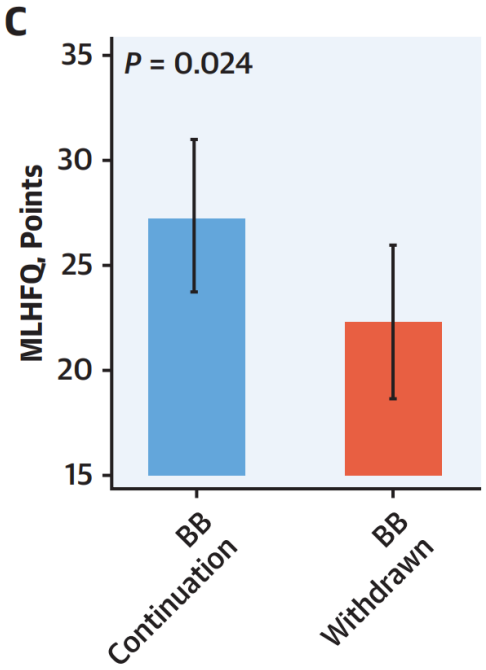


* Infographic courtesy of *Manual of Medicine* (manualofmedicine.com)

PRESERVE-HR Trial: BB Withdrawal in HFpEF

Improvement in pVO2 & Minnesota Living with HF Questionnaire





Palau et al. *JACC* 2021

Aim

We investigated withdrawal of SoC medical therapy in patients already being treated with *aficamten* in the REDWOOD-HCM Open Label Extension (OLE) study

Methods

- Observational study

- Patients were classified as receiving SoC therapy if treated with:
  - beta-blocker (BB)
  - non-dihydropyridine calcium channel blocker (CCB)
  - and/or disopyramide.

- Patients were eligible for background therapy reduction/withdrawal (BTR/W) at the discretion of the site investigator and once receiving a stable dose of *aficamten* for at ≥ 4-weeks and after Week 12 of the study

- Successful BTR/W was defined as at least a dose-reduction of one medication to ≤ 50% of baseline

Results - Baseline Characteristics

Metric, (SD)	On BT (N = 39*)	No Attempt (N = 15)	Attempt at BTR/W (N = 20)
Demographics			
Age, years	59.0 (13.1)	57.7 (13.1)	61.3 (13.6)
Female (%)	23 (59)	7 (47)	13 (65.0)
Body mass index	30.1 (6.5)	32.2 (7.9)	29.2 (5.1)
HR, BPM	64 (11)	64 (9)	64 (12)
SBP, mmHg	123 (19)	116 (19)	129 (18)
DBP, mmHg	68 (12)	66 (13)	70 (12)
HCM History			
HCM History			
Positive family history (%)	10 (26)	6 (40)	3 (15)
Known pathogenic gene (%)	9 (23)	5 (33)	1 (5)
Median Time since diagnosis, years (Min, Max)	2.9 (1, 24)	3.1 (1, 19)	2.3 (1, 13)
HCM Medication History			
Beta-Blocker Use (%)	33 (85)	12 (80)	18 (90)
Calcium Channel Blocker (%)	7 (18)	3 (20)	3 (15)
Disopyramide (%)	8 (21)	2 (13)	6 (30)

*4 patients were not eligible for BTR/W because there were on *aficamten* treatment for < 12 weeks

