The Prognostic Importance of Changes in Cardiac Structure and Function in Heart Failure with Preserved Ejection Fraction and the Impact of Spironolactone

Amil M. Shah, MD MPH; Nancy K. Sweitzer, MD; Sanjiv J. Shah, MD;

Anita Deswal, MD, MPH; Inder S. Anand, MD, PhD; Brian Claggett, PhD;

Jerome L. Fleg, MD; Bertram Pitt, MD; Marc A. Pfeffer, MD, PhD;

Scott D. Solomon, MD

SUPPLEMENTAL MATERIAL

Regional Analysis

The marked regional variation in TOPCAT makes interpretation of treatment effect difficult.[1] HF hospitalization and death rates in the Americas were consistent prior HFpEF outcomes trials, but were multifold lower in Russia and Georgia.[1] In addition, the significantly attenuated blood pressure, potassium, and creatinine responses to spironolactone among patients enrolled in Russia and Georgia compared to the Americas suggest that the physiologic response to randomization to spironolactone treatment differed between regions.[1] We therefore also performed all analyses separately by region of enrollment.

Impact of Spironolactone on Cardiac Structure and Function

134 (56%) patients were enrolled in the Americas and 105 (44%) were enrolled in Russia or Georgia. Compared to patients enrolled in Russia or Georgia, those enrolled in the Americas had smaller LV volumes and higher measures of LV filling pressure (E/A ratio, E/e' ratio, LA size; Supplemental Table 2). In the Americas, the 68 patients randomized to spironolactone were well matched to the 66 patients randomized to placebo with respect to clinical and laboratory characteristics (Table 1). No significant difference was noted in the number of interval primary events between the baseline and follow-up studies between treatment arms (9 [14%] versus 4 [6%] in the placebo and spironolactone arms respectively, p=0.15). Among patients enrolled in the Americas, randomization to spironolactone compared to placebo was associated with modest decrease in LVESV (-1.4±7.7 versus 2.4±10.2 ml, p=0.024) and E/A ratio (-0.14±0.40 versus 0.11±0.62,

p=0.053) and increase in LVEF (1.0±6.1 versus -0.4±7.2, p=0.053), but no significant difference compared to placebo in change in LV wall thickness or mass, mitral annular early relaxation velocity (e'), E/e' ratio, or LA size (Table 2). Similar findings were noted in an on-treatment analysis, excluding 27 patients who permanently discontinued study drug prior to the follow-up echocardiogram (Supplemental Table 3). Similar findings were noted in the study population overall and in the subgroup of patients enrolled in the Americas in analysis stratified by randomization strata (prior HF hospitalization versus elevated natriuretic peptide level; Supplemental Table 4). The modest decrease in LVESV and increase in LVEF observed in the Americas appeared most prominent among patients randomized through the prior HF hospitalization stratum (Supplemental Table 4).

Among patients enrolled in Russia or Georgia, the 53 randomized to spironolactone were well matched to the 52 randomized to placebo, with the exception of a modestly lower prevalence of hypertension in the spironolactone arm (Table 1). There was no significant difference in the number of interval primary events noted between the placebo and spironolactone arms (2 [4%] vs 0 respectively, p=0.24). Among patients enrolled in Russia or Georgia, randomization to spironolactone was not associated with significant changes in cardiac structure or function (Table 2).

Prognostic Relevance of Changes in Cardiac Structure and Function in HFpEF

Participants enrolled in the Americas were followed up for a median of 625 days (IQR 357 – 898 days) after the follow-up echocardiogram. Twenty primary outcome events occurred after the follow-up echocardiogram. After adjusting for baseline values,

increase in LA volume and pulmonary artery systolic pressure (PASP) and decrease in LVEF were associated with heightened risk of subsequent occurrence of the primary endpoint, each of marginal statistical significance (Table 3; Figure 1). The association between change in PASP and the primary outcome remained marginally statistically significant after further adjustment for patient demographics, and randomization strata, while changes in LA volume and LVEF did not. Changes in E/e' ratio and measures of LV structure were not associated with subsequent outcomes. Among participants enrolled in Russia or Georgia, participants were followed-up for a median of 716 day (IQR 376 – 1008 days) after the follow-up echocardiogram, and nine primary events occurred during this time. Changes in echocardiographic measures were not associated with subsequent outcomes among patients enrolled in Russia or Georgia.

