

SUPPLEMENTAL MATERIAL

Table S1. Primary and secondary outcomes in HFpEF patients with or without traditional resistant hypertension*.

Event	Resistant hypertension (+)			Resistant hypertension (-)		
	Placebo n = 457	Spirolactone n = 451	P value	Placebo n = 1,263	Spirolactone n = 1,270	P value
Primary outcome events[†]						
No. of patients	117	82		231	238	
Event rate (per 1,000 person-year)	88.9	57.5		59.3	59.1	
HR (95% CI)	1.00 (ref)	0.66 (0.50–0.88)	0.004	1.00 (ref)	1.01 (0.84–1.21)	0.90
All-cause death						
No. of patients	73	42		200	214	
Event rate (per 1,000 person-year)	48.5	27.1		46.9	50.2	
HR (95% CI)	1.00 (ref)	0.56 (0.38–0.82)	0.002	1.00 (ref)	1.07 (0.88–1.30)	0.47
Cardiovascular death						
No. of patients	44	24		132	136	
Event rate (per 1,000 person-year)	29.2	15.5		30.9	31.9	
HR (95% CI)	1.00 (ref)	0.53 (0.32–0.87)	0.01	1.00 (ref)	1.03 (0.81–1.31)	0.78
Non-cardiovascular death						
No. of patients	29	18		68	78	
Event rate (per 1,000 person-year)	19.3	11.6		15.9	18.3	
HR (95% CI)	1.00 (ref)	0.60 (0.33–1.09)	0.09	1.00 (ref)	1.15 (0.83–1.59)	0.40
Hospitalization for heart failure						
No. of patients	94	70		151	136	
Event rate (per 1,000 person-year)	71.2	49.1		37.6	33.8	
HR (95% CI)	1.00 (ref)	0.71 (0.52–0.96)	0.02	1.00 (ref)	0.89 (0.71–1.13)	0.34
Major cardiovascular events[‡]						
No. of patients	68	48		196	193	
Event rate (per 1,000 person-year)	46.9	31.8		47.3	46.3	
HR (95% CI)	1.00 (ref)	0.68 (0.47–0.99)	0.04	1.00 (ref)	0.98 (0.80–1.19)	0.83
Myocardial infarction						
No. of patients	18	18		46	47	
Event rate (per 1,000 person-year)	12.3	11.8		11.0	11.3	

HR (95% CI)	1.00 (ref)	0.98 (0.51–1.88)	0.94	1.00 (ref)	1.02 (0.68–1.53)	0.92
Stroke						
No. of patients	13	16		47	41	
Event rate (per 1,000 person-year)	8.8	10.5		11.2	9.8	
HR (95% CI)	1.00 (ref)	1.22 (0.59–2.54)	0.59	1.00 (ref)	0.87 (0.57–1.32)	0.50

*Data are presented as number or hazard ratio (95% confidence interval). Bold font denotes significance.

†The primary outcome was a composite of cardiovascular death, aborted cardiac arrest, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for the management of heart failure.

‡Major cardiovascular events included cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

HFpEF, heart failure with preserved left ventricular ejection fraction; HR, hazard ratio; CI, confidence interval.

Table S2. Primary and secondary outcomes in HFpEF patients with uncontrolled blood pressure despite the concurrent use of an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, a calcium channel blocker, and a diuretic*.

	Placebo n = 353	Spirolactone n = 343	P value
Event			
Primary outcome events[†]			
No. of patients	70	49	
Event rate (per 1,000 person-year)	63.9	43.1	
HR (95% CI)	1.00 (ref)	0.68 (0.47–0.98)	0.04
All-cause death			
No. of patients	38	27	
Event rate (per 1,000 person-year)	31.3	22.6	
HR (95% CI)	1.00 (ref)	0.72 (0.44–1.18)	0.19
Cardiovascular death			
No. of patients	26	17	
Event rate (per 1,000 person-year)	21.4	14.2	
HR (95% CI)	1.00 (ref)	0.66 (0.36–1.22)	0.18
Non-cardiovascular death			
No. of patients	12	10	
Event rate (per 1,000 person-year)	9.9	8.4	
HR (95% CI)	1.00 (ref)	0.84 (0.36–1.96)	0.69
Hospitalization for heart failure			
No. of patients	57	36	
Event rate (per 1,000 person-year)	52.0	31.6	
HR (95% CI)	1.00 (ref)	0.62 (0.41–0.94)	0.02
Major cardiovascular events[‡]			
No. of patients	38	35	
Event rate (per 1,000 person-year)	31.9	30.2	
HR (95% CI)	1.00 (ref)	0.95 (0.60–1.50)	0.81
Myocardial infarction			
No. of patients	8	13	