Results - Baseline Characteristics

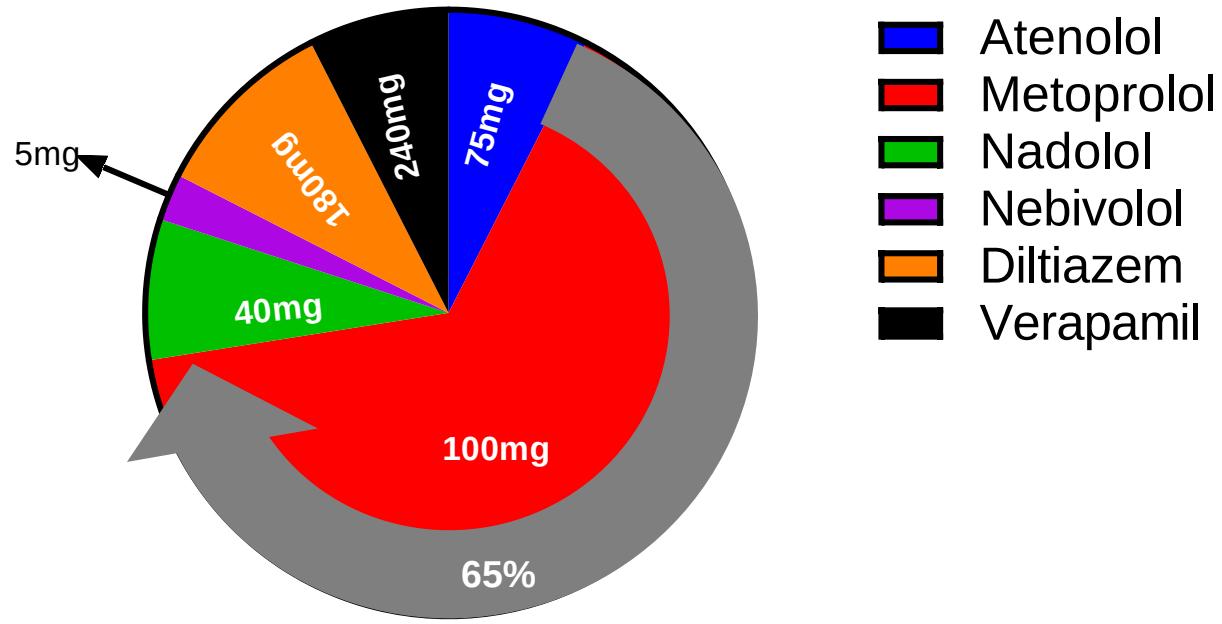
REDWOOD HCM OLE

Metric, (SD)	On BT (N = 39)	No Attempt (N = 15)	Attempt at BTR/W (N = 20)
Other Cardiovascular History			
Hypertension (%)	14 (36)	5 (33)	8 (40)
Coronary artery disease	7 (18)	1 (7)	5 (25)
Atrial fibrillation	6 (15)	3 (20)	3 (15)
Symptoms			
NYHA Class (%)			
I	0	0	0
II	19 (49)	7 (47)	8 (40)
III	20 (51)	8 (53)	12 (60)
KCCQ-OSS	64.1 (22)	65.5 (19)	58.8 (23)
LVEF, %	69 (5)	70 (5)	69 (5)
Resting LVOT-G, mmHg	52 (33)	58 (38)	47 (31)
Valsalva LVOT-G, mmHg	82 (35)	87 (31)	82 (38)
Cardiac Biomarkers			
NT-proBNP, pg/mL, median (IQR)	809 (306, 1895)	453 (306, 1921)	800 (308, 1885)
hs-cTnI, ng/L, median (IQR)	10.8 (5, 33.5)	17.7 (10.1, 75.5)	8.4 (4.5, 12.0)

Data presented as mean (SD) except where indicated, BT = Background Therapy, BTR/W = Background Therapy Reduction/Withdrawal, HR = Heart Rate, BPM = Beats per minute, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, LVEF = left ventricular ejection fraction, LVOT-G = Left ventricular outflow tract gradient, NYHA = New York Heart Association, KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire Overall symptom score, NT-proBNP = N-terminal pro B-type natriuretic peptide, hs-cTnI = high-sensitivity cardiac troponin-I

Results - Baseline Characteristics

Baseline Median Doses of Beta-Blockers and Calcuim Channel Blockers



N = 39

- 42 patients enrolled as of July 1, 2022
- 39 (93%) were taking ≥1 SoC medication (3 were on no BT at all due to intolerance)
  - 27 (69%) BB only
  - 4 (10%) CCB only
  - 7 (18%) CCB or BB + Disopyramide
  - 1 (3%) BB + CCB + Disopyramide

