Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT)

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AHA Nov 18, 2013
Late Breaking Session

Marc A. Pfeffer MD, PhD, on behalf of the TOPCAT Investigators

TOPCAT Trial Executive Committee

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ClinTrials.gov NCT00094302

HHS Contract # HHSN268200425207C

NIH National Heart, Lung, and Blood Institute

neri New England Research Institutes

BWH BRIGHAM AND WOMEN'S HOSPITAL

MRAs Beneficial in HFrEF and Post-MI LVD

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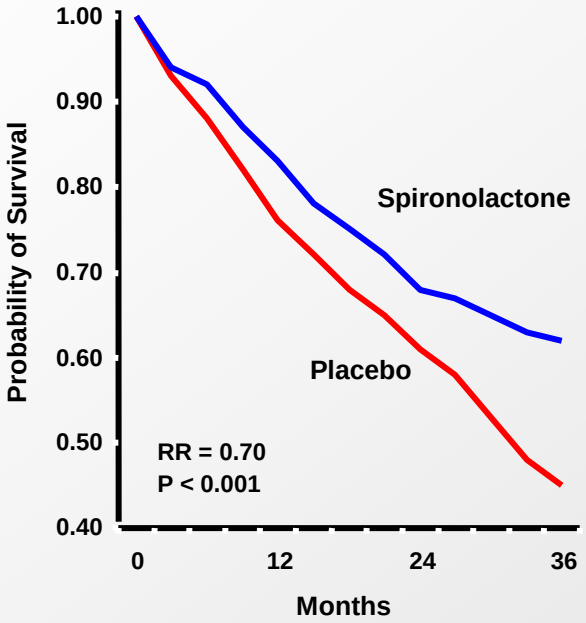
RALES
(Severe HFrEF)

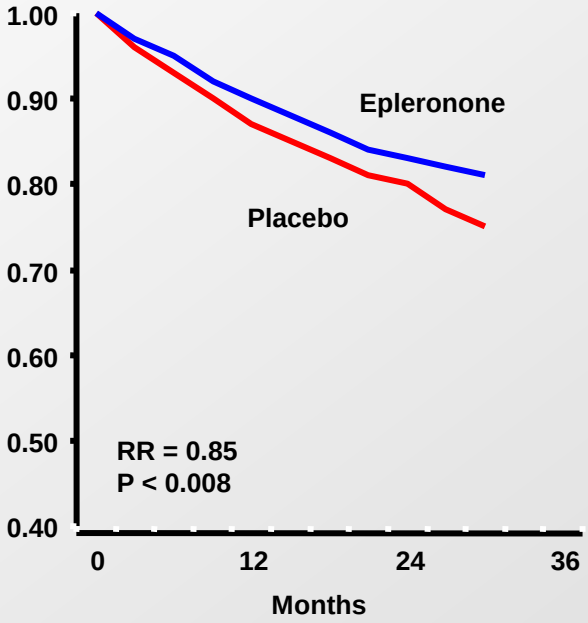
30% Risk Reduction



Pitt NEJM 1999

EPHESUS
(Post-MI)

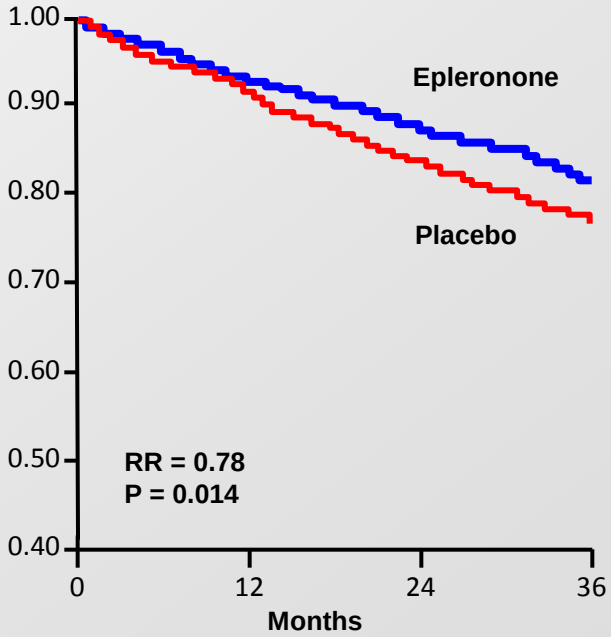
15% Risk Reduction



Pitt NEJM 2003

EMPHASIS
(Mild HFrEF)

22% Risk Reduction



Zannad NEJM 2011

Reviews of Mechanisms : Pitt Heart Fail Rev 2012; Kamalov,…,Weber JCV Pharm 2013

Treatment **O**f **P**reserved **C**ardiac Function Heart Failure with an **A**ldosterone an**T**agonist **(TOPCAT)**

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- **Objective**
  - To determine if treatment with spironolactone can produce a clinically meaningful reduction in the composite endpoint of cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of heart failure, compared with placebo, in adults with HF-Preserved EF.
- **Inclusions:**

  Symptomatic Heart Failure, Age ≥ 50, LVEF ≥ 45%, stratified according to:
  - Hospitalization within the past year for management of heart failure, or
  - Elevated natriuretic peptides (BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL)
- **Major Exclusions:**

  eGFR<30 mL/min/1.7m^2, serum potassium ≥5 mmol/L, uncontrolled hypertension, AF with rate > 90/min, recent ACS, restrictive, infiltrative, or hypertrophic cardiomyopathy

Rationale and design: (A. Desai, Am Heart J 2011)

