SUPPLEMENTAL MATERIAL

Supplemental Tables and Figures

Supplemental Figure 1. Venn diagram demonstrating the overlap between abnormal LS, LVH, and elevated E/E' patients among patients will all 3 measures available among study participants with LVEF ≥55% (n=259).

Supplemental Table 1. Clinical characteristics among patients in the TOPCAT trial without versus with strain data.

	No Strain Data (n=2,998)	Strain Data (n=447)	P value
Age (years)	68.3 ± 9. 6	70.3 ± 9.8	<0.0001
Female	1535 (51.2%)	240 (53.7%)	0.33
White	2703 (90.2%)	359 (80.3%)	<0.0001
Enrollment in Russia/Georgia	1571 (52.4%)	107 (23.9%)	<0.0001
Enrollment Strata: Prior Hospitalization	2175 (72.5%)	289 (64.7%)	0.0006
Co-morbidities			
Hypertension	2736 (91.3%)	411 (92.2%)	0.56
Myocardial Infarction	778 (26.0%)	115 (25.8%)	0.93
Coronary Revascularization	683 (22.8%)	130 (29.1%)	0.003
Stroke	218 (7.3%)	47 (10.5%)	0.016
Atrial Fibrillation	1021 (34.1%)	193 (43.3%)	0.0001
Diabetes	947 (31.6%)	171 (38.3%)	0.005
Obesity	1640 (54.9%)	262 (58.7%)	0.12
NYHA Functional Class			<0.0001
1	76 (2.5%)	33 (7.4%)	
2	1953 (65.2%)	241 (54.2%)	
3	953 (31.8%)	168 (37.8%)	

4	12 (0.4%)	3 (0.7%)	
Physical Characteristics			
BMI (kg/m^2)	32.1 ± 7.3	32.5 ± 6.9	0.28
Heart rate (bpm)	68.2 ± 12.0	67.8 ± 11.5	0.53
Systolic blood pressure (mmHg)	130 ± 14	126 ± 15	<0.0001
Diastolic blood pressure (mmHg)	76 ± 11	72 ± 11	<0.0001
Laboratory Values			
eGFR (mL/min per 1.73 m^2)	67.9 ± 19.9	66.1 ± 21.5	0.08
Creatinine (mg/dL)	1.09 ± 0.29	1.14 ± 0.34	0.0008
Hematocrit (%)	40.3 ± 5.1	38.9 ± 4.7	<0.0001

Supplemental Table 2. Clinical characteristics among patients in the TOPCAT echocardiography study without versus with acceptable image quality for strain analysis. Unacceptable image quality was defined as lack of a full cardiac cycle, more than 2 segment dropout, analog format or digital format other than DICOM, missing view, or significant foreshortening of the left ventricle.

	Inadequate Image Quality (n=488)		Adequate Image Quality (n=447)		P value
Age (years)	69.56 ± 9.61		70.27 ± 9.79		0.27
Female	222	(45.5%)	240	(53.7%)	0.01
White	411	(84.2%)	359	(80.3%)	0.12
Enrollment in Russia/Georgia	174	(35.7%)	107	(23.9%)	<0.0001
Enrollment Strata: Prior Hospitalization	333	(68.2%)	289	(64.7%)	0.25
Co-morbidities					
Hypertension	443	(90.8%)	411	(92.2%)	0.45
Myocardial Infarction	138	(28.3%)	115	(25.8%)	0.39
Coronary Revascularization	134	(27.5%)	130	(29.1%)	0.57
Stroke	30	(6.1%)	47	(10.5%)	0.01
Atrial Fibrillation	166	(34.0%)	193	(43.3%)	0.004
Diabetes	202	(41.4%)	171	(38.3%)	0.34
Obesity	276	(56.7%)	262	(58.7%)	0.52
NYHA Functional Class					0.05