Supplemental Table 1. Clinical and echocardiographic characteristics of TOPCAT patients without versus with echocardiographic data at baseline and 12 to 18 months

	No Follow-up Echo (n = 3,206)	**Follow-up Echo (n = 239)**	**P value**
Age (years)	68.5 ± 9.7	70.2 ± 9.0	0.007
Female	52%	52%	0.80
White	89%	87%	0.25
Enrollment in Russia/Georgia	49%	44%	0.13
Enrollment Strata: Prior Hospitalization	72%	62%	<0.001
Co-morbidities			
Hypertension	91%	93%	0.40
Myocardial Infarction	26%	29%	0.22
Coronary Revascularization	23%	31%	0.009
Stroke	8%	10%	0.25
Atrial Fibrillation	35%	43%	0.009
Diabetes	32%	35%	0.44
Obesity	55%	56%	0.93
NYHA Class			0.09*
1	3%	5%	

2	64%	60%	
3	33%	34%	
4	0.4%	0.8%	
Physical Characteristics			
BMI (kg/m^2)	32.1 ± 7.3	32.4 ± 7.3	0.51
Heart rate (bpm)	68 ± 12	66 ± 12	0.01
Systolic blood pressure (mmHg)	129 ± 14	126 ± 14	0.002
Diastolic blood pressure (mmHg)	76 ± 11	74 ± 11	0.001
Laboratory Values			
eGFR (mL/min per 1.73 m^2)	67.7 ± 20.3	67.8 ± 18.6	0.94
Creatinine (mg/dL)	1.09 ± 0.30	1.08 ± 0.31	0.65
Hematocrit (%)	40.2 ± 5.1	39.0 ± 4.7	<0.001

*p-value from Fisher exact test; BMI= body mass index; eGFR= estimated glomerular filtration rate.

Supplemental Table 2. Analysis of the impact of randomization to spironolactone versus placebo among patients who did not experience permanent discontinuation of study drug prior to the follow-up echocardiogram (n=201/239 [84%])

	N		Baseline			Follow-up			Change		
	Pl	**Sp**	**Placebo**	**Spirono**	**P**	**Placebo**	**Spirono**	**P**	**Placebo**	**Spirono**	**P***
LV Structure											
LVEDV (ml)	86	88	95.1 ± 33.1	101.0 ± 30.8	0.22	98.3 ± 33.0	101.3 ± 34.2	0.56	3.2 ± 15.3	0.3 ± 14.0	0.19
LVESV (ml)	86	88	39.9 ± 22.7	41.4 ± 19.4	0.63	41.5 ± 24.2	42.0 ± 21.8	0.89	1.6 ± 9.5	0.6 ± 9.1	0.45
Mean wall thickness (cm)	98	97	1.16 ± 0.20	1.12 ± 0.15	0.15	1.15 ± 0.21	1.11 ± 0.14	0.10	-0.00 ± 0.05	-0.01 ± 0.08	0.63
LV mass index (mg/m^2)	97	94	106 ± 30	103 ± 29	0.57	106 ± 34	102 ± 30	0.35	0 ± 7	-1 ± 11	0.21
Relative wall thickness	97	94	0.49 ± 0.12	0.47 ± 0.08	0.17	0.49 ± 0.12	0.47 ± 0.07	0.11	-0.00 ± 0.03	-0.00 ± 0.04	0.53
LV Function											
LVEF (%)	100	101	59.1 ± 8.5	59.6 ± 8.1	0.68	59.1 ± 9.3	59.9 ± 8.1	0.51	0.0 ± 5.7	0.3 ± 6.2	0.70