Event rate (per 1,000 person-year)	6.7	11.1	
HR (95% CI)	1.00 (ref)	1.68 (0.69–4.05)	0.25
Stroke			
No. of patients	9	10	
Event rate (per 1,000 person-year)	7.5	8.5	
HR (95% CI)	1.00 (ref)	1.14 (0.46–2.80)	0.78

*Data are presented as number or hazard ratio (95% confidence interval). Uncontrolled blood pressure was defined as systolic blood pressure ≥ 130 mm Hg and/or diastolic blood pressure ≥ 80 mm Hg. Bold font denotes significance.

[†]The primary outcome was a composite of cardiovascular death, aborted cardiac arrest, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for the management of heart failure.

[‡]Major cardiovascular events included cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. HFpEF, heart failure with preserved left ventricular ejection fraction; HR, hazard ratio; CI, confidence interval.

Table S3. Primary and secondary outcomes in HFpEF patients from the Americas with or without resistant hypertension*.

Event	Resistant hypertension (+)			Resistant hypertension (-)		
	Placebo n = 284	Spiro n = 270	P value	Placebo n = 595	Spiro n = 615	P value
Primary outcome events[†]						
No. of patients	105	73		175	169	
Event rate (per 1,000 person-year)	156.0	102.4		112.6	103.0	
HR (95% CI)	1.00 (ref)	0.66 (0.48–0.89)	0.006	1.00 (ref)	0.92 (0.74–1.13)	0.50
All-cause death						
No. of patients	66	35		139	146	
Event rate (per 1,000 person-year)	78.7	42.5		78.9	79.4	
HR (95% CI)	1.00 (ref)	0.53 (0.35–0.80)	0.002	1.00 (ref)	1.00 (0.79–1.26)	0.96
Cardiovascular death						
No. of patients	37	18		90	78	
Event rate (per 1,000 person-year)	44.1	21.9		51.1	42.4	
HR (95% CI)	1.00 (ref)	0.49 (0.27–0.86)	0.01	1.00 (ref)	0.83 (0.61–1.12)	0.23
Non-cardiovascular death						
No. of patients	29	17		49	68	
Event rate (per 1,000 person-year)	34.6	20.7		27.8	36.9	
HR (95% CI)	1.00 (ref)	0.58 (0.32–1.07)	0.08	1.00 (ref)	1.32 (0.91–1.90)	0.13
Hospitalization for heart failure						
No. of patients	87	65		129	134	
Event rate (per 1,000 person-year)	128.4	91.2		82.7	72.5	
HR (95% CI)	1.00 (ref)	0.72 (0.51–0.98)	0.04	1.00 (ref)	0.88 (0.68–1.13)	0.30
Major cardiovascular events[‡]						
No. of patients	57	37		132	115	
Event rate (per 1,000 person-year)	72.0	46.5		78.8	64.5	
HR (95% CI)	1.00 (ref)	0.65 (0.42–0.97)	0.03	1.00 (ref)	0.82 (0.64–1.05)	0.11
Myocardial infarction						
No. of patients	17	14		29	34	

Event rate (per 1,000 person-year)	21.3	17.5		17.0	19.2	
HR (95% CI)	1.00 (ref)	0.83 (0.40–1.67)	0.59	1.00 (ref)	1.11 (0.68–1.84)	0.65
Stroke						
No. of patients	10	13		29	25	
Event rate (per 1,000 person-year)	12.2	16.1		17.0	13.8	
HR (95% CI)	1.00 (ref)	1.33 (0.58–3.03)	0.49	1.00 (ref)	0.81 (0.47–1.38)	0.43

*Data are presented as number or hazard ratio (95% confidence interval). Bold font denotes significance.

