Kantonsspital
St.Gallen

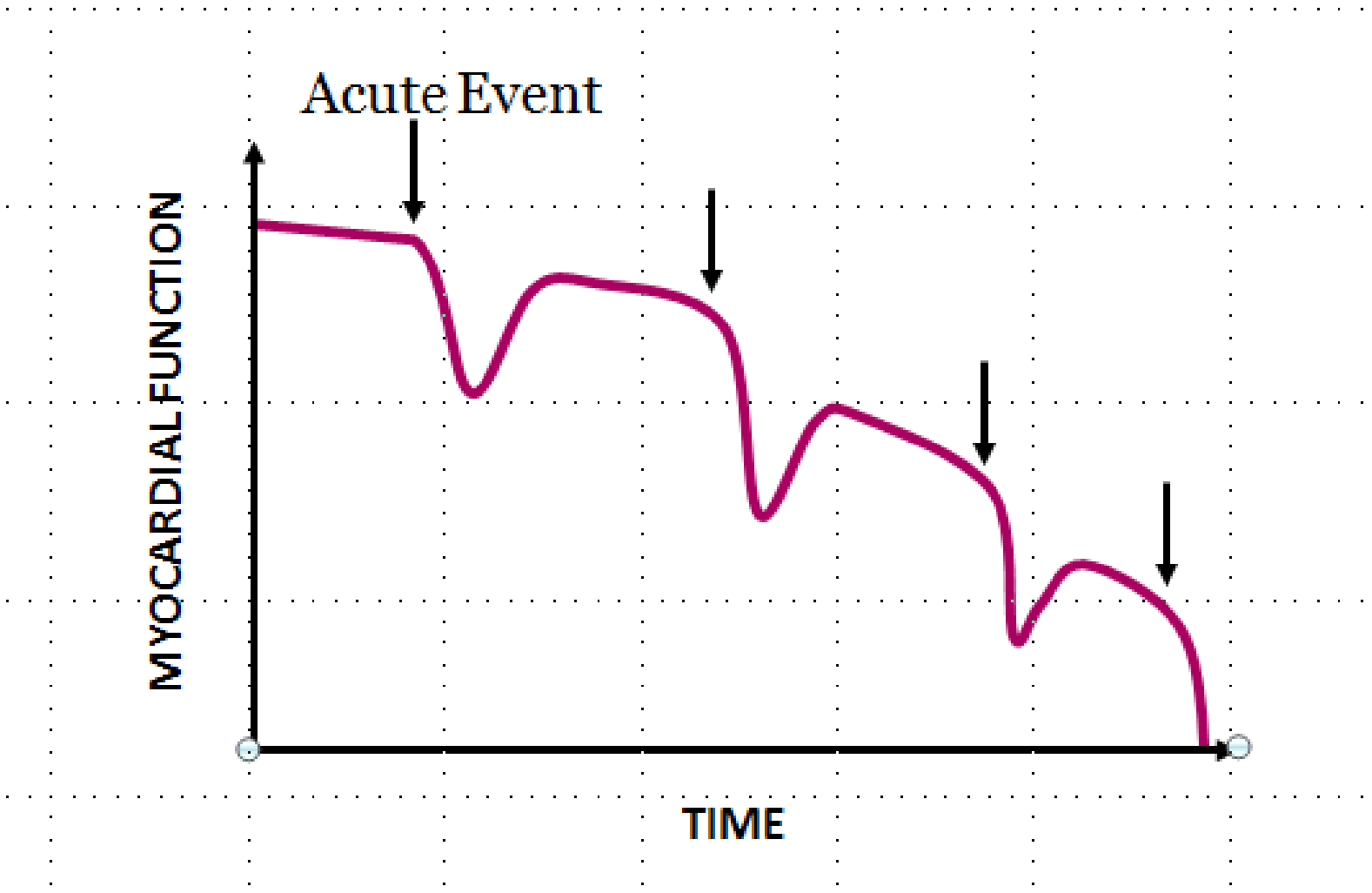
Risk Factors for Heart Failure Readmissions

Micha T. Maeder, MD, PhD
Cardiology Department
Kantonsspital St. Gallen
micha.maeder@kssg.ch

Disclosures

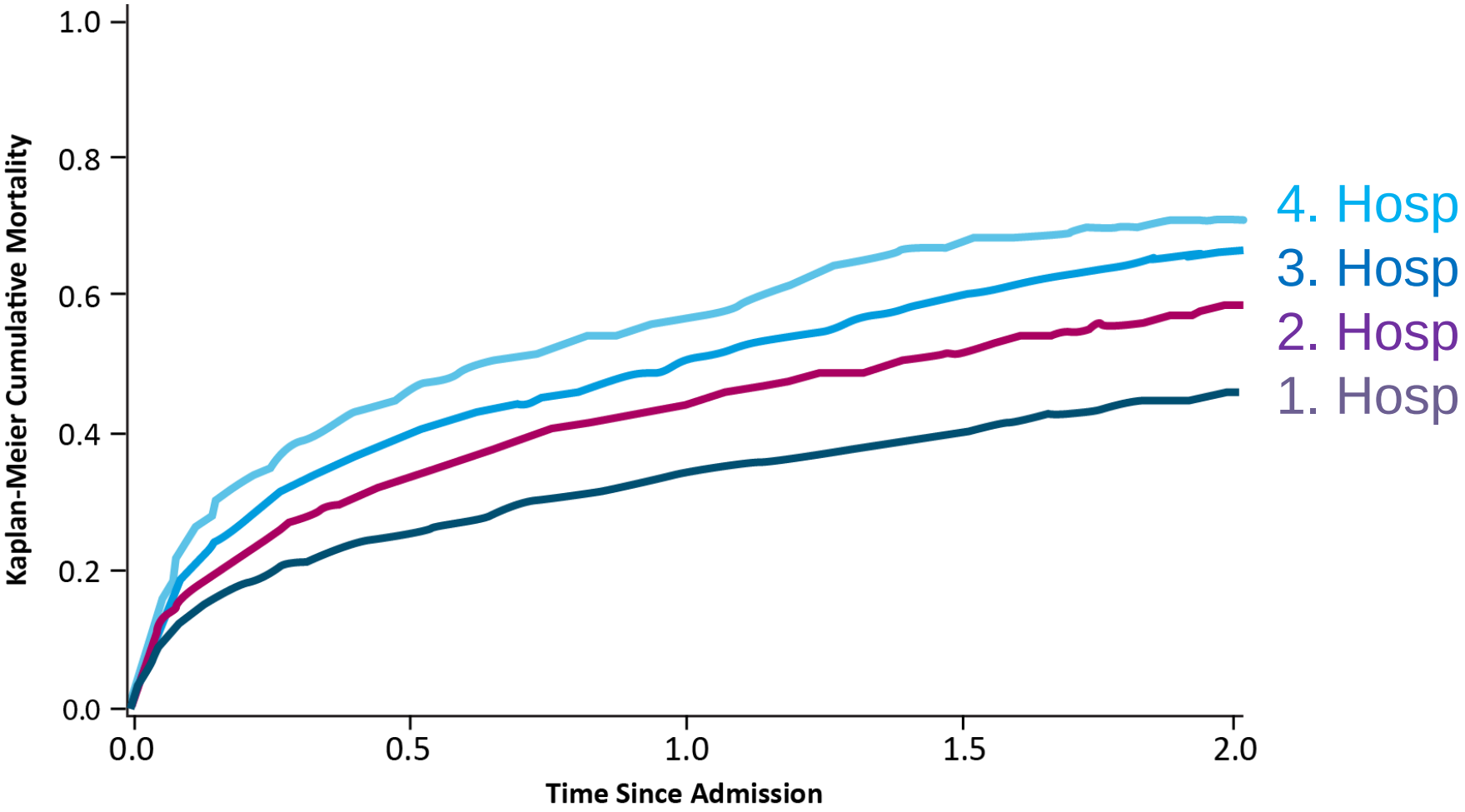
- Honoraria for talks and advisory board participation from Novartis, Servier, Vifor, AstraZena, Bayer

Natural history



Setoguchi et al. Am Heart J 2007

Hospitalisations and Mortality



Setoguchi et al. Am Heart J 2007

Advanced HF (old)

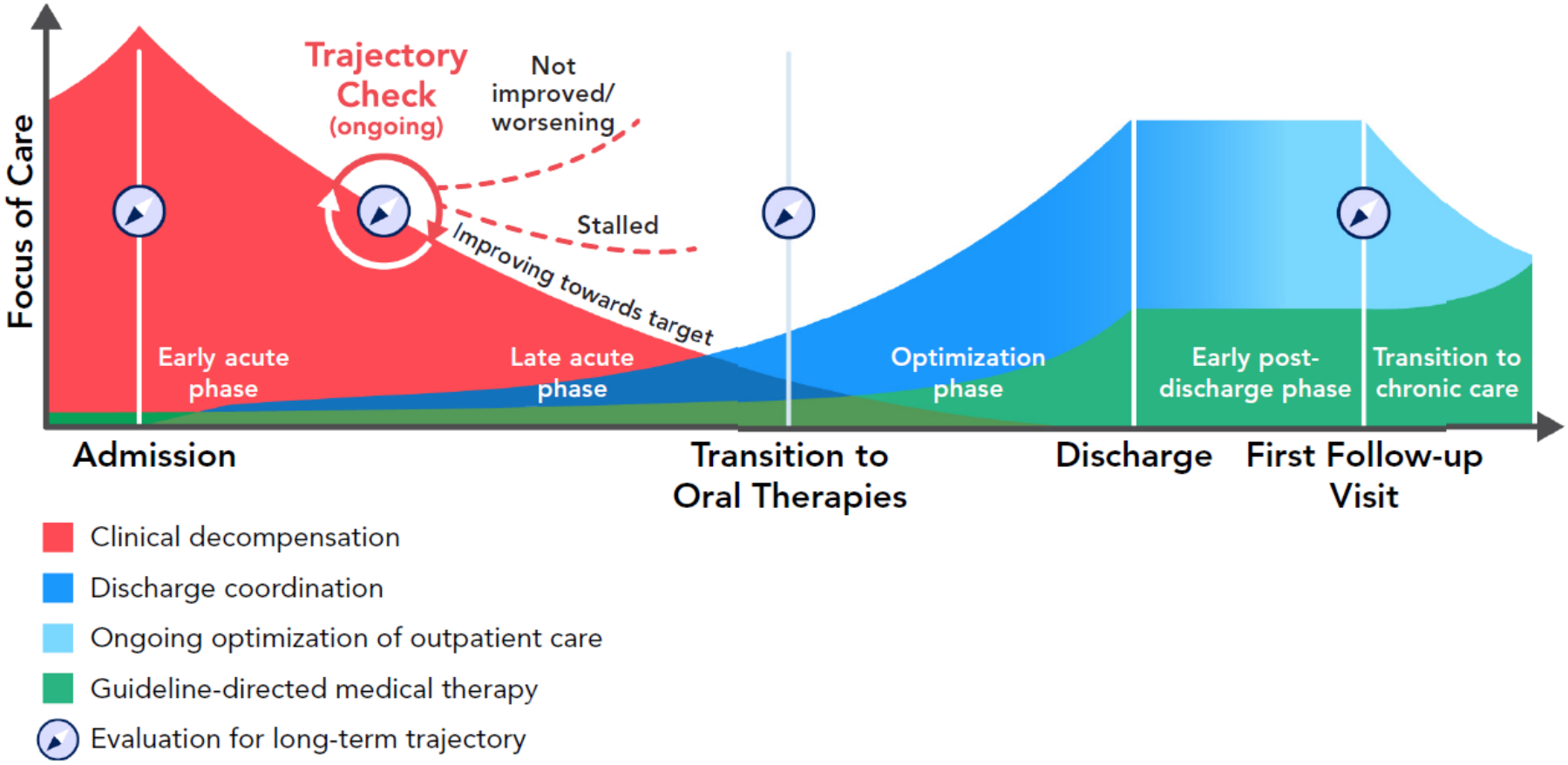
- **NYHA III/IV**
- Episodes of **congestion and/or hypoperfusion**
- **Severe cardiac dysfunction**
  - LVEF<30%
  - Diastolic dysfunction grade 2 or 3
  - Mean PAWP >16 mmHg and/or mean RAP >12 mmHg
  - «high» BNP/NT-proBNP
- **Severley impaired functional capacity**
  - 6-MWD <300 m
  - Peak VO_2 <12-14 ml/min/kg
- ≥1 HF **hospitalization** within 6 months
- Presence of these features **despite attempts to optimize therapy**

Metra M et al. Eur J Heart Fail 2007

Advanced HF (new)

- **NYHA III/IV**
- **Severe cardiac dysfunction**
  - LVEF<30%
  - Isolated RV failure
  - Non-operable valve disease or congenital heart disease
  - «severe HFpEF or HFmrEF»
  - «persistently high» BNP/NT-proBNP
- Episodes of **congestion** requiring high-dose iv diuretics or **low output** requiring inotropes or vasoactive drugs or **malignant arrhythmia** causing **>1 unplanned visit or hospitalisation in the last 12 months**
- **Severley impaired functional capacity**
  - 6-MWD <300 m or peak VO_2 <12-14 ml/min/kg

Crespo-Leiro MG et al. Eur J Heart Fail 2018



Hollenberg SM et al. JACC 2019

Predictors of Re-Hospitalization

Swiss data (TIME-CHF)

Table V. Multivariable outcome predictors

30-d outcome	OR	95% CI	P	90-d outcome	OR	95% CI	P
Angina	2.68	1.50-4.79	<.01	CAD	2.06	1.31-3.22	.02
Systolic BP (per mm Hg)	.97	0.96-0.99	<.01	PM	2.07	1.19-3.62	.01
Anemia	1.80	1.02-3.20	.04	Charlson score (per class)	1.15	1.01-1.30	.03
Edema by clinical examination (per class)	1.30	1.01-3.20	.04	Jugular veins (per class)	1.32	1.09-1.62	<.01
Creatinine (per 10 µmol/L)	1.10	1.04-1.18	<.01	Lung rales (per class)	1.34	1.02-1.75	.04
Dry cough (per class)	1.45	1.1-1.9	<.01	Prior abdominal surgery	2.34	1.42-3.86	<.01
				Age (per year)	1.04	1.01-1.07	<.01
				GDS (per class)	1.08	1.01-1.15	.02

OR, odds ratio; *CI*, confidence interval; for the abbreviations, see Tables I-IV.

Muzzarelli S et al. Am Heart J 2010

30 day readmission

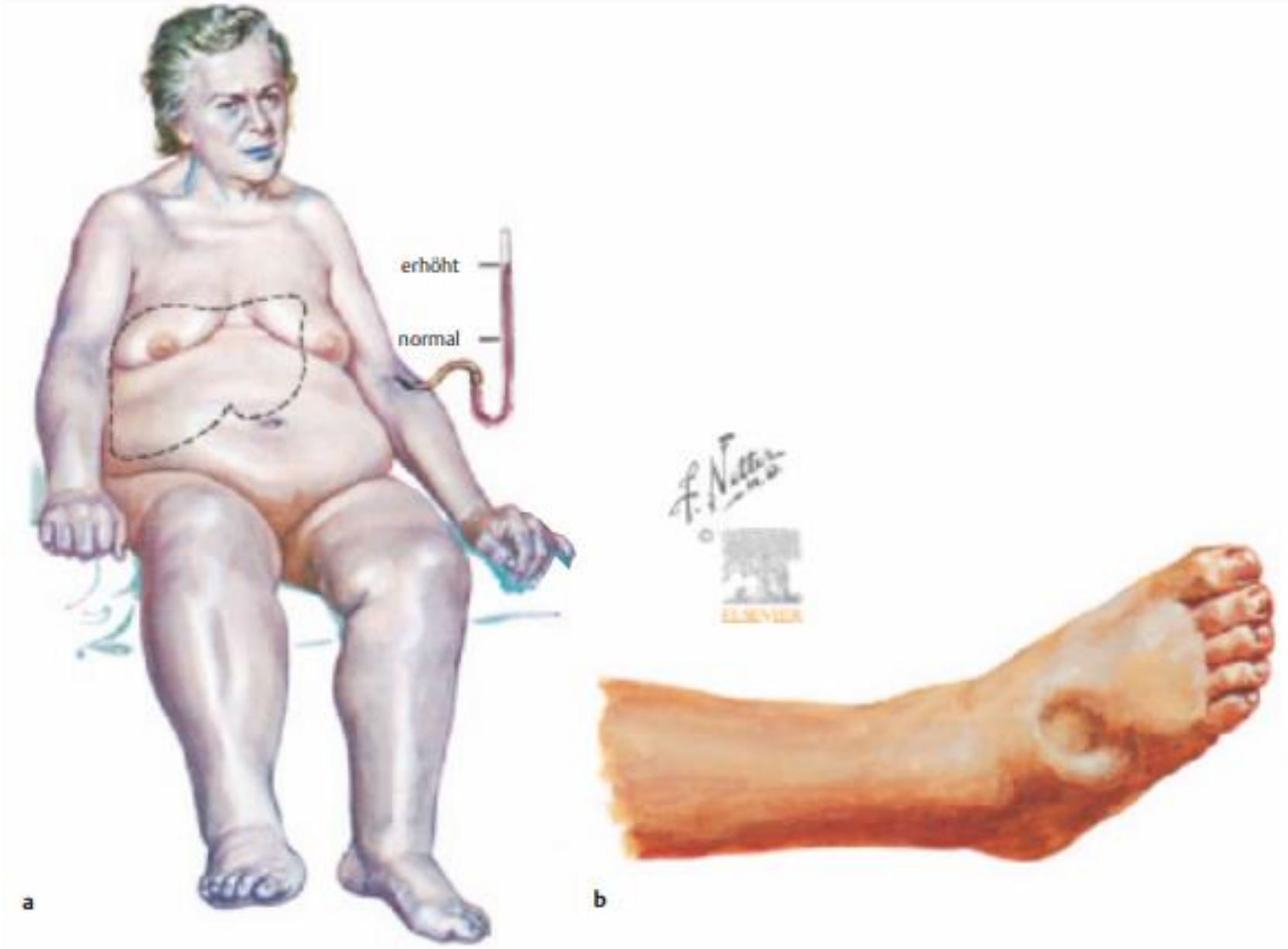
- Edema
- Lower systolic blood pressure
- Higher creatinine
- Anemia
- Angina
- Dry cough

