Gestion du traitement oral de l'insuffisance cardiaque à la sortie de réanimation

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HOMAGE FIBRO TARGETS

UNIVERSITÉ DE LORRAINE CHU NANCY www.chu-nancy.fr Instituts thématiques Inserm Institut national de la santé et de la recherche médicale Liberté • Égalité • Fraternité RÉPUBLIQUE FRANÇAISE DGOS ICALOR Réseau lorrain insuffisance cardiaque SEVENTH FRAMEWORK PROGRAMME

Heart Failure, a heterogeneous syndrome

Internists
Hypertension
Primary care
GPs

Internists
Geriatricians
Primary care
GPs

HF specialists
Transplant,
LVAD

Pre-HF	Post MI Low EF	HFPEF	CHF Mild Moderate Low EF	CHF Severe Low EF	Acute Worsening Hosp

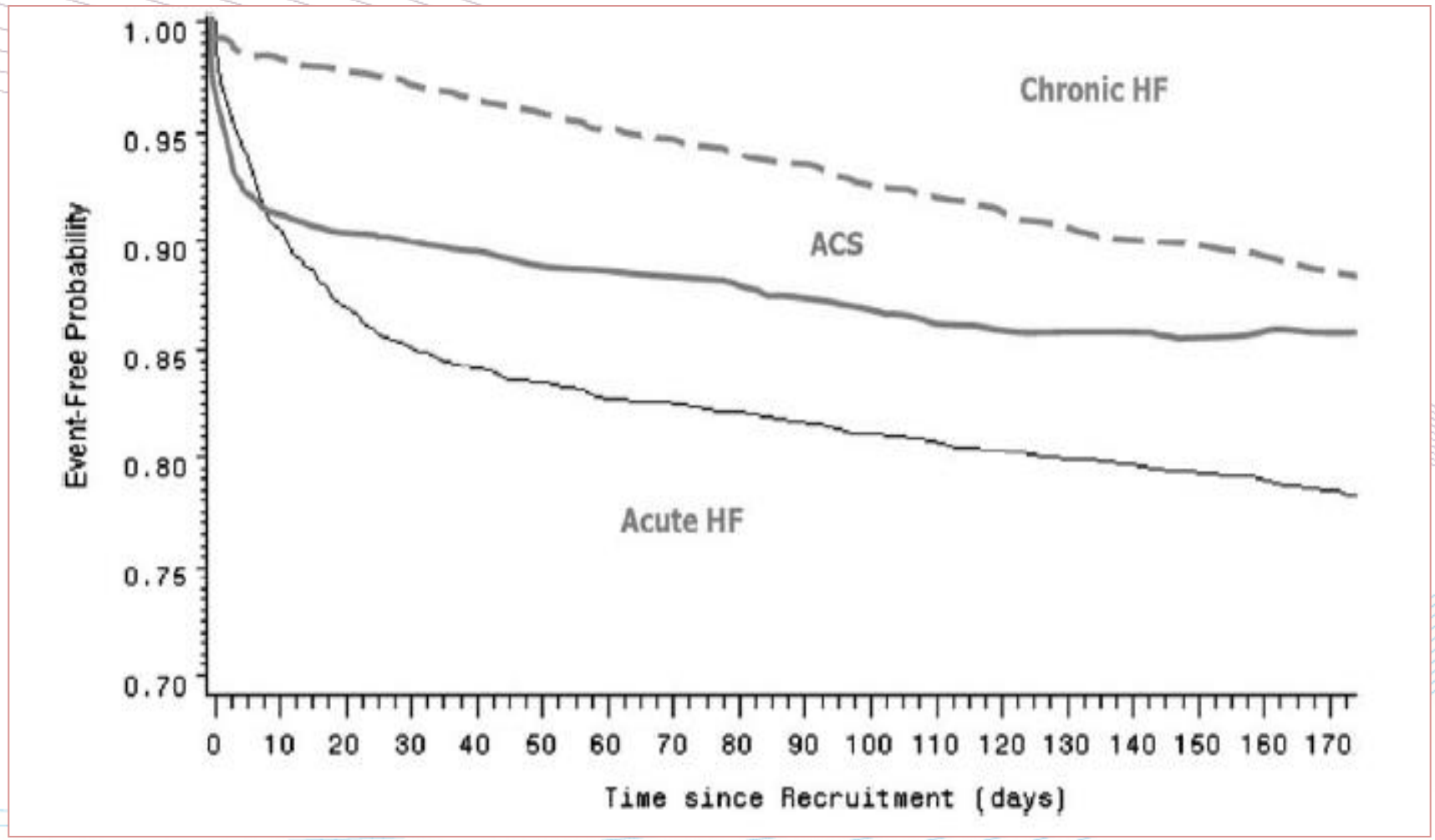
CCUs
Cath Labs

Cardiologists
Electrophysiologists

Intensivits
Emergency
departments

Stakeholders

AHF more serious than ACS



Maggioni PA et al. 2011

AHFS: An Acute EVENT
The ACS model

Pre-admission

“Golden Hours”

22%

In-Patient

4-27%

Post-Discharge

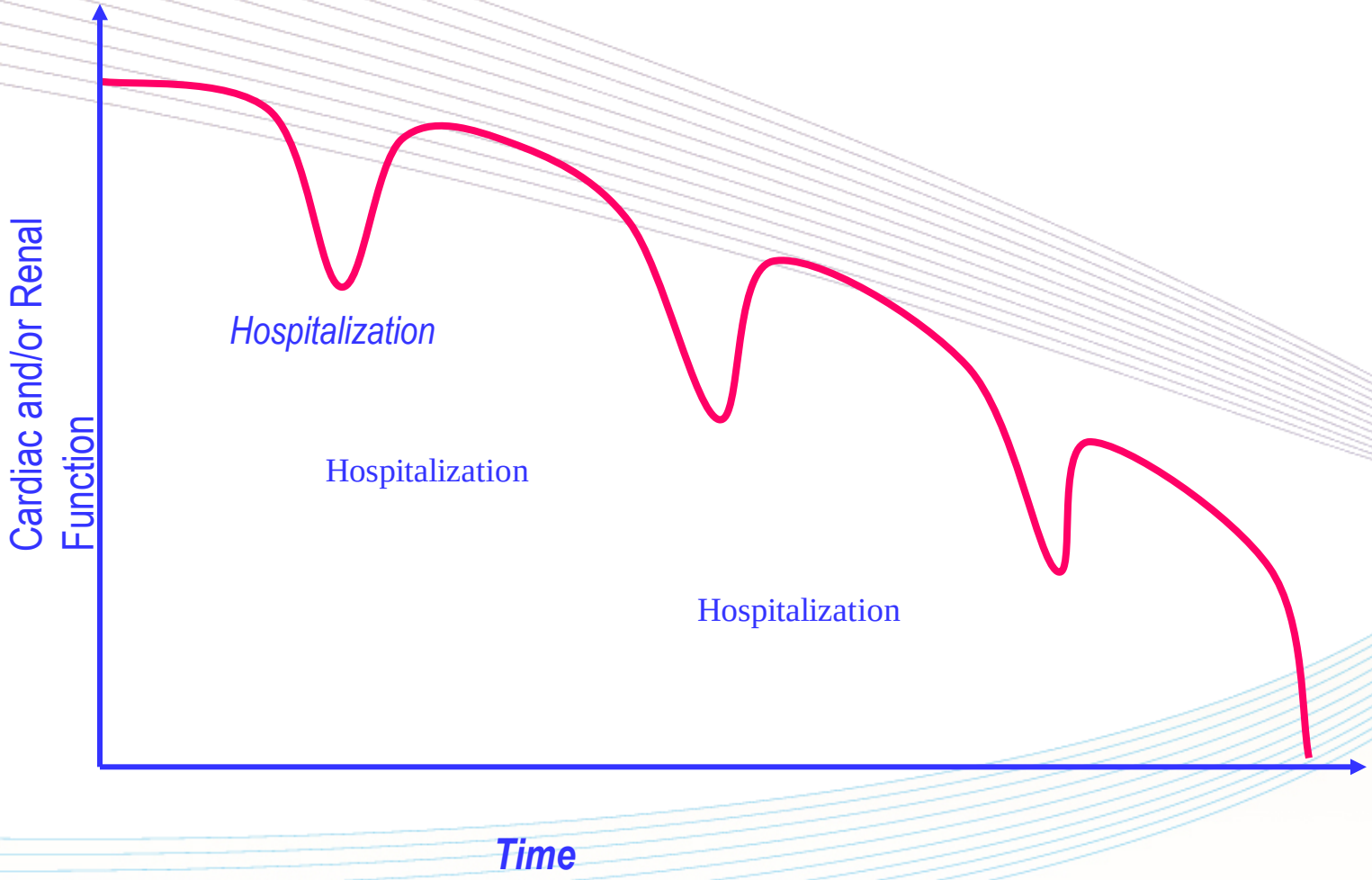
1-year Mortality 25%

1-year Re admissions 25%

Zannad et al EJHF 2008

AHFS and Progression of HF

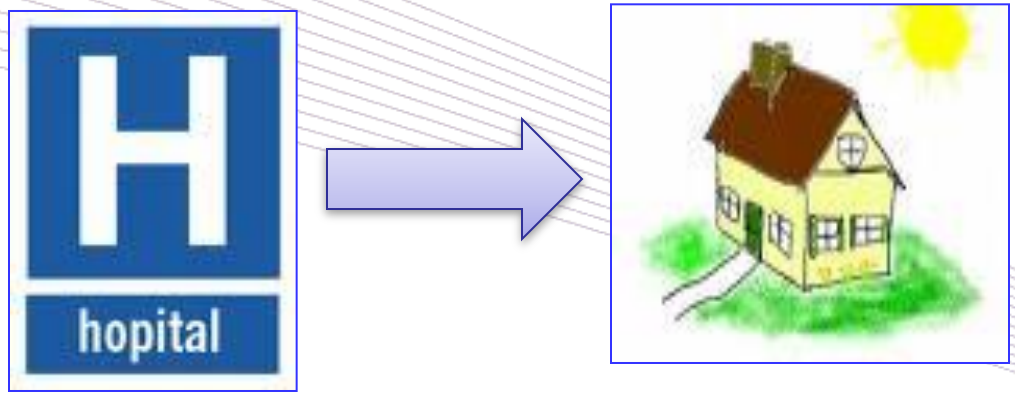
Hypothesis: With each hospitalization, there is **myocardial** and or **renal** damage



Gheorghiade M et al. *Am J Cardiol*. 2005; 96 (6A)