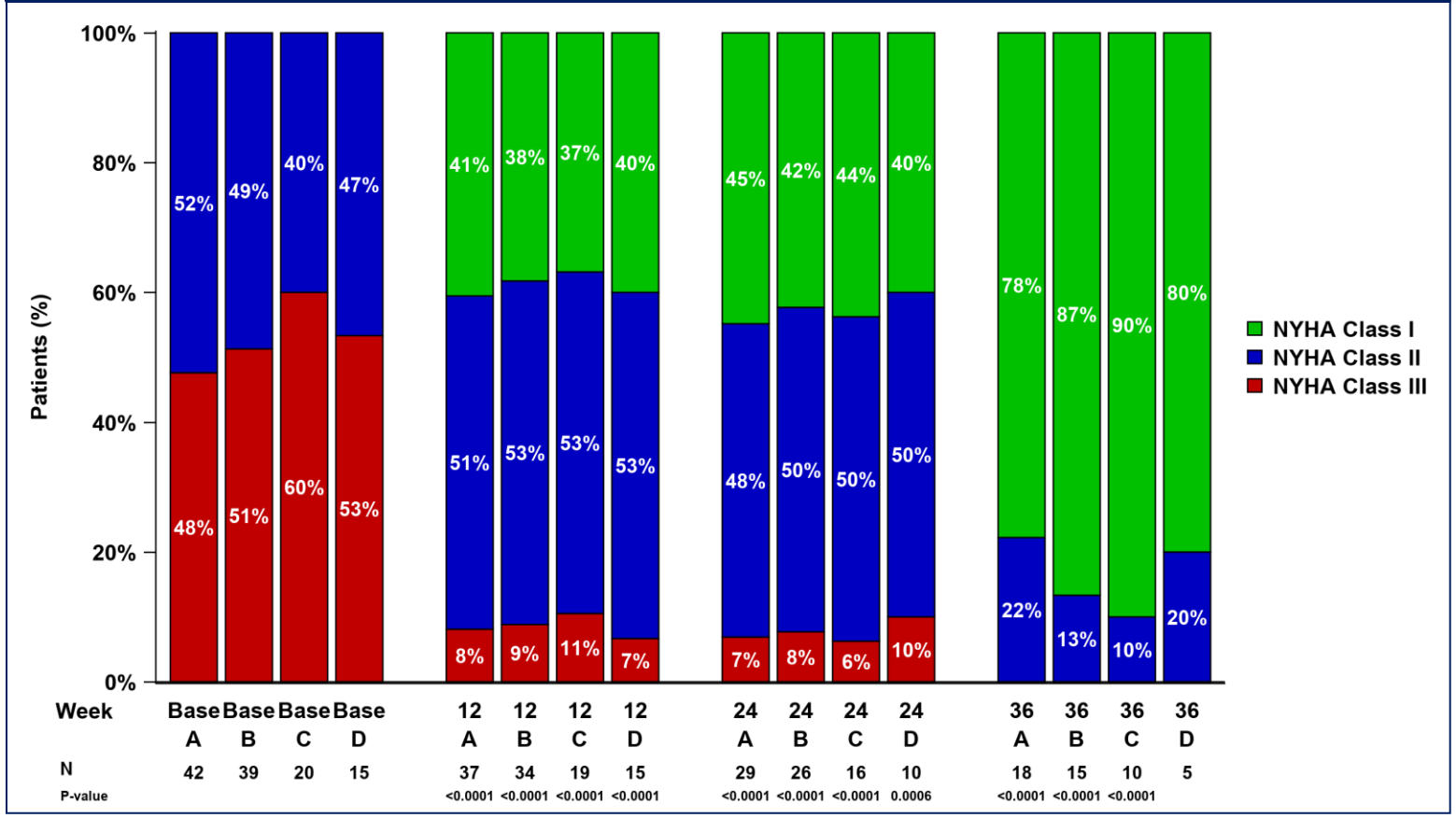
Results

- Among patients eligible for withdrawal of background therapy based on ≥12 weeks of treatment with *aficamten* (n = 35), BTR/W was attempted in 20 patients (57%):