1	19 (3.9%)	33 (7.4%)	
2	296 (60.8%)	241 (54.2%)	
3	167 (34.3%)	168 (37.8%)	
4	5 (1.0%)	3 (0.7%)	
Physical Characteristics			
BMI (kg/m^2)	32.80 ± 8.05	32.46 ± 6.91	0.49
Heart rate (bpm)	68.35 ± 13.02	67.78 ± 11.48	0.48
Systolic blood pressure (mmHg)	129.73 ± 14.35	126.37 ± 15.03	0.0005
Diastolic blood pressure (mmHg)	74.53 ± 10.53	72.48 ± 10.85	0.003
Laboratory Values			
eGFR (mL/min per 1.73 m^2)	66.73 ± 21.74	66.08 ± 21.51	0.65
Creatinine (mg/dL)	1.13 ± 0.31	1.14 ± 0.34	0.70
Hematocrit (%)	39.60 ± 5.31	38.91 ± 4.67	0.04

Supplemental Table 3. Association of LS with cardiovascular outcomes (primary composite outcomes, CV death, incident HF hospitalization, and total number of HF hospitalizations) in univariate and multivariable analysis among 354 patients with LVEF ≥55%. Multivariable analysis is adjusted for the following variables: Model 1: age, gender, race, randomization strata (prior HF hospitalization or biomarker criteria), region of enrollment (Americas versus Russia or Georgia), randomized treatment assignment, core lab LVEF, history of atrial fibrillation, heart rate, New York Heart Association class, history of stroke, creatinine, and hematocrit; Model 2: Model 1 + LV mass, LVESVi; Model 3: Model 2 + E/E' ratio. For dichotomous analysis, abnormal LS was defined as LS > -15.8% (see text for details). LS is shown as absolute value.

	Normal LS (≥15.8)			Abnormal LS (<15.8)			Dichotomous		Continuous (per 1% ↓)	
	N	*Events*	*Rate*	*N*	*Events*	*Rate*	*HR (95% CI)*	*P*	*HR (95% CI)*	*P*
Primary										
Unadjusted	202	36	6.1 (4.4-8.5)	152	51	13.5 (10.3-17.8)	2.18 (1.42-3.34)	<0.001	1.20 (1.12-1.28)	<0.001
Model 1	190	35	6.3 (4.6-8.8)	148	50	13.6 (10.3-17.9)	2.38 (1.42-3.97)	0.001	1.21 (1.12-1.32)	<0.001
Model 2	146	27	6.4 (4.4-9.3)	103	34	13.6 (9.7-19.1)	2.37 (1.30-4.33)	0.005	1.24 (1.11-1.39)	<0.001

	N			N			HR/IRR (95% CI)	P	HR/IRR (95% CI)	P
CV death										
Unadjusted	202	14	2.2 (1.3-3.8)	152	26	6.1 (4.1-8.9)	2.80 (1.46-5.37)	0.002	1.25 (1.13-1.39)	<0.001
Model 1	190	14	2.4 (1.4-4.0)	148	25	6.0 (4.0-8.8)	3.60 (1.66-7.81)	0.001	1.34 (1.19-1.51)	<0.001
Model 2	146	11	2.4 (1.3-4.4)	103	20	7.1 (4.6-11.0)	4.13 (1.67-10.2)	0.002	1.46 (1.23-1.73)	<0.001
Incident HF Hosp										
Unadjusted	202	25	4.3 (2.9-6.3)	152	36	9.6 (6.9-13.2)	2.17 (1.30-3.62)	0.003	1.19 (1.10-1.29)	<0.001
Model 1	190	24	4.4 (2.9-6.5)	148	36	9.8 (7.1-13.6)	2.39 (1.27-4.50)	0.007	1.20 (1.09-1.32)	<0.001
Model 2	146	18	4.3 (2.7-6.8)	103	24	9.6 (6.5-14.4)	2.64 (1.25-5.58)	0.011	1.24 (1.07-1.43)	0.004
Total HF Hosp							*IRR (95% CI)*	*P*	*IRR (95% CI)*	*P*
Unadjusted	202	-	-	152	-	-	2.68 (1.37-5.26)	0.004	1.24 (1.11-1.39)	<0.001
Model 1	190	-	-	148	-	-	3.80 (1.74-8.29)	0.001	1.31 (1.15-1.50)	<0.001
Model 2	146	-	-	103	-	-	5.27 (2.01-13.8)	0.001	1.34 (1.14-1.58)	<0.001