E/A ratio	62	63	1.00 ± 0.43	1.05 ± 0.49	0.59	1.08 ± 0.59	0.93 ± 0.37	0.10	0.07 ± 0.48	-0.12 ± 0.35	0.01
TDI E' (septal) (cm/sec)	77	82	5.76 ± 1.74	6.16 ± 2.05	0.18	5.63 ± 1.92	6.10 ± 2.12	0.15	-0.12 ± 1.52	-0.07 ± 1.81	0.83
E/E' (septal)	72	78	14.8 ± 4.9	13.8 ± 5.5	0.24	14.9 ± 5.3	13.6 ± 6.6	0.18	0.1 ± 4.3	-0.2 ± 5.0	0.68
LAV (ml)	83	81	58.5 ± 19.7	59.0 ± 23.4	0.88	60.7 ± 21.0	59.6 ± 24.6	0.76	2.2 ± 12.6	0.6 ± 15.3	0.46
LA diameter (cm)	100	99	4.08 ± 0.56	4.03 ± 0.51	0.49	4.11 ± 0.54	4.02 ± 0.48	0.27	0.02 ± 0.21	-0.01 ± 0.19	0.31
RV and Pulmonary Vascular											
TR jet velocity (m/sec)	30	27	2.75 ± 0.48	2.82 ± 0.41	0.51	2.61 ± 0.41	2.72 ± 0.47	0.34	-0.14 ± 0.55	-0.10 ± 0.49	0.80
RVFAC (%)	60	53	0.48 ± 0.06	0.49 ± 0.07	0.65	0.48 ± 0.06	0.49 ± 0.07	0.25	-0.00 ± 0.08	0.00 ± 0.09	0.58

Supplemental Table 3. Change in echocardiographic measures by treatment arm and by randomization strata (prior HF hospitalization or, if no prior HF hospitalization, elevated natriuretic peptide level) in the study population overall

	Prior HF Hospitalization (n=147)					**Elevated Natriuretic Peptide Level (n=92)**					**P for**
	Placebo (n=76)		**Spirono (n=71)**			**Placebo (n=42)**		**Spirono (n=50)**			**inter**
	N	**Mean**±SD	**N**	**Mean**±SD	**P**	**N**	**Mean**±SD	**N**	**Mean**±SD	**P**	**-act**
LV Heart Structure											
LVEDV (ml)	60	3.8±13.6	57	1.44±12.8	0.43	40	2.7±16.5	44	-0.7±15.5	0.39	0.85
LVESV (ml)	60	3.6±8.6	57	0.4±8.5	0.05	40	-0.2±9.6	44	0.6±8.9	0.68	0.12
Mean wall thickness (cm)	74	0.00±0.05	68	-0.01±0.08	0.21	41	-0.01±0.05	49	-0.01±0.07	0.91	0.48
LV mass index (mg/m^2)	73	1±7	65	-1±14	0.19	41	-1±6.8	48	-1±11	0.75	0.53
Relative wall thickness	73	0.00±0.03	65	-0.01±0.04	0.19	41	0.00±0.04	48	-0.00±0.04	0.66	0.71
LAV (ml)	61	1.3±11.1	53	2.7±14.0	0.56	36	3.8±13.5	40	-1.1±16.8	0.19	0.14
LA diameter	75	0.03±0.22	69	0.01±0.19	0.70	42	0.02±2.0	50	-0.04±0.20	0.11	0.35

(cm)											
LV Function											
LVEF (%)	76	-1.4±6.5	71	0.4±6.7	0.11	42	1.2±5.6	50	-0.2±5.2	0.32	0.10
E/A ratio	49	0.06±0.49	45	-0.03±0.34	0.26	24	0.04±0.39	26	-0.20±0.37	0.05	0.45
TDI E' (septal) (cm/sec)	63	-0.27±1.65	62	-0.08±1.68	0.25	28	-0.09±1.43	33	-0.15±2.01	0.96	0.51
E/E' (septal)	58	0.5±4.1	59	0.5±4.8	0.73	28	0.4±5.5	32	0.0±5.8	0.76	0.86
RV and Pulmonary Vascular											
TR jet velocity (m/sec)	18	-0.08±0.53	20	0.11±0.48	0.40	18	-0.05±0.58	17	-0.16±0.50	0.62	0.79
RVFAC (%)	43	-0.00±0.09	32	0.01±0.07	0.34	28	0.00±0.08	34	-0.00±0.10	0.85	0.51

Table 4. Baseline characteristics by randomization treatment arm in the study population overall and stratified by region of enrollment