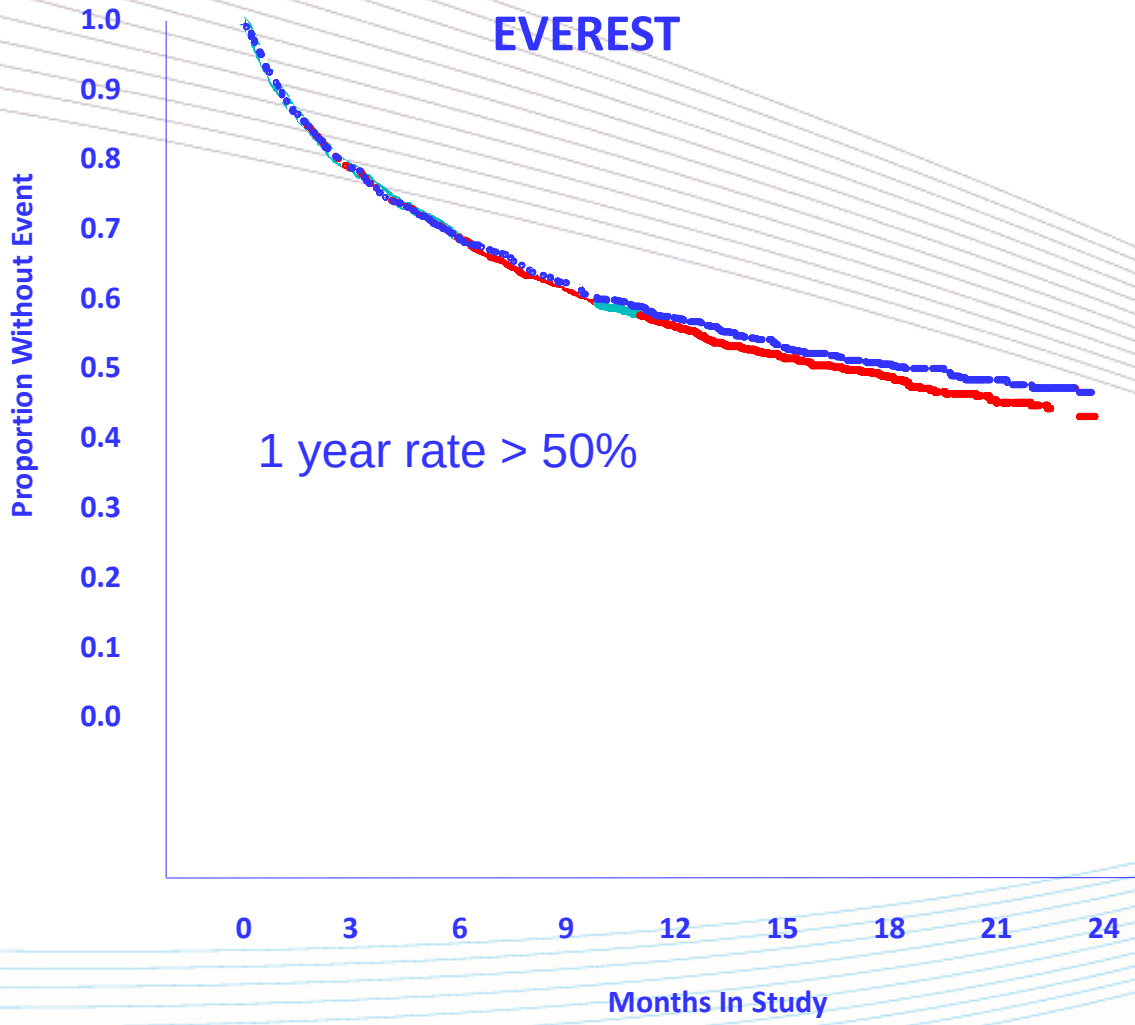
D'après F Zannad

Discharge



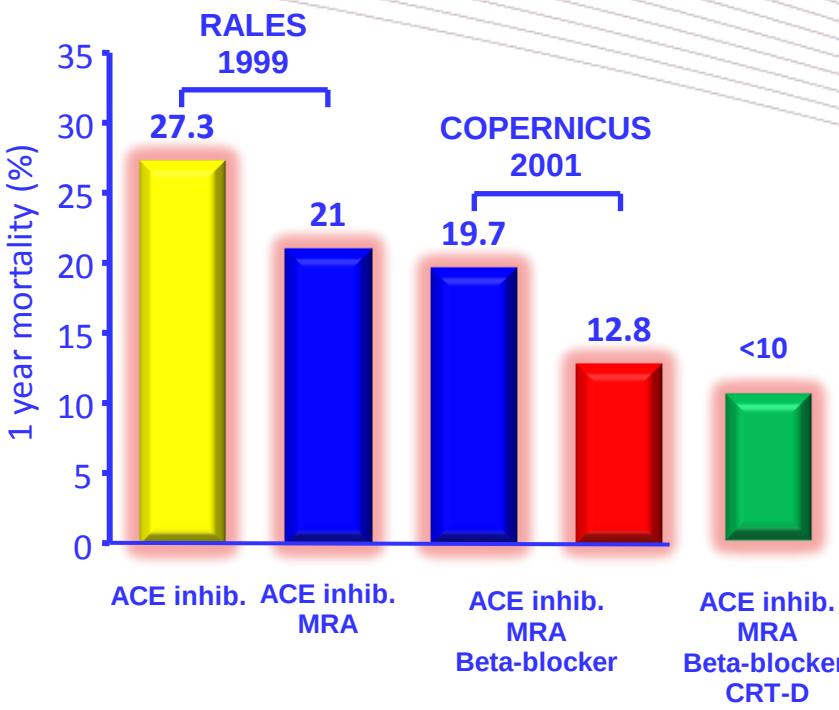
And what happens after discharge?

CV Mortality or HF Hospitalisation



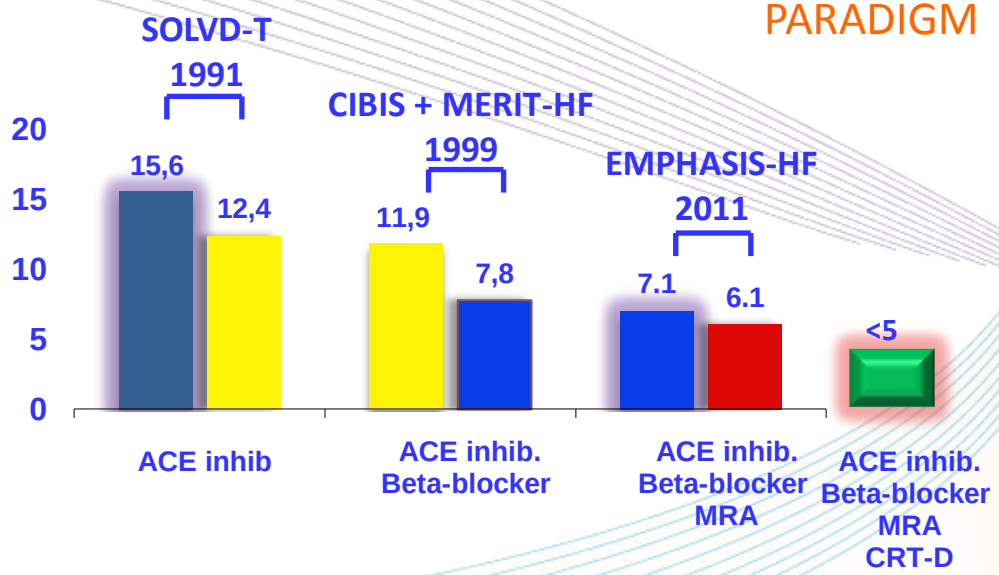
1-year mortality in patients with systolic heart failure decreased three fold.

Moderate to severe symptoms.



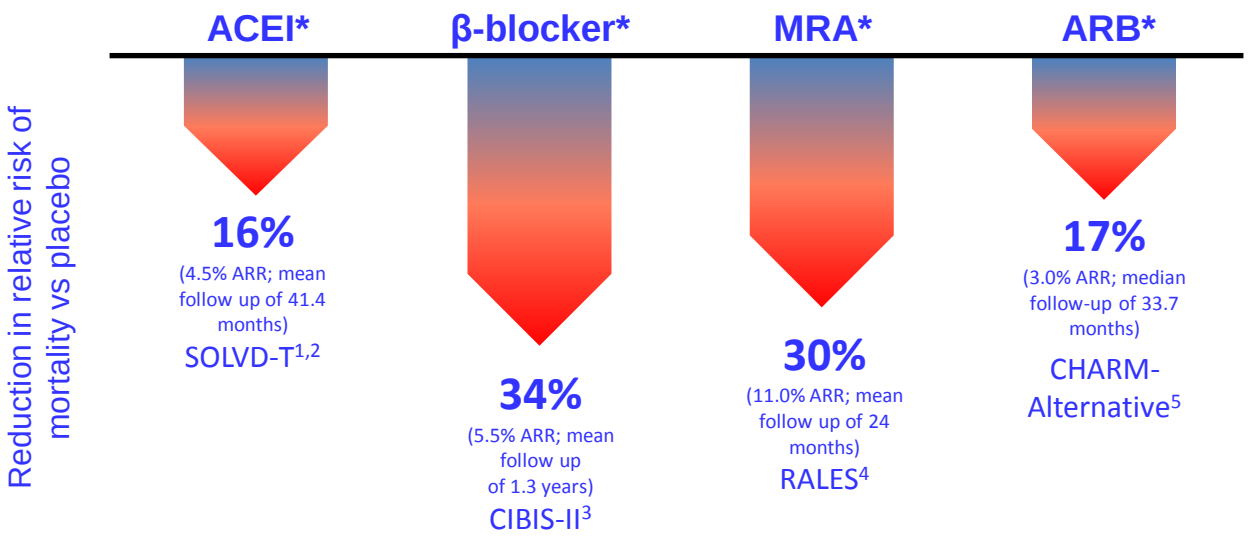
Mild symptoms.

