



Evaluation Of The Mechanism Of Benefit For Dapagliflozin In HFpEF: An Invasive Hemodynamic Randomized Trial

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Disclosure

Financial Relationships

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Consulting/Advisory Board:

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Background

- HFpEF is >50% of all HF, few effective treatments
- SGLT2i dapagliflozin and empagliflozin ↓risk of HF hospitalizations & CV death and ↑ QOL in HFpEF, but mechanisms remain unclear
- Elevation in left heart filling pressures at rest and during exercise represents the signature hemodynamic perturbation in HFpEF

Hypothesis

Treatment with dapagliflozin for 24 weeks will favorably reduce rest and exercise left heart filling pressures in patients with HFpEF

Methods

- Single-Center, Double-Blinded, RCT testing the effects of dapagliflozin on rest and exercise hemodynamics in HFpEF
- Primary endpoint: pulmonary capillary wedge pressure (PCWP) incorporating measurements at rest and peak exercise
- Secondary endpoints
 - Rest/exercise RA and PA pressures
 - Directly measured plasma, blood, and red cell volumes
 - Body weight

Methods

- Patients: HFpEF ($\geq 50\%$), NYHA 2-3
 - PCWP ≥ 25 mmHg during exercise
- Excluded: Type I DM, cardiomyopathies, pericardial disease, other causes of dyspnea or HF not due to HFpEF
- Intervention: Dapagliflozin 10 mg qd or matching placebo for 24 weeks
- Assessments at Baseline and 24 weeks:
 - Invasive exercise testing
 - Hemodynamics by high fidelity micromanometer catheters
 - Total blood, plasma, and RBC volumes (Daxor, New York, NY)

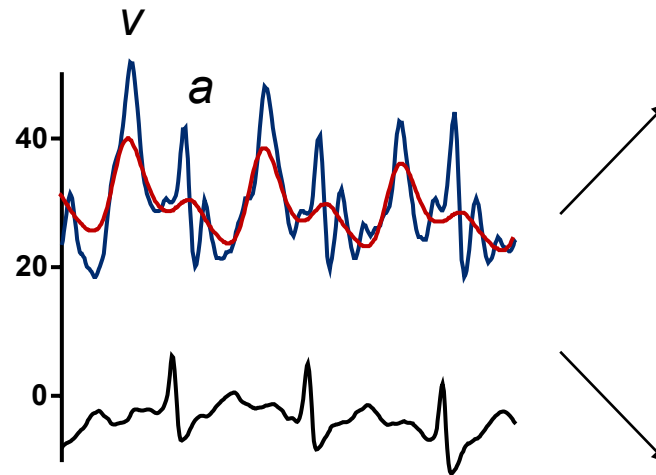
Primary Endpoint:

Change in PCWP measured by micromanometer at end-expiration, mid-a wave, mean of ≥ 3 beats, at rest **and peak exercise** after 24 weeks

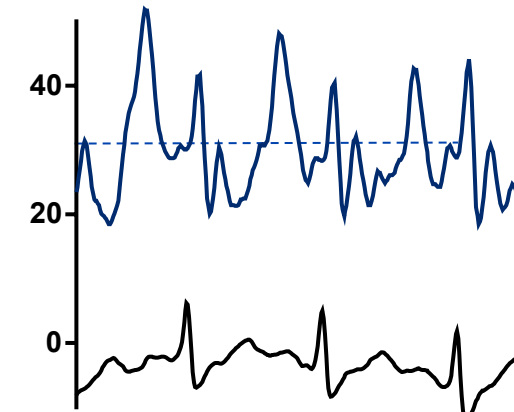
Statistical Analysis:

ITT analysis using linear mixed model consisting of repeated measures of PCWP at rest and peak exercise

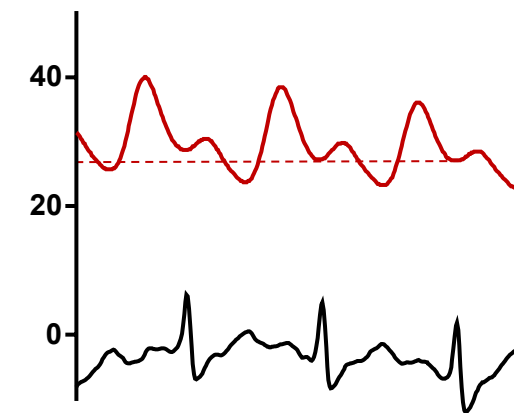
Statistical significance according to a LR test with maximum likelihood estimation