	Americas			**Russia/Georgia**		
	Placebo (n=66)	**Spirono (n=68)**	**P value**	**Placebo (n=52)**	**Spirono (n=53)**	**P value**
Age (years)	72.2 ± 8.6	70. 6 ± 10.0	0.32	68.9 ± 7.8	68.6 ± 8.8	0.83
Female	47%	49%	0.86	62%	55%	0.48
White	80%	72%	0.26	100%	100%	-
Enrollment Strata: Prior Hospitalization	52%	49%	0.73	81%	72%	0.28
Co-morbidities						
Hypertension	94%	90%	0.53*	100%	89%	0.03*
Myocardial Infarction	14%	18%	0.52	44%	49%	0.62
Coronary Revascularization	27%	31%	0.65	33%	32%	0.95
Stroke	5%	9%	0.32	10%	17%	0.27
Atrial Fibrillation	55%	52%	0.72	31%	30%	0.95

Diabetes	50%	46%	0.61	14%	23%	0.22
Obesity	67%	71%	0.62	37%	42%	0.60
NYHA Functional Class			0.60*			0.68*
1	9%	6%		2%	4%	
2	59%	68%		58%	53%	
3	32%	27%		40%	40%	
4	0%	0%		0%	4%	
Physical Characteristics						
BMI (kg/m^2)	34.1 ± 8.8	35.0 ± 8.4	0.56	29.4 ± 4.0	30.0 ± 4.0	0.43
Heart rate (bpm)	69± 12	65 ± 12	0.09	66± 11	64± 11	0.29
Systolic blood pressure (mmHg)	123 ± 14	124± 15	0.75	130 ± 12	131 ± 12	0.61
Diastolic blood pressure (mmHg)	69 ± 12	71 ± 10	0.50	78 ± 7	78 ± 8	0.78
Laboratory Values						
eGFR (mL/min per 1.73 m^2)	63.2 ± 18.5	64.4 ± 21.2	0.71	73.2 ± 16.1	72.4 ± 15.0	0.80

Creatinine (mg/dL)	1.17 ± 0.33	1.19 ± 0.36	0.71	0.95 ± 0.18	0.97 ± 0.21	0.46
Hematocrit (%)	37.8 ± 4.7	38.4 ± 4.0	0.46	39.5 ± 4.9	40.8 ± 5.0	0.20

*P value from Fisher exact test; BMI=body mass index; eGFR= estimated glomerular filtration rate

Supplemental Table 5. Baseline echocardiographic measures by region. Adjusted P value adjusts for age, randomization strata, prior MI, diabetes, BMI, and eGFR

	Americas (n=134)	**Russia/Georgia (n=105)**	**Unadjusted P**	**Adjusted P**
LVEDV (ml)	90.6 ± 28.1	106.7 ± 36.4	<0.001	0.007
LVESV (ml)	36.9 ± 15.9	46.1 ± 25.0	<0.001	0.054
Mean WT (cm)	1.18 ± 0.20	1.13 ± 0.17	0.046	0.12
LV mass index (g/m^2)	104 ± 30	108 ± 28	0.25	0.93
RWT	0.51 ± 0.11	0.47 ± 0.10	0.004	0.065
LVEF (%)	60.1 ± 7.8	58.7 ± 8.3	0.21	0.91
E/A ratio	1.30 ± 0.63	0.88 ± 0.36	<0.001	<0.001
TDI e’	6.34 ± 2.09	5.32 ± 1.40	<0.001	0.003
E/e’ ratio	16.3 ± 6.5	13.5 ± 5.2	<0.001	0.032
LA volume (ml)	65.5 ± 24.2	54.6 ± 20.3	<0.001	0.033

LA diameter (cm)	4.15 ± 0.54	4.00 ± 0.53	0.028	0.25
PASP (mmHg)	41 ± 9	38 ± 9	0.031	0.79
RVFAC (%)	48.8 ± 7.4	48.5 ± 5.9	0.71	0.99

LVEDV – left ventricular end diastolic volume, LVESV – left ventricular end-systolic volume, LVEF – left ventricular ejection fraction; TDI E' – tissue Doppler early diastolic relaxation velocity; LAV – left atrial volume; TR – tricuspid regurgitation; RVFAC – right ventricular fractional area chance

Supplemental Table 6. Baseline, Follow-up, and Change in echocardiographic measures by treatment arm separately among patients enrolled in the Americas and in Russia/Georgia. *P value for between treatment group differences in change is based on linear regression models adjusting for the baseline value