PARADIGM



Mortality in HFrEF remains high despite the introduction of new therapies that improve survival

- Survival rates in chronic HF have improved with the introduction of new therapies[1]



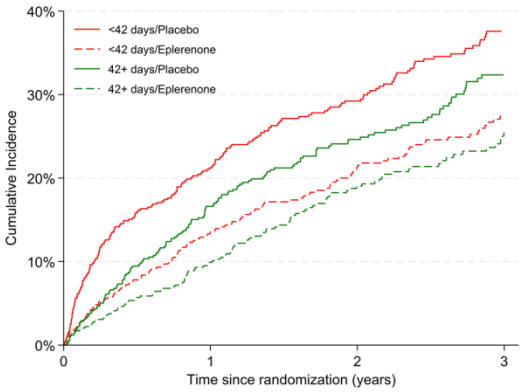
- However, significant mortality remains: ~50% of patients die within 5 years of diagnosis[6–8]

*On top of standard therapy at the time of study (except in CHARM-Alternative where background ACEI therapy was excluded). Patient populations varied between trials and as such relative risk reductions cannot be directly compared. SOLVD (Studies of Left Ventricular Dysfunction), CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) and RALES (Randomized Aldactone Evaluation Study) enrolled chronic HF patients with LVEF≤35%. CHARM-Alternative (Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity) enrolled chronic HF patients with LVEF≤40%

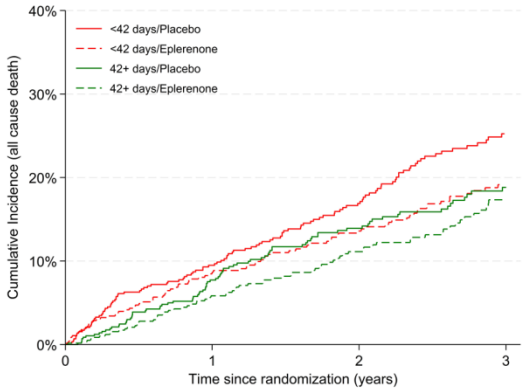
1. McMurray et al. Eur Heart J 2012;33:1787–847; 2. SOLVD Investigators. N Engl J Med 1991;325:293–302;
3. CIBIS-II Investigators. Lancet 1999;353:9–13; 4. Pitt et al. N Engl J Med 1999;341:709-17;–50;
5. Granger et al. Lancet 2003;362:772–6; 6. Go et al. Circulation 2014;129:e28-e292;
7. Yancy et al. Circulation 2013;128:e240–327; 8. Levy et al. N Engl J Med 2002;347:1397–402

EMPHASIS-HF Eplerenone early after discharge from CV hospitalisation

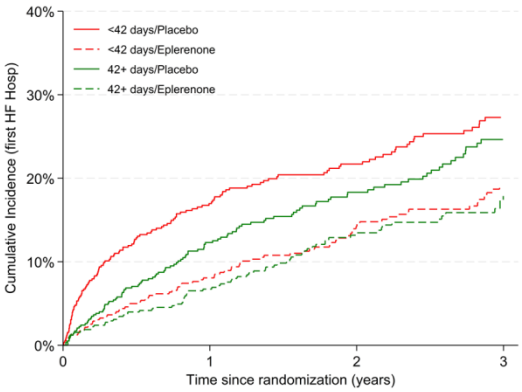
Cardiovascular deaths or Hospitalization for Heart Failure



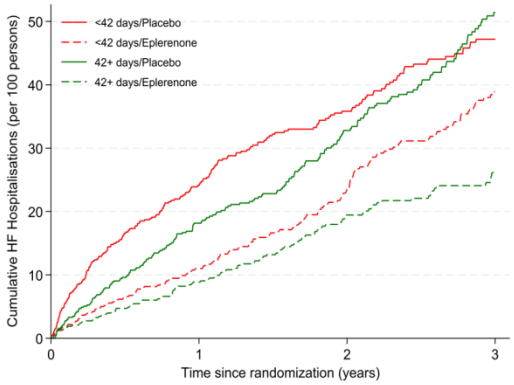
All-cause mortality



Heart failure hospitalization



Heart failure hospitalization (including repeats)



Girerd N AHA 2013

Prevent HF	Post MI Low EF	CHF Preserved EF	CHF Mild Moderate Low EF	CHF Severe Low EF	Acute Worsening Hosp
HOPE EUROPA	AIRE/SAVE	PEP-CHF (Perindopril)	SOLVD	CONSENSUS	-----?------
-----?------	CAPRICORN	SENIORS	US Carvedilol MERIT CIBIS SENIORS	COPERNICUS	-----?------
ONTARGET TRANSCEND	OPTIMAAL VALIANT	CHARM I-PRESERVE	ELITE HEAAL VALHeft CHARM	-----?------	-----?------
REMINDER ALBATROSS	EPHESUS	TOPCAT	EMPHASIS	RALES	-----?------
	ASPIRE		ATMOSPHERE		ASTRONAUT

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

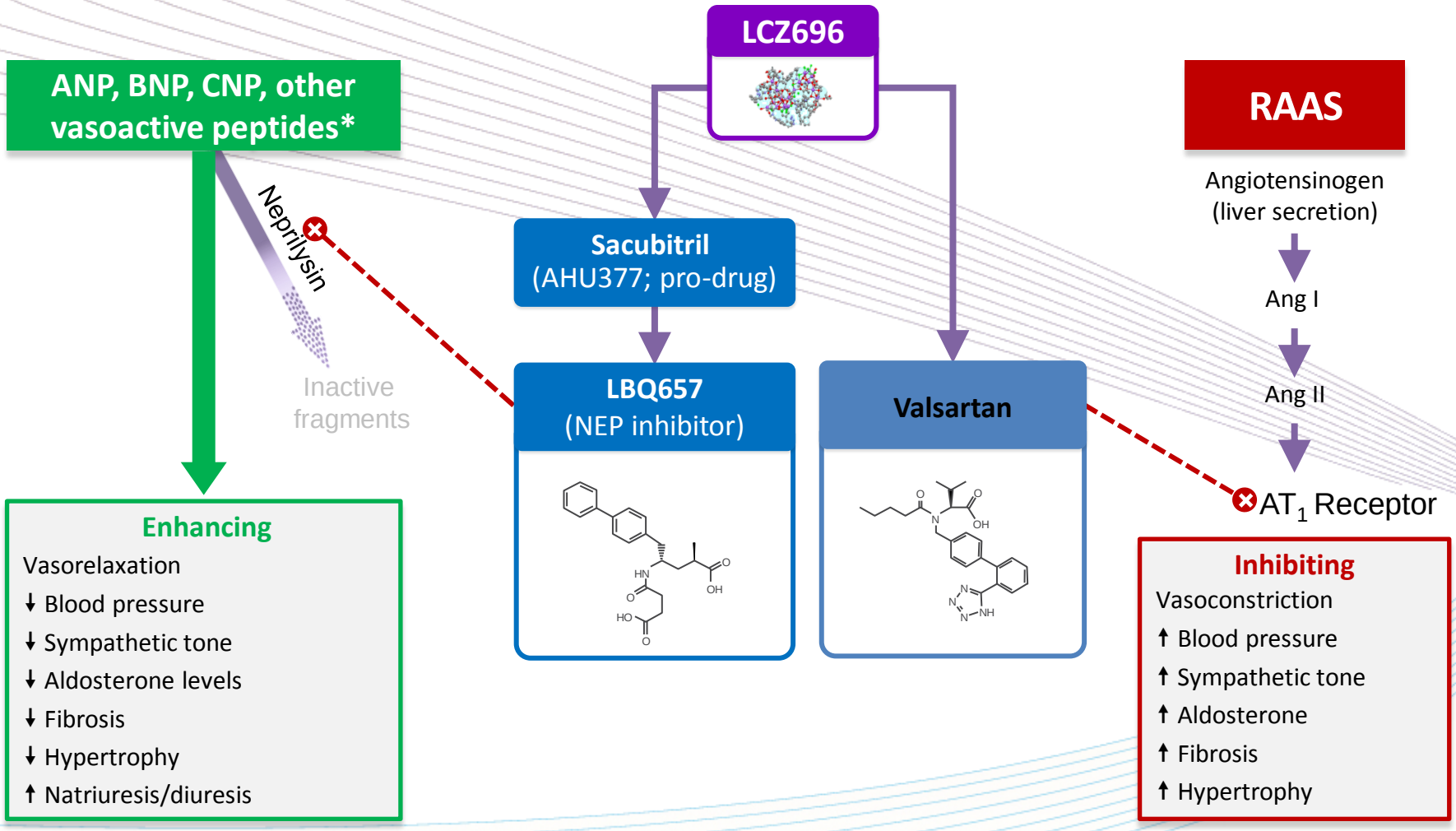
EUROPEAN SOCIETY OF CARDIOLOGY®

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC.

Pharmacological treatments indicated in potentially all patients with symptomatic (NYHA functional class II–IV) systolic HF			
Recommendations	**Class[a]**	**Level[b]**	**Ref.[c]**
An ACE inhibitor is recommended for all patients with an EF ≤ 40% to reduce the risk of HF hospitalization and the risk of premature death.	I	A	SOLVD CONSENSUS ATLAS
A beta-blocker is recommended in addition to an ACE inhibitor (or ARB if ACE inhibitor not tolerated) for all patients with an EF ≤ 40% to reduce the risk of HF hospitalization and the risk of premature death.	I	A	CIBIS MERIT Carvedillol Copernicus SENIORS
An MRA is recommended for all patients with persisting symptoms (NYHA class II–IV) and an EF ≤ 35% despite treatment with an ACE inhibitor (or ARB) to reduce the risk of HF hospitalization and the risk of premature death.	I	A	RALES EPHESUS EMPHASISS