Design / Statistical Considerations

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- **International (6) multi-center (270), double-blind, placebo-controlled randomized trial**
- **Randomization, 1:1 within each stratum, to either**
  - Spironolactone, 15, 30, 45 mg daily, or matching placebo
- **80% power to detect a 20% relative reduction in primary events (CVD, HF hosp, or aborted cardiac arrest): 551 adjudicated primary events (approximately 3,515 subjects)**
  - Assuming 3-year placebo primary outcome rate of 17.4%
  - Log-rank test, two-sided $p<0.05$, ITT

A.Desai Am Heart J 2011

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Baseline

*Variable**	Spironolactone N = 1722	Placebo N = 1723
NYHA Class		
II	63.3%	64.3%
III	33.0%	32.2%
LVEF %	56 (51, 61)	56 (51, 62)
Stratum		
Hosp. for HF	71.5%	71.5%
Natriuretic Peptide**	28.5%	28.5%
Age	69 (61, 76)	69 (61, 76)
Female	52%	51%
Hypertension	91%	92%
Coronary Artery Disease	57%	60%
Myocardial Infarction	26%	26%
Stroke	7%	8%
Atrial Fibrillation	35%	35%
Diabetes Mellitus	33%	32%
Smoking (current)	10%	11%

*Reported as % or median (Q1, Q3)

**(BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL)

S. Shah Circ HF 2012

Baseline (2)

*Variable**	Spironolactone N = 1722	Placebo N = 1723
Systolic Blood Pressure	130 (120, 139)	130 (120, 140)
Diastolic Blood Pressure	80 (70, 80)	80 (70, 80)
Heart Rate	68 (62, 76)	68 (62, 76)
BMI (kg/m^2)	31 (27, 36)	31 (27, 36)
eGFR ($ml/min/1.73m^2$) < 60 ($ml/min/1.73m^2$)	65 (54, 79) 39%	66 (54, 79) 38%
Serum Potassium (mEq/L)	4.3 (4.0, 4.6)	4.3 (4.0, 4.6)
Hemoglobin (g/dl)	13.2 (12.1, 14.4)	13.3 (12.2, 14.5)
Medications		
ACE-I or ARB	84%	84%
Beta-blocker	78%	77%
Diuretic	81%	82%
Statin	53%	52%
Anticoagulant	23%	22%

*Reported as % or median (Q1, Q3)

A. Shah Circ HF 2013 (echo)
S. Shah Circ HF 2012 (baseline)

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Patient Participation

Randomized: N=3445; **Mean follow-up:** 3.3 years

US (1,151); **Russia** (1,066); **Rep. of Georgia** (612);
Canada (326); **Brazil** (167); **Argentina** (123)

Mean Dose at 8 months: spironolactone 25 mg; placebo 28 mg

Spironolactone N=1,722

% discontinued study medication:
1 year: 17.0%
2 year: 25.1%
End: 34.3%

Vital status unknown: 67 (3.9%)

Placebo N=1,723

% discontinued study medication:
1 year: 13.5%
2 year: 20.1%
End: 31.4%

Vital status unknown: 65 (3.8%)

1° Outcome
(CV Death, HF Hosp, or Resuscitated Cardiac Arrest)

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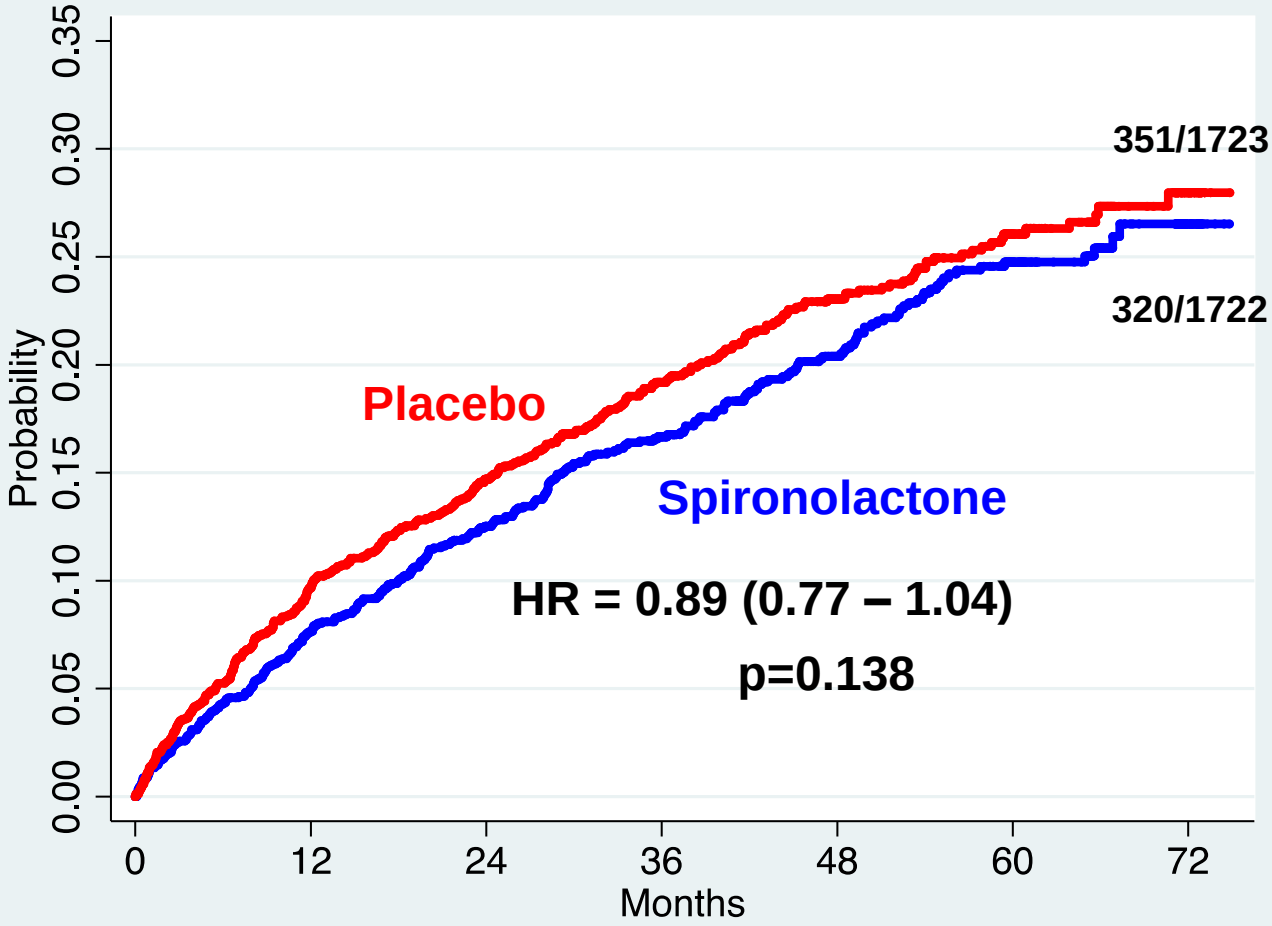