	N		Baseline			Follow-up			Change		
	Placebo	**Spirono**	**Placebo**	**Spirono**	**p**	**Placebo**	**Spirono**	**p**	**Placebo**	**Spirono**	**P***
Enrollment in the Americas (n=134)											
Left Heart Structure											
LVEDV (ml)	57	54	86.8 ± 23.4	90.2 ± 28.7	0.48	91.0 ± 28.7	89.1 ± 28.7	0.73	4.3 ± 16.2	-1.0 ± 13.5	0.073
LVESV (ml)	57	54	35.7 ± 14.7	34.6 ± 13.9	0.66	38.1 ± 18.0	33.1 ± 13.1	0.10	2.4 ± 10.2	-1.4 ± 7.7	0.024
Mean wall thickness (cm)	65	64	1.19 ± 0.22	1.16 ± 0.16	0.37	1.19 ± 0.22	1.14 ± 0.16	0.22	-0.00 ± 0.05	-0.01 ± 0.08	0.25
LV mass index (mg/m^2)	64	61	106 ± 31	103 ± 28	0.57	106 ± 31	101 ± 30	0.37	0 ± 7	-2 ± 13	0.27
Relative wall thickness	64	61	0.51 ± 0.13	0.50 ± 0.08	0.40	0.52 ± 0.13	0.49 ± 0.08	0.23	0.00 ± 0.04	0.00 ± 0.04	0.24
LAV (ml)	51	51	64.5 ± 21.3	63.9 ± 25.9	0.90	66.9 ± 23.4	62.8 ± 26.9	0.41	2.4 ± 13.8	-1.1 ± 15.7	0.21
LA diameter (cm)	66	66	4.21 ± 0.55	4.12 ± 0.53	0.31	4.23 ± 0.56	4.11 ± 0.50	0.20	0.02 ± 0.23	-0.01 ± 0.18	0.37
LV Function											

LVEF (%)	66	68	59.0 ± 8.3	61.1 ± 7.3	0.11	58.6 ± 9.6	62.1 ± 6.3	0.01	-0.4 ± 7.2	1.0 ± 6.1	0.053
E/A ratio	35	38	1.16 ± 0.52	1.24 ± 0.54	0.53	1.27 ± 0.69	1.09 ± 0.45	0.20	0.11 ± 0.62	-0.14 ± 0.40	0.052
TDI E' (septal) (cm/sec)	46	52	6.20 ± 1.92	6.62 ± 2.26	0.33	5.79 ± 2.04	6.44 ± 2.16	0.13	-0.41 ± 1.79	-0.18 ± 1.97	0.24
E/E' (septal)	46	52	16.4± 5.5	15.5 ± 6.3	0.48	17.1 ± 6.1	15.7 ± 8.5	0.35	0.8 ± 5.6	0.2 ± 6.1	0.53
RV and Pulmonary Vascular											
TR jet velocity (m/sec)	28	27	2.76 ± 0.45	2.88 ± 0.38	0.26	2.71 ± 0.50	2.78 ± 0.43	0.57	-0.05 ± 0.57	-0.11 ± 0.46	0.82
RVFAC (%)	44	38	0.48 ± 0.08	0.50 ± 0.07	0.22	0.49 ± 0.06	0.50 ± 0.07	0.65	0.02 ± 0.08	0.00 ± 0.09	0.90
Enrollment in Russia or Georgia (n=105)											
Left Heart Structure											
LVEDV (ml)	43	47	101.3 ± 39.7	109.7 ± 32.9	0.27	103.3 ± 35.7	112.0 ± 35.1	0.25	2.1 ± 12.7	2.3 ± 14.5	0.73
LVESV (ml)	43	47	42.9 ± 28.0	47.4 ± 22.2	0.40	44.5 ± 28.3	50.1 ± 25.2	0.32	1.7 ± 7.6	2.8 ± 9.2	0.56
Mean wall thickness (cm)	50	53	1.13 ± 0.16	1.13 ± 0.18	0.94	1.13 ± 0.16	1.13 ± 0.18	0.95	0.00 ± 0.05	-0.00 ± 0.08	0.73
LV mass index (mg/m^2)	50	52	107 ± 26	110 ± 30	0.61	108 ± 25	109 ± 32	0.83	1 ± 7	-1 ± 12	0.46
Relative wall	50	52	0.47 ± 0.10	0.46 ± 0.10	0.67	0.47 ± 0.10	0.46 ± 0.10	0.57	-0.00 ± 0.02	-0.00 ± 0.04	0.63