Mc Murray J et al EHJ 2012

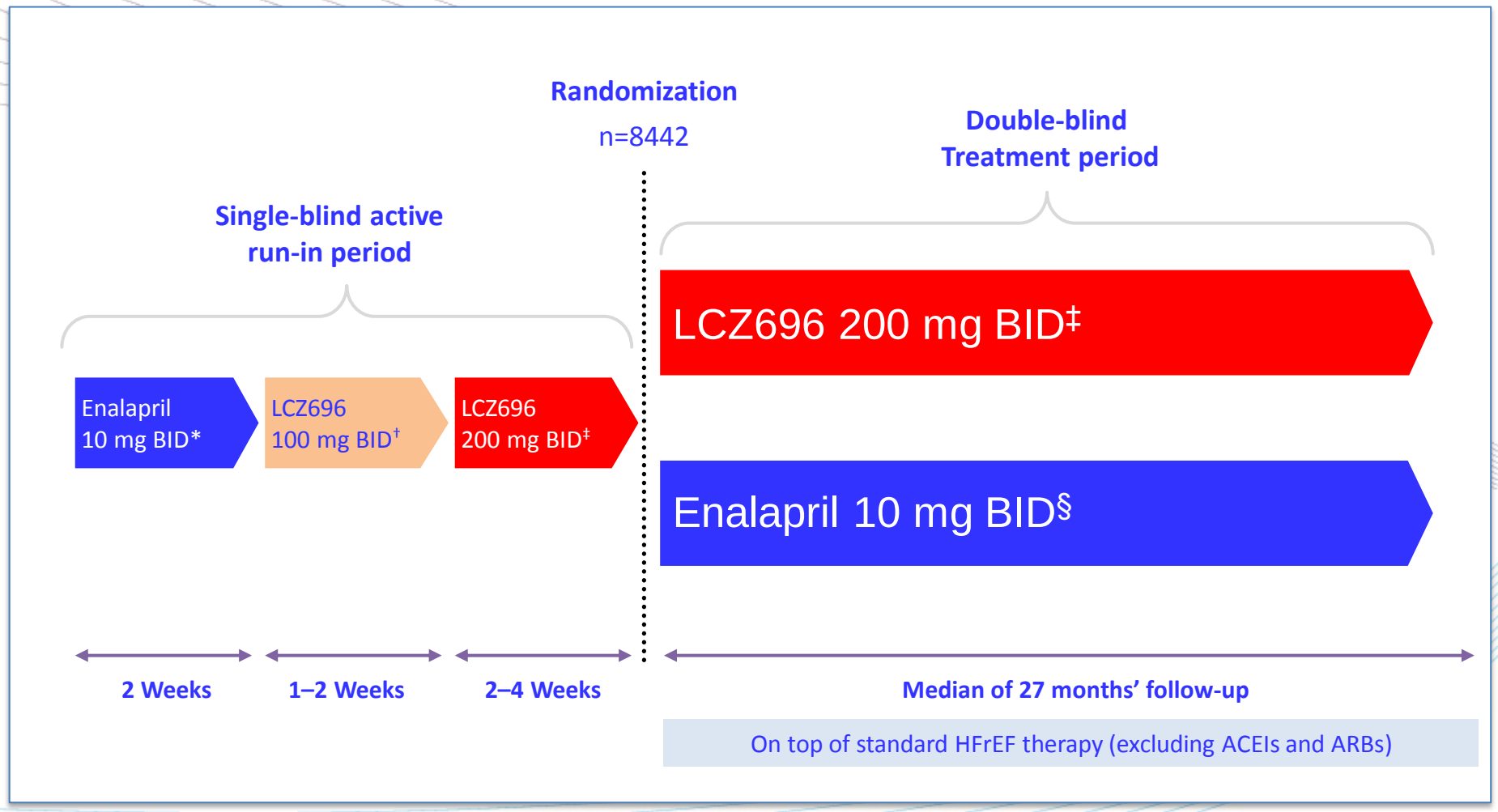
Following oral administration LCZ969 dissociates into the pro-drug sacubitril (AHU377), which is further metabolized to LBQ657, and valsartan



*Neprilysin substrates listed in order of relative affinity for NEP: ANP, CNP, Ang II, Ang I, adrenomedullin, substance P, bradykinin, endothelin-1, BNP
Ang=angiotensin; ANP=atrial natriuretic peptide; AT_1=angiotensin II type 1; BNP=B-type natriuretic peptide; CNP=C-type natriuretic peptide; NEP=neprilysin; RAAS=renin angiotensin aldosterone system

Levin et al. N Engl J Med 1998;339:321–8;
Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42;
Schrier & Abraham N Engl J Med 2009;341:577–85;
Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9;
Feng et al. Tetrahedron Letters 2012;53:275–6

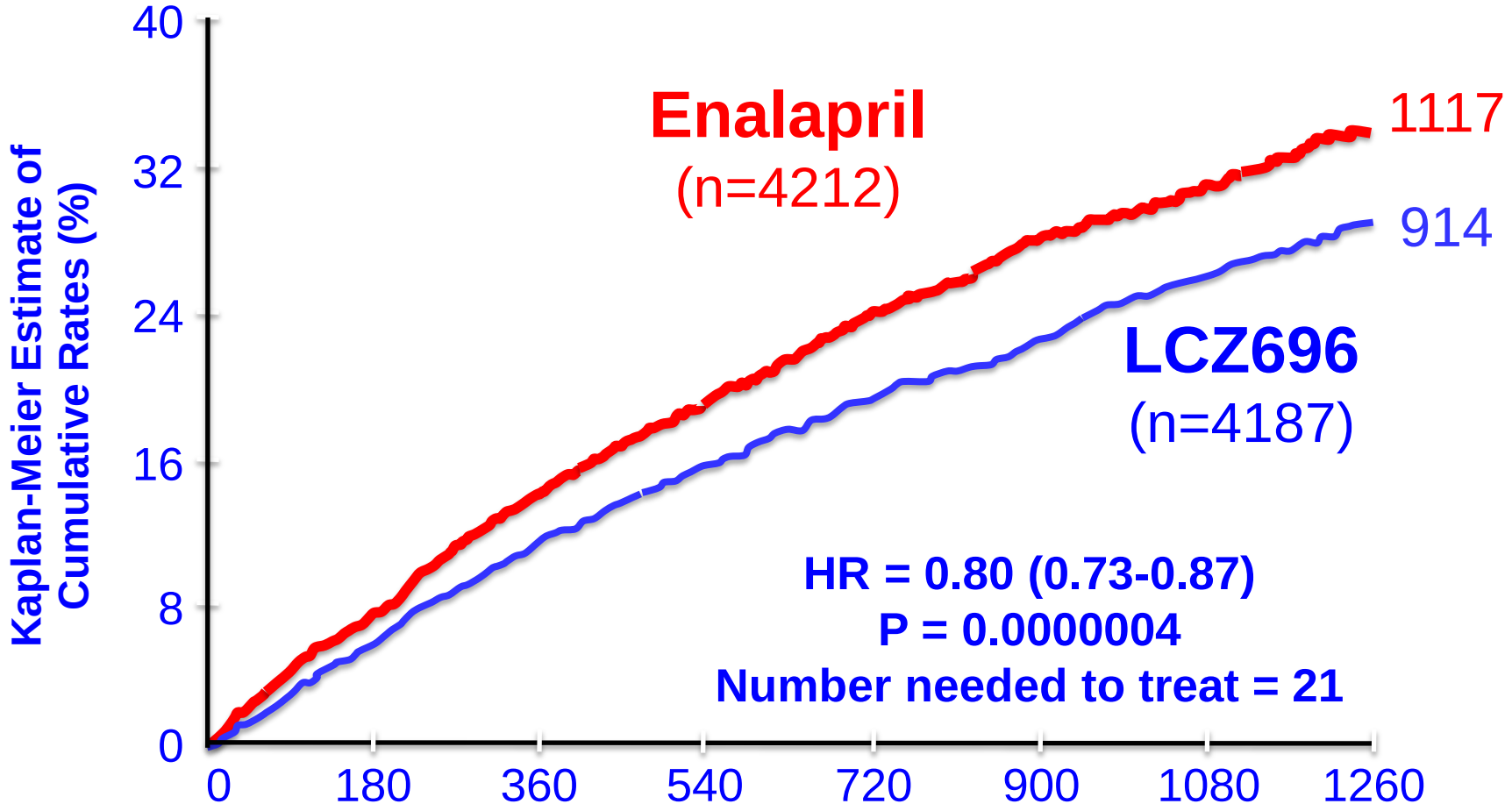
PARADIGM-HF: Study design



*Enalapril 5 mg BID (10 mg TDD) for 1–2 weeks followed by enalapril 10 mg BID (20 mg TDD) as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEI; †200 mg TDD; ‡400 mg TDD; §20 mg TDD.

McMurray et al. Eur J Heart Fail. 2013;15:1062–73; McMurray et al. Eur J Heart Fail. 2014;16:817–25; McMurray, et al. N Engl J Med 2014; ePub ahead of print: DOI: 10.1056/NEJMoa1409077.

PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)



Patients at Risk

LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

Prospectively defined safety events
Renal, Potassium

Event, n (%)	LCZ696 (n=4187)	Enalapril (n=4212)	p-value‡
Elevated serum creatinine			
≥2.5 mg/dL	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dL	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/L	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/L	181 (4.3)	236 (5.6)	0.007

McMurray, et al. N Engl J Med 2014; ePub ahead of print: DOI: 10.1056/NEJMoa1409077.

PARADIGM-HF: LCZ696 dose selection rationale

AT_1 receptor blockade

- LCZ696 200 mg BID delivers similar exposures to valsartan as Diovan® 160 mg BID, the dose recommended for treatment of HF and MI (based on Val-HeFT and VALIANT)[1–3]

