Prognostic Value of Albuminuria and Influence of Spironolactone in Heart Failure with Preserved Ejection Fraction: The TOPCAT Trial

Supplemental Material

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Supplementary Figure Legend

Supplementary Figure 1:

Title: *Treatment Effect of Spironolactone by Baseline Urinary Albumin to Creatinine Ratio for the Primary Outcome*

Caption: Interaction spline for the treatment effect (hazard ratio) of spironolactone is shown by baseline urinary albumin to creatinine ratio (mg/g) for the primary outcome of cardiovascular death, aborted cardiac arrest, or heart failure hospitalization. Spironolactone demonstrated a consistent effect across baseline urinary albumin to creatinine ratio (p=1.00).

Supplementary Figure 2:

Title: *Relationship between Change in Systolic Blood Pressure and Change in Albuminuria*

Caption: A linear relationship is demonstrated between change in systolic blood pressure and ratio of albuminuria between the 1-year and baseline visits, adjusted for baseline systolic blood pressure and baseline urinary albumin to creatinine ratio. P-value shown for linear trend.

Table S1. Characteristics of Participants with and without Baseline Albuminuria Measurements

	Missing Baseline UACR Measurements N=590		Available Baseline UACR Measurements N=1175		P-value*
Randomization to spironolactone, n (%)	288	(48.8%)	597	(50.8%)	0.43
Age, years	71 ± 10		72 ± 10		0.06
Female, n (%)	318	(53.9%)	562	(47.8%)	0.016
White race, n (%)	447	(75.8%)	936	(79.7%)	0.06
NYHA Class III or IV, n (%)	221	(37.6%)	398	(33.9%)	0.12
Enrollment through HF hospitalization stratum, n (%)	307	(52.0%)	668	(56.9%)	0.05
Physical Characteristics					
Systolic blood pressure, mmHg	128 ± 15		127 ± 16		0.72
Diastolic blood pressure, mmHg	71 ± 11		72 ± 12		0.2
Heart rate (beats/min)	69 ± 11		69 ± 11		0.63
Body mass index (kg/m^2)	34.2 ± 9.1		33.7 ± 8.1		0.26
Comorbidities, n (%)					
Hypertension	539	(91.7%)	1047	(89.1%)	0.09
Atrial fibrillation	198	(33.7%)	544	(46.3%)	0.001
Diabetes mellitus	272	(46.3%)	515	(43.8%)	0.33
Myocardial Infarction	124	(21.1%)	235	(20.0%)	0.59
COPD	101	(17.2%)	190	(16.2%)	0.59
Stroke	48	(8.2%)	110	(9.4%)	0.41
Peripheral artery disease	79	(13.4%)	128	(10.9%)	0.12
Chronic kidney disease	296	(50.2%)	558	(47.5%)	0.29
Current smoker	43	(7.3%)	73	(6.2%)	0.39
Medication Use, n (%)					
ACE-I and/or ARB	457	(77.6%)	936	(79.9%)	0.30
Beta-blocker	478	(81.2%)	907	(77.3%)	0.06
Calcium channel blocker	220	(37.4%)	461	(39.3%)	0.44
Diuretic	520	(88.3%)	1051	(89.5%)	0.43

Other anti-hypertensive medication	96 (16.3%)	198 (16.9%)	0.76
Statin	390 (66.2%)	758 (64.5%)	0.47
Laboratory Testing			
Estimated glomerular filtration rate (mL/min/1.78 m^2)	63 ± 22	65 ± 21	0.18
Hemoglobin (mg/dL)	12.7 ± 1.7	12.9 ± 1.7	0.004
Electrocardiographic and Imaging Data			
Ejection fraction (%)	58 ± 8	58 ± 7	0.30
ECG Left ventricular hypertrophy (%)	53 (12.4%)	114 (12.7%)	0.91

UACR, urine albumin to creatinine ratio; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; HF, heart failure.
*P-value shown for trend.

Table S2. **Crude and Adjusted Hazard Ratios for Efficacy and Safety Outcomes by Continuous Urinary Albumin to Creatinine Ratio**

Outcomes, n (%)	Hazard Ratio per Doubling of UACR (95% CI), P-value	Baseline Albuminuria x treatment interaction P-value
Composite endpoint		1.00
• Crude model	1.11 (1.07, 1.16), p<0.001	
• Multivariable adjusted model	1.08 (1.04, 1.13), p<0.001	
Cardiovascular mortality		0.68
• Crude model	1.07 (1.01, 1.13), p=0.019	
• Multivariable adjusted model	1.06 (1.00, 1.12), p=0.068	
HF hospitalization		0.91
• Crude model	1.14 (1.10, 1.20), p<0.001	
• Multivariable adjusted model	1.11 (1.06, 1.16), p<0.001	
All cause mortality		0.90
• Crude model	1.05 (1.01, 1.110, p=0.023	
• Multivariable adjusted model	1.05 (1.00, 1.10), p=0.041	
Doubling of creatinine		0.54
• Crude model	1.06 (1.00, 1.12), p=0.043	
• Multivariable adjusted model	1.04 (0.98, 1.10), p=0.19	
Hyperkalemia		0.29
• Crude model	1.11 (1.05, 1.16), p<0.001	
• Multivariable adjusted model	1.10 (1.04, 1.16), p=0.001	
Study drug discontinuation		0.22
• Crude model	1.04 (1.00, 1.07), p=0.32	
• Multivariable adjusted model	1.02 (0.99, 1.06), p=0.23	