Muzzarelli S et al. Am Heart J 2010

30 day readmission

- Edema
- Lower systolic blood pressure
- Higher creatinine
- Anemia
- Angina
- Dry cough

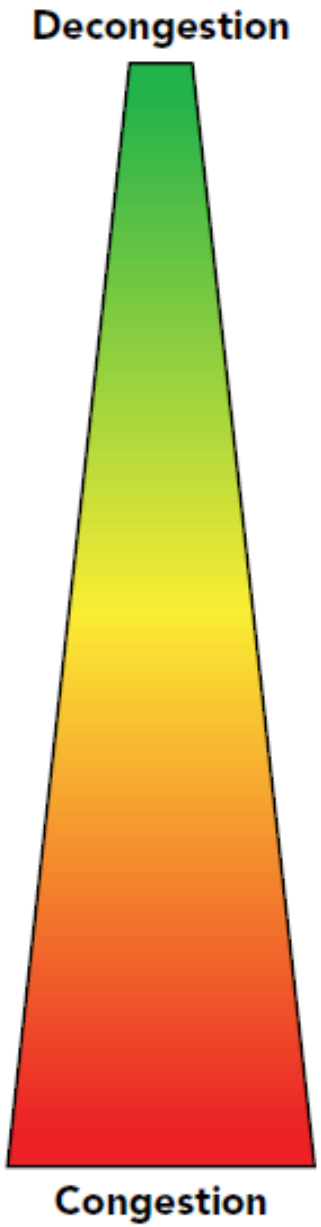
Muzzarelli S et al. Am Heart J 2010


erhöht
normal
a
b

Clinical Findings and Hemodynamics

PARAMETER	Estimation of	Sens (%)	Spec (%)
JVP	RAP	48	78
Edema		10	94
BP amplitude	Cardiac Index	27	69
S3	PAWP	36	81
Rales		13	90

Capomolla et al. Eur J Heart Fail 2005



Freedom from clinical congestion

No peripheral edema

No rales

No dyspnea on minimal exertion

No hepatomegaly or congestive GI symptoms

No orthopnea or bendopnea

Jugular venous pressure ≤6-8 mm Hg

No hepatojugular reflex

Common reasons for Residual Congestion

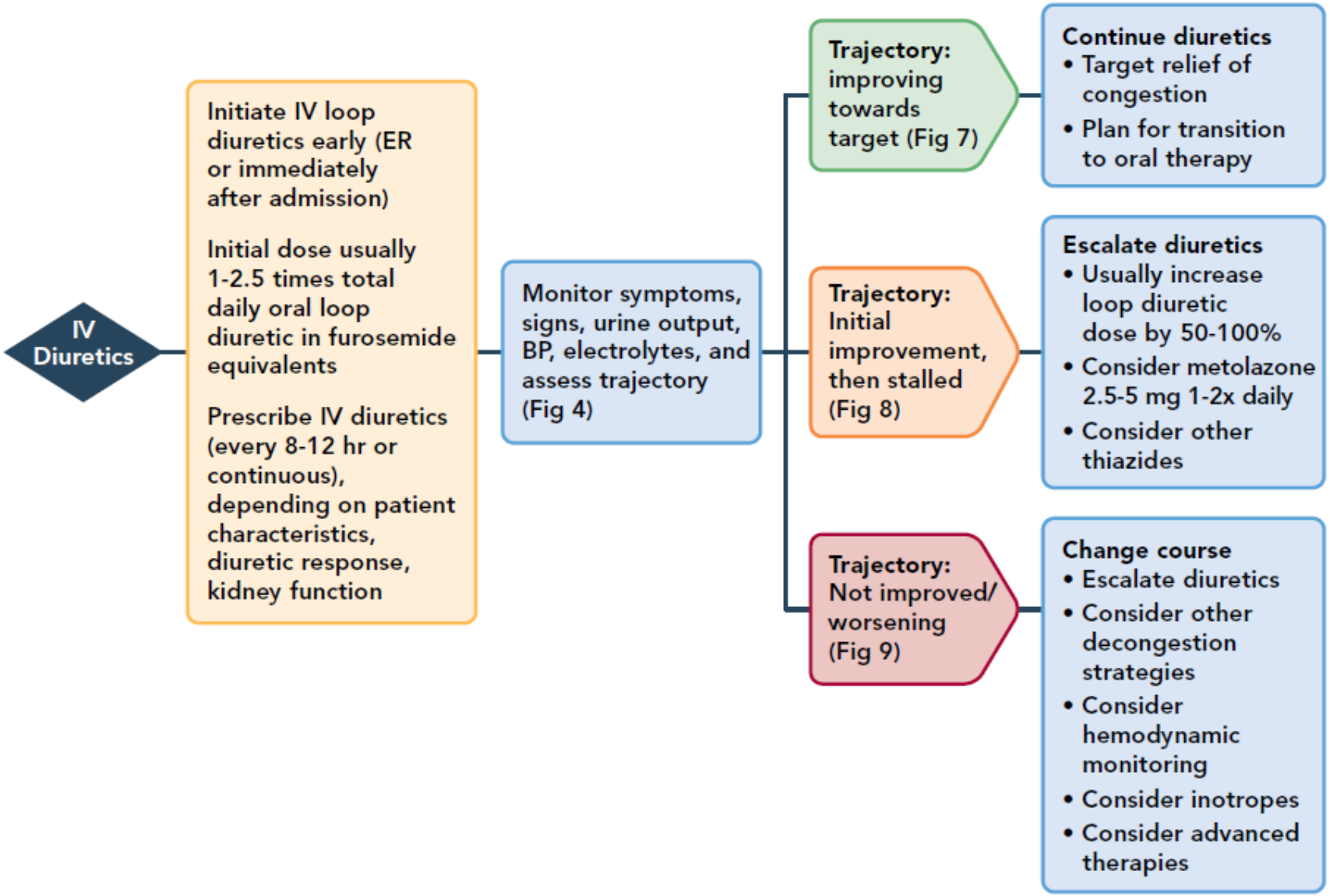
Low cardiac output state
Dominant right heart failure
Advanced renal disease
Symptomatic hypotension
Limitations to patient engagement in self-care