Supplemental Table 4. Association of LS with cardiovascular outcomes (primary composite outcomes, CV death, incident HF hospitalization, and total number of HF hospitalizations) stratified by region of enrollment: the Americas (United States, Canada, Argentina, Brazil) versus Russia or Georgia. Multivariable analysis is adjusted for the following variables: Model 1: age, gender, race, randomization strata (prior HF hospitalization or biomarker criteria), randomized treatment assignment, core lab LVEF, history of atrial fibrillation, heart rate, New York Heart Association class, history of stroke, creatinine, and hematocrit; Model 2: Model 1 + LV mass, LVESVi; Model 3: Model 2 + E/E' ratio. Given the small number of events in Russia and Georgia, only unadjusted analyses are presented for this region. The number of HF hospitalizations was insufficient to assess the association of LS with total number of HF hospitalizations in Russia and Georgia. For dichotomous analysis, abnormal LS was defined as an absolute LS <15.8% (see text for details).

	Normal LS (≥15.8)			Abnormal LS (<15.8)			Dichotomous		Continuous (per 1% ↓)	
	N	*Events*	*Rate*	*N*	*Events*	*Rate*	*HR (95% CI)*	*P*	*HR (95% CI)*	*P*
Enrollment in the United States, Canada, Argentina, or Brazil (n=340)										
Primary										
Unadjusted	160	33	7.5 (5.3-10.5)	180	67	15.4 (12.1-19.6)	2.05 (1.35-3.11)	0.001	1.13 (1.07-1.19)	<0.001

	N	n	Rate (95% CI)	N	n	Rate (95% CI)	HR (95% CI)	p	HR (95% CI)	p
Model 1	151	32	7.6 (5.4-10.8)	177	66	15.5 (12.1-19.7)	2.05 (1.25-3.34)	0.004	1.14 (1.06-1.23)	<0.001
Model 2	149	32	7.7 (5.5-10.9)	175	66	15.7 (12.3-19.9)	1.91 (1.14-3.18)	0.013	1.13 (1.04-1.22)	0.002
Model 3	107	24	8.3 (5.5-12.3)	120	47	17.1 (12.8-22.7)	1.96 (1.08-3.56)	0.027	1.11 (1.01-1.22)	0.026
CV death										
Unadjusted	160	12	2.5 (1.4-4.41)	180	30	5.9 (4.1-8.5)	2.40 (1.23-4.70)	0.010	1.15 (1.06-1.25)	0.001
Model 1	151	12	2.6 (1.5-4.6)	177	29	5.8 (4.0-8.3)	2.53 (1.15-5.58)	0.021	1.22 (1.09-1.36)	0.001
Model 2	149	12	2.7 (1.5-4.7)	175	29	5.9 (4.1-8.4)	2.50 (1.11-5.64)	0.027	1.22 (1.09-1.37)	0.001
Model 3	107	9	2.8 (1.5-5.4)	120	22	6.7 (4.4-10.2)	2.80 (1.07-7.36)	0.037	1.26 (1.08-1.46)	0.003
Incident HF Hosp										
Unadjusted	160	24	5.4 (3.6-8.1)	180	50	11.5 (8.7-15.1)	2.08 (1.28-3.38)	0.003	1.12 (1.05-1.19)	0.001
Model 1	151	23	5.5 (3.7-8.3)	177	50	11.7 (8.8-15.4)	2.29 (1.29-4.04)	0.004	1.13 (1.04-1.23)	0.004
Model 2	149	23	5.6 (3.7-8.4)	175	50	11.8 (9.0-15.6)	2.21 (1.22-3.99)	0.009	1.12 (1.02-1.22)	0.012
Model 3	107	17	5.8 (3.6-9.4)	120	36	13.0 (9.4-18.0)	2.43 (1.23-4.83)	0.011	1.10 (0.99-1.23)	0.082

Total HF Hosp							IRR (95% CI)	P	IRR (95% CI)	P
Unadjusted	160	-	-	180	-	-	2.18 (1.20-3.95)	0.011	1.15 (1.04-1.26)	0.005
Model 1	151	-	-	177	-	-	3.65 (1.78-7.46)	<0.001	1.20 (1.08-1.34)	0.001
Model 2	149	-	-	175	-	-	3.76 (1.82-7.76)	<0.001	1.21 (1.08-1.36)	0.001
Model 3	107	-	-	120	-	-	5.74(2.27-14.5)	<0.001	1.21 (1.05-1.39)	0.008
Enrollment in Russia or Georgia (n=107)										
Primary										
Unadjusted	56	4	2.1 (0.8-5.6)	51	11	7.8 (4.2-13.7)	3.31(1.05-10.4)	0.04	1.16 (1.02-1.31)	0.025
CV death										
Unadjusted	56	3	1.6 (0.5-4.9)	51	9	5.9 (3.1-11.3)	3.56 (0.96-13.1)	0.06	1.20 (1.04-1.38)	0.015
Incident HF Hosp										