Number at risk

Spiro	1722	1502	1168	870	614	330	53
Placebo	1723	1462	1145	834	581	331	53

1° and Components

Outcome	# and % of Subjects with Event, and Event Rate		Hazard Ratio (95% CI) p-value
	Spironolactone (N = 1722)	Placebo (N = 1723)	
Primary Outcome	**320 (18.6%)** 5.9/100pt-yr	**351 (20.4%)** 6.6/100pt-yr	**0.89** (0.77-1.04) P=0.138
Primary Components			
CV Mortality	**160 (9.3%)** 2.8/100pt-yr	**176 (10.2%)** 3.1/100pt-yr	**0.90** (0.73-1.12) P=0.354
Aborted Cardiac Arrest	**3 (<1%)** 0.05/100pt-yr	**5 (<1%)** 0.09/100pt-yr	**0.60** (0.14-2.50) P=0.482
Hospitalization for Heart Failure	**206 (12.0%)** 3.8/100pt-yr	**245 (14.2%)** 4.6/100pt-yr	**0.83** (0.69-0.99) P=0.042

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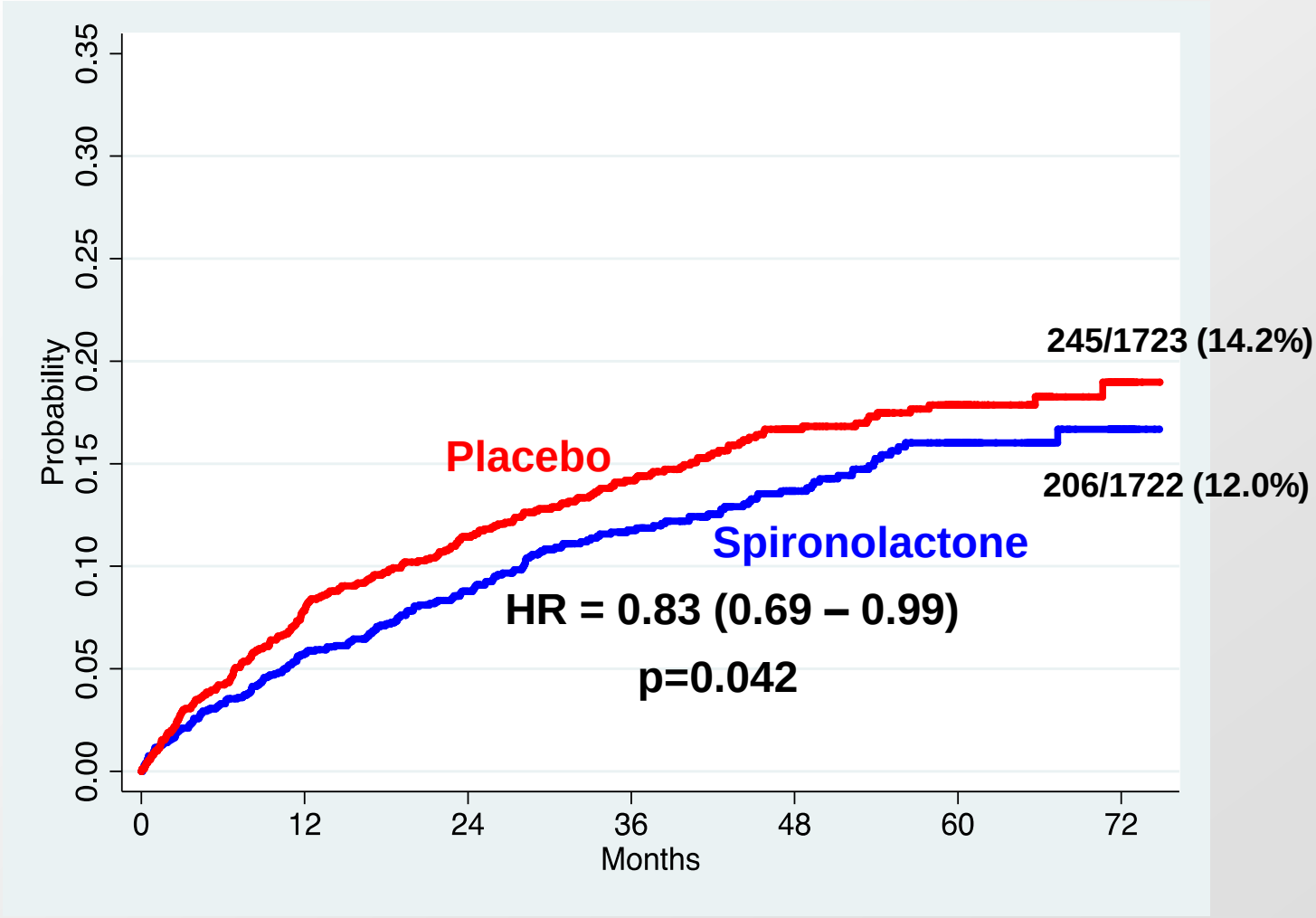
Heart Failure Hospitalizations