  - 17 (85%) achieved any successful BTR/W
  - 10 (50%) completely discontinued at least one medication
  - 5 (25%) withdrew from all SoC (*aficamten* monotherapy)

Results

NYHA Class



A → All Patients (including 3 patients not on SoC therapy)

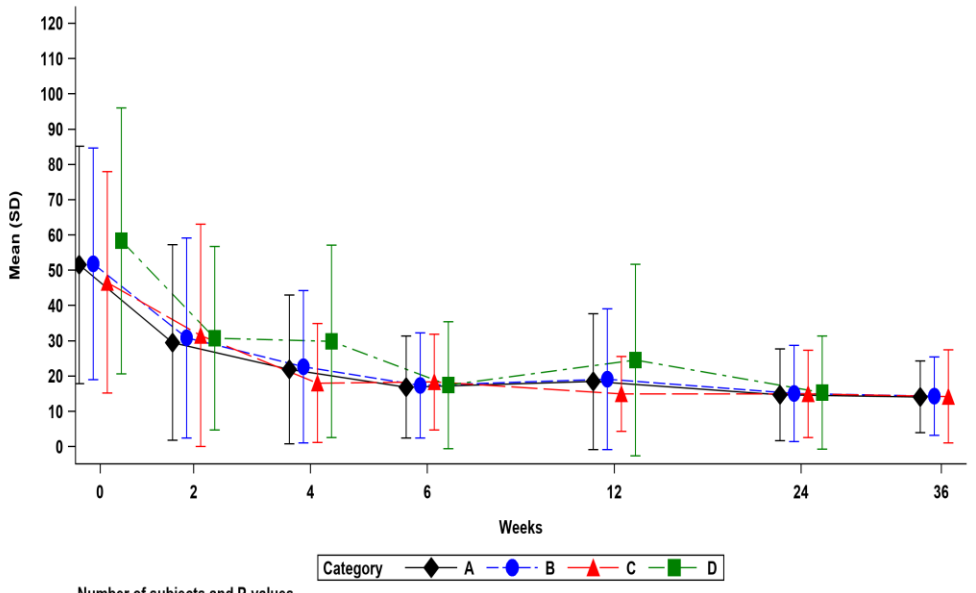
B → All Patients on Background Therapy

C → Patients with Background Therapy Withdrawal Attempt

D → Patients without Background Therapy Withdrawal Attempt

Results

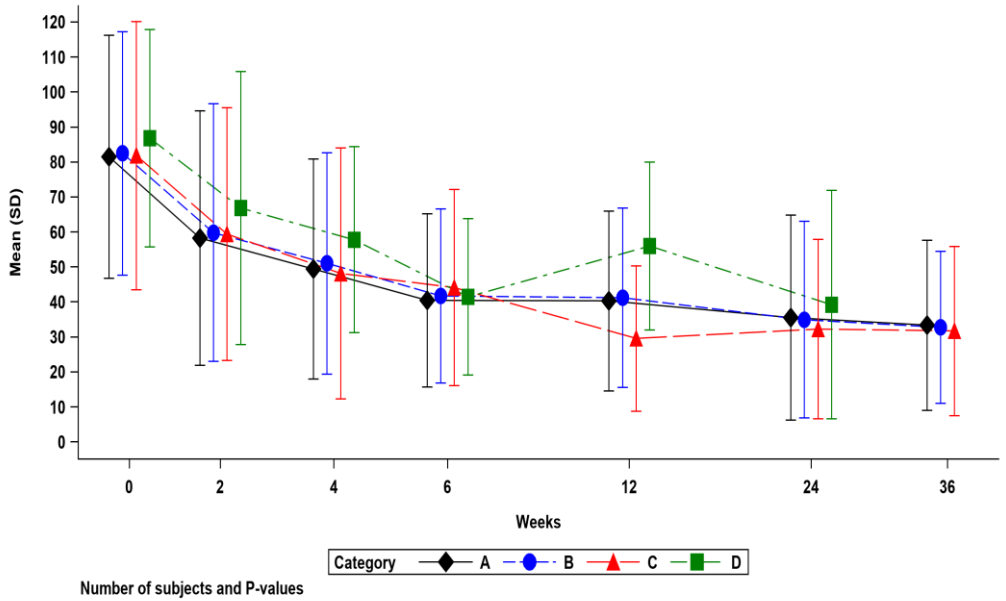
Resting LVOT-G



Number of subjects and P-values

A	42	42 ****	41 ****	41 ****	37 ****	29 ****	18 ***