†The primary outcome was a composite of cardiovascular death, aborted cardiac arrest, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for the management of heart failure.

‡Major cardiovascular events included cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

HFpEF, heart failure with preserved left ventricular ejection fraction; HR, hazard ratio; CI, confidence interval.

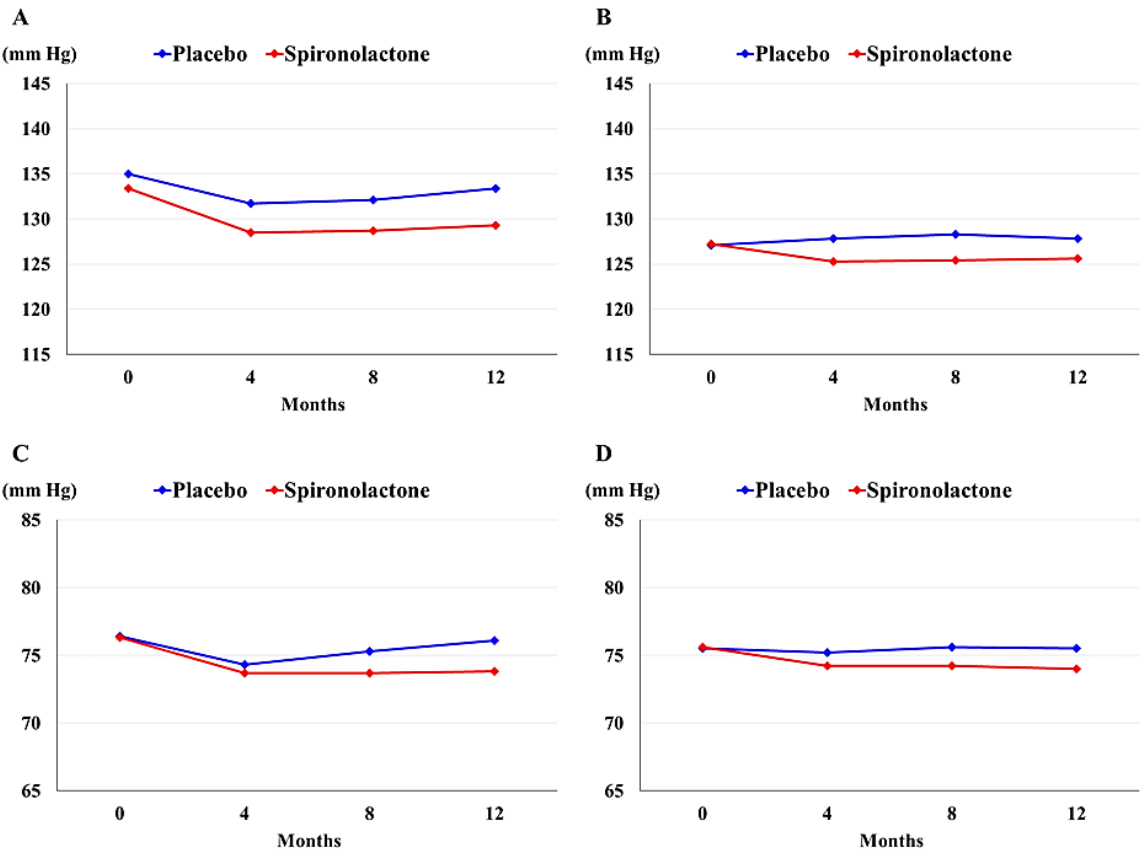
Table S4. Spironolactone use and study discontinuation in HFpEF patients with or without resistant hypertension*.