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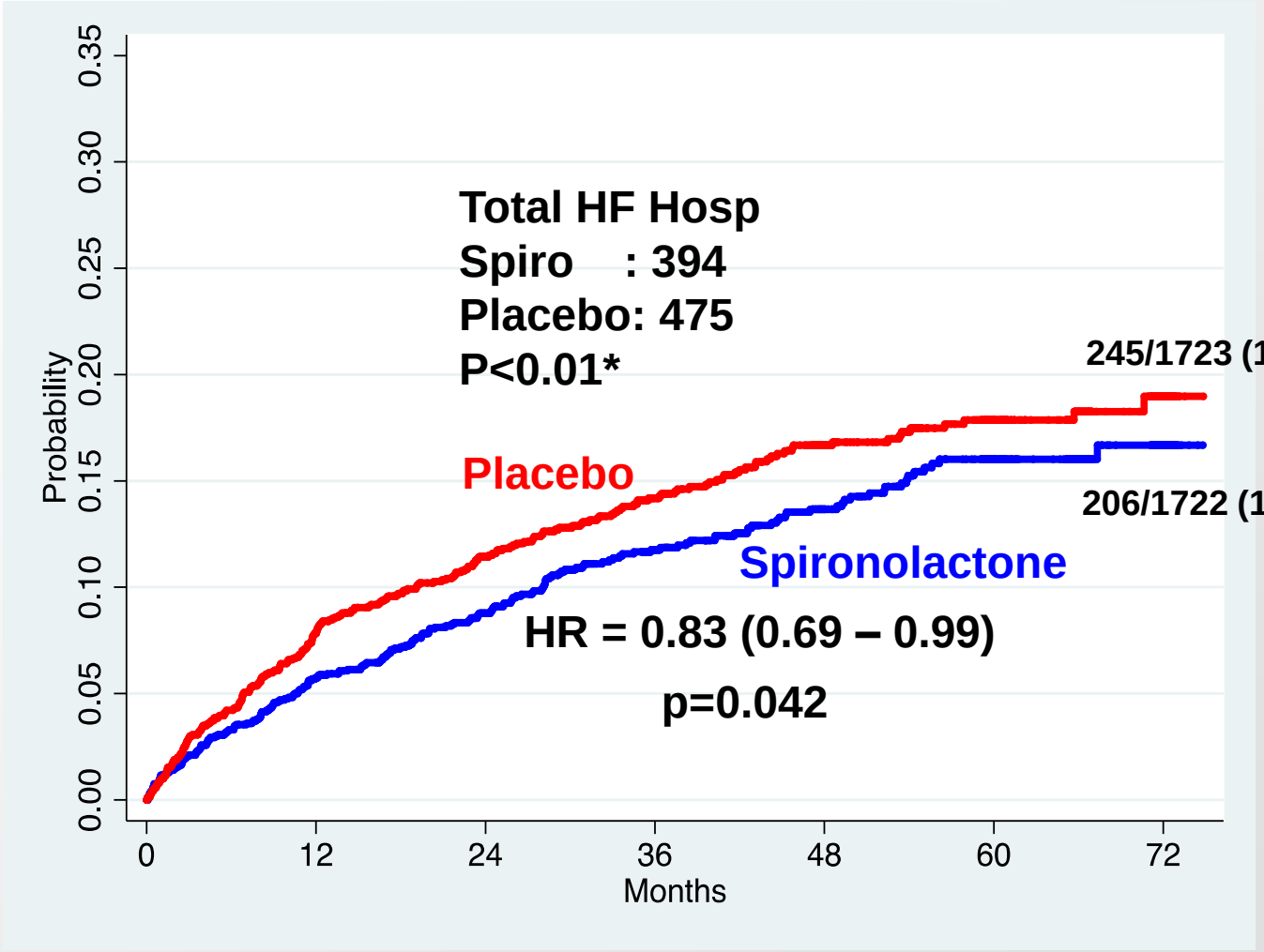
Heart Failure Hospitalizations