Fluid-filled catheter
Micromanometer
ECG



PCWP 32 mmHg



PCWP 27 mmHg

Key Secondary Endpoints

- **Secondary Endpoints:**
 - Changes in RA and PA pressures (rest and exercise) measured & compared in the same way
 - Changes in Plasma, red cell, and total blood volume
 - Change in Body weight

Sample Size Assumptions and Power

SD of exercise PCWP ~5 mmHg based upon prior studies

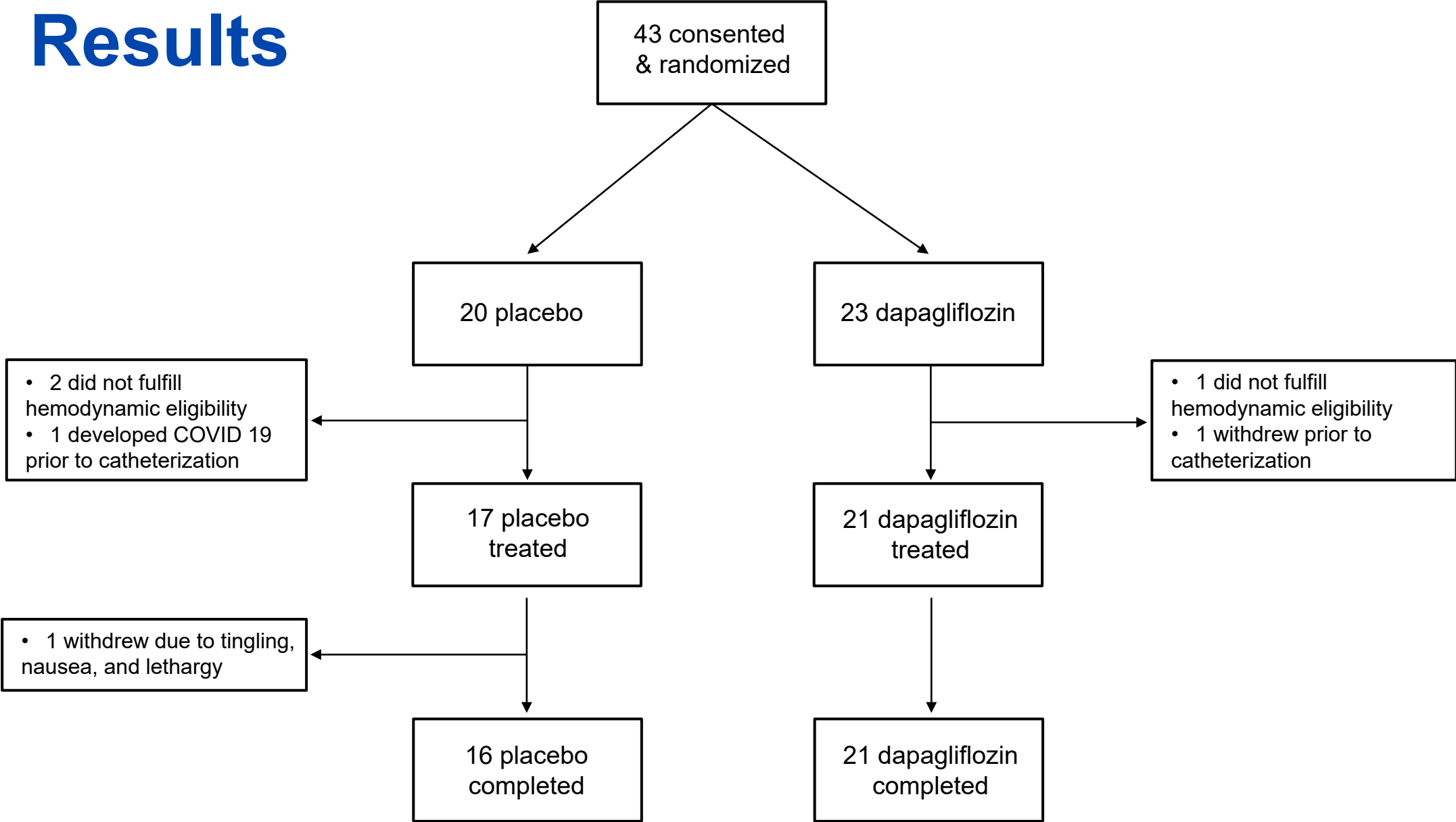
Expectations:

Mean exercise PCWP of 30 mmHg in patients at enrollment

Mean reduction in exercise PCWP of 20% (~ 6 mmHg) with dapagliflozin

Based upon a 2-sample t test, 36 patients (18 per group) provides 93% power to detect a difference of 6 mmHg or higher in exercise PCWP at 0.05 significance level

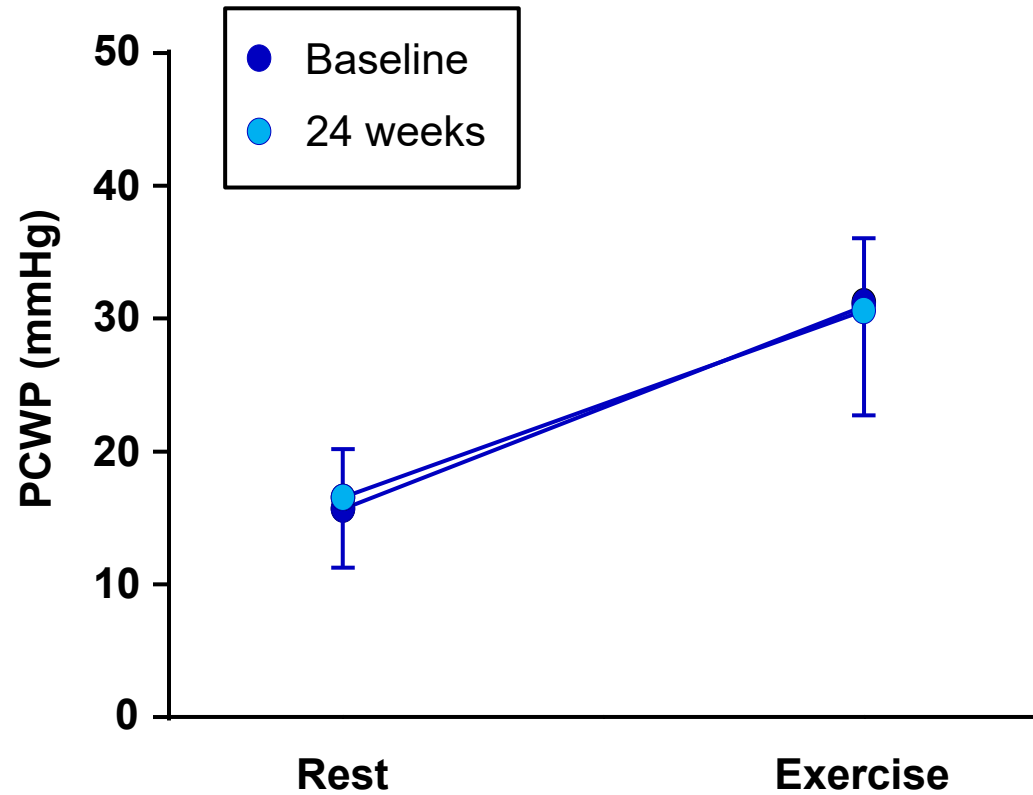
Results



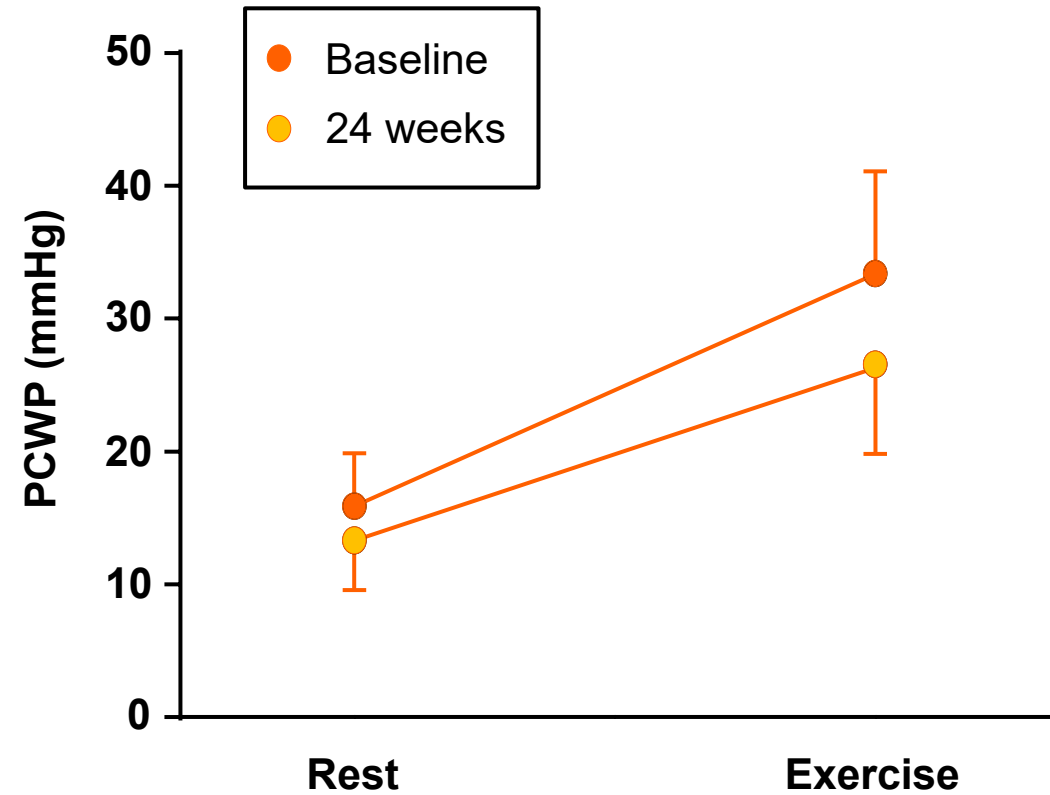
Results

	Placebo (n=17)	Dapagliflozin (n=21)
Age, years	67 (9)	67 (9)
Women, n (%)	11 (65%)	14 (67%)
Body mass index, kg/m ²	34.5 (5.7)	35.0 (7.2)
NYHA functional class III, n (%)	12 (71%)	14 (67%)
Obesity (BMI≥30), n (%)	12 (71%)	15 (71%)
Hypertension, n (%)	10 (59%)	14 (67%)
Atrial Fibrillation, n (%)	6 (35%)	8 (38%)
NTproBNP, pg/ml	118 (76, 226)	235 (102, 394)
LVEF, %	63 (6)	61 (6)