	Resistant hypertension (+)			Resistant hypertension (-)		
	Placebo n = 499	Spironolactone n = 505	P value	Placebo n = 1,221	Spironolactone n = 1,216	P value
Serum potassium ≥ 5.5 mmol/L on lowest spironolactone dose (15 mg)						
No. of patients	4	40		16	62	
Event rate (per 1,000 person-year)	3.0	30.0		4.7	19.6	
HR (95% CI)	1.00 (ref)	9.97 (3.57–27.88)	<0.001	1.00 (ref)	4.00 (2.31–6.94)	<0.001
Serious hyperkalemia						
No. of patients	2	17		15	29	
Event rate (per 1,000 person-year)	1.5	12.7		4.4	9.2	
HR (95% CI)	1.00 (ref)	8.66 (2.00–37.50)	0.003	1.00 (ref)	2.02 (1.08–3.77)	0.02
Breast tenderness or enlargement						
No. of patients	1	9		4	34	
Event rate (per 1,000 person-year)	0.7	6.7		1.2	10.7	
HR (95% CI)	1.00 (ref)	9.15 (1.16–72.23)	0.03	1.00 (ref)	8.86 (3.14–24.97)	0.34
Anaphylactoid reaction or intolerance[†]						
No. of patients	2	1		8	5	
Event rate (per 1,000 person-year)	1.5	0.7		2.4	1.6	
HR (95% CI)	1.00 (ref)	0.49 (0.04–5.46)	0.56	1.00 (ref)	0.63 (0.21–1.94)	0.42

*Data are presented as number or hazard ratio (95% confidence interval). Serious hyperkalemia was defined as potassium ≥ 6.0 mmol/L based on a non-hemolyzed sample.

[†]None were anaphylactoid reaction.

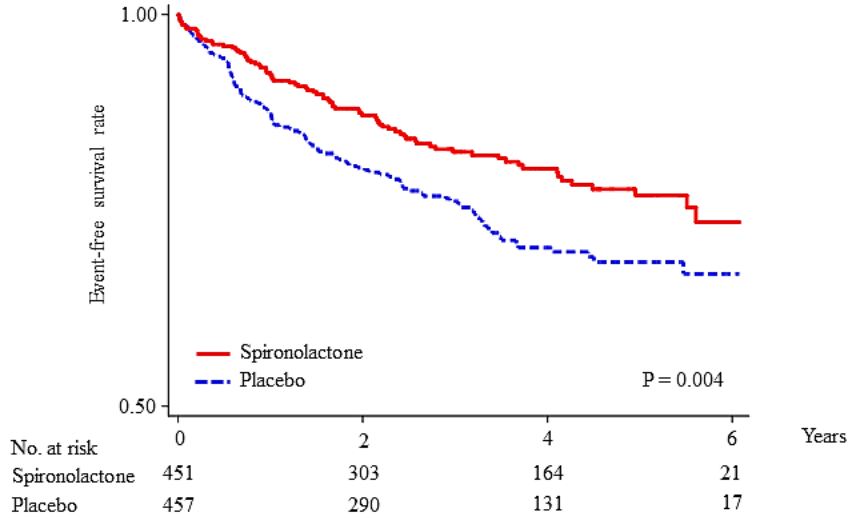
Figure S1. Mean systolic and diastolic blood pressure levels during follow-up in HFpEF patients with and without resistant hypertension.



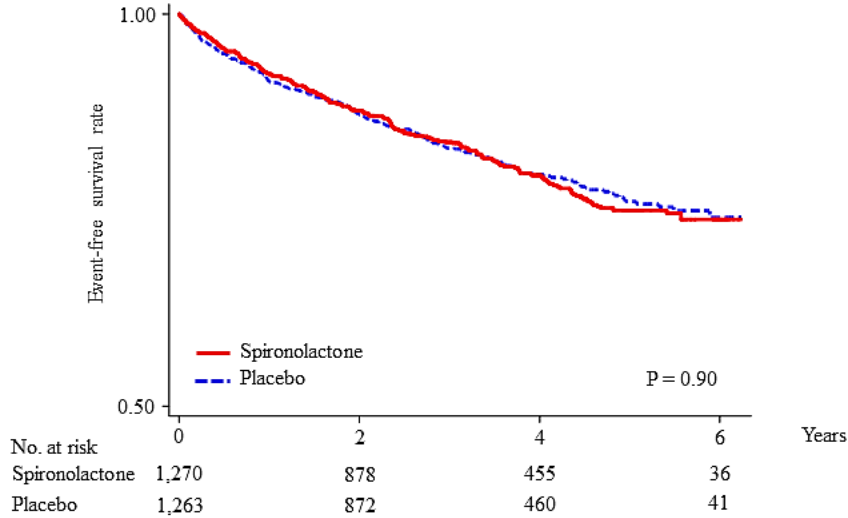
Mean systolic and diastolic blood pressure levels during follow-up in HFpEF patients, with (A and C) and without (B and D) resistant hypertension. HFpEF, heart failure with preserved ejection fraction.