Lack of improvement in signs/symptoms of HF

Lack of decrease in natriuretic peptide levels

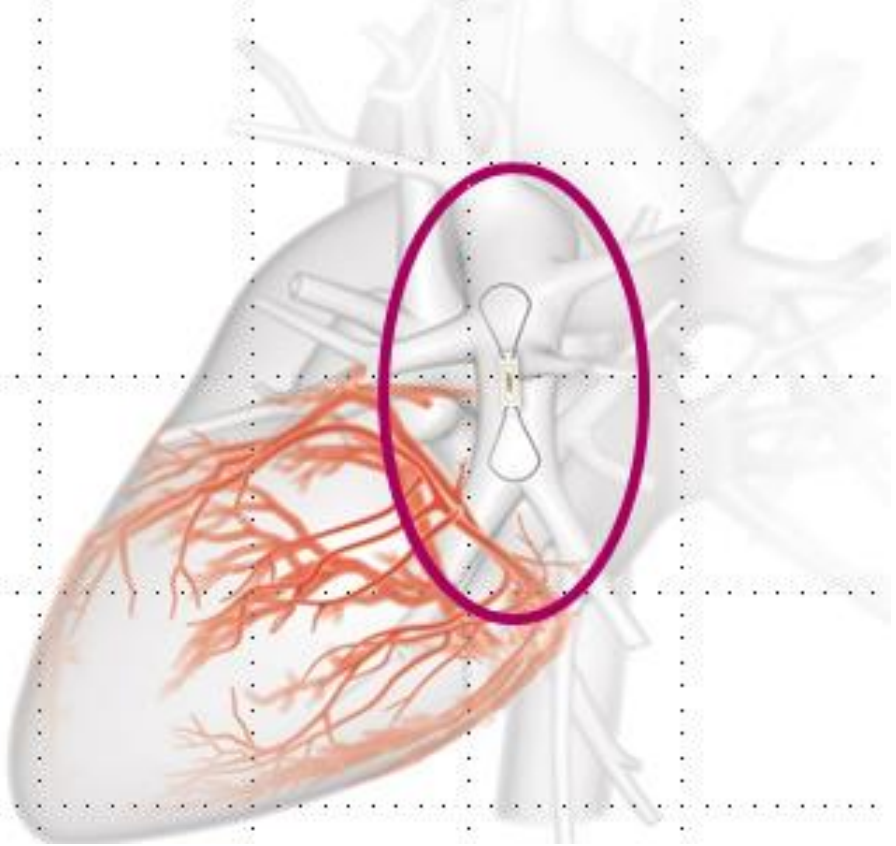
Lack of decrease in weight

Hollenberg SM et al. JACC 2019

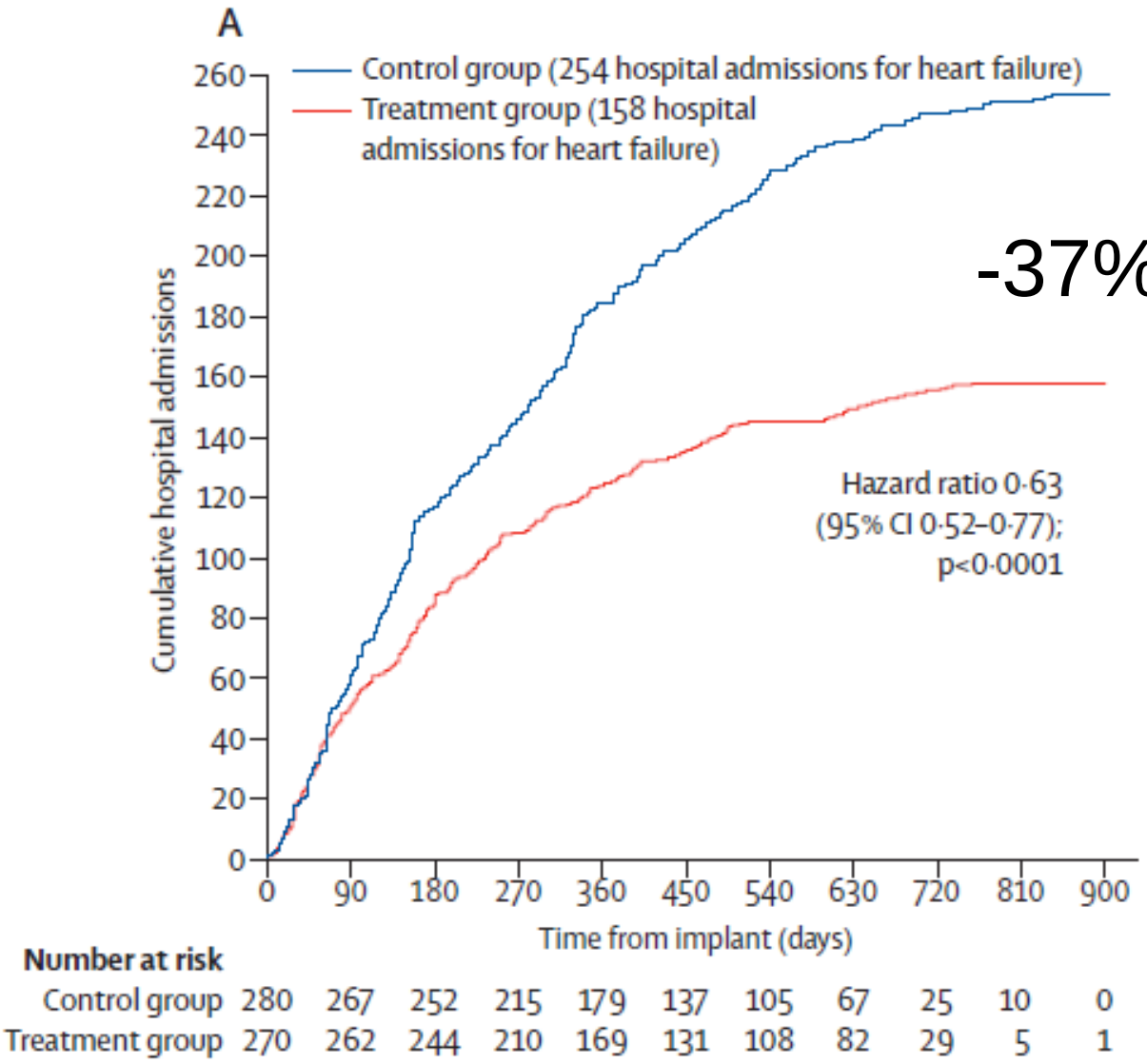


Hollenberg SM et al. JACC 2019

TARGET LOCATION FOR PA PRESSURE SENSOR

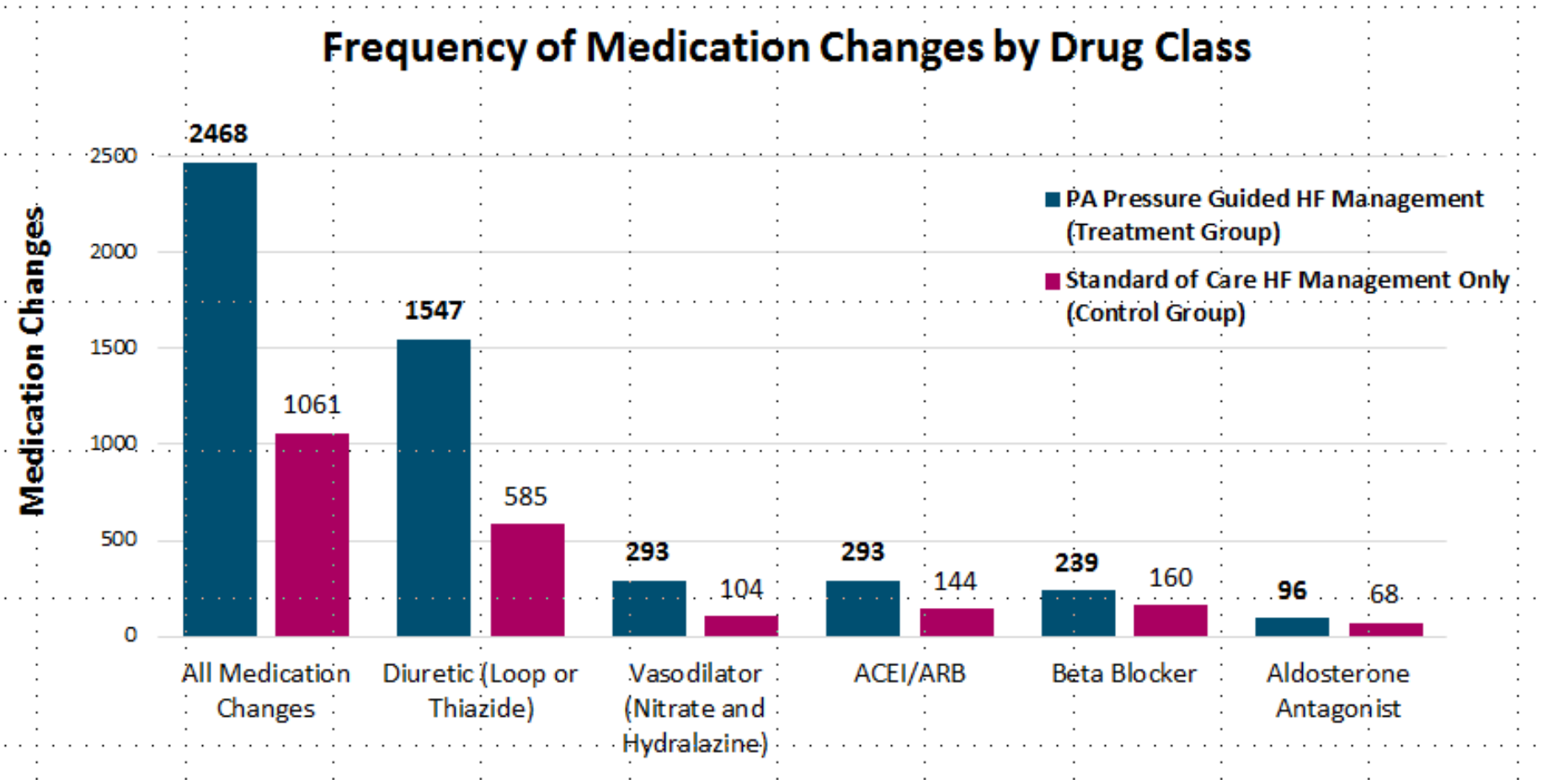


Primary EP: HF Hospitalizations



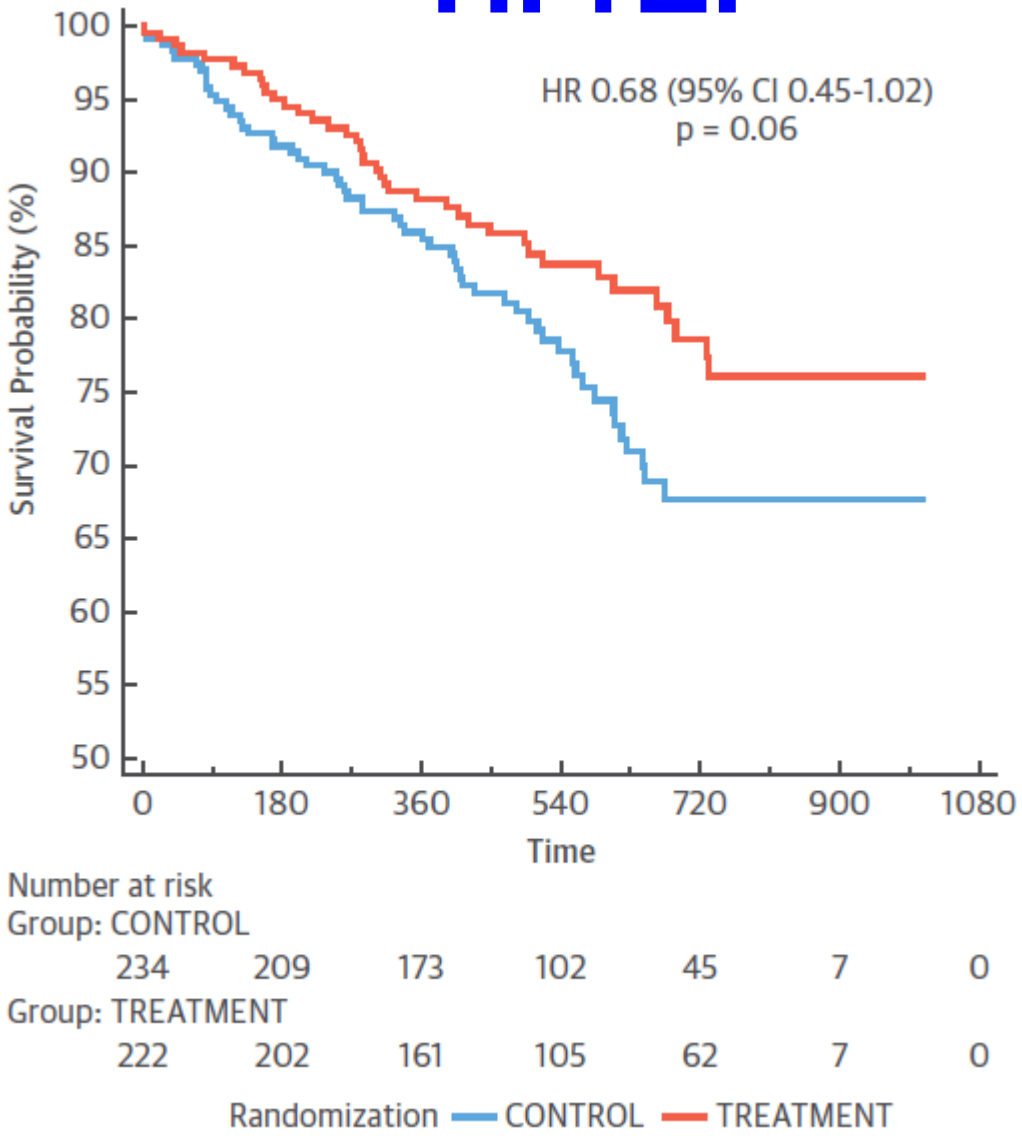
-37%

Abraham et al. Lancet 2011



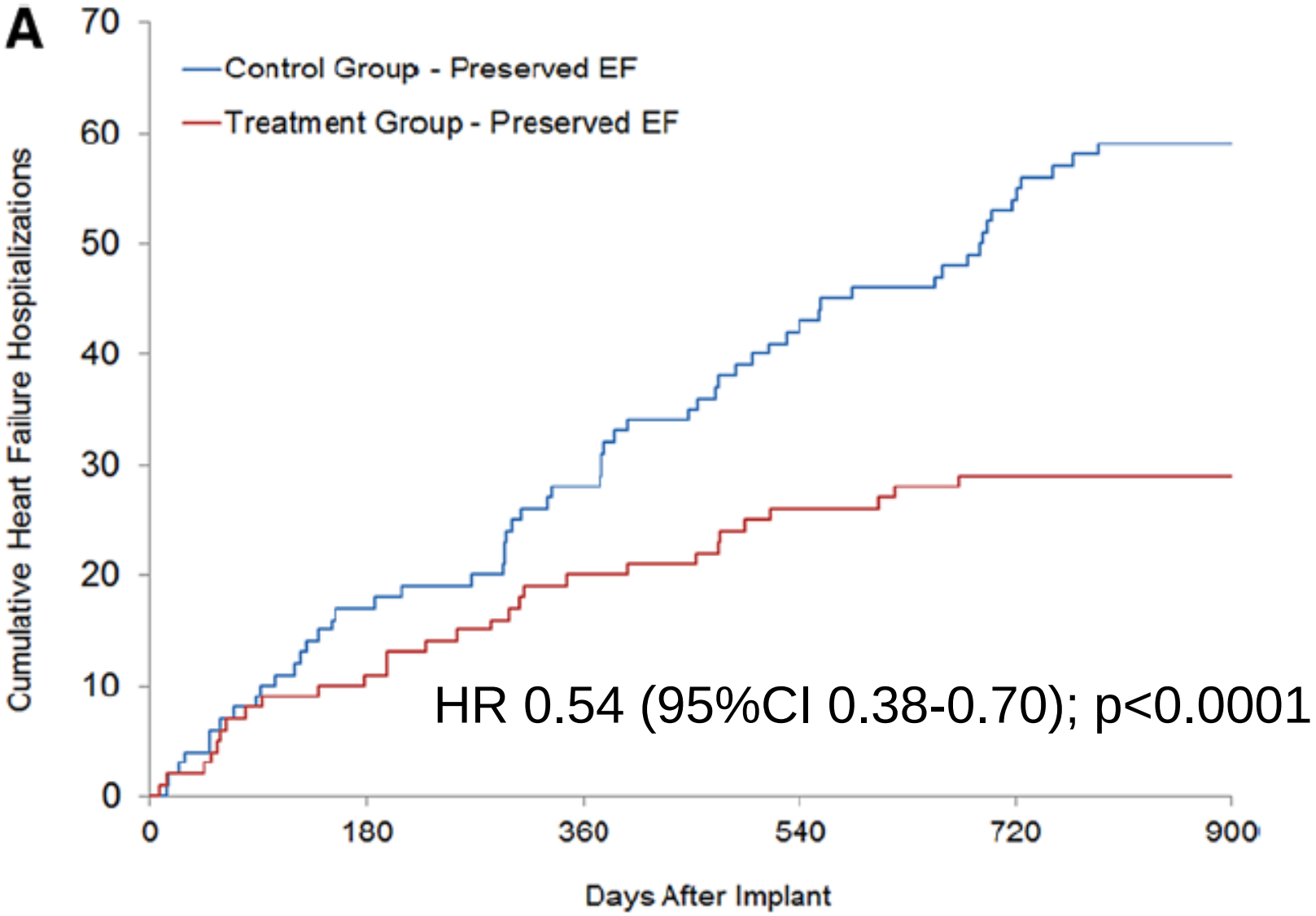
Costanzo et al. JACC HF 2016

HFrEF



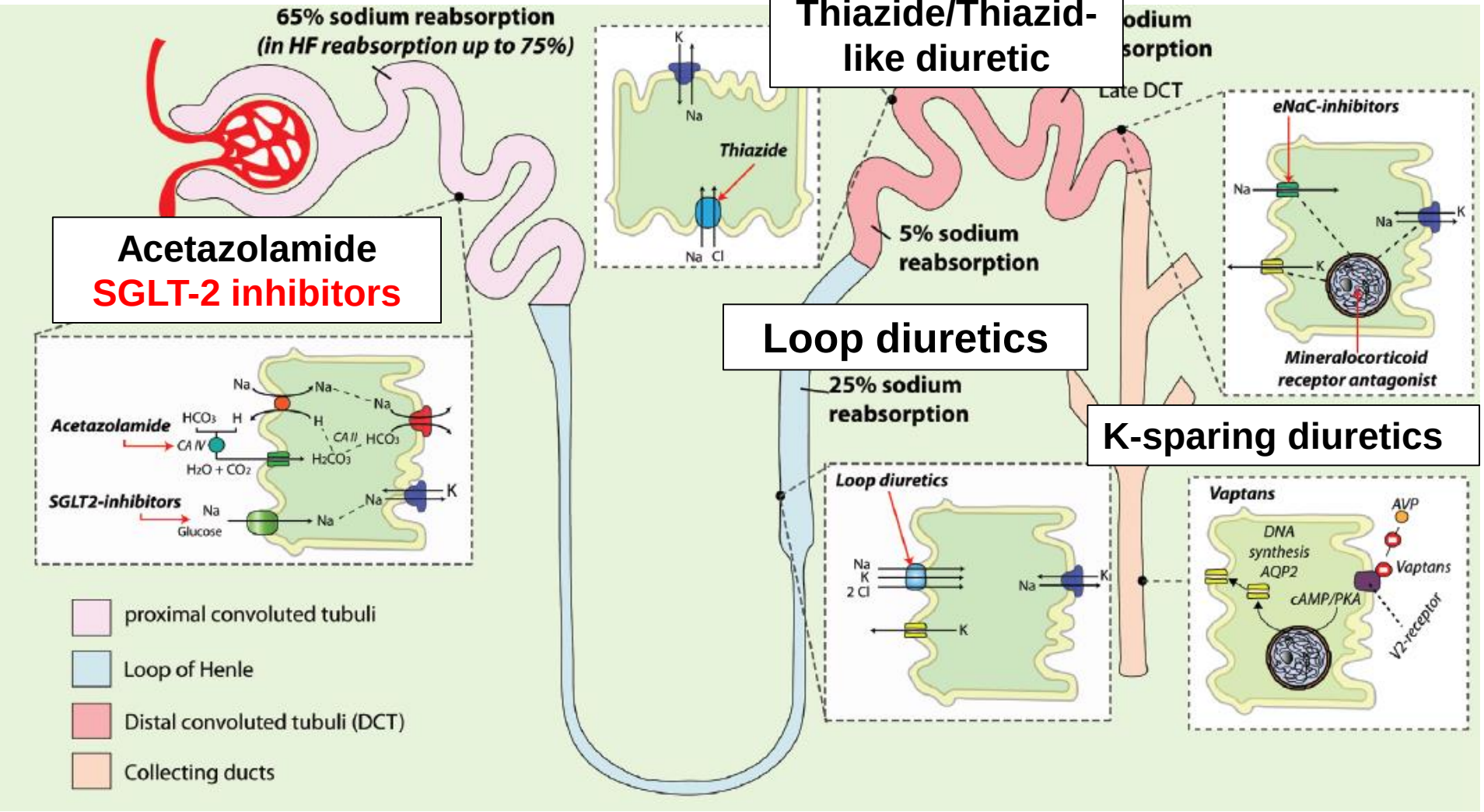
Givertz et al. JACC 2017

HFpEF

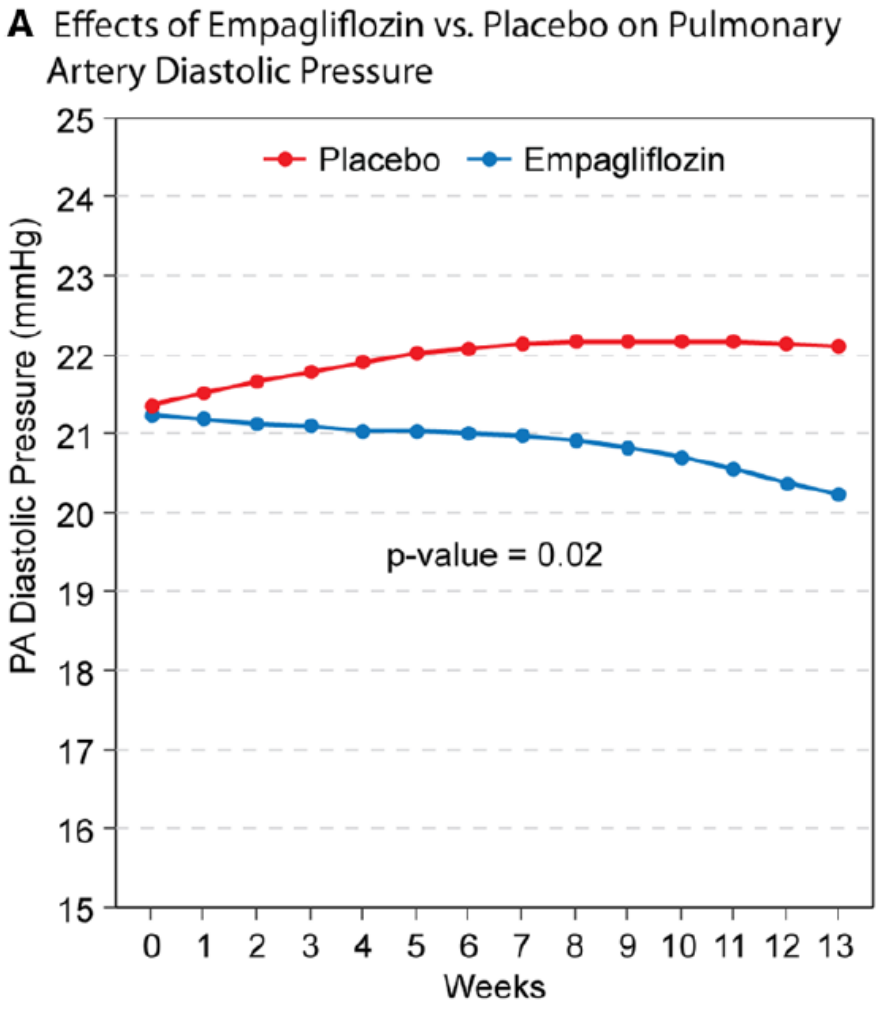


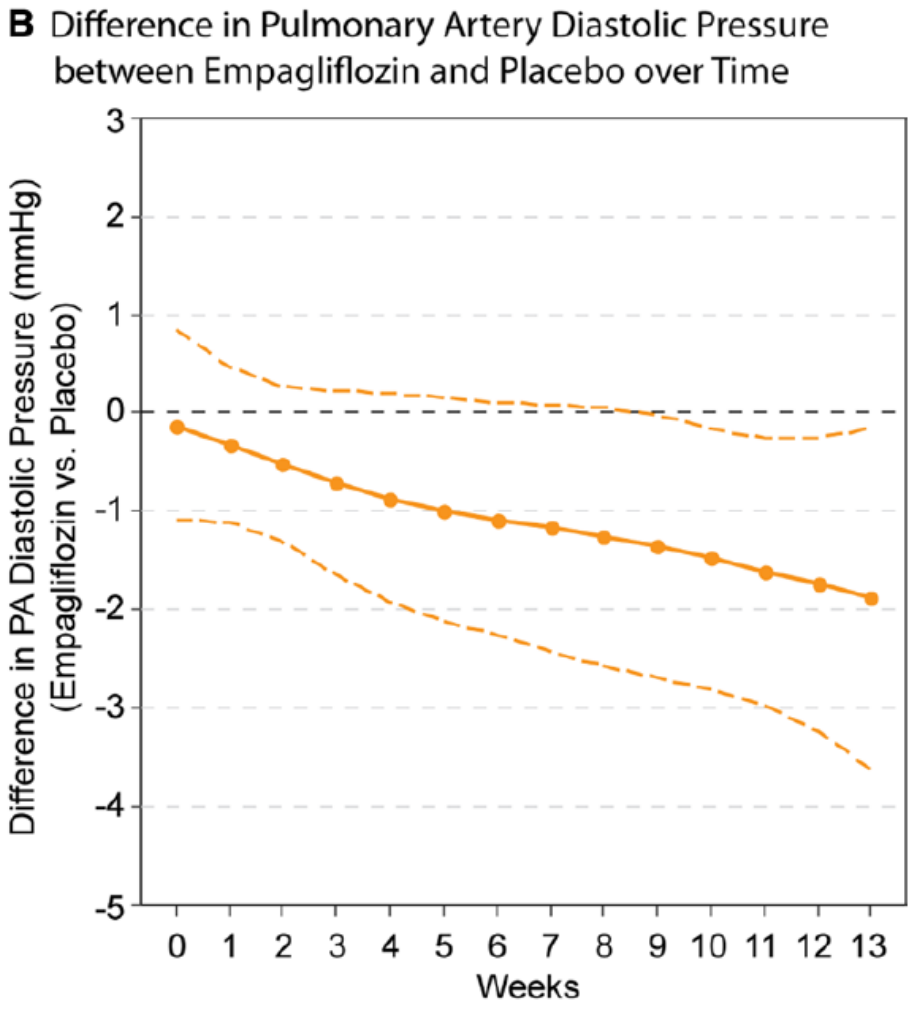
Adamson et al. Circ HF 2014

SGLT2- inhibitors: Diuretic effect



Empagliflozin: Effect on pulmonary pressure





Nassif ME et al. Circulation 2021

30 day readmission

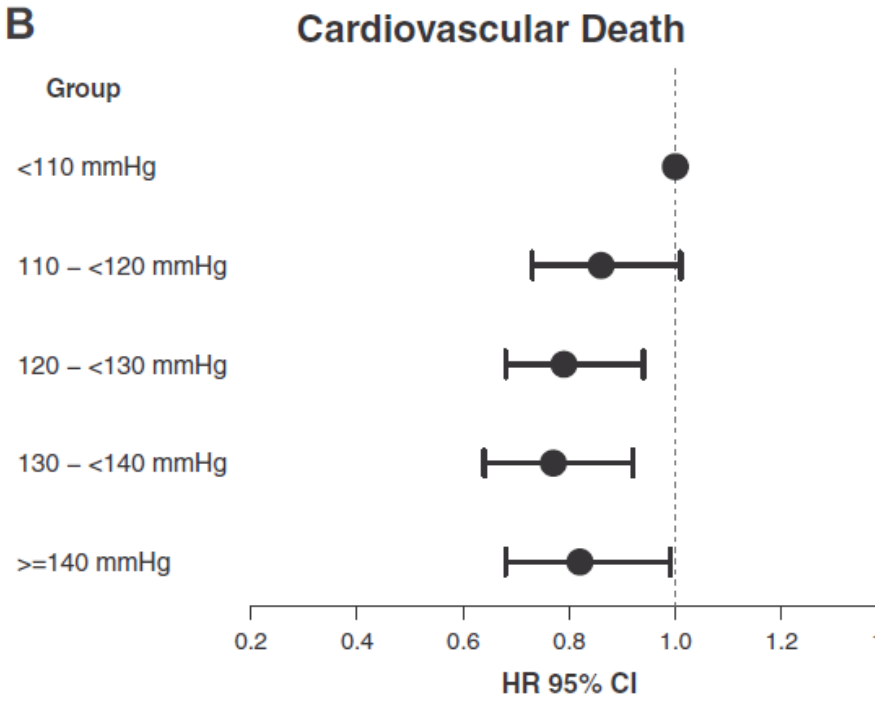
- Edema
- Lower systolic blood pressure
- Higher creatinine