CI, confidence interval; UACR, urinary albumin to creatinine ratio; HF, heart failure

Table S3. Ratio of Urinary Albumin to Creatinine Ratio at the 1-Year Visit vs. Baseline by Treatment Arm in Subgroup Analysis
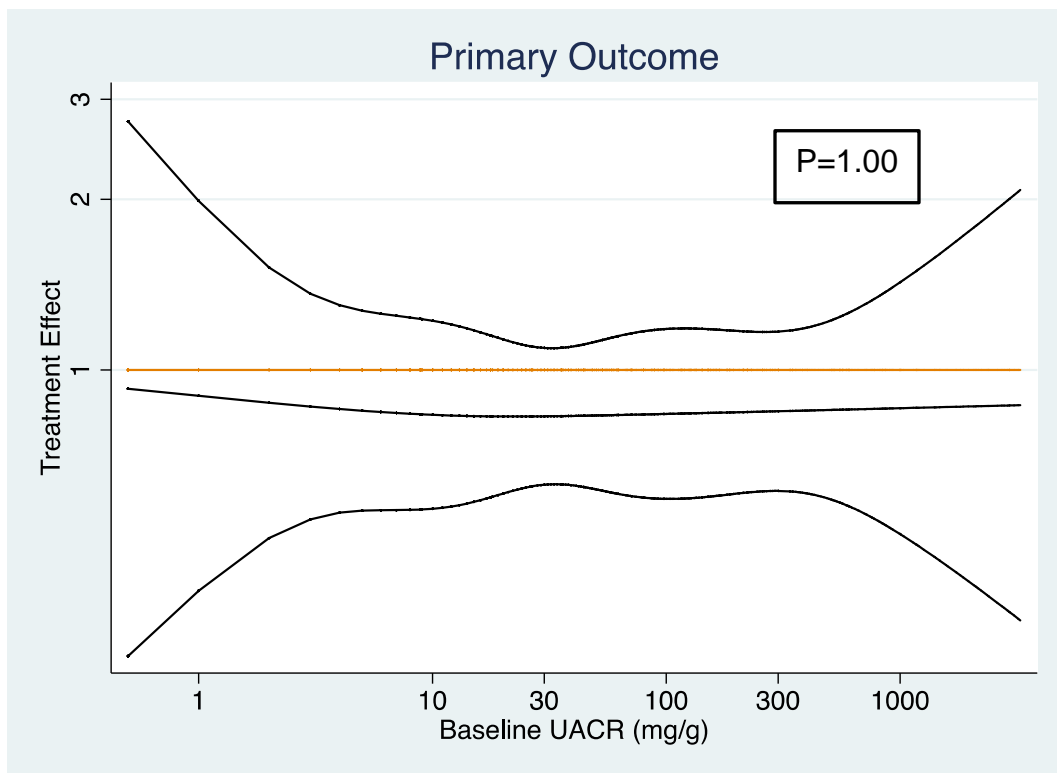
	Treatment Effect of Spironolactone vs. Placebo	
	Geometric Mean Ratio of 1-Year to Baseline UACR in Spironolactone Arm (95% CI), P-value	Geometric Mean Ratio of 1-Year to Baseline UACR in Placebo Arm (95% CI), P-value
All Patients	0.71 (0.58, 0.88), p=0.001	0.97 (0.83, 1.18), p=0.88
Albuminuria Status		
Normalbuminuria	1.39 (1.09, 1.77), p=0.008	1.97 (1.55, 2.51), p<0.001
Microalbuminuria	0.50 (0.38, 0.66), p<0.001	0.63 (0.49, 0.79), p<0.001
Macroalbuminuria	0.06 (0.02, 0.12), p<0.001	0.24 (0.14, 0.41), p<0.001

Table S4. Baseline Clinical and Laboratory Characteristics and Association with Change in Urinary Albumin to Creatinine Ratio at the 1-Year Visit after Multivariable Adjustment

	Percent Change	95% Confidence Interval	|Z|	P-value
Baseline UACR (per doubling)	+31%	+25%, +37%	11.82	<0.001
eGFR (per 10 ml/min/1.73m^2)	-9%	-14, -4%	3.19	0.001
Diabetes mellitus	+32%	+3%, +70%	2.21	0.028
Systolic blood pressure (per 10 mmHg)	+8%	-0%, +17%	1.84	0.07
Age (per year)	-1%	-3%, 0%	1.71	0.09
Female gender	-13%	-32%, +10%	1.19	0.24
Current smoker	+33%	-28%, +127%	1.03	0.30
Heart rate (per 10 beats per minute)	+5%	-5%, +17%	0.93	0.35
White race	+10%	-20%, +50%	0.57	0.57
NYHA class III or IV	+6%	-17%, +37%	0.48	0.63
ACE-I or ARB use	+1%	-25%, +36%	0.08	0.93

UACR, urinary albumin to creatinine ratio; ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate

Supplementary Figure 1.

Primary Outcome

P=1.00

Treatment Effect

Baseline UACR (mg/g)

Supplementary Figure 2.