Unadjusted	56	1	0.5 (0.1-3.8)	51	3	2.1 (0.7-6.4)	3.53 (0.37-34.0)	0.27	1.13 (0.87-1.45)	0.36

Supplemental Table 5. Association of LS with cardiovascular outcomes (primary composite outcomes, CV death, incident HF hospitalization, and total number of HF hospitalizations) in univariate and multivariable analysis using multiple imputation by chained equations to account for variable missing data. N=444 for all analyses using the overall study population; N=341 for all analyses using the subgroup with LVEF ≥55%. Multivariable analysis is adjusted for the following variables: Model 1: age, gender, race, randomization strata (prior HF hospitalization or biomarker criteria), randomized treatment assignment, core lab LVEF, history of atrial fibrillation, heart rate, New York Heart Association class, history of stroke, creatinine, and hematocrit; Model 2: Model 1 + LV mass, LVESVi; Model 3: Model 2 + E/E' ratio. For dichotomous analysis, abnormal LS was defined as an absolute LS <15.8%.

	Dichotomous		Continuous (per 1% ↓)	
	HR (95% CI)	*P*	*HR (95% CI)*	*P*
Overall Study Population (n=444)				
Primary *(events = 115)*				
Model 1	2.16 (1.38-3.39)	0.001	1.15 (1.08-1.23)	<0.001
Model 2	2.17 (1.36-3.45)	0.001	1.15 (1.07-1.23)	<0.001
Model 3	2.10 (1.32-3.34)	0.002	1.14 (1.06-1.22)	0.001

CV death *(events = 54)*

Model 1	2.92 (1.47-5.79)	0.002	1.23 (1.12-1.36)	<0.001
Model 2	3.21 (1.59-6.47)	0.001	1.25 (1.13-1.38)	<0.001
Model 3	3.12 (1.55-6.31)	0.001	1.24 (1.12-1.38)	<0.001

Incident HF Hosp

(events = 78)

Model 1	2.10 (1.22-3.63)	0.008	1.12 (1.04-1.22)	0.005
Model 2	2.04 (1.16-3.58)	0.014	1.11 (1.02-1.21)	0.014
Model 3	1.93 (1.10-3.39)	0.022	1.09 (0.99-1.19)	0.066

Subgroup with LVEF ≥55% (n=351)

Primary *(events = 87)*

Model 1	2.21 (1.37-3.58)	0.001	1.19 (1.11-1.28)	<0.001
Model 2	2.37 (1.42-3.93)	0.001	1.22 (1.13-1.32)	<0.001
Model 3	2.26 (1.36-3.78)	0.002	1.22 (1.11-1.33)	<0.001

CV death *(events = 40)*				
Model 1	3.05 (1.45-6.41)	0.003	1.27 (1.14-1.42)	<0.001
Model 2	3.55 (1.66-7.62)	0.001	1.33 (1.18-1.50)	<0.001
Model 3	3.48 (1.61-7.52)	0.002	1.35 (1.18-1.54)	<0.001
Incident HF Hosp *(events = 61)*				
Model 1	2.21 (1.23-3.99)	0.008	1.19 (1.09-1.30)	<0.001
Model 2	2.26 (1.21-4.22)	0.011	1.21 (1.09-1.33)	<0.001
Model 3	2.12 (1.13-3.99)	0.019	1.19 (1.07-1.33)	0.001

Supplemental Table 6. Association of LS with the primary composite outcome of CV death, incident HF hospitalization, and aborted cardiac arrest in univariate and multivariable analysis among 259 patients with data for natriuretic peptide level. Multivariable analysis is adjusted for the following variables: Model 1: age, gender, race, randomization strata (prior HF hospitalization or biomarker criteria), region of enrollment (Americas versus Russia or Georgia), randomized treatment assignment, core lab LVEF, history of atrial fibrillation, heart rate, New York Heart Association class, history of stroke, creatinine, hematocrit, *and natriuretic peptide level*; Model 2: Model 1 + LV mass, LVESVi; Model 3: Model 2 + E/E' ratio. For dichotomous analysis, abnormal LS was defined as an absolute LS <15.8% (see text for details).