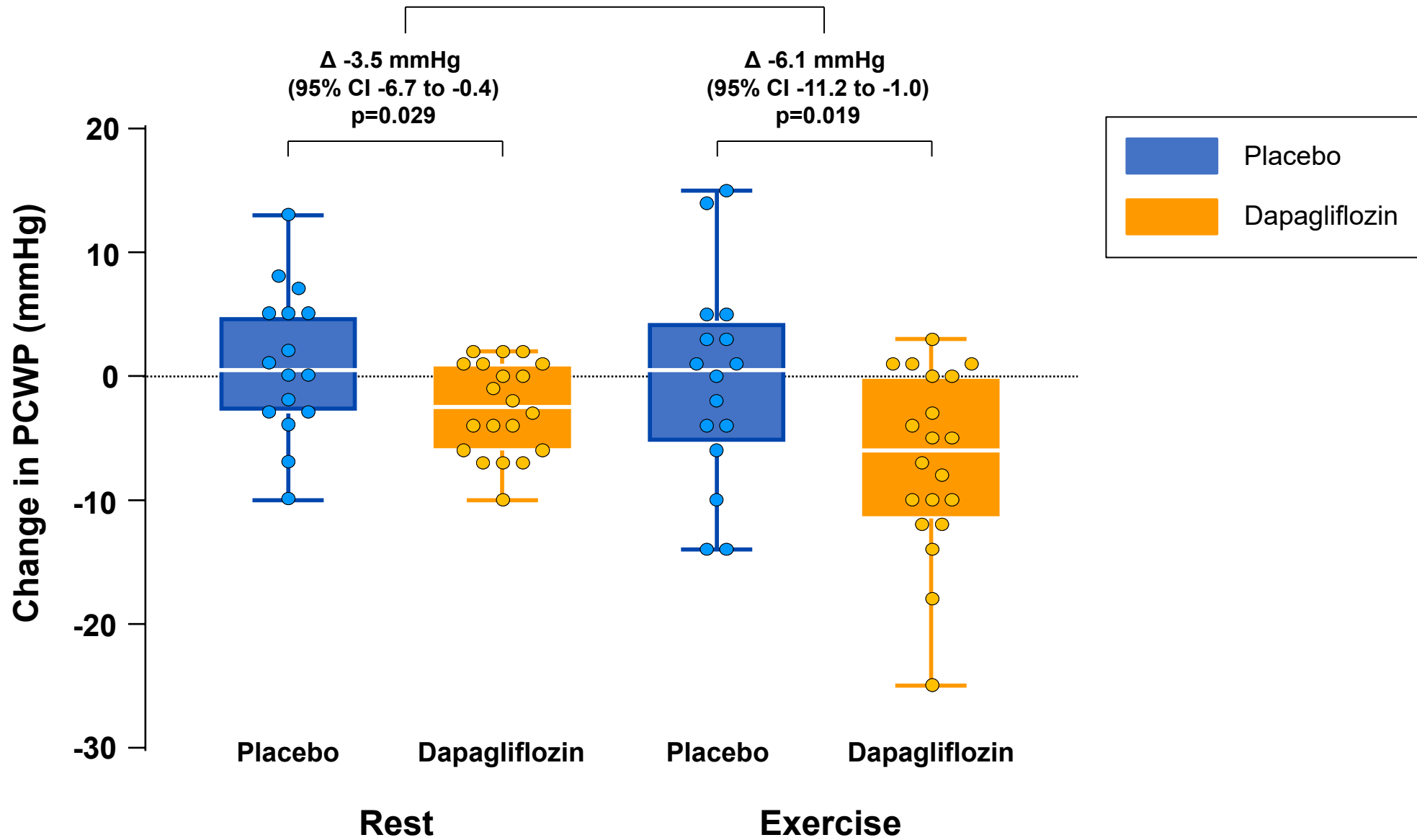
Placebo



Dapagliflozin



Overall Mixed Model LR $p < .001$



Effects on RA and PA pressures

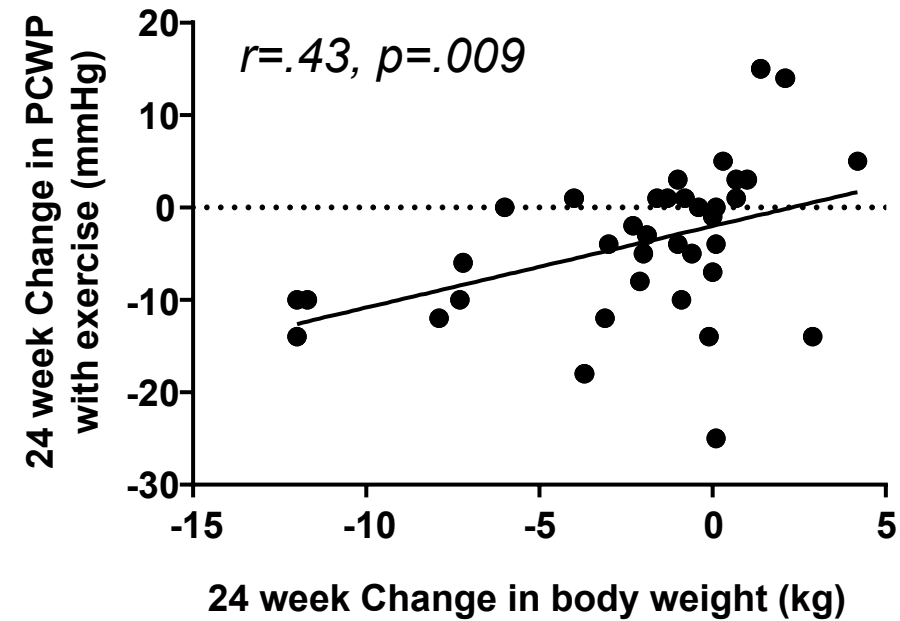
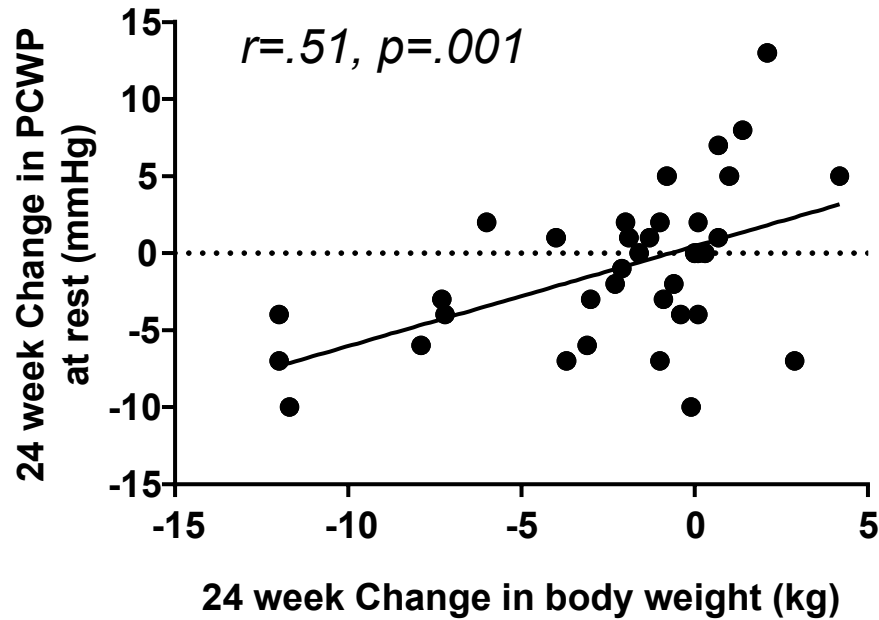
	Study Period	Dapagliflozin Mean (SD)	Placebo Mean (SD)	Treatment Effect Estimate (95% CI)	P-value
<i>Exercise</i>					
RA pressure, mmHg	Baseline	19.9 (7.0)	18.2 (6.3)	--	--
	Change from baseline	-3.4 (4.0)	0.8 (5.6)	-4.2 (-7.3 to -1.0)	.010
Mean PA pressure, mmHg	Baseline	49.9 (10.2)	49.4 (10.6)	--	--
	Change from baseline	-5.2 (6.6)	0.7 (8.6)	-5.9 (-10.9 to -0.9)	.022
<i>Rest</i>					
RA pressure, mmHg	Baseline	10.4 (2.4)	9.6 (3.2)	--	--
	Change from baseline	-1.6 (2.6)	0.3 (4.0)	-1.9 (-4.1 to 0.2)	.077
Mean PA pressure, mmHg	Baseline	26.5 (6.9)	26.2 (7.6)	--	--
	Change from baseline	-1.8 (4.0)	1.1 (7.4)	-2.8 (-6.6 to 1.0)	.14