Figure S2. Kaplan–Meier survival curves for primary outcome in HFpEF patients with or without traditional resistant hypertension.

A. Primary outcome events in patients with resistant hypertension



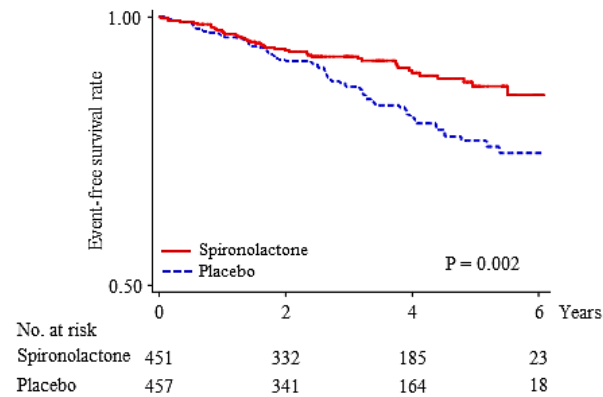
B. Primary outcome events in patients without resistant hypertension



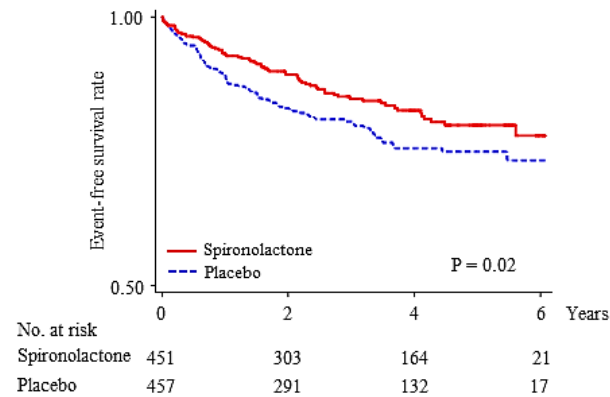
Rates of freedom from primary outcome events in HFpEF patients, with (A) and without (B) traditional resistant hypertension. The primary outcome was a composite of cardiovascular death, aborted cardiac arrest, or hospitalization for heart failure. HFpEF, heart failure with preserved ejection fraction.

Supplemental Figure 3. Kaplan–Meier survival curves for all-cause death and heart failure hospitalization in HFpEF patients with or without traditional resistant hypertension.

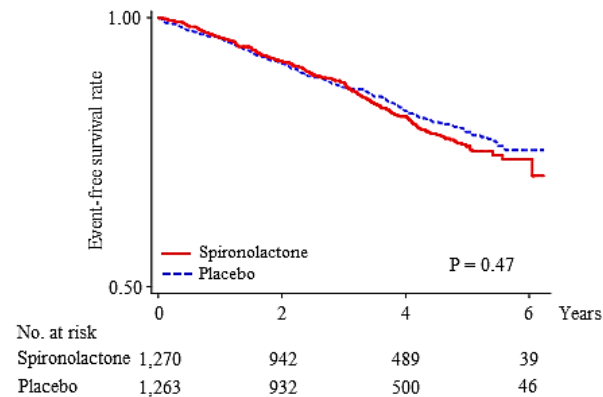
A. All-cause death in patients with resistant hypertension