- Anemia
- Angina
- Dry cough

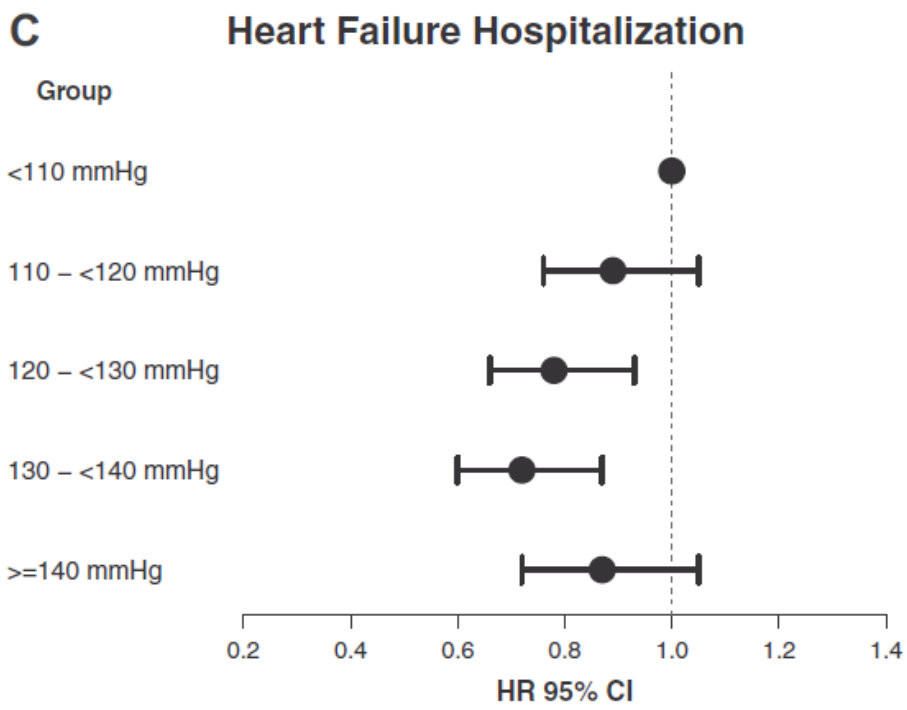
Muzzarelli S et al. Am Heart J 2010

Systolic BP

- Depends on stroke volume and systemic vascular resistance
- Low systolic BP = marker of poor prognosis
- Difficult to manage
- Risk of side effects
- Risk of undertreatment

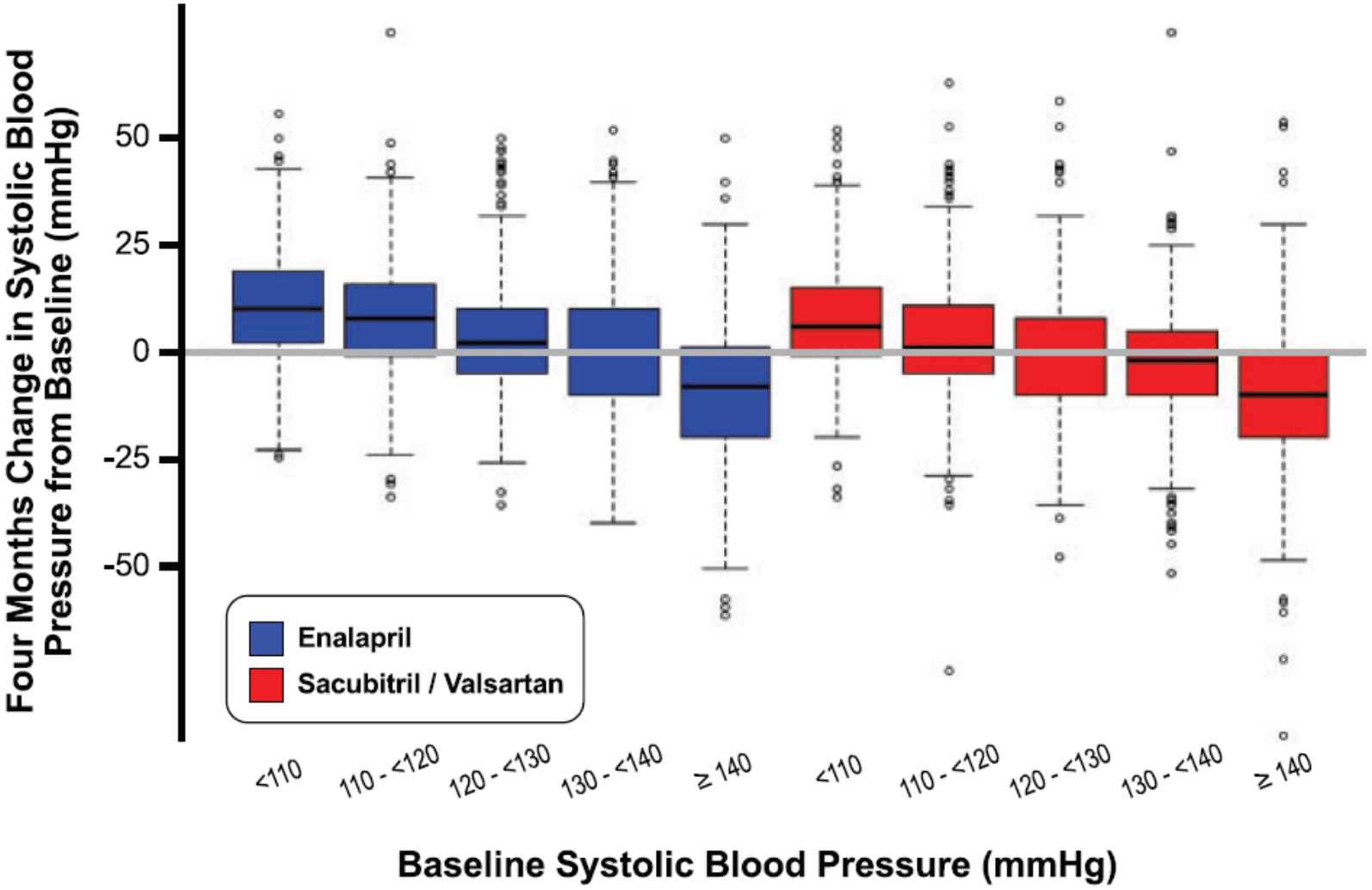
Baseline Systolic Blood Pressure and Outcome





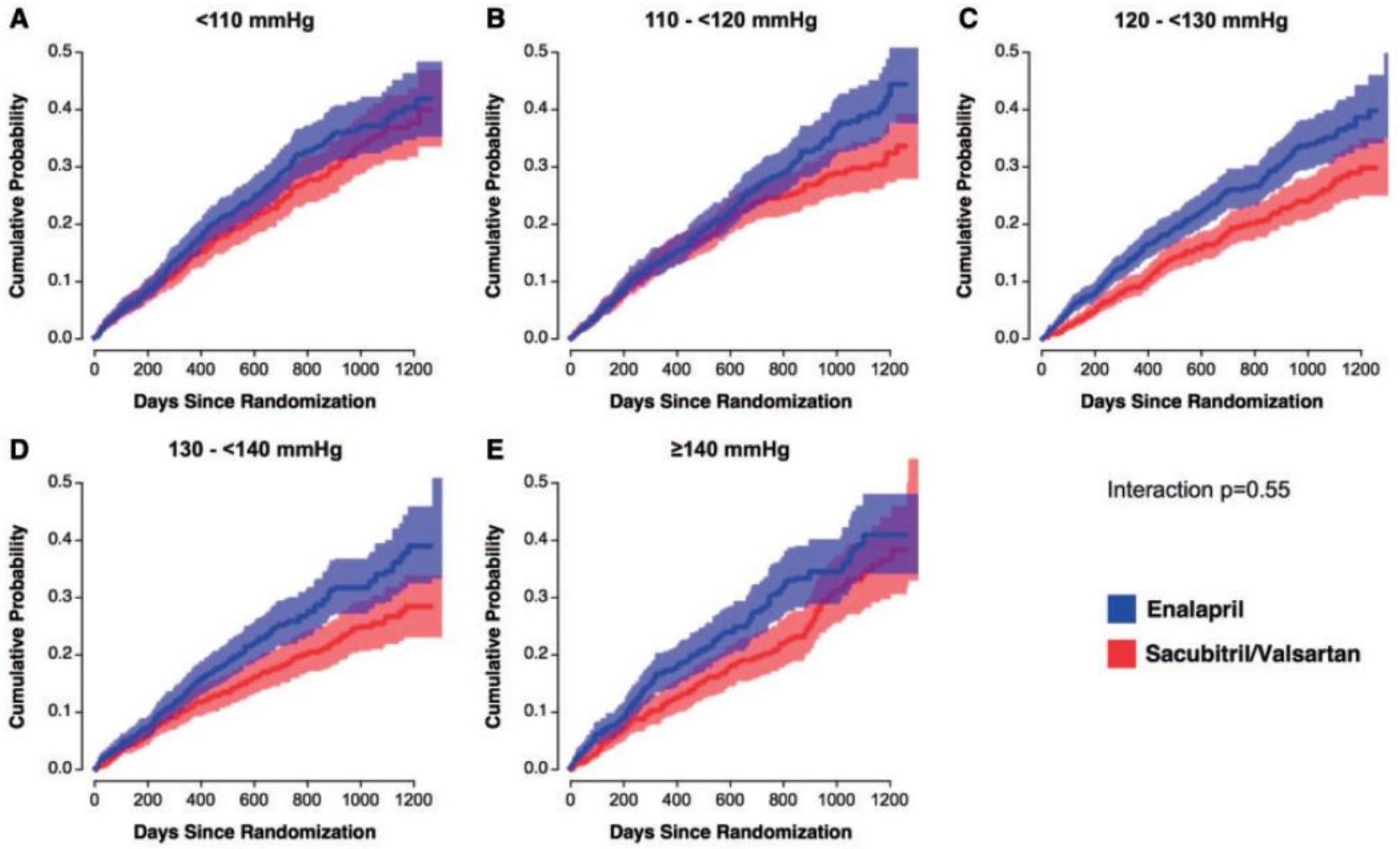
Böhm M et al. Eur Heart J 2017

Change in Systolic Blood Pressure



Böhm M et al. Eur Heart J 2017

Baseline Systolic Blood Pressure and Treatment Effect



Böhm M et al. Eur Heart J 2017

Low BP: practical aspects

- Correct measurement?
- Volume status: hypovolemia?
- Co-medication that is not absolutely neccessary?
  - Nitrates
  - Calcium channel blockers
  - Alpha-blockers

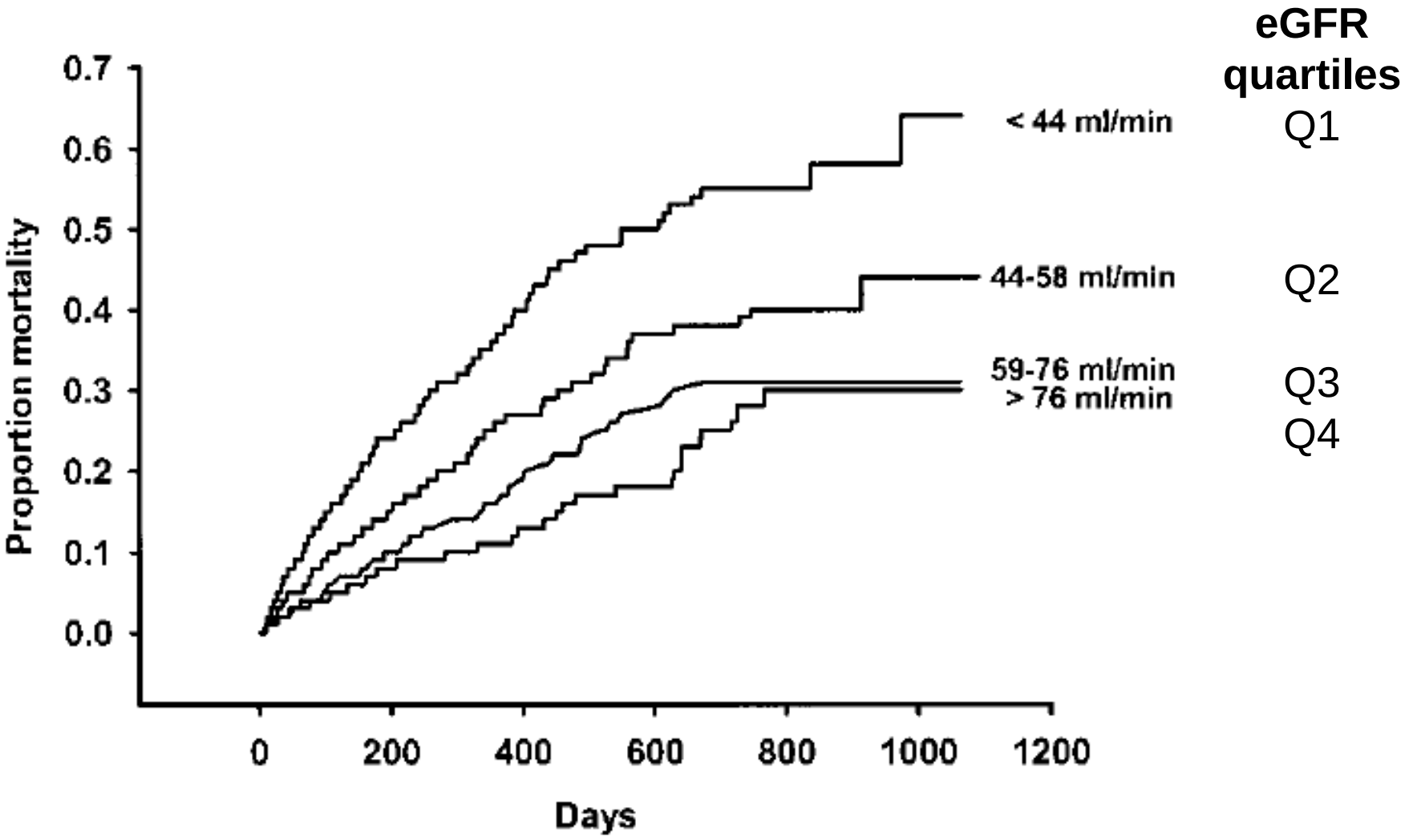
30 day readmission

- Edema
- Lower systolic blood pressure
- Higher creatinine
- Anemia
- Angina
- Dry cough