*poisson regression

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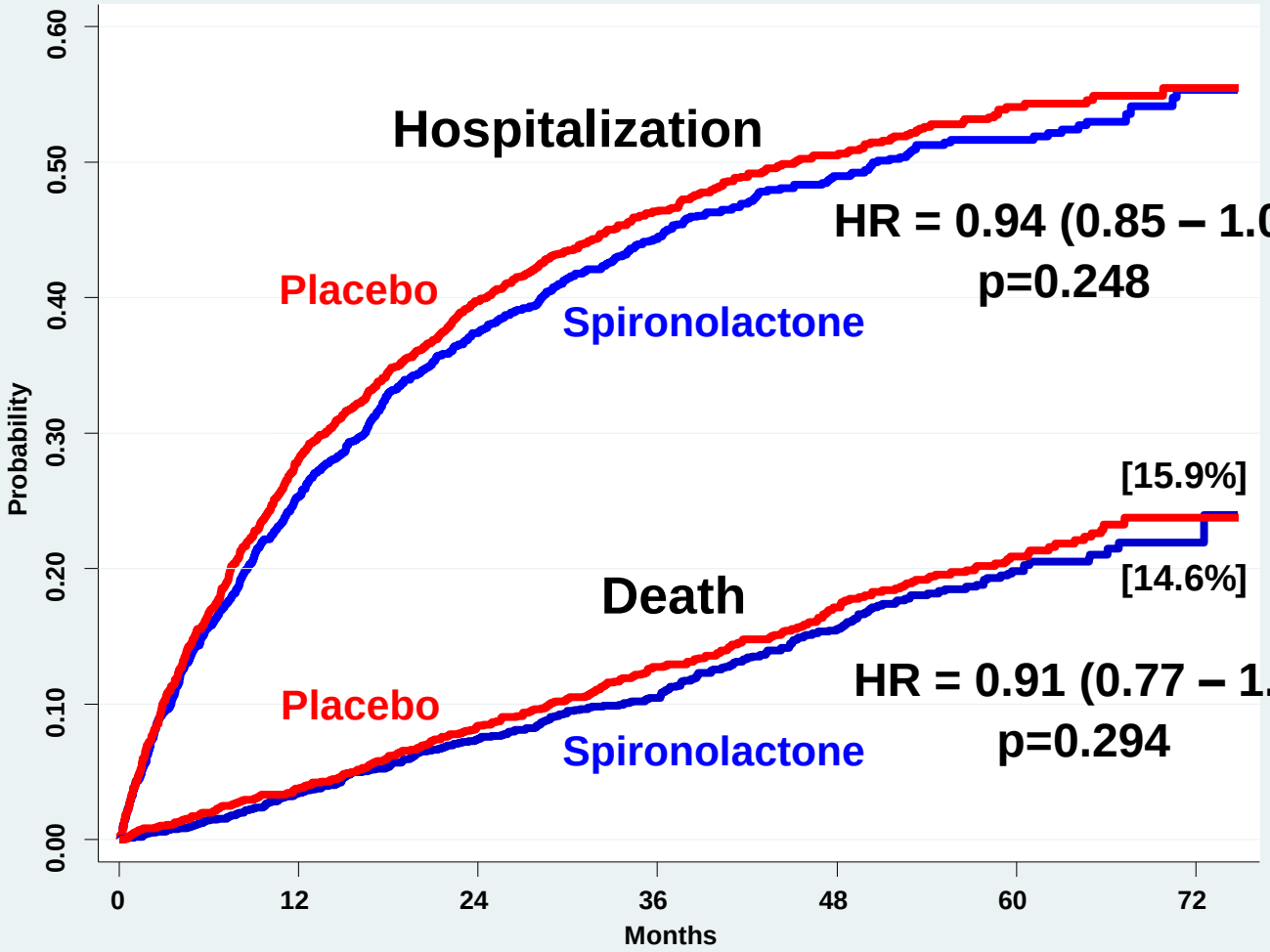
Deaths, Hospitalization – all causes



Serious Adverse Events (SAEs)

No significant differences were found in either:

- **The number of patients**
  - spironolactone 835 (48.5%) vs. placebo 855 (49.6%)

  or

- **The total reports of SAEs**
  - spironolactone 2395 vs. placebo 2387

However, . . .

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Serum Potassium*

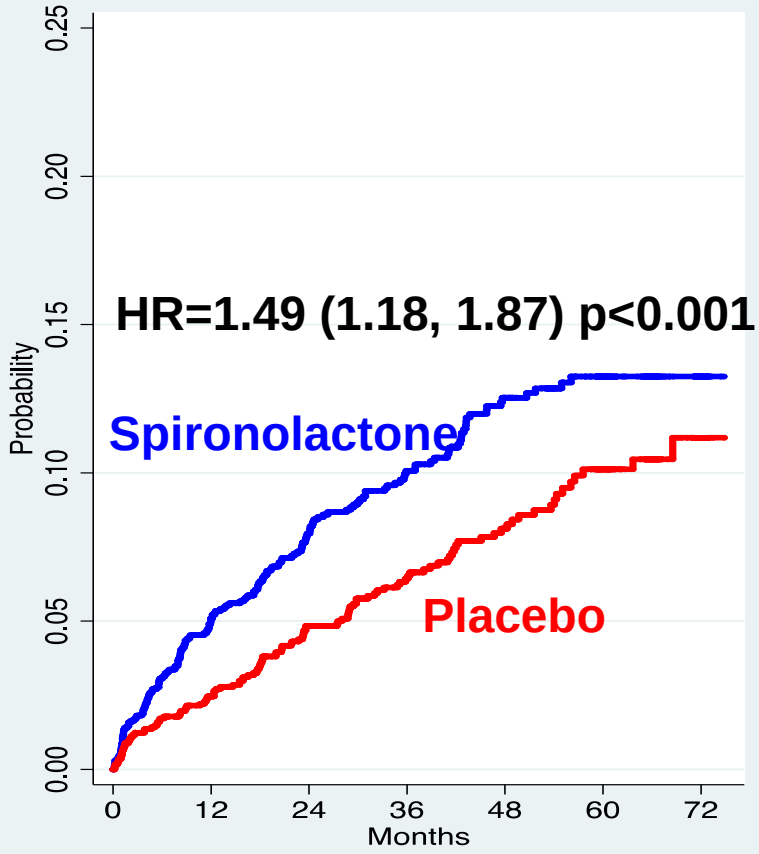
Potassium	Spiro	Placebo	P (chi-sq)
Hyperkalemia (≥ 5.5 mmol/L)	**322** (18.7%)	**157** (9.1%)	**<0.001**
Hypokalemia (<3.5 mmol/L)	**279** (16.2%)	**394** (22.9%)	**<0.001**

No deaths related to hyperkalemia were reported.