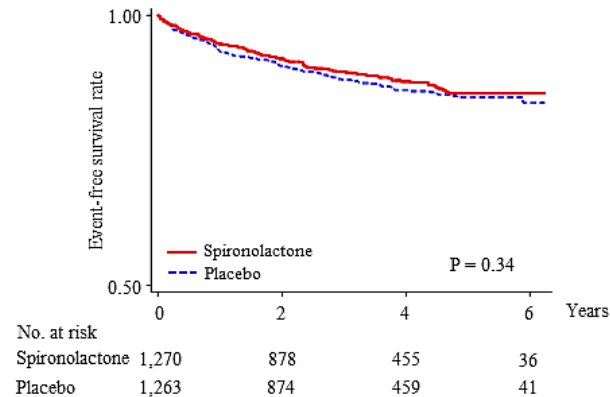
B. Hospitalization for HF in patients with resistant hypertension



C. All-cause death in patients without resistant hypertension



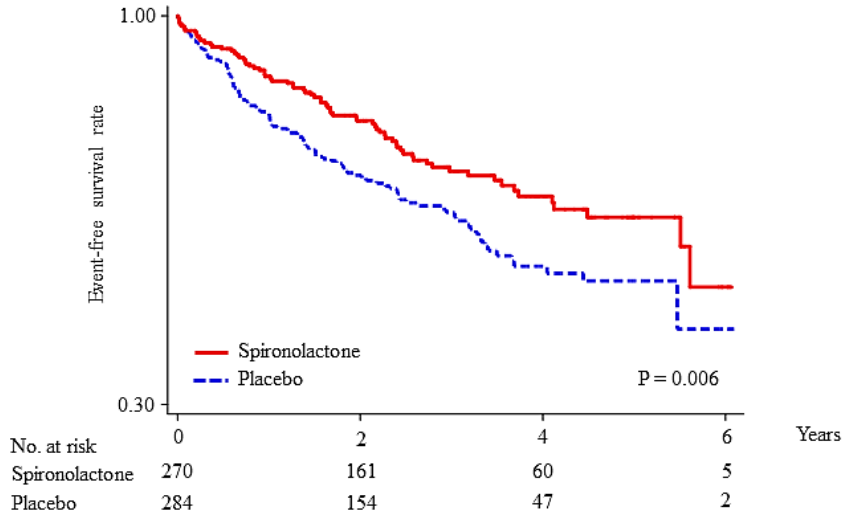
D. Hospitalization for HF in patients without resistant hypertension



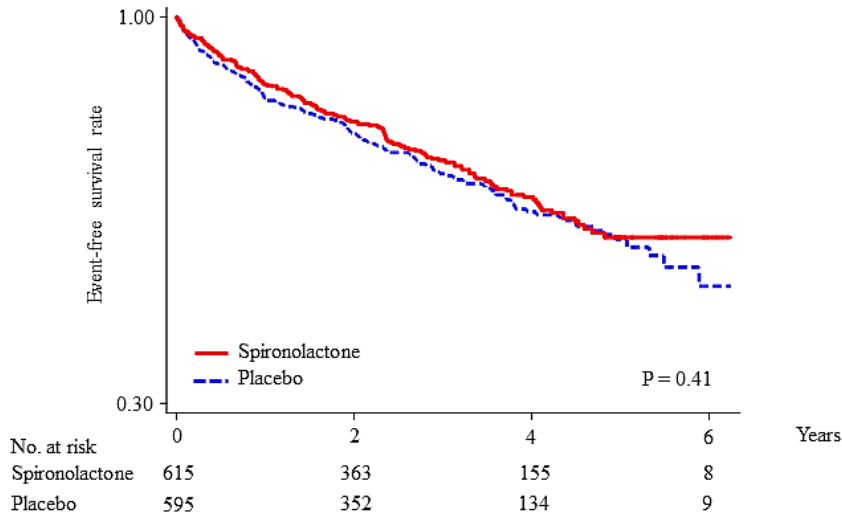
Rates of freedom from all-cause death (A and C) and hospitalization for heart failure (B and D). HFpEF, heart failure with preserved ejection fraction; HF, heart failure.

Figure S4. Kaplan–Meier survival curves for primary outcome in HFpEF patients from the Americas with or without resistant hypertension.