Muzzarelli S et al. Am Heart J 2010

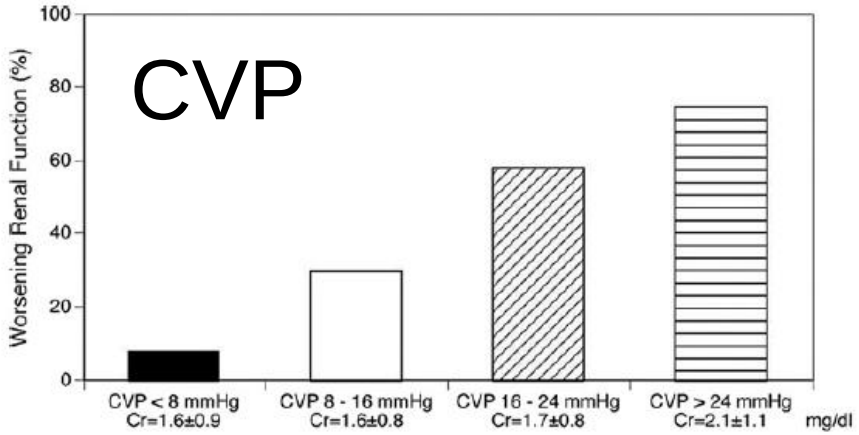
n=1906, age 65±10 years, median eGFR ≅59 ml/min/1.73 m^2

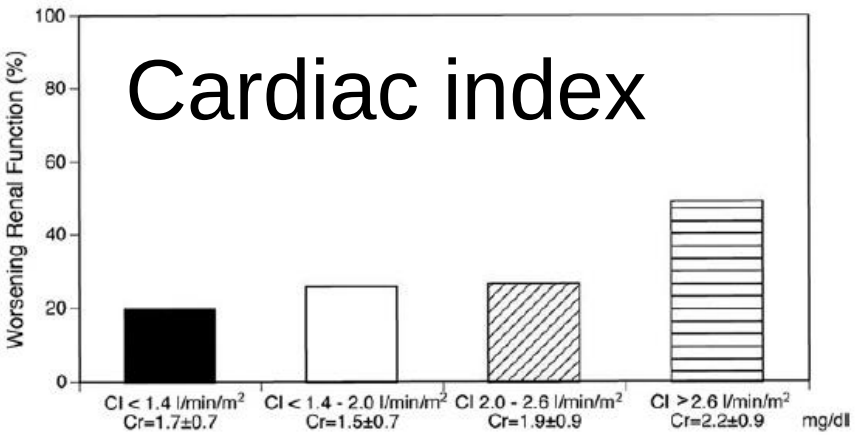
eGFR Q1: threefold risk of death compared to Q4

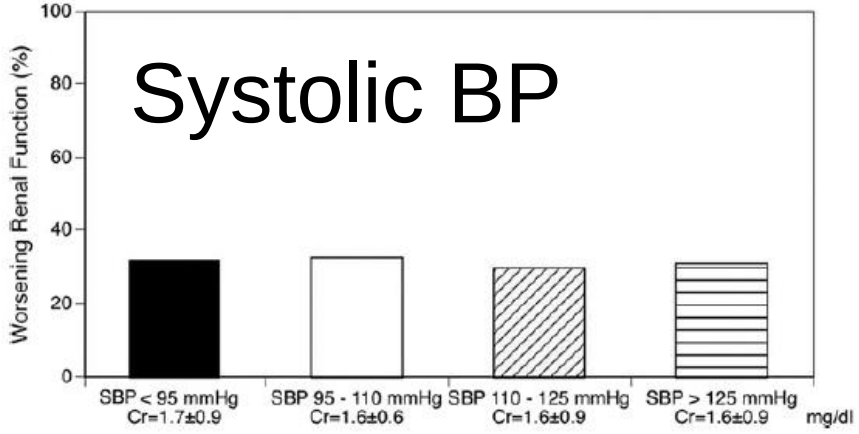


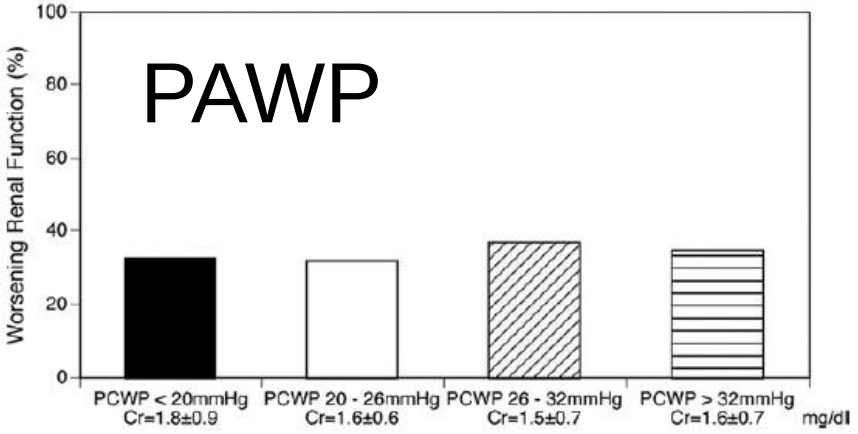
Hillege HL et al. Circulation 2000

Hemodynamics and occurrence of worsening renal function





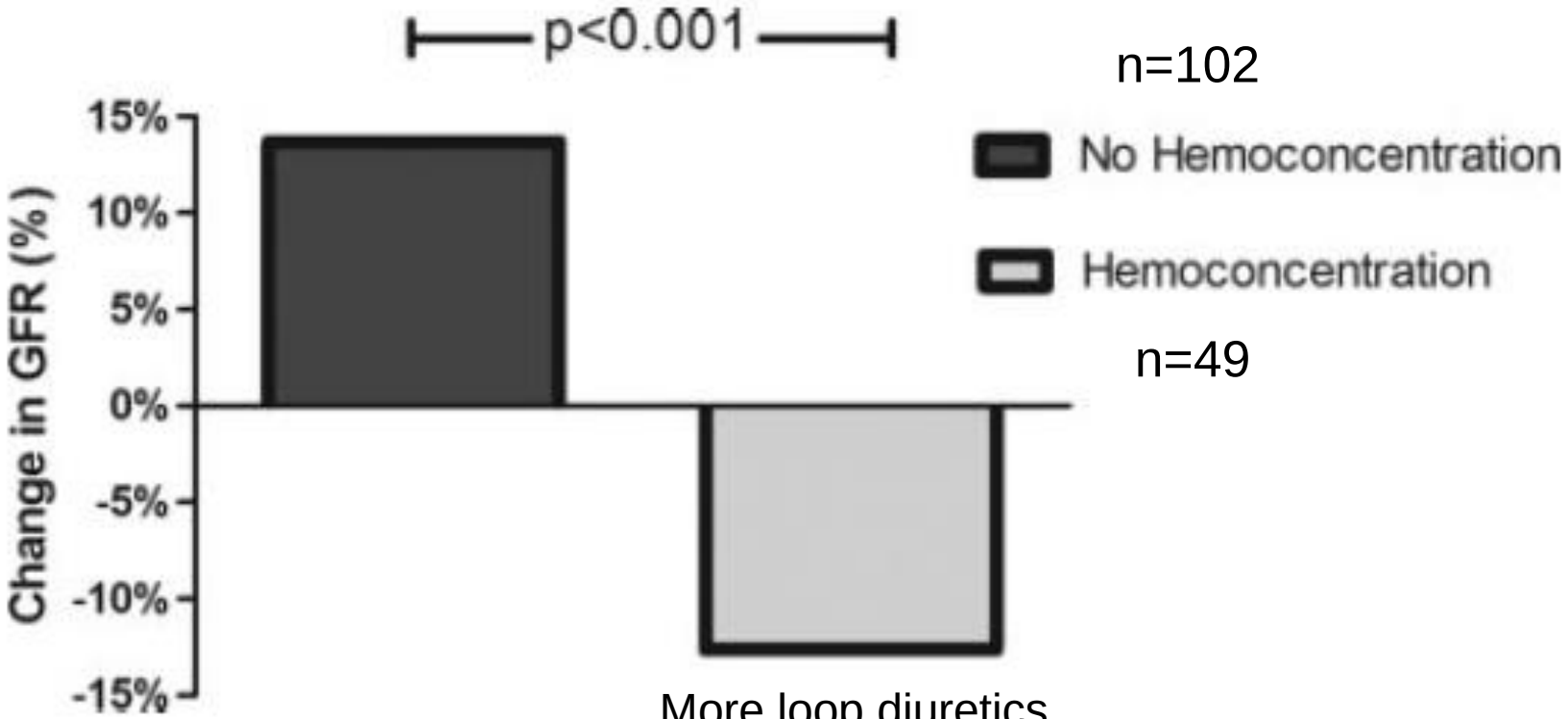




WRF = rise in sCR by ≥0.3 mg/dl

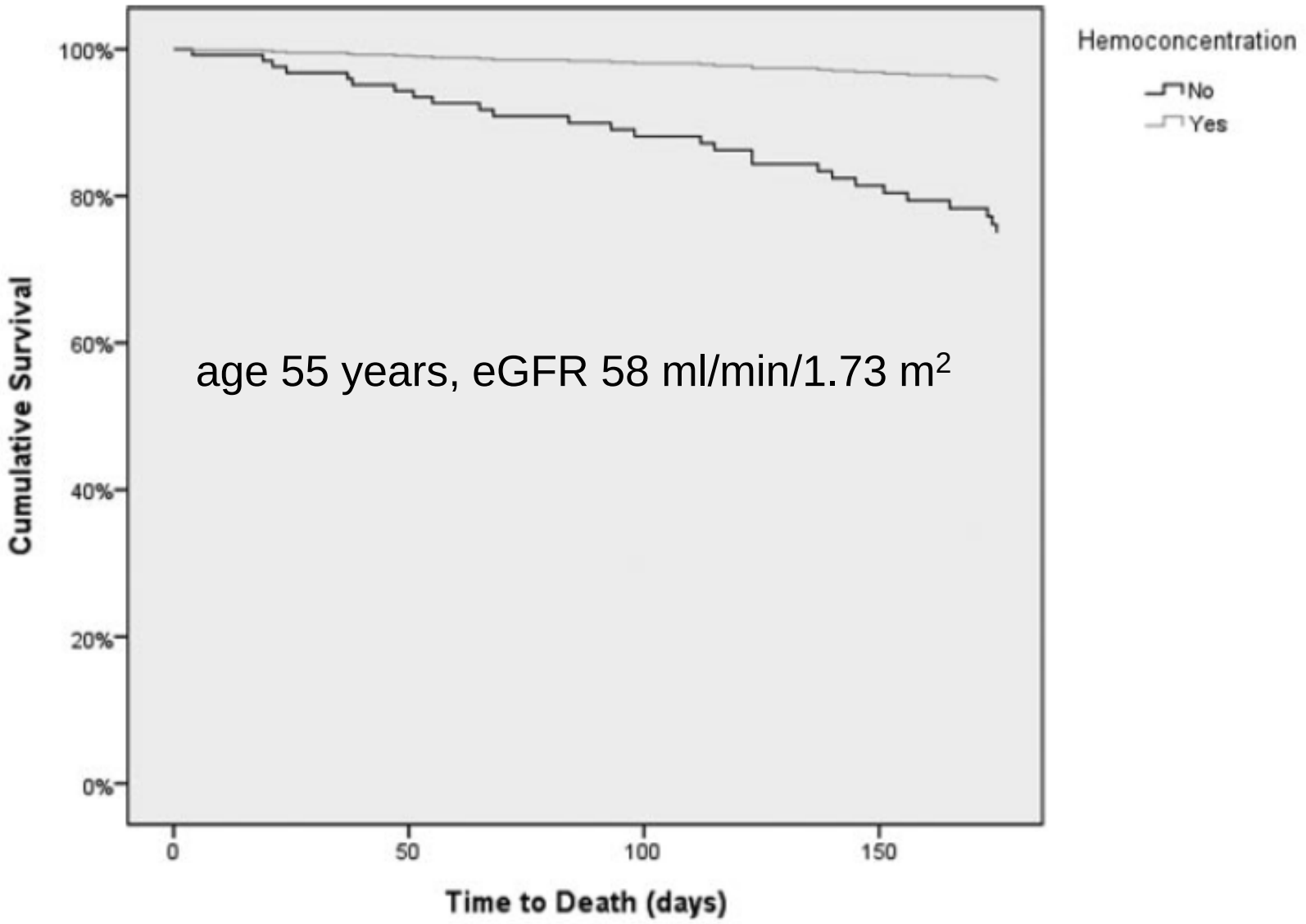
Mullens W et al. J Am Coll Cardiol 2009

Baseline – discharge changes in hematocrit, albumine, total proteine (≥2 parameters in top tertile → hemoconcentration)



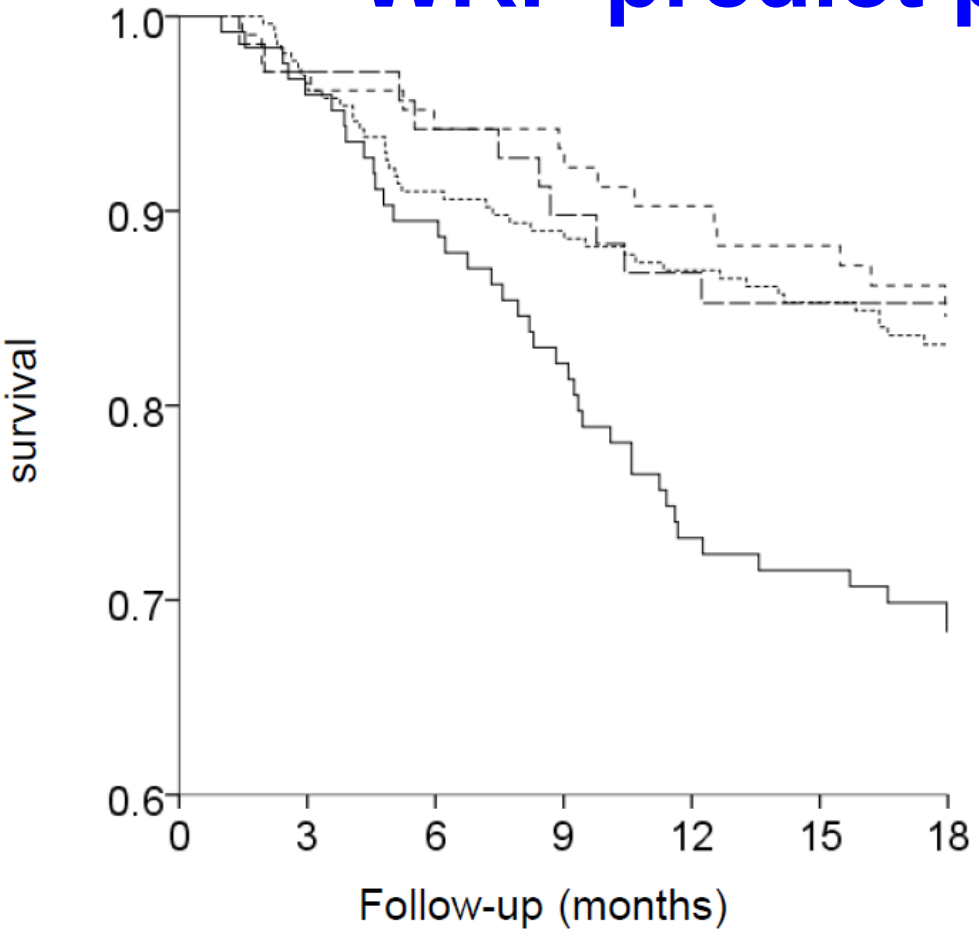
More loop diuretics
More weight loss
Greater reduction in filling pressures

Testani JM et al. Circulation 2010



Testani JM et al. Circulation 2010

WRF III but not milder forms of WRF predict prognosis



Number at risk						
No WRF	267	249	225	218	212	205
WRF I	70	65	63	60	57	52
WRF II	105	100	94	93	89	86
WRF III	124	118	109	100	88	85