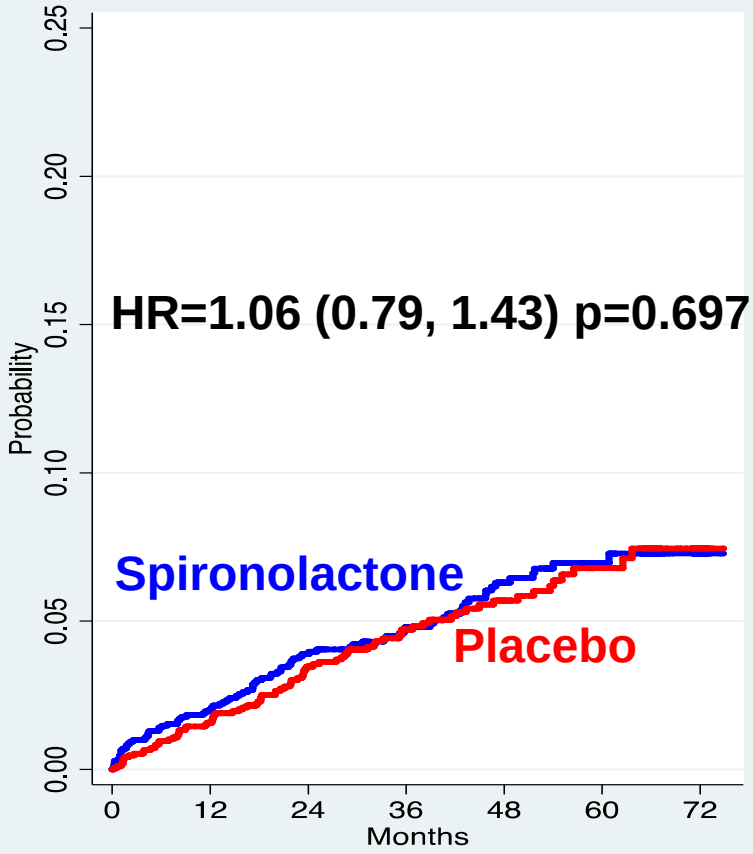
***Monitoring at each dose change and visit (algorithm in Desai Am Heart J 2011)**

Creatinine

Doubling above ULN

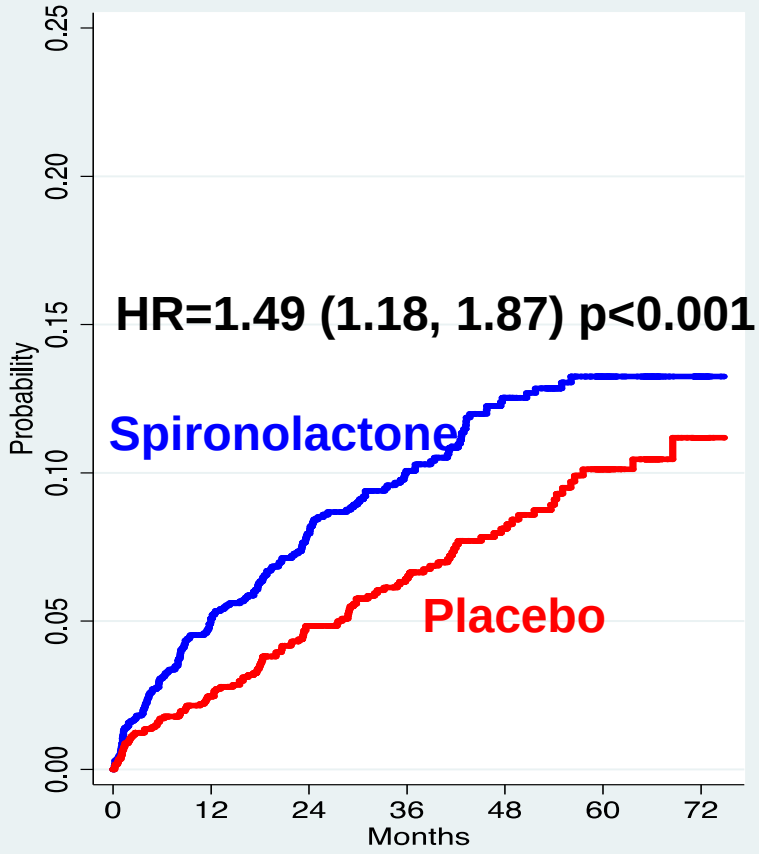


At least 3.0 mg/dl (265 ug/L)