Neprilysin (NEP) inhibition

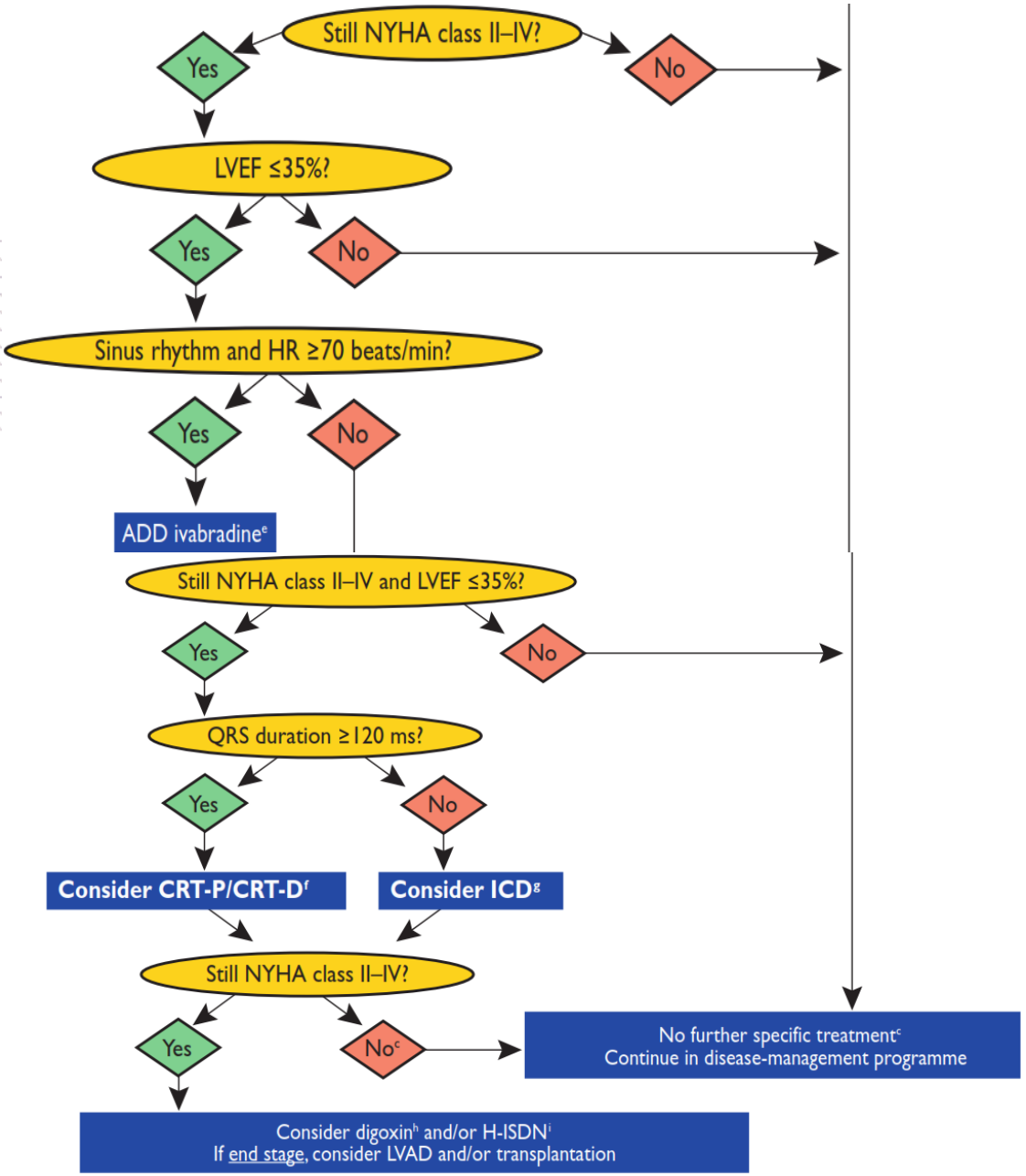
- Biomarker analysis indicates that LCZ696 200 mg provides ~90% of its maximal NEP inhibition[4,5]
- Both LCZ696 400 and 200 mg QD (but not 100 mg LCZ696) provided meaningful pharmacodynamic effect (BP lowering) attributable to NEP inhibtion[5]
- BID dosing is considered essential to obtain 24-hour NEP inhibition[1,6]
- BID dosing mitigates risk of post-dose hypotension (two smaller doses, compared to one larger once-daily dose, as used in the OVERTURE study with omapatrilat)[1,6]

1. McMurray et al. Eur J Heart Fail. 2013;15:1062–732; 2. Valsartan Heart Failure Trial Investigators. N Engl J Med 2001;345:1667–75;
3. Valsartan in Acute Myocardial Infarction Trial Investigators. N Engl J Med 2003;349:1893–1906; 4. Gu et al. J Clin Pharmacol 2010;50:401–14;
5. Ruilope et al. Lancet 2010;375:1255–1266; 6. Packer et al. Circulation 2002;106:920–6.