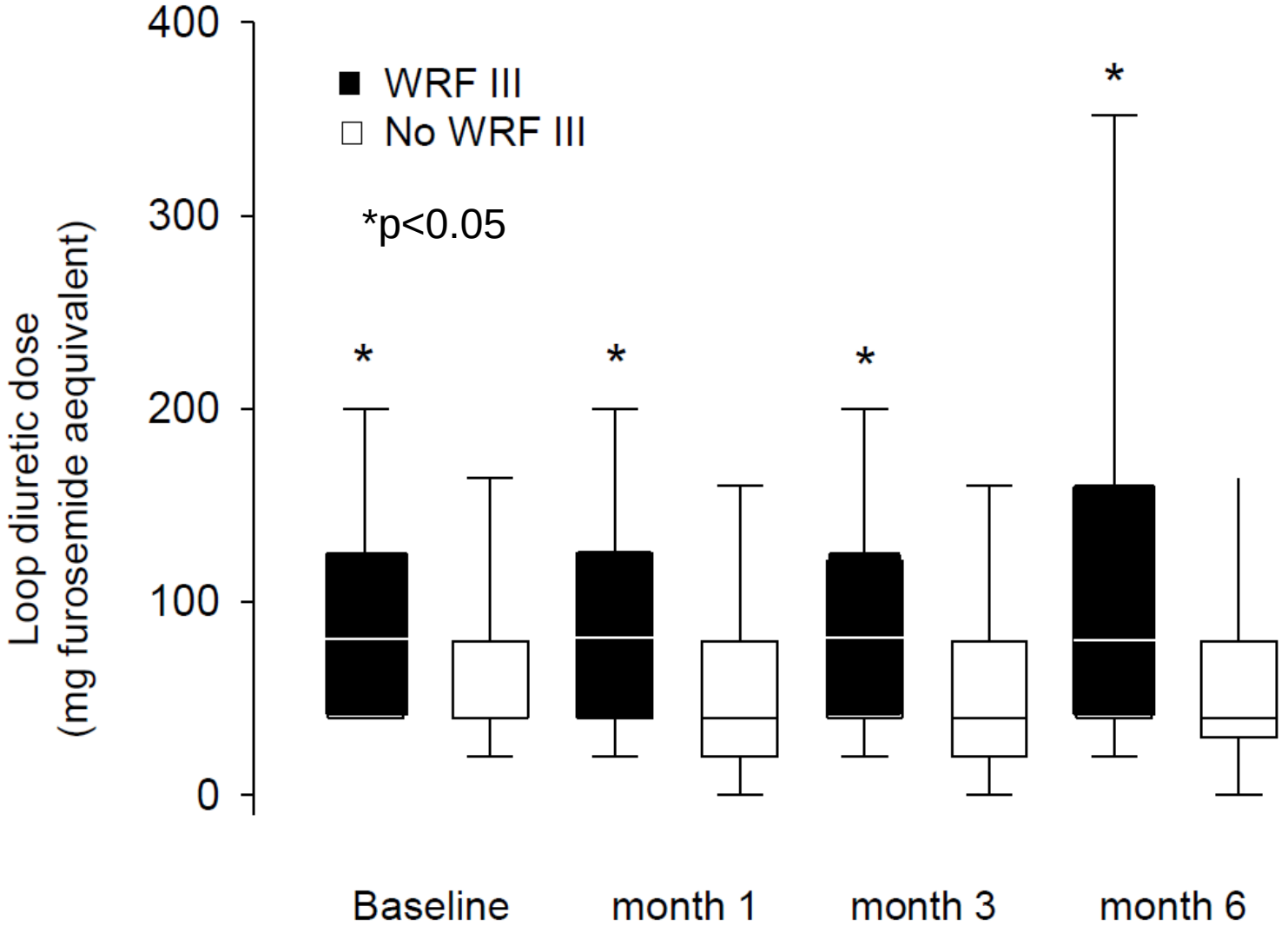
No WRF
WRF I: creatinine↑ 0.2-0.3 mg/dl
WRF II: creatinine↑ 0.3-0.5 mg/dl

WRF III: creatinine↑ ≥ 0.5 mg/dl

Conversion: 1 mg/dl = 88.4 μmol/l

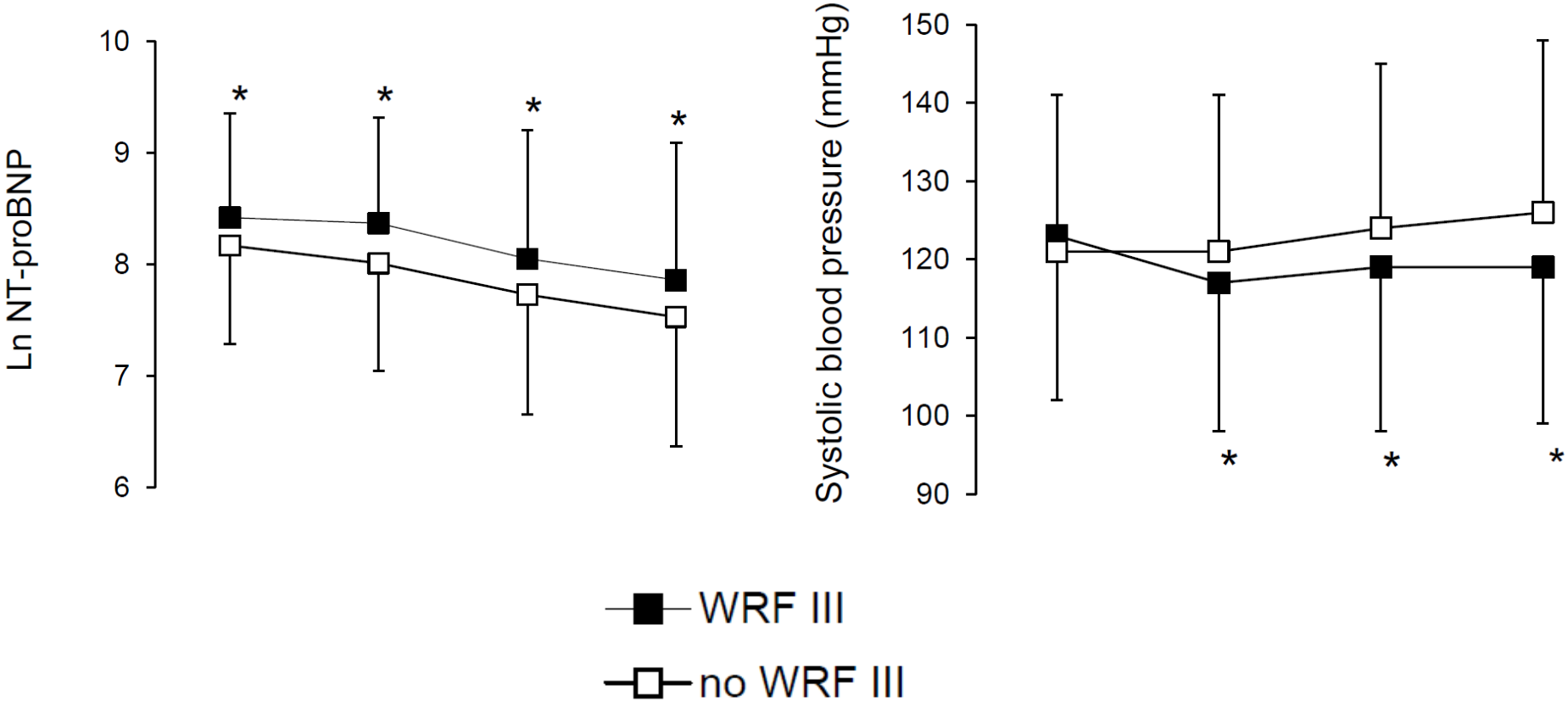
Maeder MT et al. Am Heart J 2012

Loop diuretic use and dose escalation predict WRF III



Maeder MT et al. Am Heart J 2012

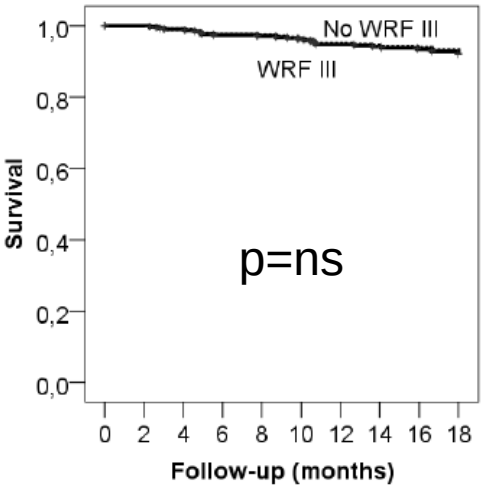
Despite more aggressive diuretic therapy a difference in NT-proBNP persists, but blood pressure falls

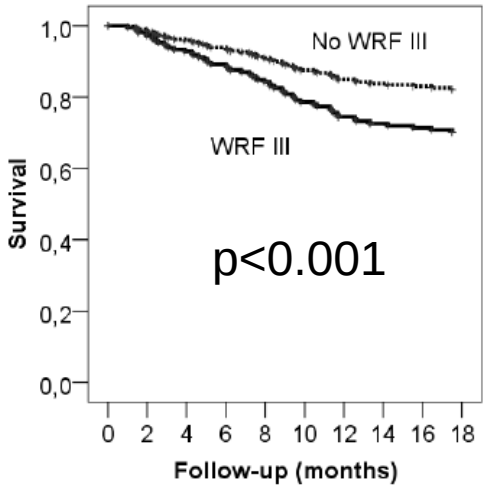


Maeder MT et al. Am Heart J 2012

The prognostic impact of WRF during loop diuretic or spironolactone therapy differs fundamentally

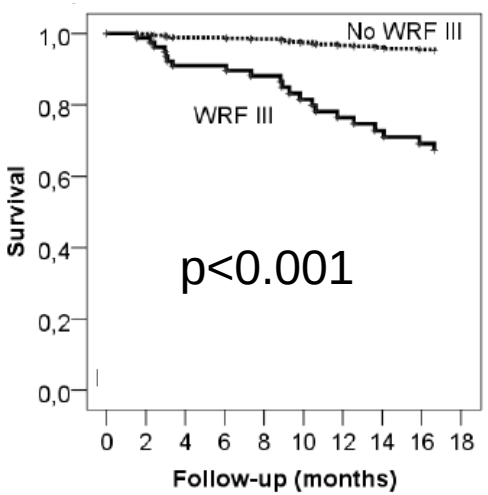
Low dose loop diuretic therapy (median furosemide equivalent doses 37 mg)

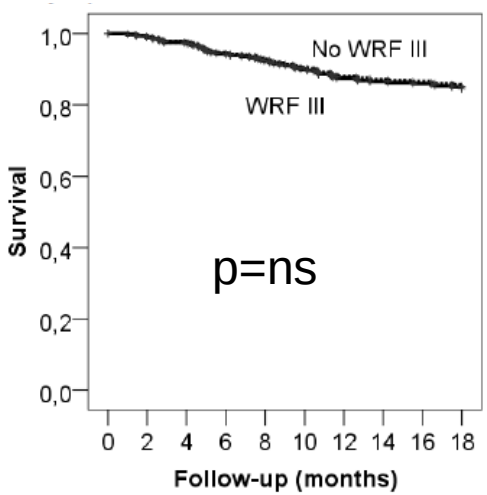




High dose loop diuretic therapy (median furosemide equivalent dose 97 mg)

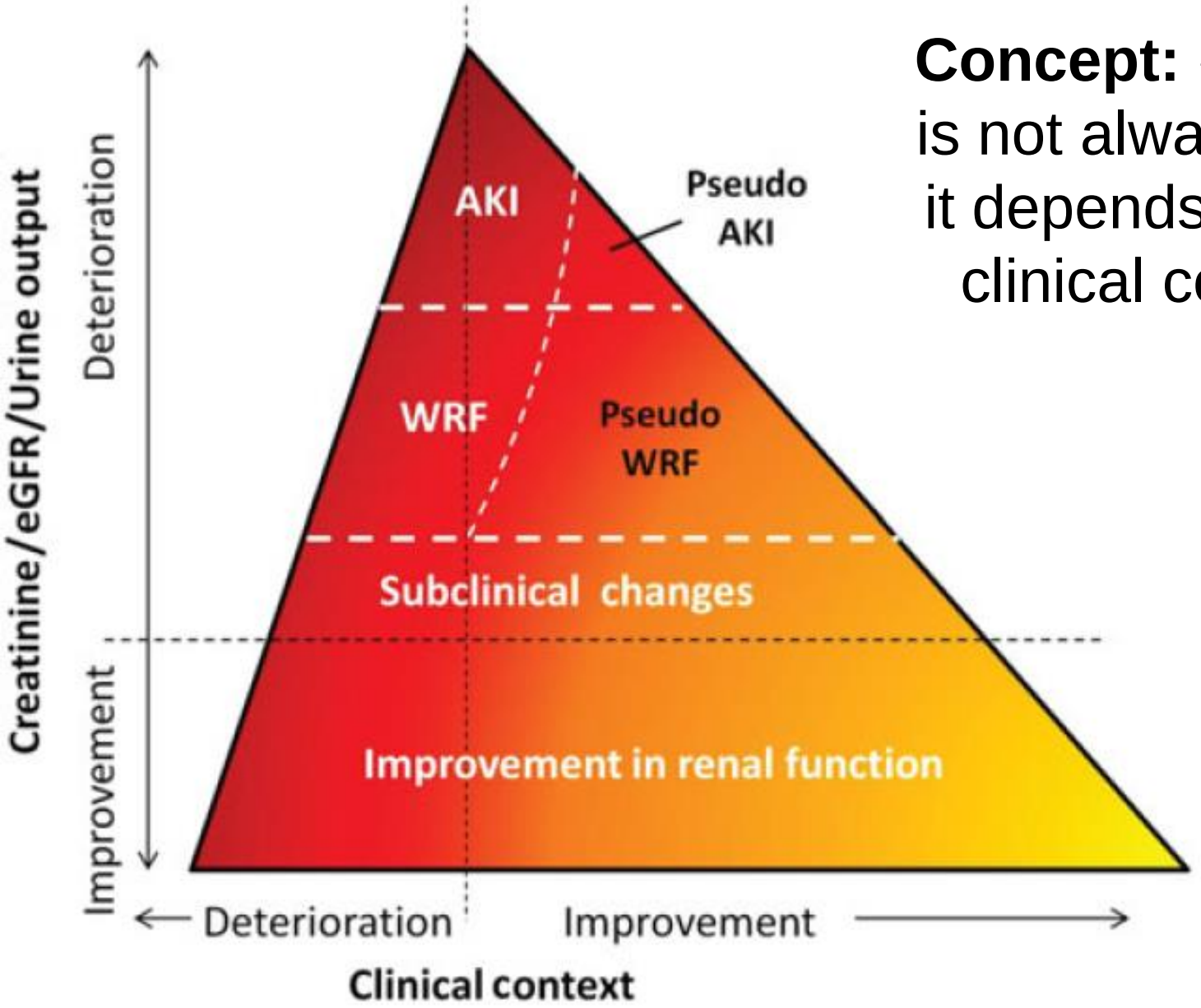
No spironolactone





spironolactone

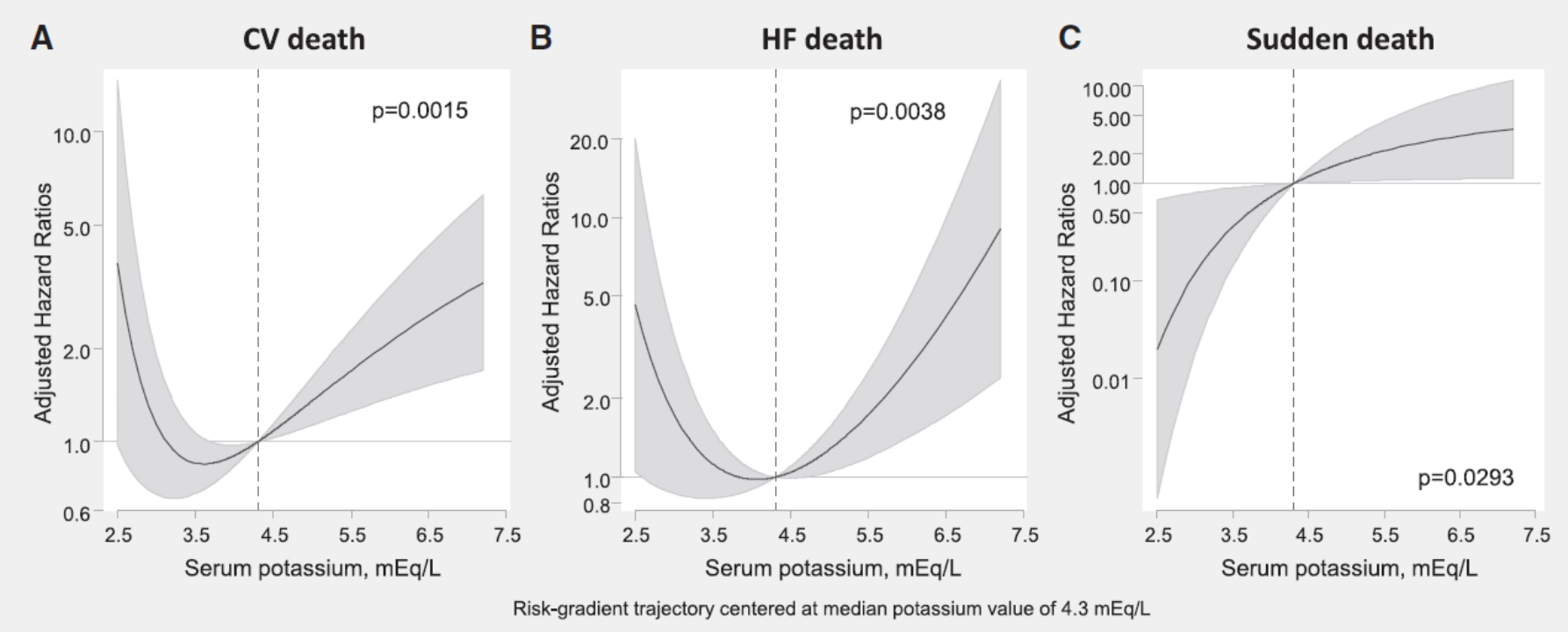
Brunner-La Rocca HF, …, Maeder MT. Eur J Heart Fail 2016