Creatinine

Doubling above ULN



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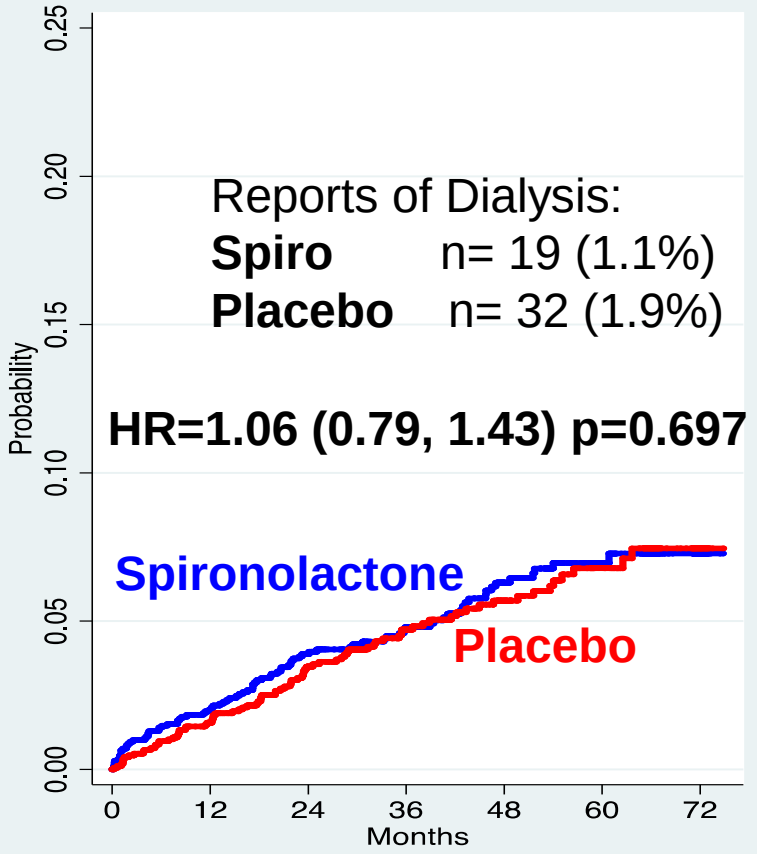

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Subgroups

Of 22 pre-specified, only 1 - Stratum - showed a significant interaction with treatment

Enrolled by:	Spiro	Placebo	Hazard Ratio (95% CI) P-value
Natriuretic peptide	**78/490** (15.9%)	**116/491** (23.6%)	**0.65** (0.49-0.87) **0.003**
Heart Failure Hosp	**242/1232** (19.6%)	**235/1232** (19.1%)	**1.01** (0.84-1.21) **0.923**

***P=0.013 for interaction**

Placebo Rates:

Primary Outcome, by region

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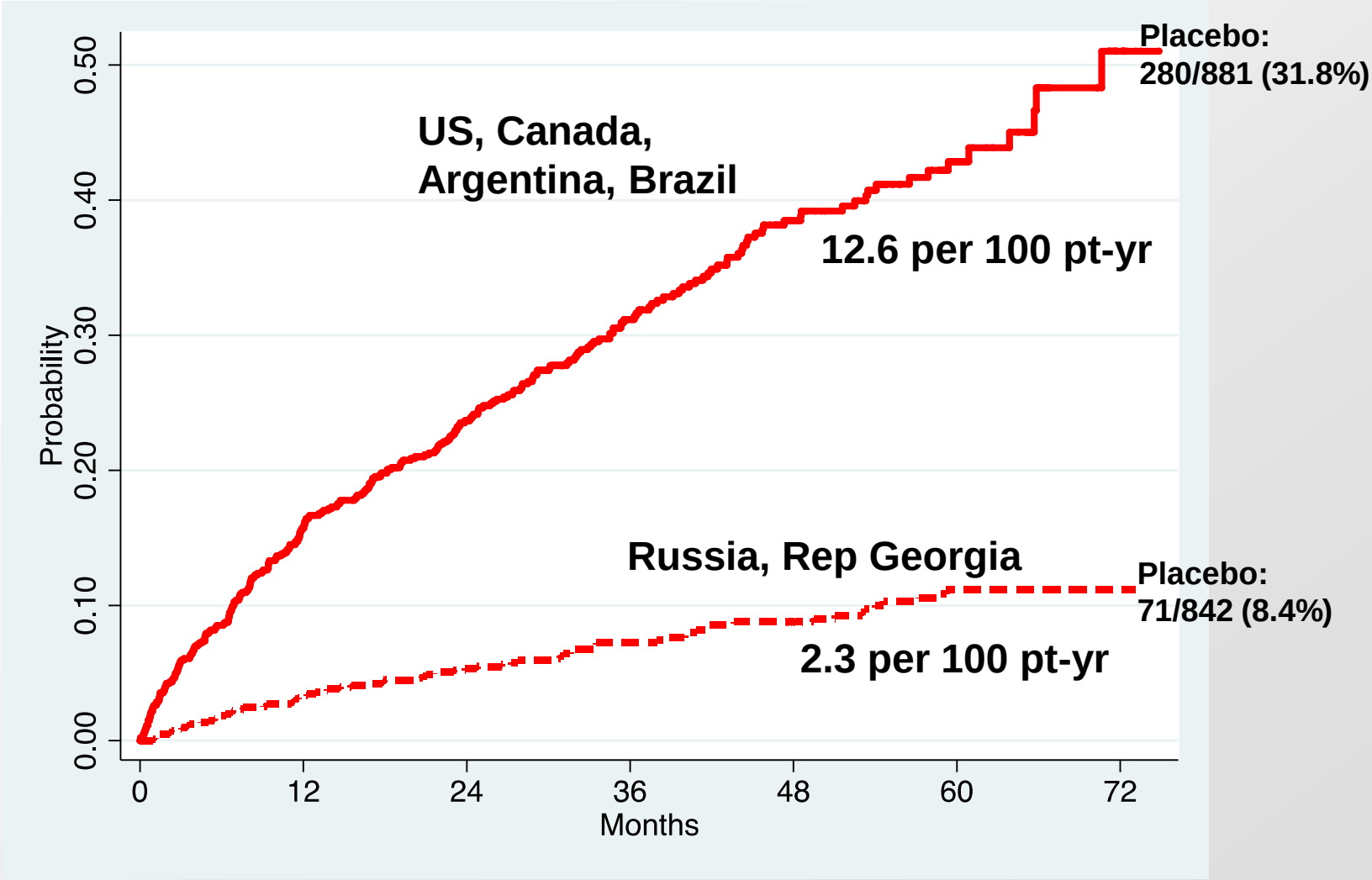