thickness											
LAV (ml)	46	42	51.0 ± 16.8	53.7 ± 16.2	0.45	53.0 ± 15.4	57.4 ± 21.5	0.27	2.0 ± 10.0	3.7 ± 14.5	0.41
LA diameter (cm)	51	53	3.92 ± 0.52	4.08 ± 0.53	0.13	3.95 ± 0.51	4.06 ± 0.51	0.28	0.03 ± 0.18	-0.01 ± 0.20	0.37
LV Function											
LVEF (%)	52	53	59.4 ± 8.4	58.1 ± 8.2	0.41	58.8 ± 9.3	57.1 ± 9.1	0.34	-0.6 ± 5.0	-1.0 ± 6.0	0.64
E/A ratio	38	33	0.84 ± 0.24	0.82 ± 0.28	0.77	0.84 ± 0.27	0.79 ± 0.28	0.41	0.01 ± 0.24	-0.03 ± 0.30	0.44
TDI E' (septal) (cm/sec)	45	43	5.30 ± 1.39	5.48 ± 1.49	0.55	5.29 ± 1.67	5.47 ± 1.83	0.64	-0.01 ± 1.33	-0.01 ± 1.56	0.89
E/E' (septal)	40	39	13.4 ± 4.3	12.2 ± 3.5	0.16	13. 6 ± 4.2	12.8 ± 4.3	0.38	0.2 ± 3.0	0.6 ± 3.7	0.94
RV and Pulmonary Vascular											
TR jet velocity (m/sec)	8	10	2.64 ± 0.52	2.55 ± 0.32	0.65	2.51 ± 0.32	2.77 ± 0.56	0.26	-0.12 ± 0.49	0.22 ± 0.55	0.21
RVFAC (%)	27	28	0.49 ± 0.05	0.49 ± 0.08	1.00	0.46 ± 0.06	0.48 ± 0.06	0.24	-0.02 ± 0.08	-0.00 ± 0.07	0.22

LVEDV – left ventricular end diastolic volume, LVESV – left ventricular end-systolic volume, LVEF – left ventricular ejection fraction; TDI E' – tissue Doppler early diastolic relaxation velocity; LAV – left atrial volume; TR – tricuspid regurgitation; RVFAC – right ventricular fractional area chance

Supplemental Table 7. Change in echocardiographic measures of cardiac structure and function and subsequent outcomes stratified by region of enrollment. Fully adjusted analysis adjusts for baseline value, age, gender, race, randomization strata, and region of enrollment (for analysis of overall study population). After multivariable adjustment: *HR 0.93 (0.85-1.00), p=0.06; §HR 1.03 (1.00-1.06), p=0.09; ¥HR 1.12 (1.03-1.23), p=0.01

Measure	Enrolled in the Americas				Enrolled in Russia or Georgia			
	N	Events	Baseline-adjusted HR	P value	N	Events	Baseline-adjusted HR	P value
ΔLVEDV (per ml)	99	16	1.02 (0.99-1.05)	0.29	87	7	0.98 (0.93-1.03)	0.43
ΔLVESV (per ml)	99	16	1.03 (0.98-1.08)	0.30	87	7	0.98 (0.91-1.05)	0.59
ΔLVMi (per g/m^2)	109	20	1.00 (0.96-1.05)	0.84	99	9	1.00 (0.94-1.06)	0.96
ΔLVEF (per 1%)	117	20	0.92 (0.85-0.99)	0.03*	102	9	1.09 (0.97-1.23)	0.16
ΔE/A ratio (per 0.1 unit)	66	9	1.08 (0.98-1.19)	0.11	69	6	0.92 (0.67-1.25)	0.59
Δe' (per cm/s)	86	15	1.03 (0.77-1.39)	0.84	85	7	1.10 (0.61-2.02)	0.74
ΔE/e' ratio (per 1 unit)	86	15	0.98 (0.91-1.07)	0.72	77	7	0.75 (0.56-1.00)	0.05
ΔLAV (per ml)	91	16	1.03 (1.00 – 1.07)	0.04§	85	8	1.05 (0.99-1.12)	0.10
ΔPASP (per mmHg)	47	7	1.08 (1.01-1.16)	0.02¥	18	1	0.92 (0.63-1.33)	0.65
ΔRVFAC (per 1%)	70	7	0.92 (0.81-1.05)	0.24	54	5	0.89 (0.75-1.04)	0.14