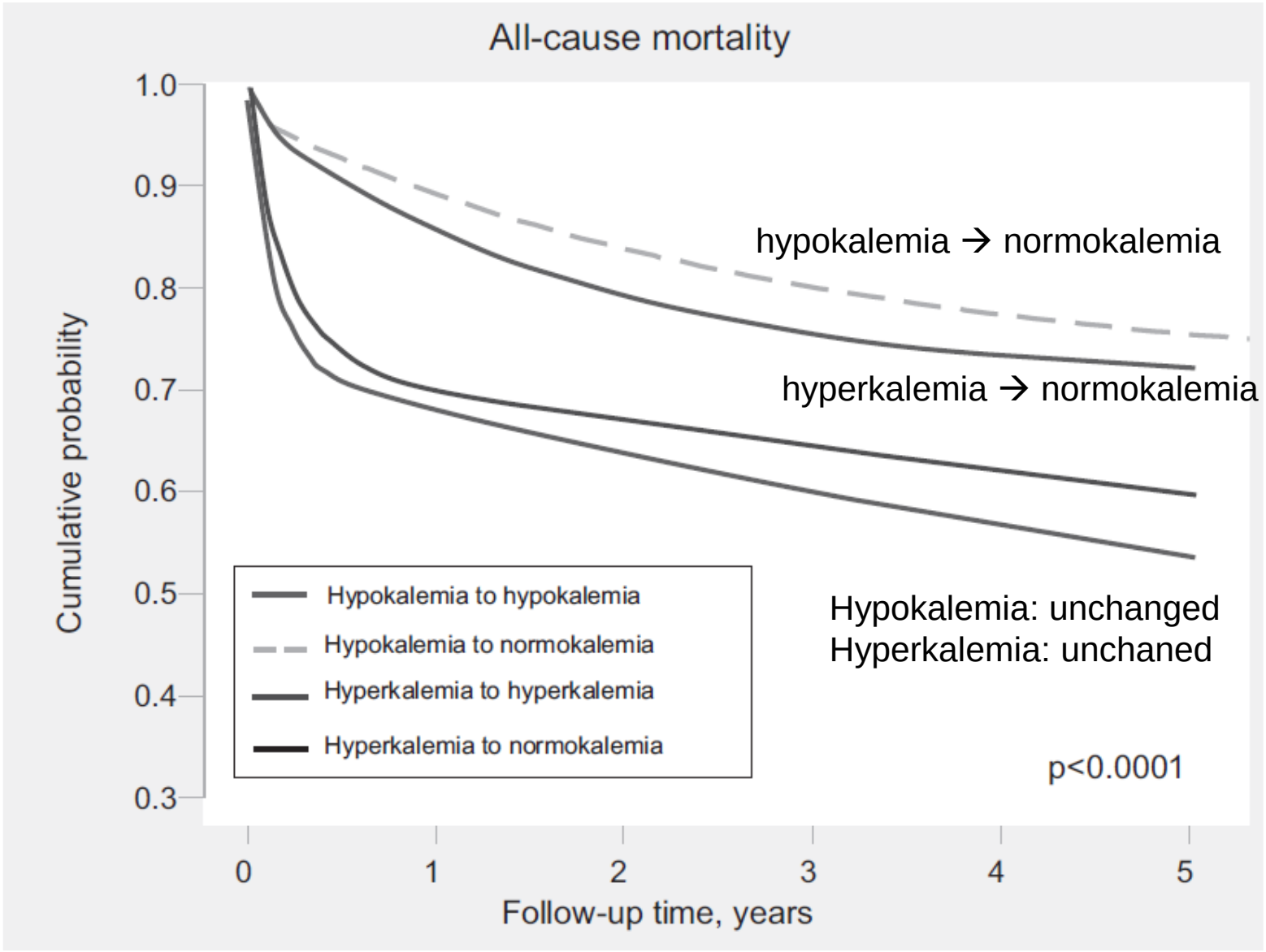
Concept: «WRF» is not always bad, it depends on the clinical context

Damman&Testani. Eur Heart J 2015

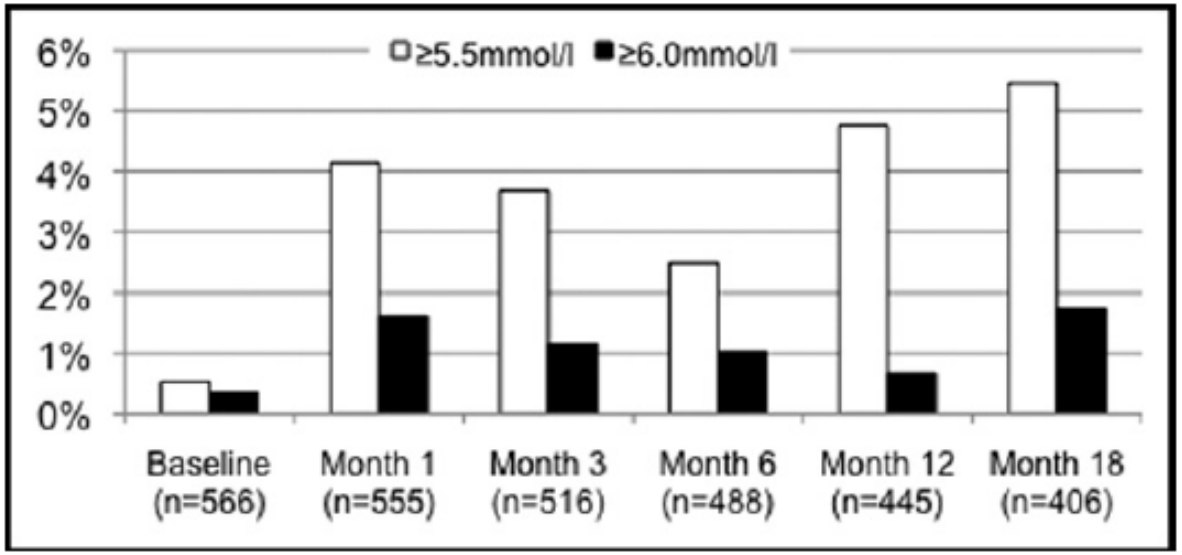
Serum potassium and prognosis



Nunes et al. Circulation 2018



Nunes et al. Circulation 2018



Multivariable baseline predictors of hyperkalemia

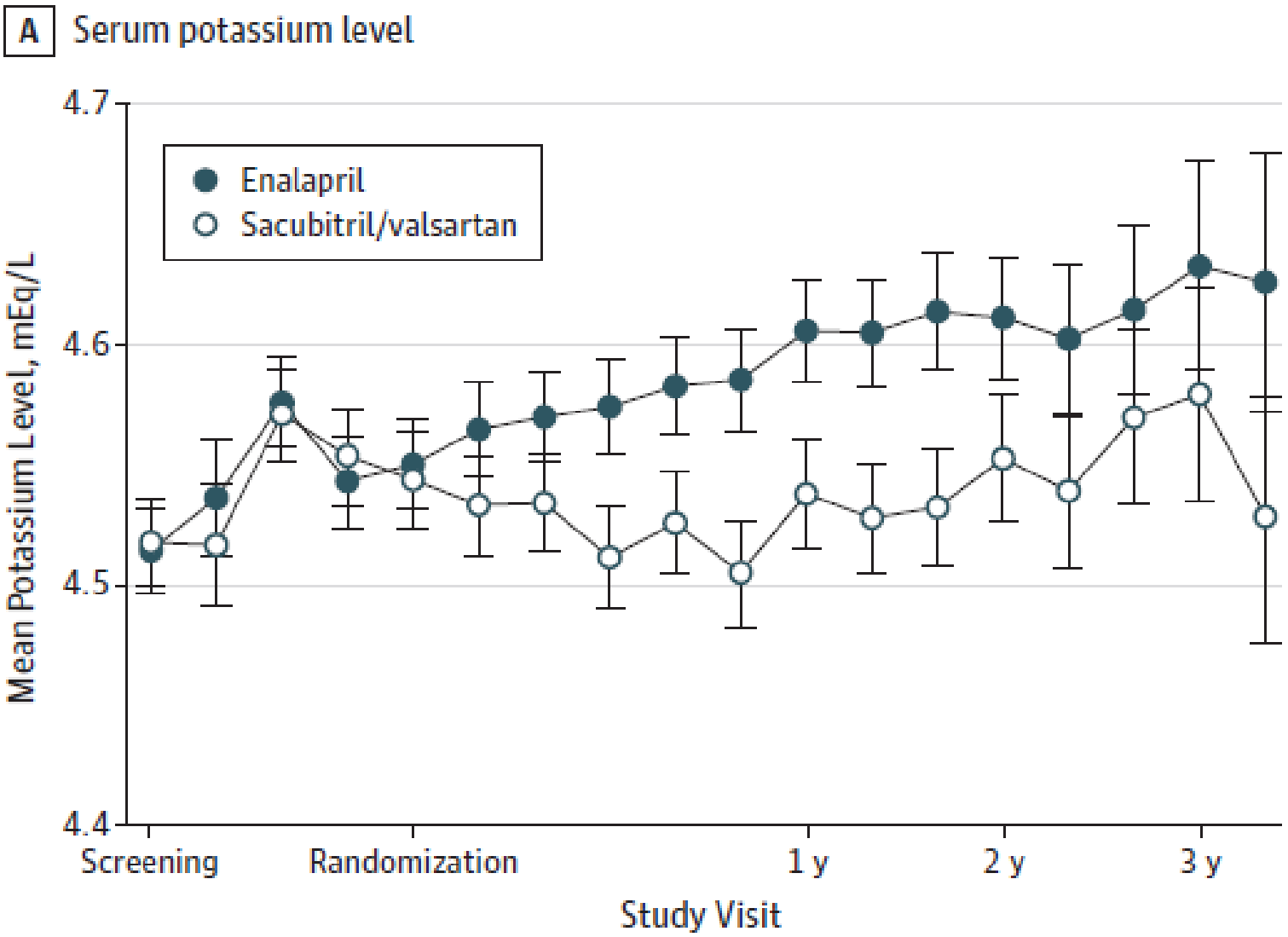
Variable	OR	95% CI	p Value
Potassium (per mmol/L)	2.92	1.75–4.89	<0.001
Gout	2.56	1.22–5.38	0.01
New York Heart Association class vs class II			0.02
Class III	1.33	0.69–2.59	0.39
Class IV	3.08	1.37–6.95	0.007
Creatinine (per 10 μmol/L)	1.11	1.04–1.19	0.001
Dose of spironolactone (per 12.5 mg)	1.20	1.00–1.42	0.05

Muzzarelli S et al. Am J Cardiol 2012

Restricting dietary potassium intake	• Salt substitutes should be avoided due to K+ content[23] • **Observational studies reporting association between worse outcomes and higher mortality in CKD patients and low K+ intake[23]** • **Many cardio-renal patients already have other restricted diets[23]** • **K+ is a common ingredient in many healthy foods[23]**
Loop diuretics	• Increase urinary K+ excretion and may thereby reduce K+ levels[23] • **Efficacy depends on residual renal function[23]** • **Guidelines for chronic stable HF recommend use of loop diuretics at the lowest necessary dose to maintain fluid balance[6]**
Avoid drugs with nephrotoxic potential	• Avoid all drugs with nephrotoxic potential[23] (e.g. non-steroidal anti-inflammatory drugs)
Reduce RAAS inhibitors	• Current guidelines recommend halving RAAS inhibitors if K+ > 5.5 mmol/L, to monitor K+ closely, and to stop RAAS inhibitors if K+ > 6.0 mmol/L[6] • **Suboptimal doses of RAAS inhibitors have been associated with poor outcomes – including mortality – in HF patients[12]**
Favour sacubitril-valsartan and/or dapaglifozin	• Sacubitri-Valsartan seem less associated with hyperkalemia than ACEI[25] • Dapagliflozin does not interfere with the RAAS[26] • **Not specifically studied in patients with hyperkalemia yet**
Potassium-binding resins (SPS, CPS)	• Used for decades[24] • **Limited safety and efficacy data[27]** • **Poorly tolerated and use associated with life-threatening side effects including intestinal necrosis[28]** • **Need for discontinuation if K^+ < 5.0 mmol/L (risk of hypokalemia)[29]** • **SPS: caution in severe HF patients due to relatively high sodium content (~ 100 mg per g of SPS)[29]**