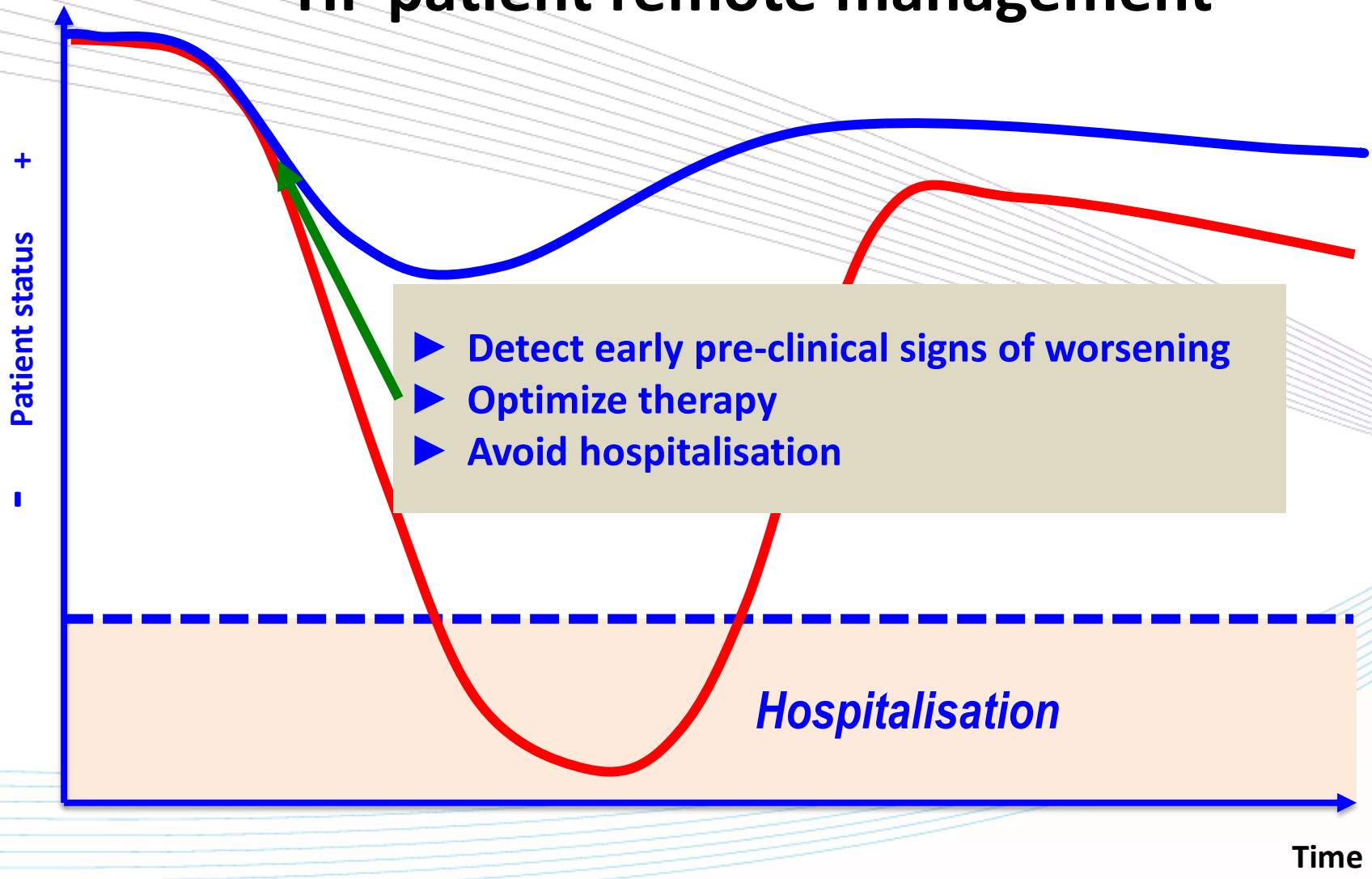
LVEF

Heart Rate

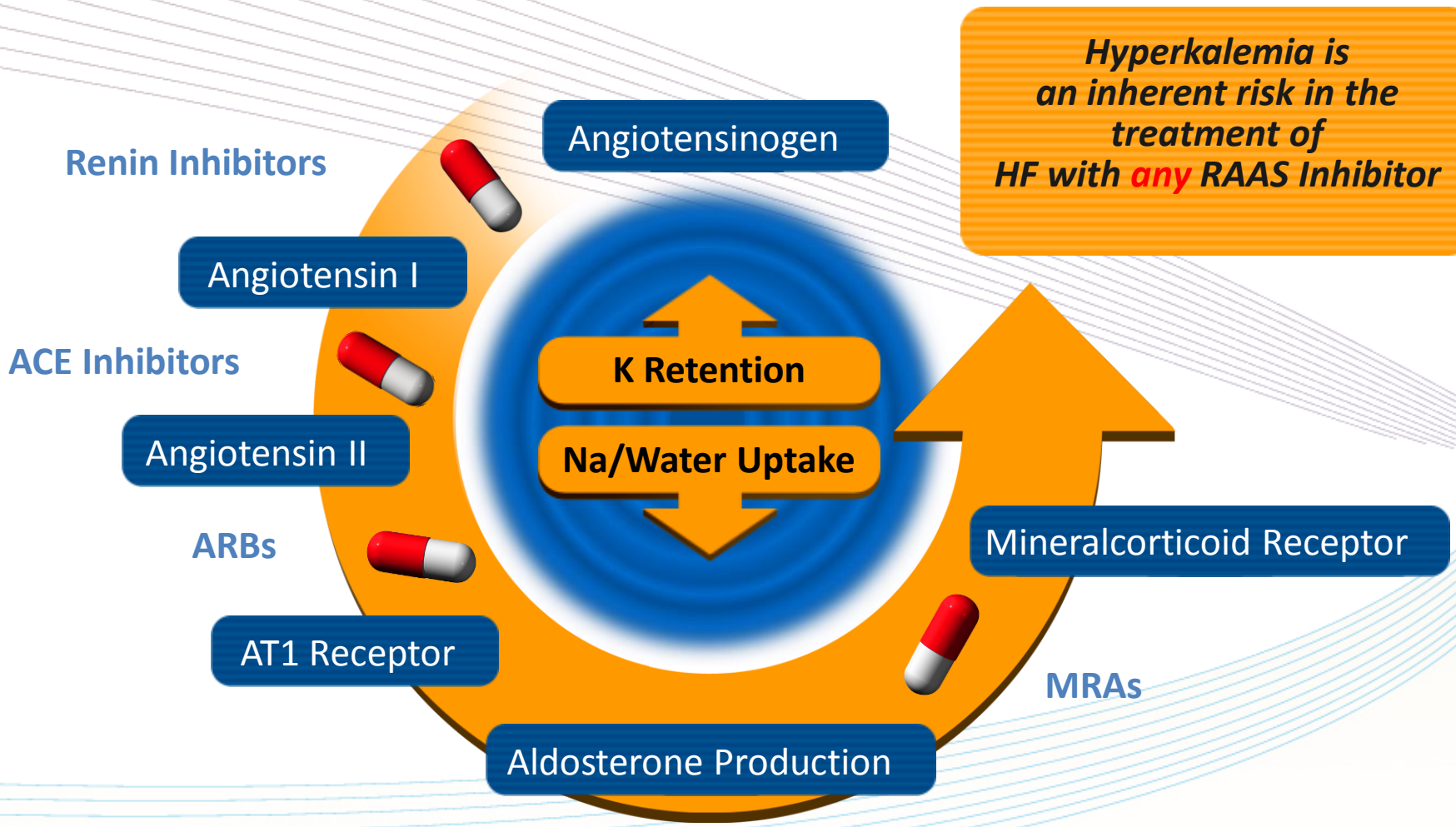
ECG – QRS, LBBB



Potential Solution:
telemonitoring-enabled
HF patient remote management



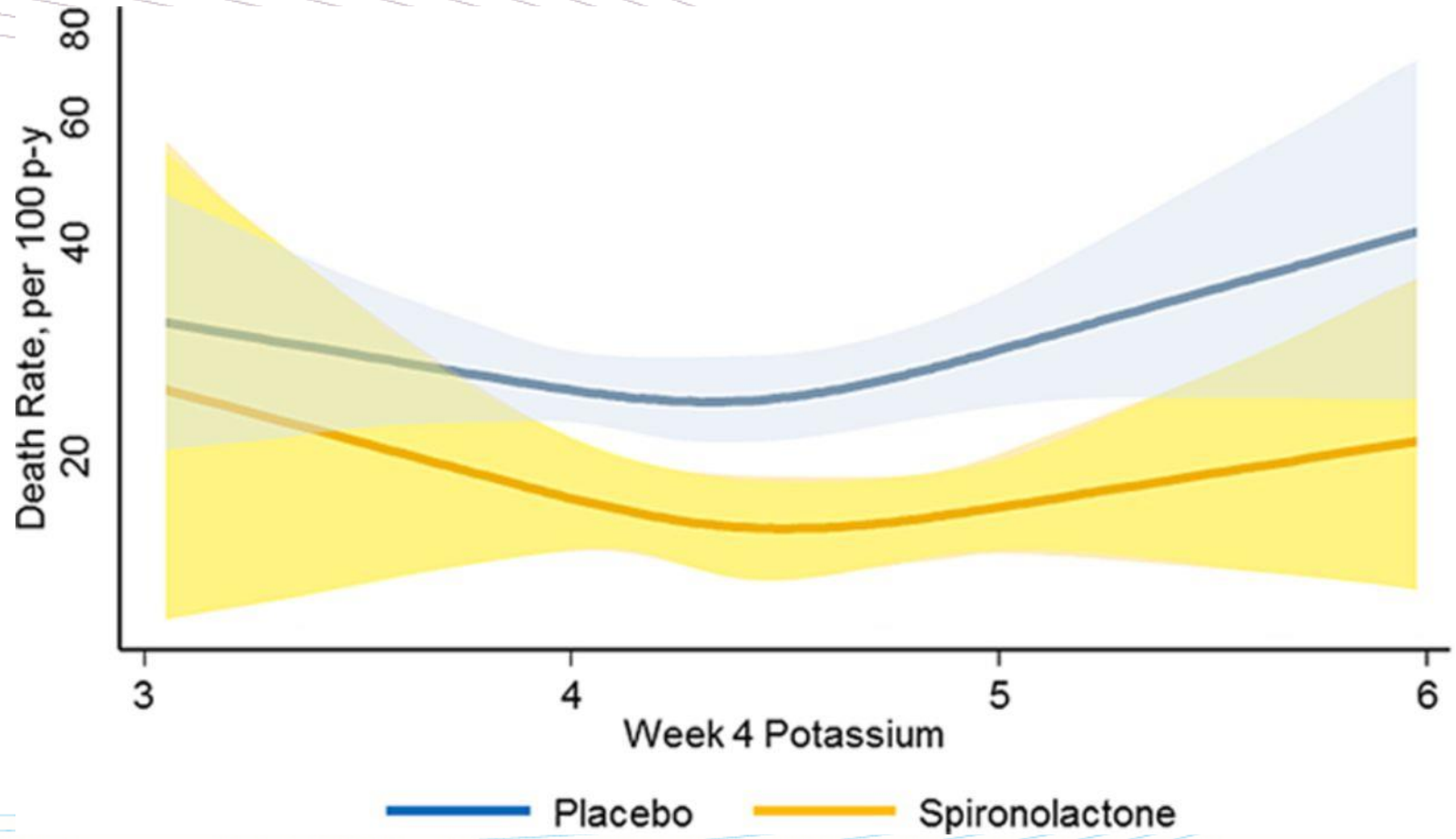
Treatment with Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors Reduces Water and Sodium, But Increases Potassium



Hyperkalemia is an inherent risk in the treatment of HF with any RAAS Inhibitor

RALES

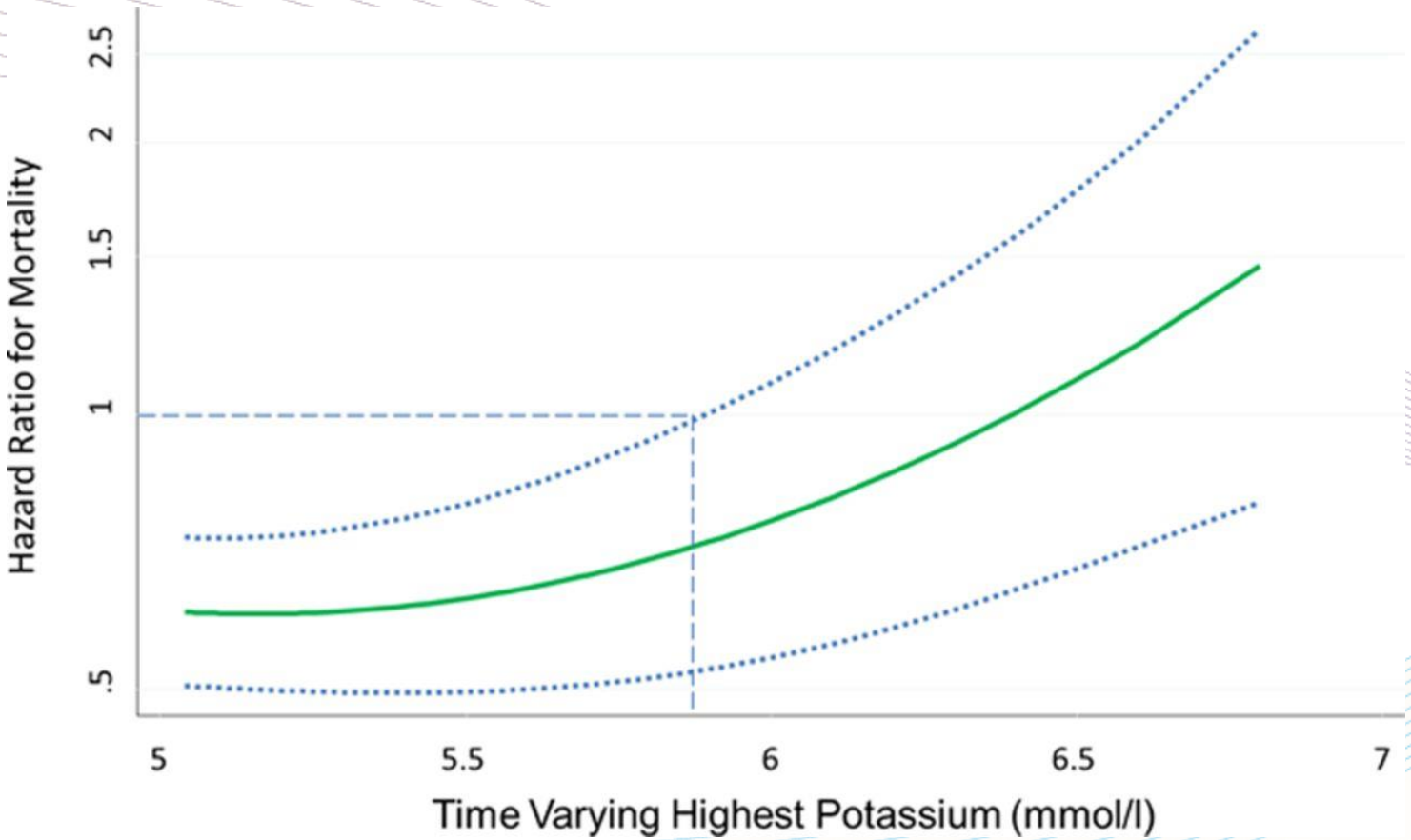
Rates of death after visit 2 (4 weeks) by treatment, based on serum potassium levels at visit 2.



Vardeny O et al. Circ Heart Fail. 2014;7:573-579

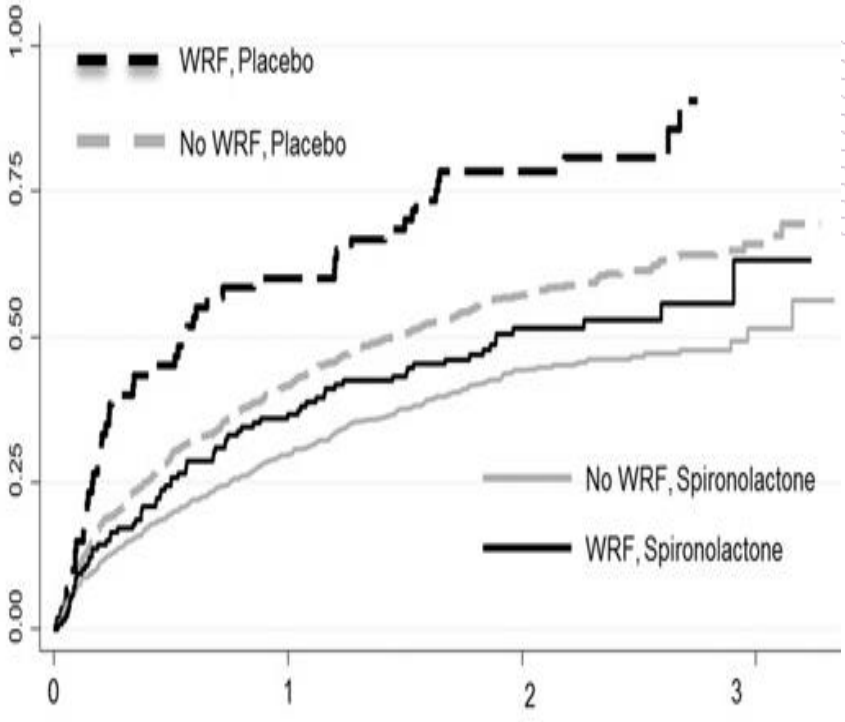
RALES

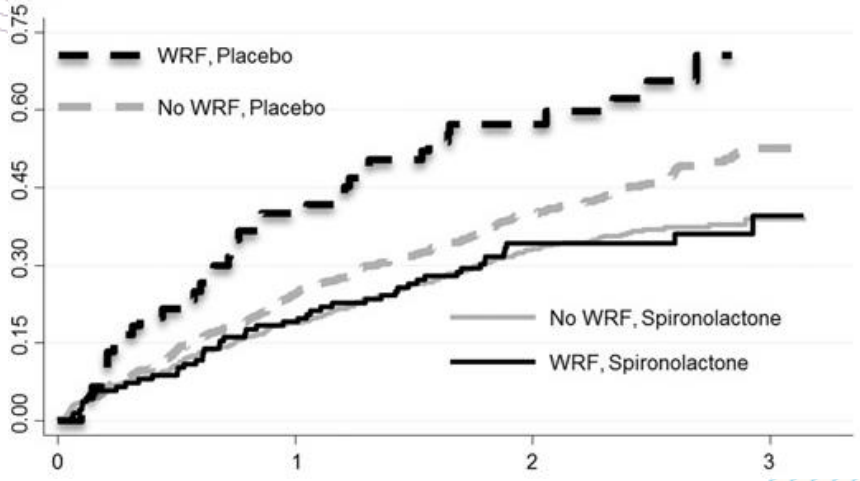
Mortality in the spironolactone group based on time-varying maximum potassium level when compared with a referent participant on placebo who never experienced potassium levels ≥5.0 mEq/L, adjusting for age, estimated glomerular filtration rate, baseline potassium, and diabetes mellitus.