Exploratory (post-hoc): Placebo vs. Spiro by region

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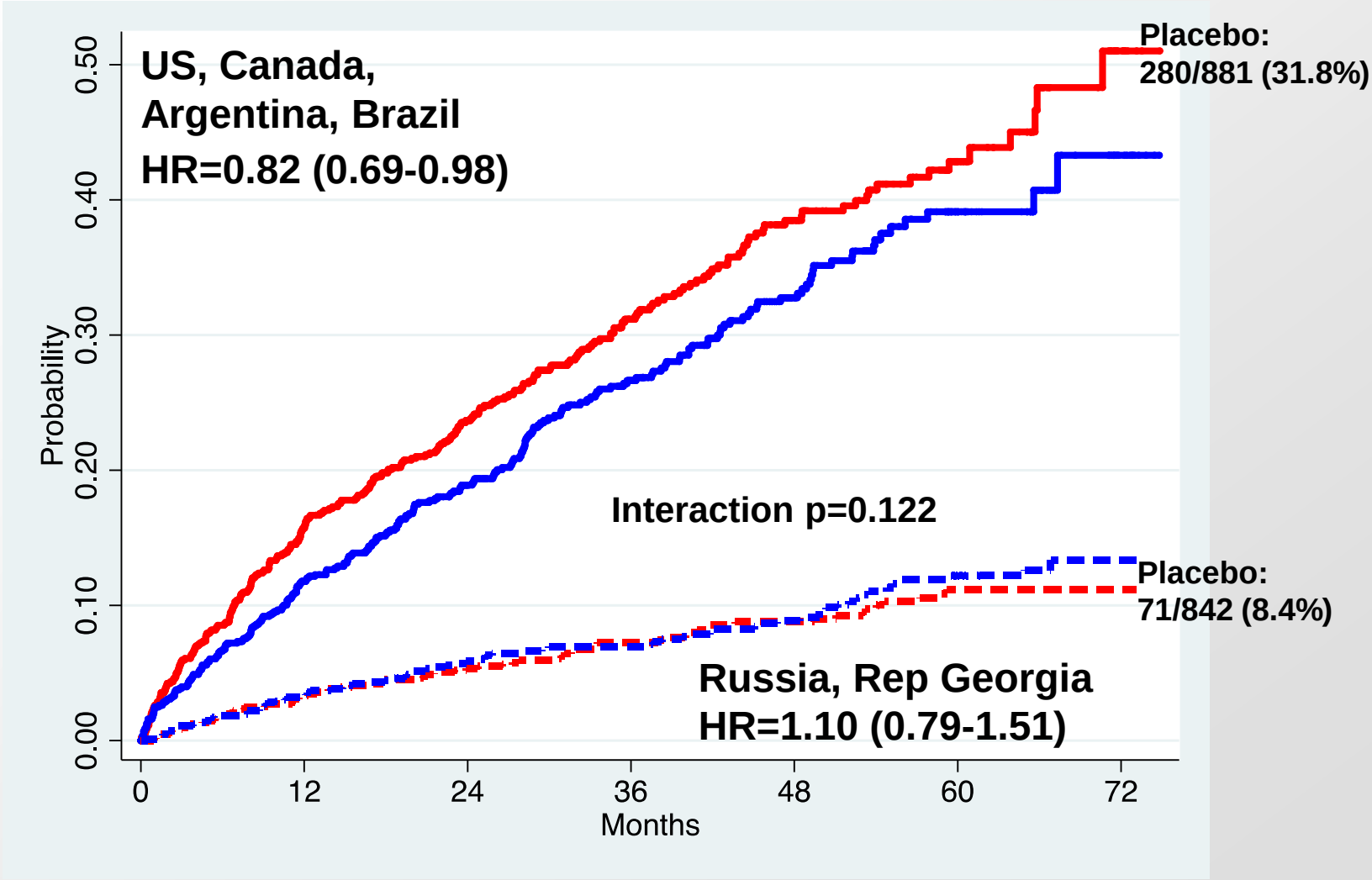

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Summary

	Spironolactone (N = 1722)	Placebo (N = 1723)	HR (95% CI)
Primary Outcome	**320 (18.6%)** 5.9/100pt-yr	**351 (20.4%)** 6.6/100pt-yr	**0.89 (0.77-1.04) P=0.138**
Hospitalization for Heart Failure	**206 (12.0%)** 3.8/100pt-yr	**245 (14.2%)** 4.6/100pt-yr	**0.83 (0.69-0.99) P=0.042 Multiple HF Hosp P<0.01**

Conclusions: TOPCAT population with HFpEF:

- **Rx with spironolactone did not alter the 1° composite**
- Reductions in heart failure were observed
- Use of spironolactone in these patients requires careful monitoring of K^+ and creatinine

Thank you

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Patients and Investigators

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Country Leaders: Argentina- Raphael Diaz; Brazil- Nadine Clausell; Canada- Eileen O'Meara, Jean Rouleau; Rep. Georgia- Tomas Shaburishvili; Russia- Ivan Gordeev; USA- Inder Anand, John Heitner, Jeff Probstfield, David Whellan

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