	Normal LS (≥15.8)			Abnormal LS (<15.8)			Dichotomous		Continuous (per 1% ↓)	
	N	Events	Rate	N	Events	Rate	HR (95% CI)	P	HR (95% CI)	P
Sub-group with data on BNP/NT-proBNP (n=259)										
Unadjusted	125	21	6.0 (3.9-9.2)	134	43	14.4 (10.7-19.4)	2.32 (1.37-3.91)	0.002	1.13 (1.05-1.21)	0.001
Model 1	117	20	6.0 (3.9-9.3)	132	42	14.2 (10.5-19.2)	2.07 (1.10-3.91)	0.024	1.12 (1.03-1.23)	0.011

Model 2	115	20	6.1 (3.9-9.5)	131	42	14.4 (10.6-19.5)	2.15 (1.13-4.10)	0.020	1.13 (1.03-1.24)	0.013
Model 3	93	17	6.4 (4.0-10.3)	96	32	15.1 (10.7-21.3)	1.98 (0.94-4.17)	0.072	1.11 (0.98-1.25)	0.094

Supplemental Table 7. Incremental value of LS in predicting cardiovascular outcomes (primary composite outcomes, CV death, incident HF hospitalization, and total number of HF hospitalizations) beyond clinical and echocardiographic variables among 249 patients with LVEF ≥55%. Clinical variables were: age, gender, race, randomization strata (prior HF hospitalization or biomarker criteria), region of enrollment (Americas versus Russia or Georgia), randomized treatment assignment, core lab LVEF, history of atrial fibrillation, heart rate, New York Heart Association class, history of stroke, creatinine, and hematocrit. Echocardiographic variables of LV structure were LV mass and LVESVi. Only individuals with no missing data for any clinical or echocardiographic variables were included.

	Base cross-validated C statistic	+LS cross-validated C statistic	P value	IDI (95% CI)	P value	NRI (95% CI)	P value
Primary (*events =61*)							
Clinical	0.70 (0.64-0.77)	0.75 (0.68-0.81)	0.026	6.7 (1.3-14.8)	0.016	27.7 (-1.4-47.1)	0.056
Clinical + structure	0.72 (0.66-0.79)	0.76 (0.70-0.83)	0.040	6.6 (1.1-13.8)	0.016	27.6 (2.8-48.4)	0.032
Clinical + structure + E/E'	0.73 (0.66-0.79)	0.76 (0.69-0.82)	0.14	5.6 (0.8-12.3)	0.016	26.6 (2.6-42.9)	0.020

CV death *(events = 31)*

Clinical	0.59 (0.48-0.71)	0.68 (0.56-0.80)	0.024	10.5 (2.2-22.5)	0.02	37.8 (12.2-60.6)	0.012
Clinical + structure	0.61 (0.49-0.72)	0.69 (0.57-0.81)	0.042	10.9 (2.2-22.8)	0.012	42.9 (10.0-62.4)	0.016
Clinical + structure + E/E'	0.57 (0.45-0.69)	0.70 (0.58-0.81)	0.015	12.7 (2.9-24.2)	0.02	41.3 (12.9-61.6)	0.012

HF Hosp *(events = 42)*

Clinical	0.74 (0.65-0.82)	0.76 (0.68-0.84)	0.20	6.2 (0.4-15.0)	0.032	29.7 (-2.1-49.0)	0.084
Clinical + structure	0.75 (0.67-0.83)	0.77 (0.70-0.85)	0.15	6.3 (0.3-14.0)	0.032	32.1 (-0.3-50.1)	0.052
Clinical + structure + E/E'	0.75 (0.67-0.83)	0.77 (0.69-0.85)	0.20	4.5 (0.0-10.7)	0.052	24.2 (-5.9-45.0)	0.11

Supplemental Table 8. Baseline clinical and echocardiographic characteristics among patients with both baseline and follow-up LS values by treatment group (spironolactone versus placebo) enrolled in the Americas or in Russia and Georgia.