Vardeny O et al. Circ Heart Fail. 2014;7:573-579

If any sprionlocatone was most beneficial in patients with WRF (RALES)





"The absolute benefit of spironolactone was greatest in patients with reduced eGFR. Worsening renal function was associated with a negative prognosis, yet the mortality benefit of spironolactone was maintained"

Vardeny O et al J Am Coll Cardiol 2012

Contents lists available at ScienceDirect

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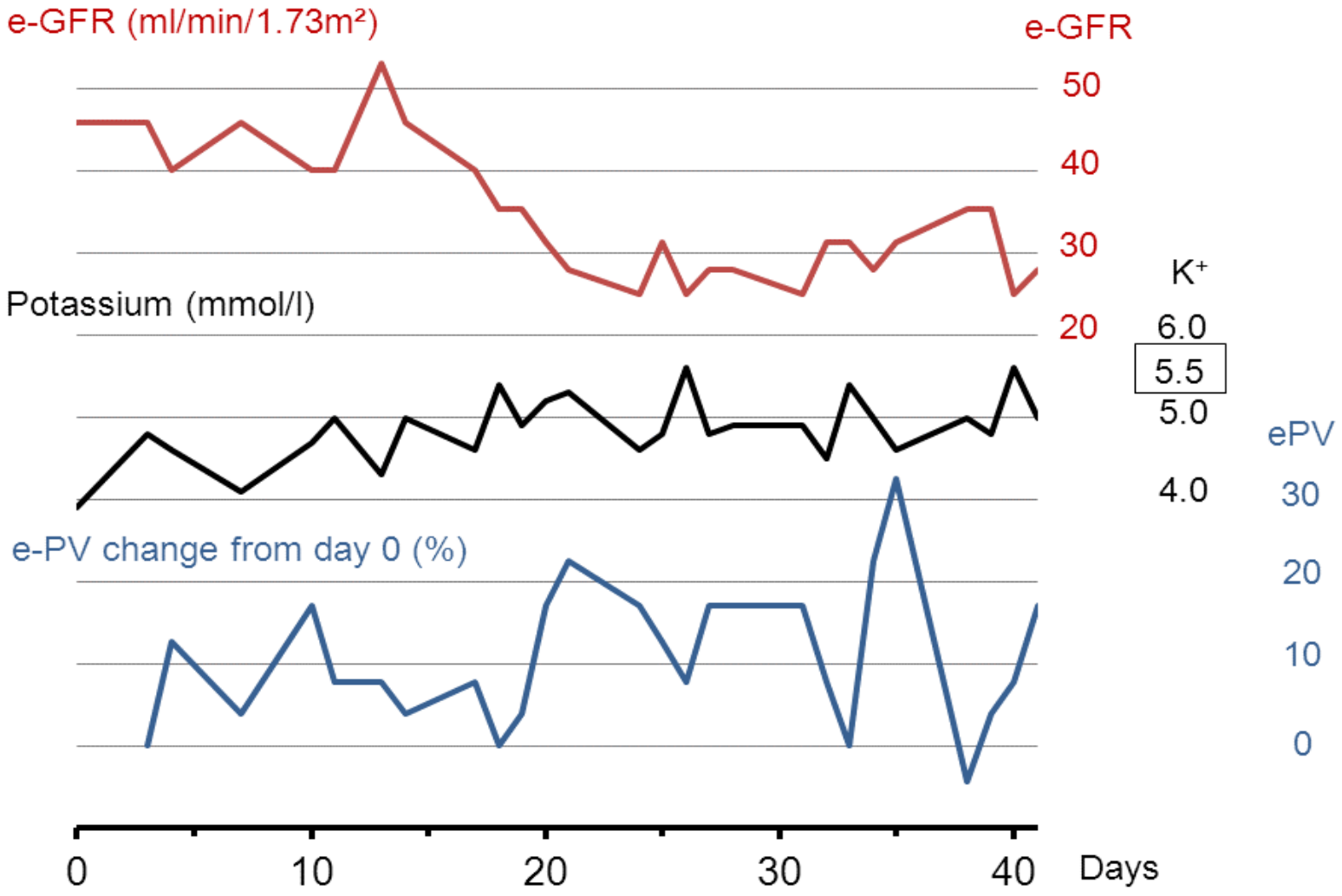
Editorial

Time to retrieve the best benefits from renin angiotensin aldosterone system (RAAS) inhibition in heart failure patients with reduced ejection fraction: Lessons from randomized controlled trials and registries

Patrick Rossignol [a,b,c,d,*], Faiez Zannad [a,b,c,d], Bertram Pitt [e], as a writing group of the 10th Global Cardio Vascular Clinical Trialist forum held on December 6th–7th 2013 in Paris, France

Although the use of multiple renin angiotensin aldosterone system-inhibitors is associated with the development of worsening renal function and hyperkalemia in patients with heart failure and reduced ejection fraction, increased efforts should be expended to initiate and maintain target doses of these agents so as to provide their benefits on mortality and hospitalizations for heart failure.

Furosemide 120 mg/d
Fosinopril 20 mg/d
Spironolactone 25 mg/d



Telemedicine to allow for dynamic optimisation of therapy

Patients

Coordination
Alert check reminders
compliance

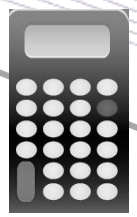
Prescription

Hospital

Signs/symptoms

Call center
Multiple HCPs

Interface
DSS



Reminders
alerts

GP
Specialist

TM Box

Transmission

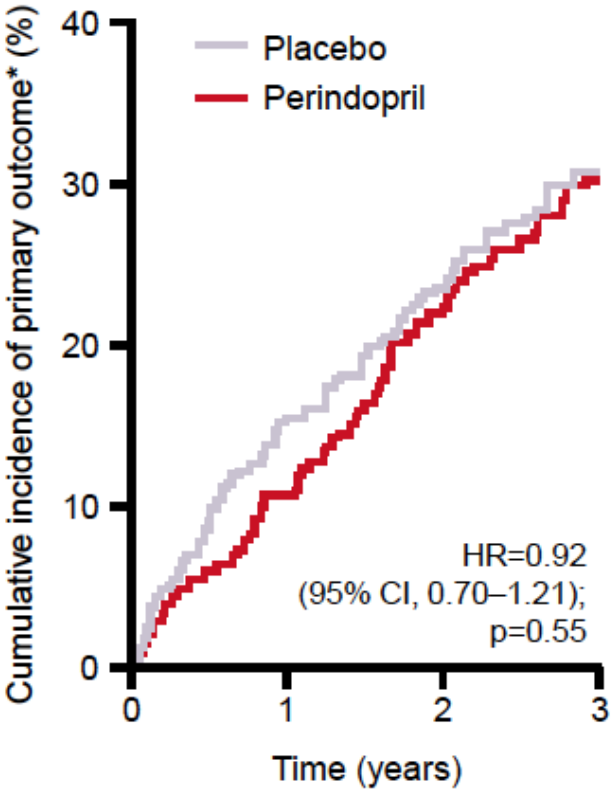
Server
Expert system

Electronic medical
record

DSS=Decision Support System; GP=general practitioner; HCP=healthcare practitioner; TM=telemedicine

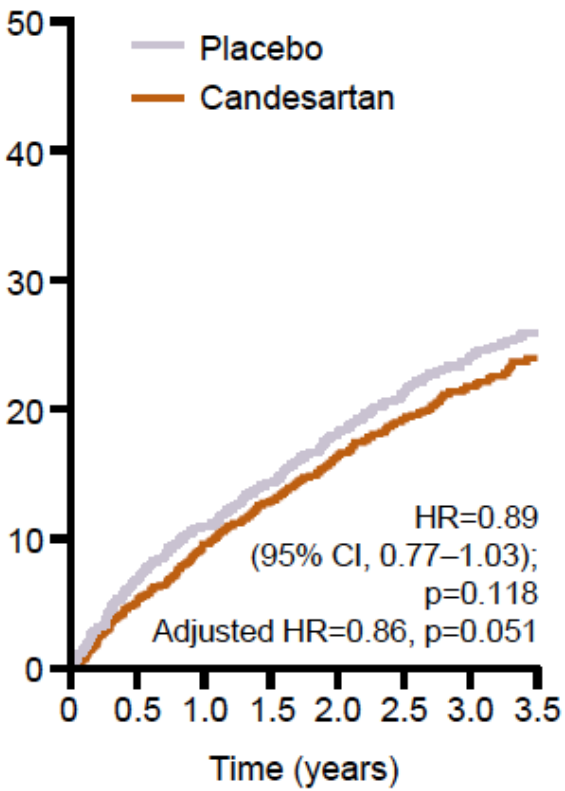
No proven therapy in HFpEF

ACEI: PEP-CHF[1]