Supplemental Table 8. Studies of the impact of aldosterone antagonist therapy on cardiac structure and function in HFpEF and TOPCAT Echo among patients enrolled in the Americas, comparing magnitude of observed effect on LVESV, E/A ratio, and LVEF

			Observed between group change in		
Author (year)	**N**	**Endpoints**	**LVESV**	**E/A ratio**	**LVEF**
Daniel et al 2009[2]	11	**↓ E/e'** No change in E/A ratio, e', LV dimension or WT	24±7 to 26±6 p=0.57	0.95±0.53 to 0.71±0.16 p=0.52	NR
Mak et al 2009[3]	44	**↓DT** No change in E/A ratio, e', E/e', LAVi, LVMi	NR	0.80±0.31 to 0.83±0.57 vs 0.89±0.38 to 0.95±0.39 btw grp p = NS	64±9.6 to 67±11.3 vs 63±9.0 to 67±7.9 btw grp p = NS
Deswal et al 2011[4]	44	**↓E/e'** No change in E/A ratio, e', LAV, LV dimension, LVMi	NR	1.22±0.66 to 1.11±0.47 vs 1.41±0.98 to 1.23±0.72 btw grp p = NS	NR
Kurrelmeyer et al 2014[5]	48	**↓E/e', ↓e', ↓LV mass** No change in E/A ratio, LAV, LV dimension	NR	NR	NR
ALDO-DHF 2013[6]	422	**↓E/e' , ↓e', ↓LVMi, ↓LV dimension, ↑LVEF** No change in E/A ratio, LAV	NR	0.92±0.34 to 0.96 vs 0.90±0.31 to 0.91 btw grp p = 0.08	68±7 to 65.9 vs 67±8 to 67.2 btw grp p = 0.04
TOPCAT Echo (Americas only)	134	↓LVESV, marginal ↓E/A ratio, marginal ↑LVEF No change in e', E/e', LAV, LVMi	35.7 ± 14.7 to 38.1 ± 18.0 vs 34.6 ± 13.9 to 33.1 ± 13.1 btw grp p = 0.02	1.16 ± 0.52 to 1.27 ± 0.69 vs 1.24 ± 0.54 to 1.09 ± 0.45 btw grp p = 0.05	59.0 ± 8.3 to 58.6 ± 9.6 vs 61.1 ± 7.3 to 62.1 ± 6.3 btw grp p = 0.05

Values are listed as baseline to follow-up with placebo on top line and active therapy on the bottom line; NR – not reported

Supplemental Reference

1. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner J, Lewis EF, O'Meara E, Rouleau JL, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer N, McKinlay S, Pitt B. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial. *Circulation* 2015;131:34-42.
2. Daniel KR, Wells G, Stewart K, Moore B, Kitzman DW. Effect of aldosterone antagonism on exercise tolerance, Doppler diastolic funciton, and quality of life in older women with diastolic heart failure. *Congest Heart Fail* 2009;15:68-74.
3. Mak GJ, Ledwidge MT, Watson CJ, Phelan DM, Dawkins IR, Murphy NF, Patle AK, Baugh JA, McDonald KM. Natural history of markers of collagen turnover in patients with early diastolic dysfunction and impact of eplerenone. *J Am Coll Cardiol* 2009;54:1674-82.
4. Deswal A, Richardson P, Bozkurt B, Mann DL. Results of the Randomized Aldosterone Antagonism in heart failure with Preserved Ejection Fraction trial (RAAM-PEF). *J Cardiac Fail* 2011;17:634-42.
5. Kurrelmeyer KM, Ashton Y, Xu J, Nagueh SF, Torre-Amione G, Deswal A. Effects of spironolactone treatment in elderly women with heart failure and preserved left ventricular ejection fraction. *J Cardiac Fail* 2014;20:560-8.
6. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Loffler M, Dungen HD, Tschope C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: The ALDO-DHF randomized controlled trial. *JAMA* 2013;209:781-91.