A. Primary outcome in patients from the Americas with resistant hypertension



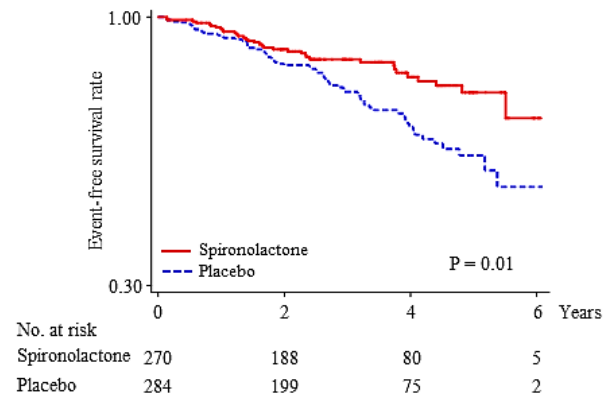
B. Primary outcome in patients from the Americas without resistant hypertension



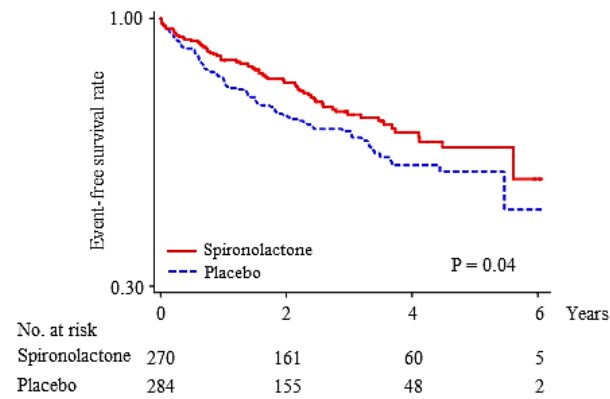
Rates of freedom from primary outcome events in HFpEF patients from Americas, with (A) and without (B) resistant hypertension. The primary outcome was a composite of cardiovascular death, aborted cardiac arrest, or hospitalization for heart failure. HFpEF, heart failure with preserved ejection fraction.

Figure S5. Kaplan–Meier survival curves for all-cause death and heart failure hospitalization in HFpEF patients from the Americas with or without resistant hypertension.

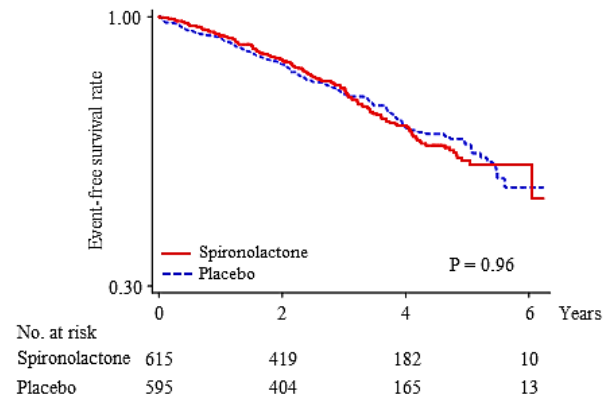
A. All-cause death in patients with resistant hypertension



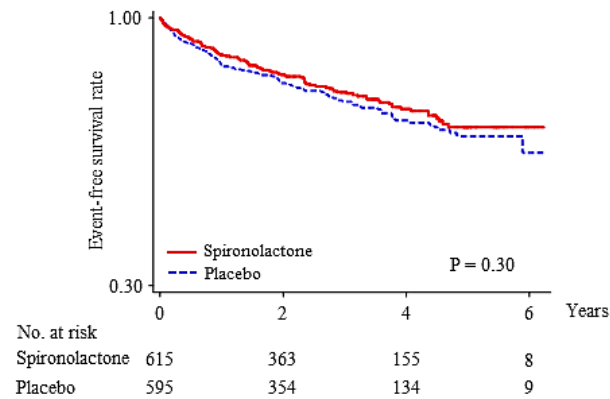
B. Hospitalization for HF in patients with resistant hypertension



C. All-cause death in patients without resistant hypertension



D. Hospitalization for HF in patients without resistant hypertension



Rates of freedom from all-cause death (A and C) and hospitalization for heart failure (B and D). HFpEF, heart failure with preserved ejection fraction; HF, heart failure.