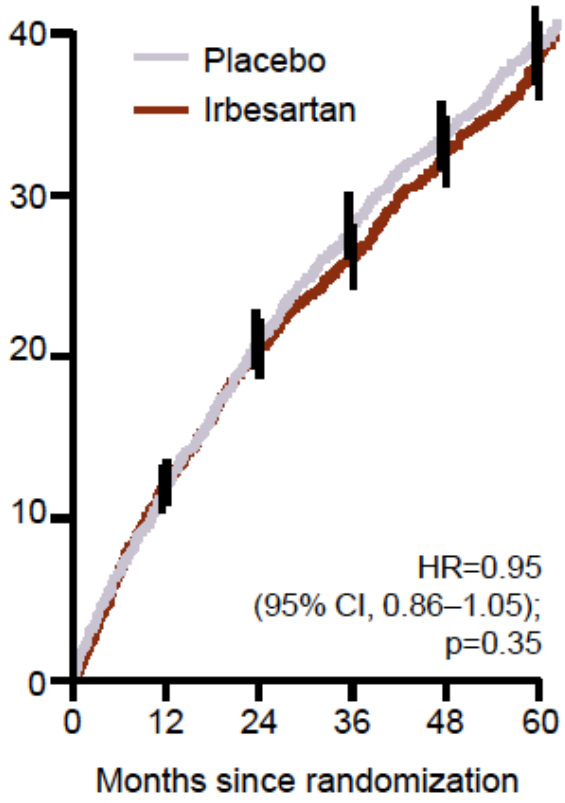
*Primary composite endpoint of all-cause mortality and unplanned HF-related hospitalization in HF patients with LV diastolic dysfunction (wall motion index of 1.4–1.6, roughly equivalent to LVEF 40–50%; [median LVEF: 64%])

ARB: CHARM-preserved[2]



*Primary composite outcome of CV death or admission to hospital for chronic HF in HF patients with LVEF >40%

ARB: I-PRESERVE[3]



*Primary outcome of death from any cause or hospitalization for pre-specified CV causes (worsening HF, myocardial infarction, stroke, atrial or ventricular arrhythmia, and myocardial infarction or stroke occurring during hospitalization for any cause)

TOPCAT

Funded by the NHLBI

- HF with a LVEF>45%
- Age ≥ 50 years
- At least 1 hospitalization for HF within 12 months
- or a BNP>100 pg/ml within 30 days
- Serum K < 5.0 meq/L
- Systolic BP < 140 mmHg

Placebo (n=2250)

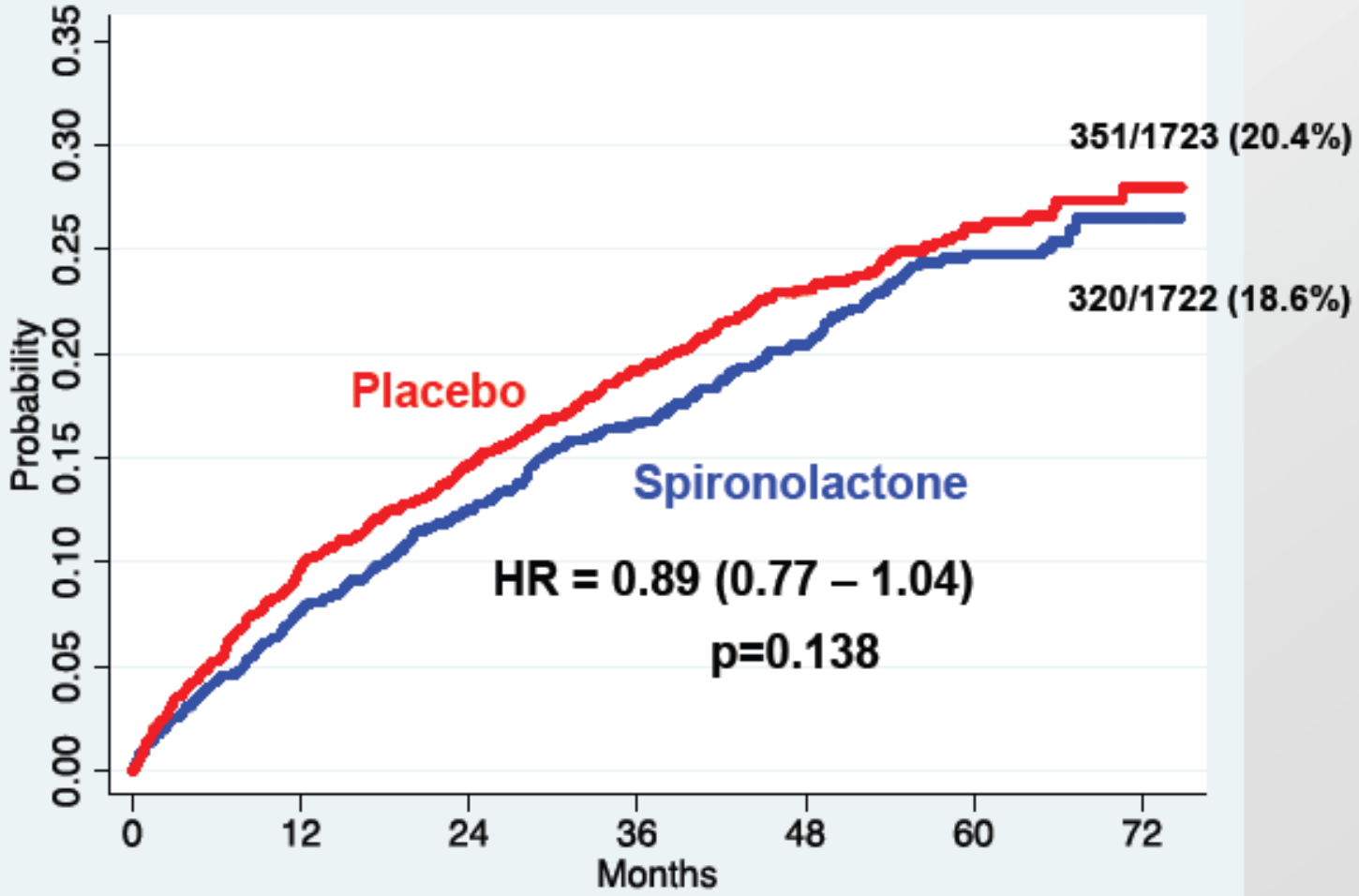
4.5 years

Spironolactone 15-30-45 mg/day (n=2250)

CV death/Hospitalization for HF

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

TOPCAT
Funded by the NHLBI

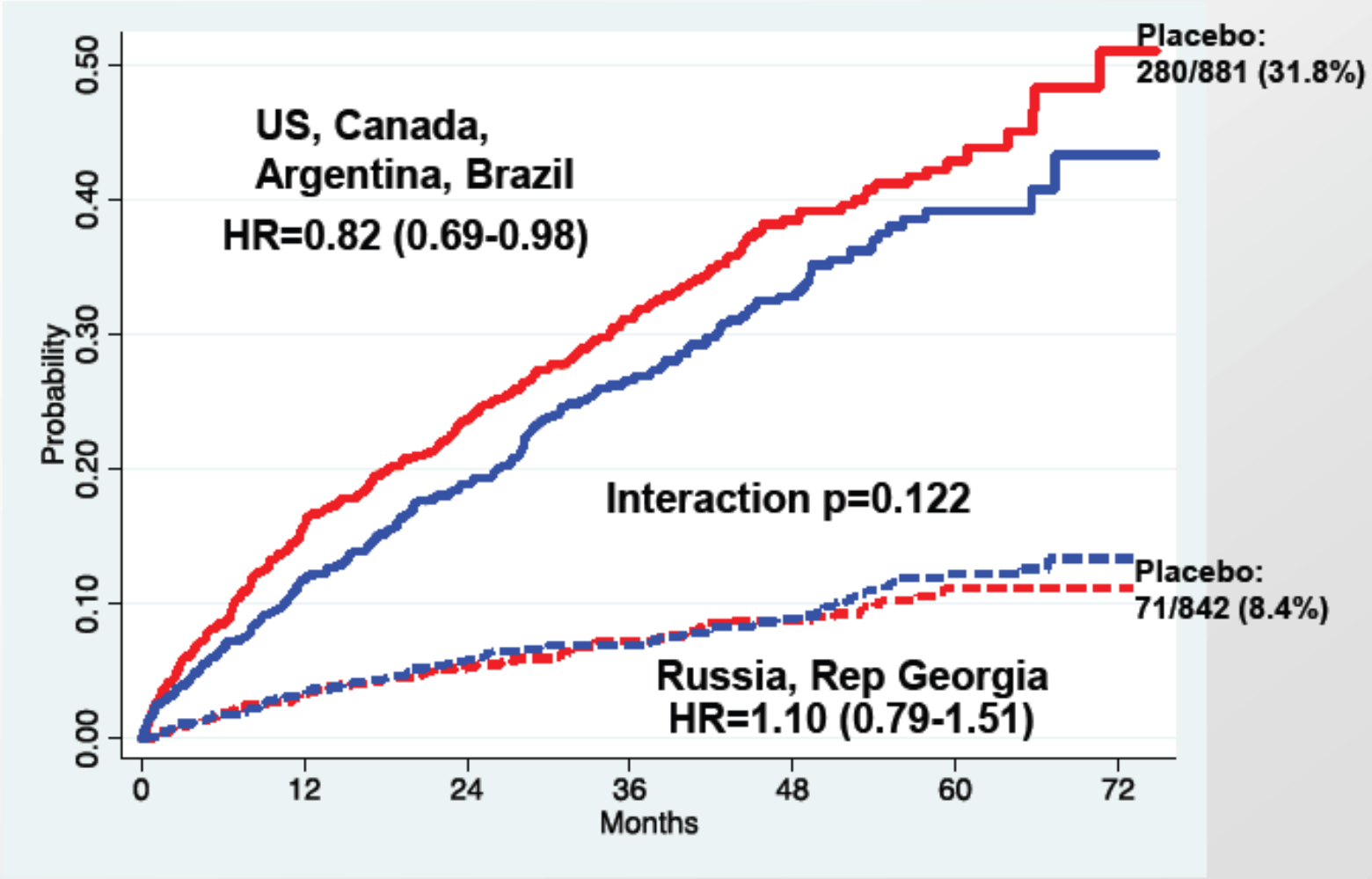


Number at risk

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

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

TOPCAT
Funded by the NHLBI



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**

No lack of creativity

Autonomic nerve modulation
Auto Serve Ventilation breathing
A1 agonist, A2b anatgonists
Biased ligand (Trevena)
Finerenone
Mitochondrial targeting peptide (stealth, and perhexilene)
Myocardial matrices: cell therapies
Natriuretic peptides
Neuregulin
NOACS
Omecamtiv mecabril
PDE inhibitors
Serelaxin
Stresscopin
Vericiguat
…/…