	Americas			Russia/Georgia		
	Placebo (n=34)	Spirono (n=30)	P value	Placebo (n=36)	Spirono (n=31)	P value
Age (years)	73.6 ± 7.8	68.5 ± 10.2	0.02	68.9 ± 8.2	67.3 ± 8.6	0.42
Female	16 (47%)	13 (43%)	0.77	21 (58%)	17 (55%)	0.77
White	30 (88%)	20 (67%)	0.04	36 (100%)	31 (100%)	-
Enrollment Strata: Prior Hospitalization	15 (44%)	16 (53%)	0.46	30 (83%)	24 (77%)	0.54
Co-morbidities						
Hypertension	33 (97%)	28 (93%)	0.48	36 (100%)	26 (84%)	0.01

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Myocardial Infarction	8 (24%)	5 (17%)	0.50	13 (36%)	17 (55%)	0.12
Stroke	2 (6%)	3 (10%)	0.54	4 (11%)	6 (19%)	0.35
Atrial Fibrillation	20 (59%)	18 (60%)	0.92	13 (36%)	8 (26%)	0.36
Diabetes	14 (41%)	17 (57%)	0.22	4 (11%)	5 (16%)	0.55
Obesity	19 (56%)	23 (77%)	0.08	15 (42%)	14 (45%)	0.77
NYHA Functional Class			0.53			0.37
1	2 (6%)	3 (10%)		1 (3%)	2 (7%)	
2	20 (59%)	20 (67%)		19 (53%)	16 (52%)	
3	12 (35%)	7 (23%)		16 (44%)	11 (36%)	
4	0	0		0	2 (7%)	
Physical Characteristics						
BMI (kg/m^2)	32.3 ± 8.3	35.5 ± 8.5	0.13	29.9 ± 4.4	30.4 ± 4.1	0.66

Heart rate (bpm)	69.8 ± 10.3	63.7 ± 12.3	0.03	67.4 ± 11.9	64.7 ± 10.5	0.33
Systolic blood pressure (mmHg)	119.8 ± 15.9	124.3 ± 15.8	0.26	128.9 ± 10.7	128.4 ± 12.5	0.85
Laboratory Values						
eGFR (mL/min per 1.73 m^2)	61.5 ± 17.4	63.7 ± 22.3	0.65	73.1 ± 16.7	71.8 ± 16.0	0.75
Creatinine (mg/dL)	1.2 ± 0.3	1.2 ± 0.4	0.40	1.0 ± 0.2	1.0 ± 0. 2	0.51
Hematocrit (%)	38.0 ± 4.3	39.2 ± 3.7	0.23	40.2 ± 4.9	40.7 ± 4.8	0.66
Echocardiographic Findings						
LVEDVi (ml/m^2)	41.7 ± 10.6	48.4 ± 12.3	0.02	54.4 ± 19.8	59.5 ± 17.1	0.27
LVESVi (ml/m^2)	17.3 ± 7.3	18.1 ± 6.5	0.64	23.0 ± 14.2	27.2 ± 11.8	0.20
Mean WT (cm)	1.19 ± 0.26	1.18 ± 0.17	0.88	1.11 ± 0.13	1.08 ± 0.13	0.31
LV mass index (g/m^2)	103.9 ± 34.2	99.5 ± 25.8	0.57	102.7 ± 20.7	106.2 ± 25.8	0.54

LVH	14 (41%)	11 (37%)	0.71	15 (42%)	16 (52%)	0.42
RWT	0.53 ± 0.15	0.51 ± 0.09	0.51	0.47 ± 0.09	0.44 ± 0.08	0.10
LVEF (%)	59.4 ± 8.4	63.1 ± 5.9	0.05	59.9 ± 8.1	55.6 ± 8.3	0.04
e' (cm/sec)	6.4 ± 2.0	7.2 ± 2.5	0.19	5.4 ± 1.5	5.4 ± 1.5	0.98
E/e' (cm/sec)	15.8 ± 7.1	15.6 ± 7.3	0.89	13.9 ± 5.5	12.6 ± 3.1	0.27
LA volume (ml/m^2)	63.9 ± 21.5	63.2 ± 20.0	0.90	52.7 ± 19.4	57.4 ± 18.2	0.33

Supplemental Figure

Study Participants with LVEF ≥55 (N=259)