B	39	39 ****	38 ****	38 ****	34 ****	26 ****	15 ***
C	20	20 *	20 ****	20 ***	19 ***	16 **	10 **
D	15	15 **	15 **	15 **	15 ***	10 **	

Valsalva LVOT-G



Number of subjects and P-values

A	42	42 ***	41 ****	41 ****	37 ****	29 ****	18 ****
B	39	39 ***	38 ****	38 ****	34 ****	26 ****	15 ****
C	20	20 *	20 ****	20 **	19 ****	16 ***	10 ***
D	15	15 (p=0.0926)	15 **	15 ***	15 **	10 ***	

**** = p <0.0001
*** = p <0.001
** = p <0.005
* = p < 0.05

A → All Patients (including 3 patients not on SoC therapy)

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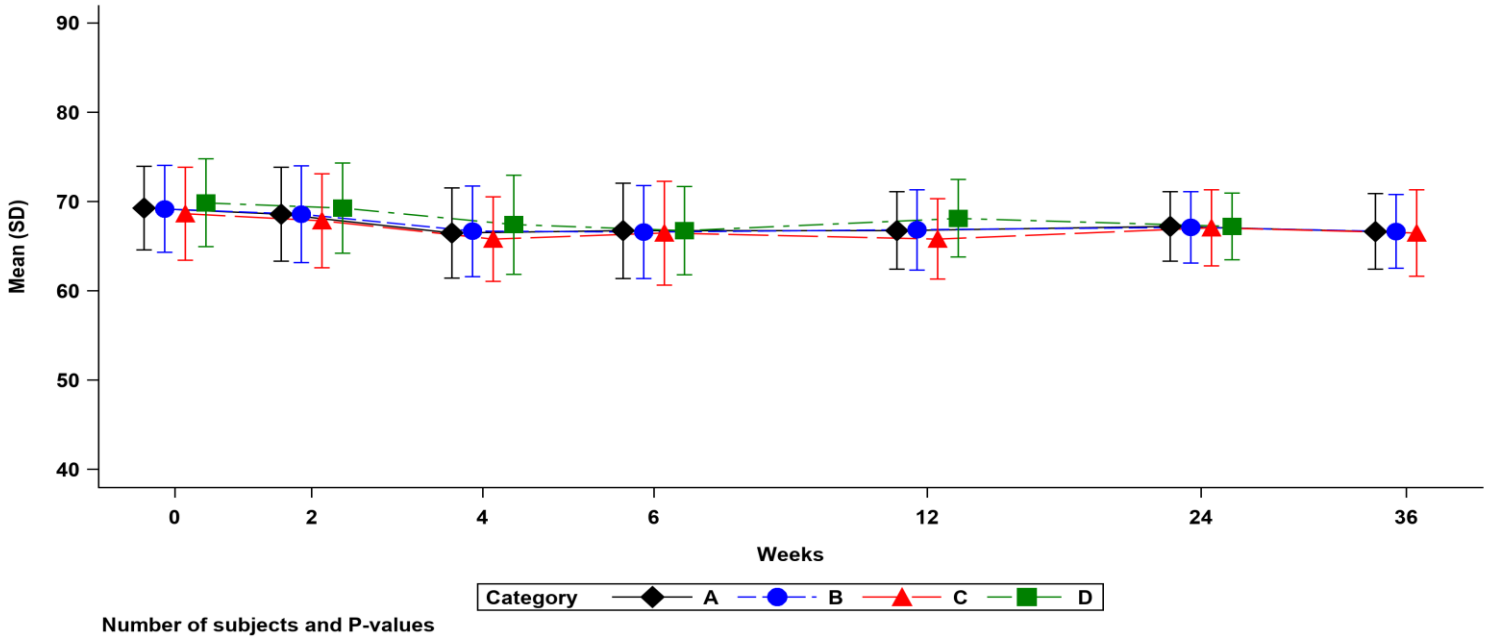
Results