LR test $p < .001$ for both RA and mean PA pressures incorporating rest and exercise data

Effects on Vascular Constituents & Weight

Measurement	Study Period	Dapagliflozin Mean (SD)	Placebo Mean (SD)	Treatment Effect Estimate (95% CI)	P-value
Body weight, kg	Baseline	100.8 (26.5)	98.1 (18.2)	--	--
	Change	-3.7 (4.2)	-0.2 (2.6)	-3.5 (-5.9 to -1.1)	.006
Total blood volume, ml	Baseline	5639 (1405)	5533 (1088)	--	--
	Change	-118 (542)	142 (399)	-260 (-587 to 68)	.12
Red cell volume, ml	Baseline	1859 (514)	1889 (1709)	--	--
	Change	52 (285)	26 (129)	25 (-131 to 181)	.75
Plasma volume, ml	Baseline	3779 (946)	3643 (755)	--	--
	Change	-170 (343)	115 (322)	-285 (-510 to -60)	.015

Changes in PCWP correlated with ↓ Weight



Changes in rest and exercise PCWP were poorly correlated with the change in plasma volume ($r=0.29$, $p=.08$ and 0.34 , $p=.04$)

Effect on Laboratories

	Placebo n=17	Dapagliflozin n=21	p
Change in hematocrit (%)	+0.3 (2.9)	+2.2 (2.5)	.046
Change in NTproBNP (pg/ml)	22 (1, 67)	-7 (-75, 7)	.037
Change in eGFR, mL/min*1.73 m ²	-5 (10)	-2 (9)	.35

Safety

	Placebo n=17	Dapagliflozin n=21
Serious adverse events, n	0	4
Minor bruising or bleeding following catheterization, n	2	2
Adverse events leading to discontinuation, n	1	0

Conclusions

- Treatment with dapagliflozin for 24 weeks favorably reduced PCWP at rest and during exercise in HFpEF, improving the fundamental hemodynamic abnormality underlying this disorder.
- Dapagliflozin also decreased exertional RA and PA pressures
- Dapagliflozin led to reductions in body weight and plasma volume, and changes in body weight were correlated with changes in PCWP.
- These findings provide new insight into the mechanisms underlying the favorable clinical effects of dapagliflozin in patients with HFpEF.

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