LVEF



Number of subjects and P-values

A	42	42 (p=0.3749)	41 ***	41 **	37 **	29 **	18 *
B	39	39 (p=0.4649)	38 **	38 **	34 *	26 **	15 *
C	20	20 (p=0.4262)	20 **	20 *	19 (p=0.0578)	16 (p=0.0748)	10 (p=0.2320)
D	15	15 (p=0.6614)	15 *	15 *	15 (p=0.2291)	10 *	

A → All Patients (including 3 patients not on SoC therapy)

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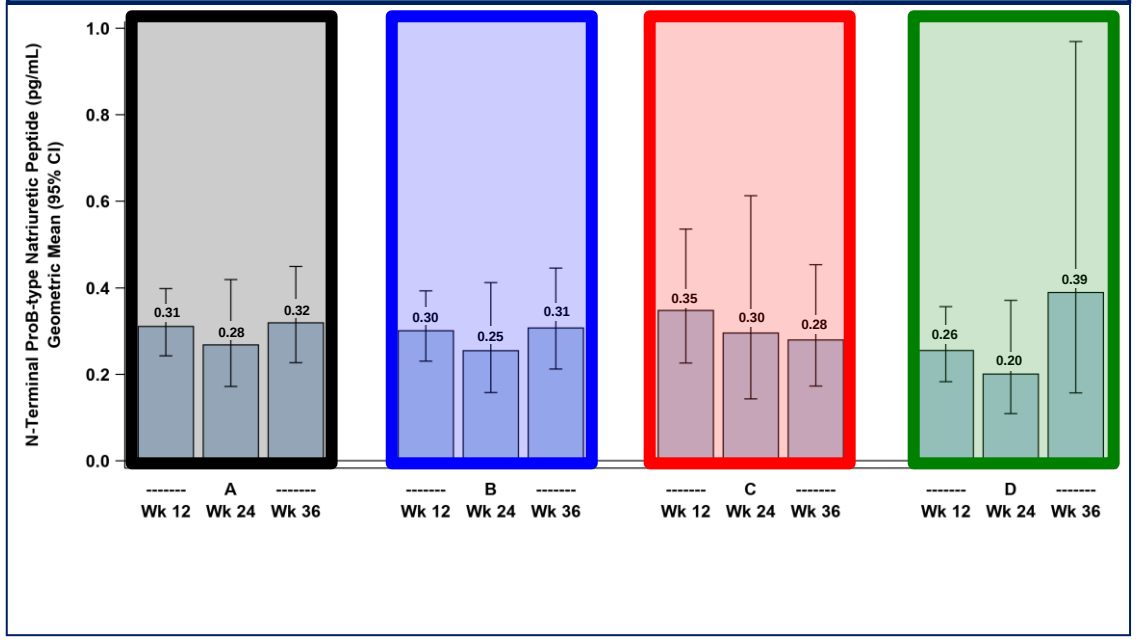
C → Patients with Background Therapy Withdrawal Attempt

D → Patients without Background Therapy Withdrawal Attempt

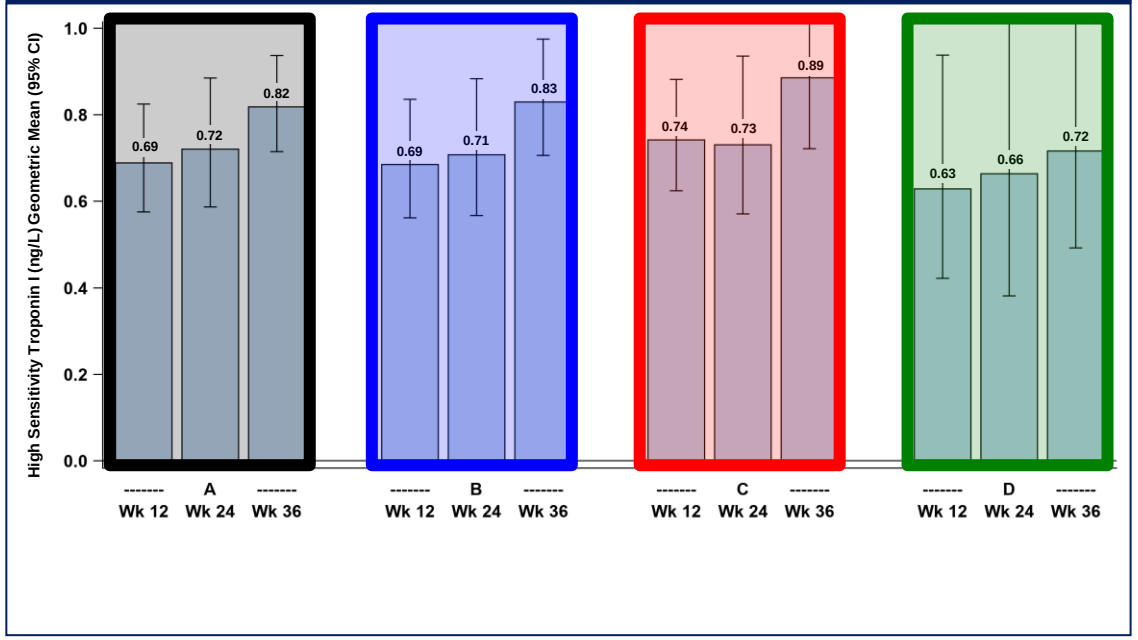
**** = p <0.0001
*** = p <0.001
** = p <0.005
* = p < 0.05

Results

Proportional Change from Baseline - **NT-Pro BNP**



Proportional Change from Baseline - **hs-Troponin I**



A → All Patients

B → All Patients on Background Therapy

C → Patients with Background Therapy Withdrawal Attempt

D → Patients without Background Therapy Withdrawal Attempt

0.31

Results

- In patients where there was an available assessment, both pre- and post-BTR/W (N =14):
  - Increased resting HR of 12 bpm (mean HR = 74 ±10 bpm, p = 0.0001)
  - No change in brachial blood pressure (128/70 to 126/74 mmHg, p = ns)
  - Increase Valsalva LVOT-G of 15 mmHg (mean Valsalva LVOT-G = 42 ±26 mmHg, p = 0.02) – although on average remaining below 50 mmHg

- Three patients underwent attempted BTR/W unsuccessfully, with reinstitution of BB as a result of recurrence of symptoms or elevated left ventricular outflow tract gradients (LVOT-G)

Conclusions

- In this pilot observational study, withdrawal or decrease in SoC medical therapies after treatment with *aficamten* did not adversely impact NYHA functional class, LVOT gradients, or biomarkers

- Importantly, some of these patients may have benefited further from dose escalation of *aficamten* up to 20 mg, which was not uniformly available at the time of this analysis

- Withdrawal or reduction of current SoC medical therapies in REDWOOD-HCM OLE is feasible.