Meyer P et al. Swiss Med Wkly 2020

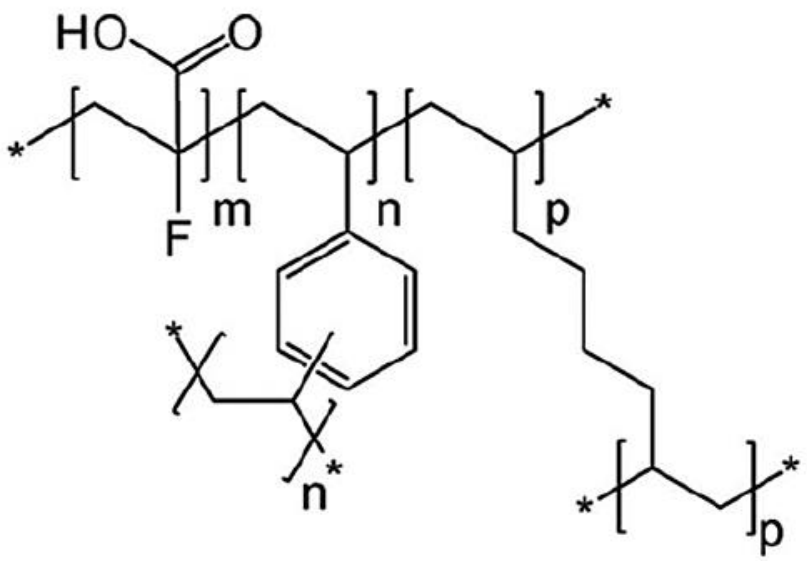
Potassium: Sac/Val vs. Enalapril



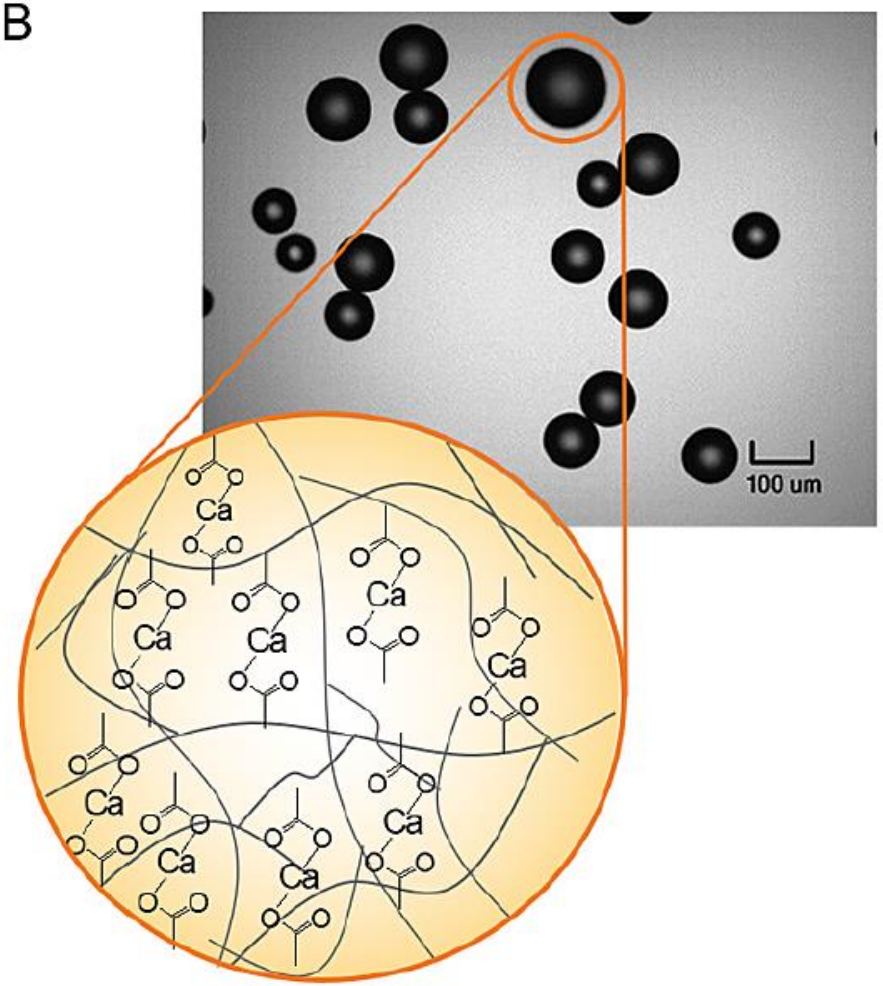
Desai AS et al. JAMA Cardiol 2016

Patiromer: new oral potassium binder

A

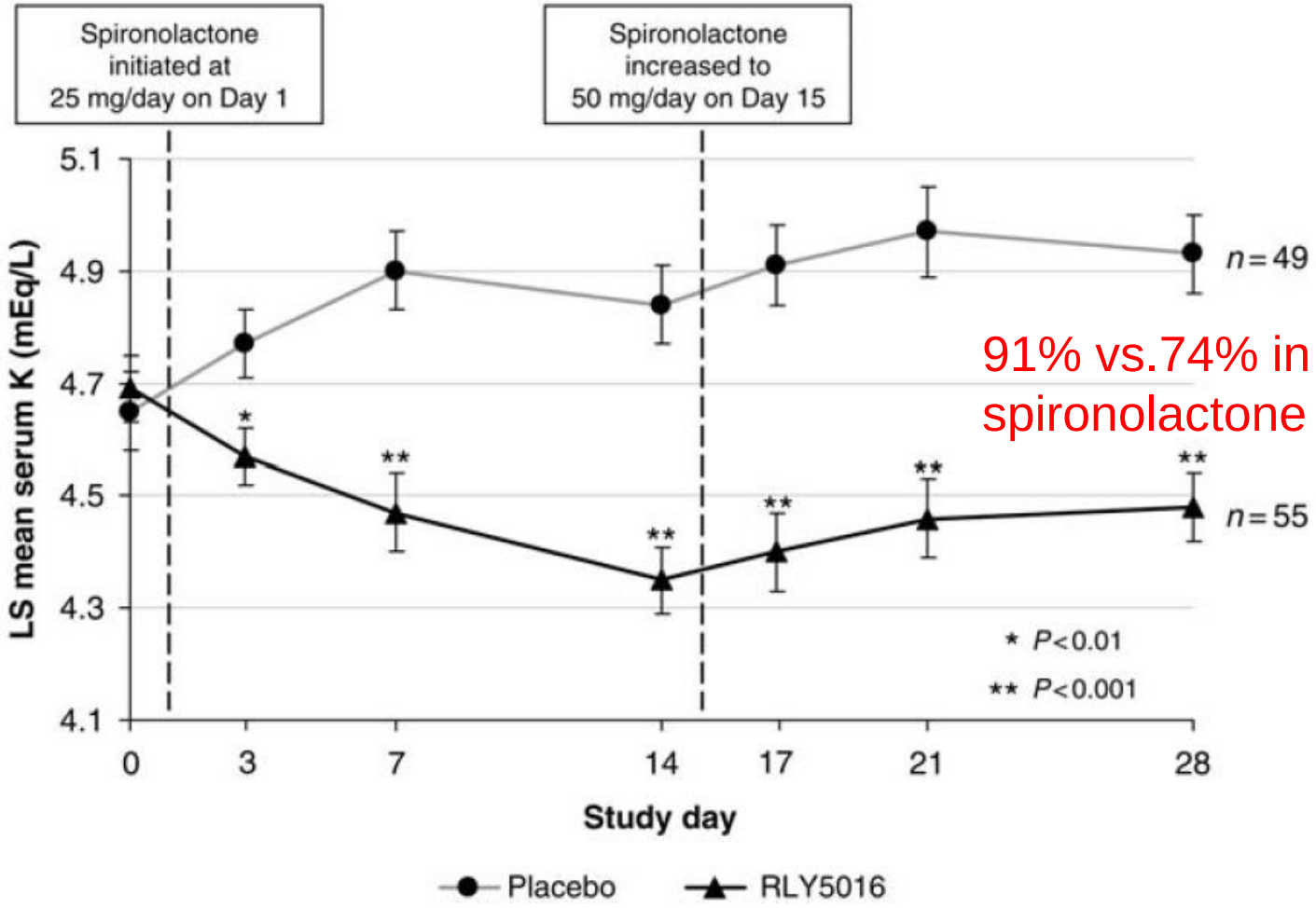


B



Meyer P et al. Swiss Med Wkly 2020

Patiromer in patients with HF and history of hyperkalemia



91% vs.74% in spironolactone 50 mg/d

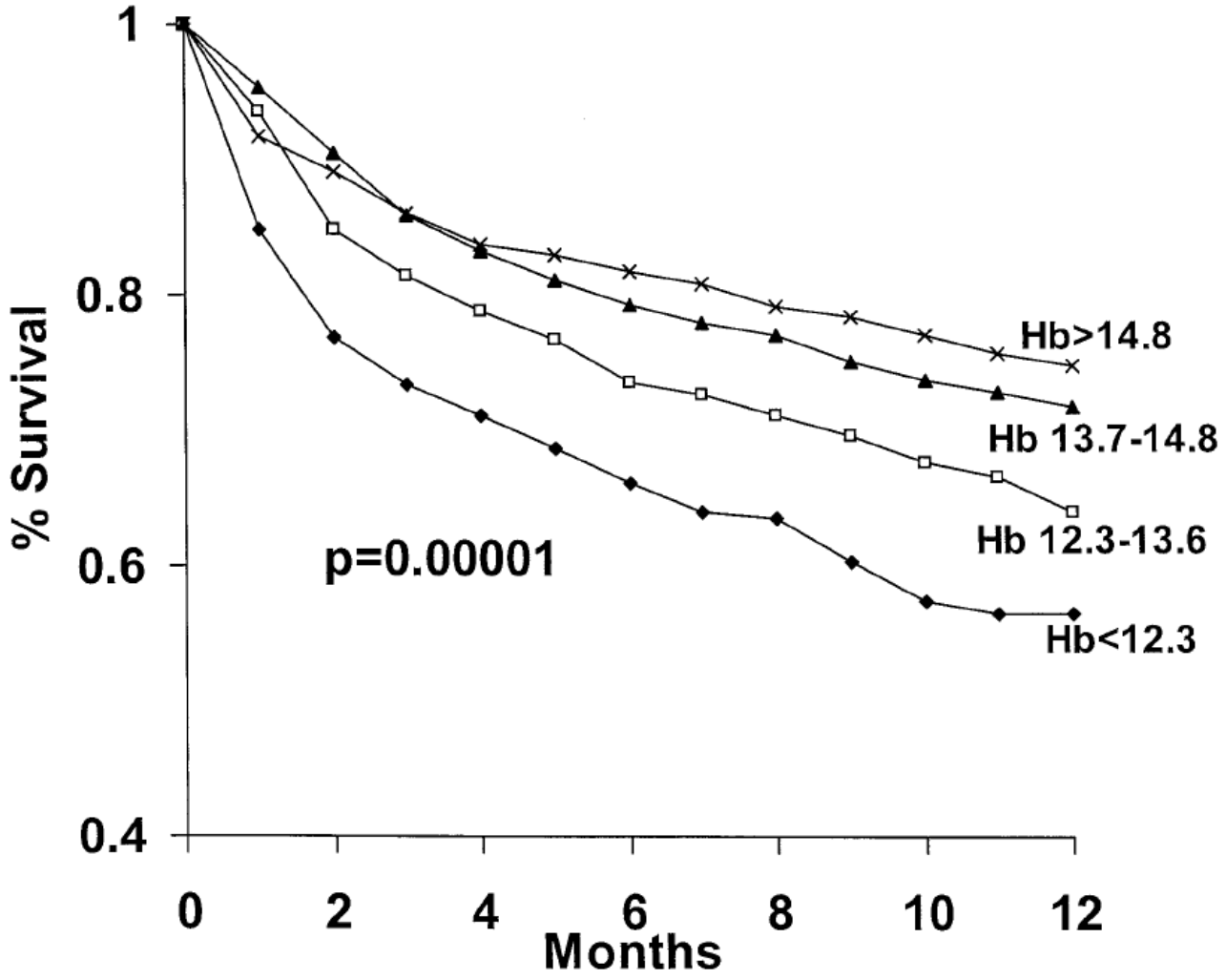
Pitt B et al. Eur Heart J 2011

30 day readmission

- Edema
- Lower systolic blood pressure
- Higher creatinine
- Anemia
- Angina
- Dry cough

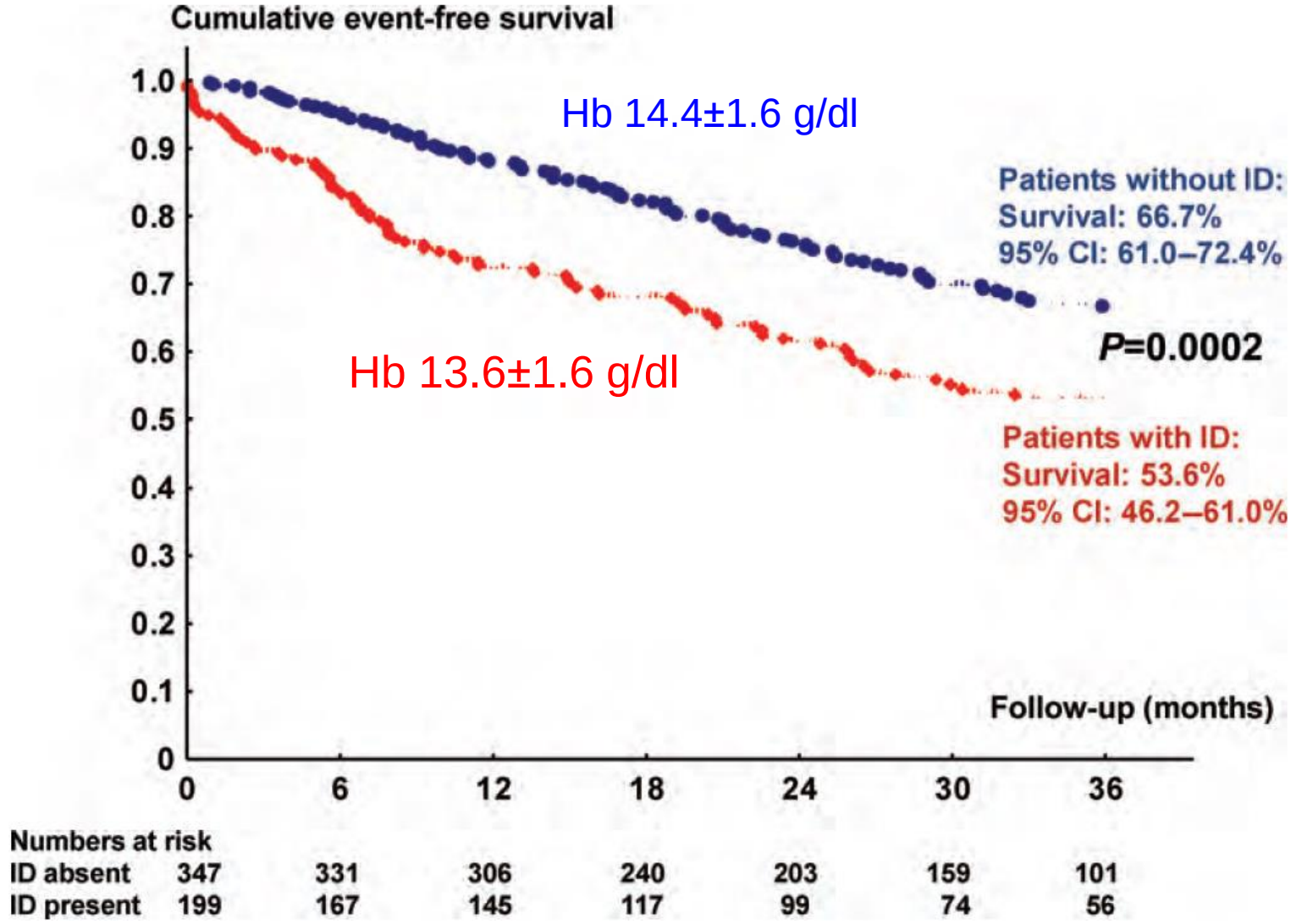
Muzzarelli S et al. Am Heart J 2010

Anemia und Outcome bei HFrEF



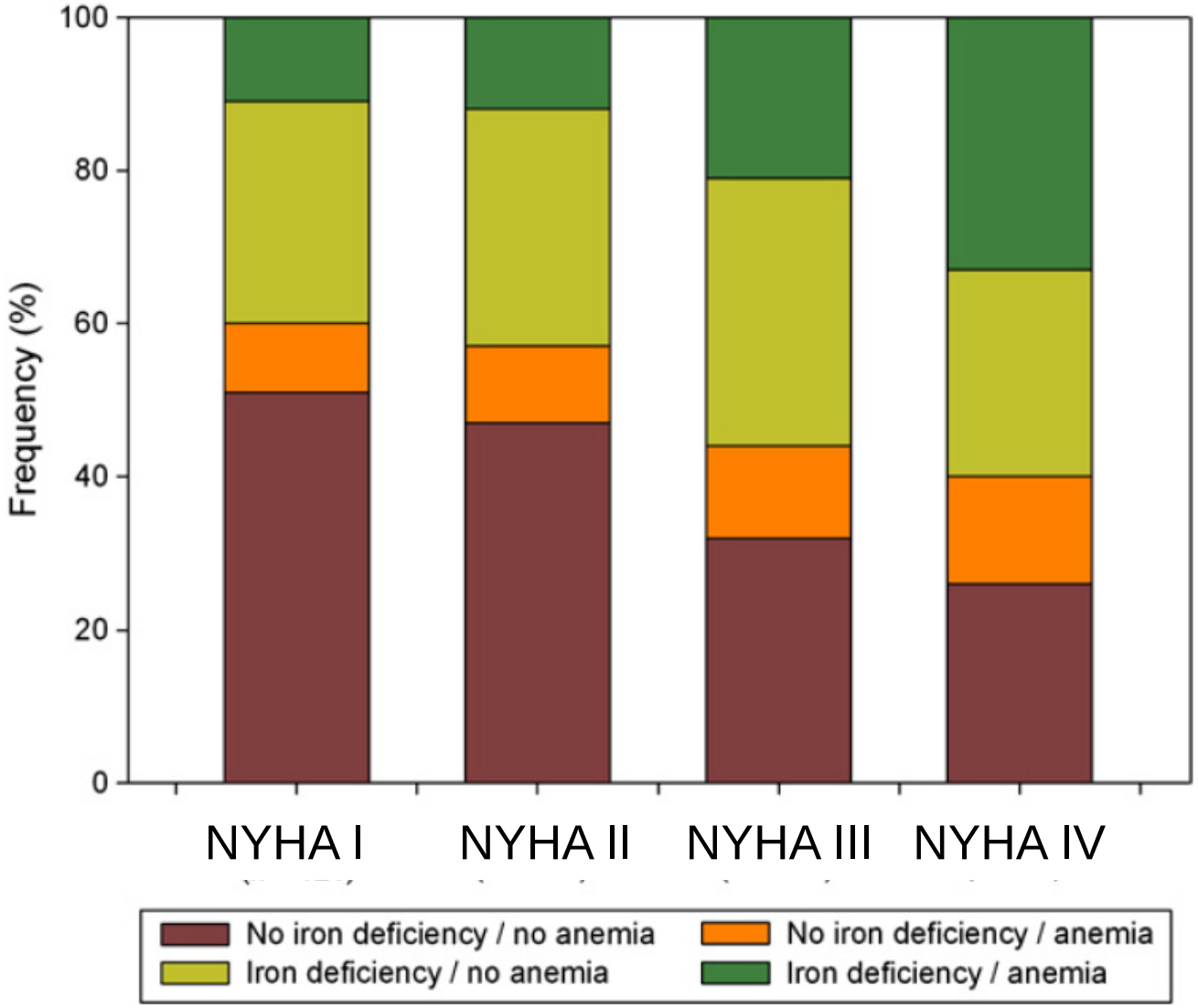
Horwich et al. J Am Coll Cardiol 2002

Iron Deficiency and Prognosis



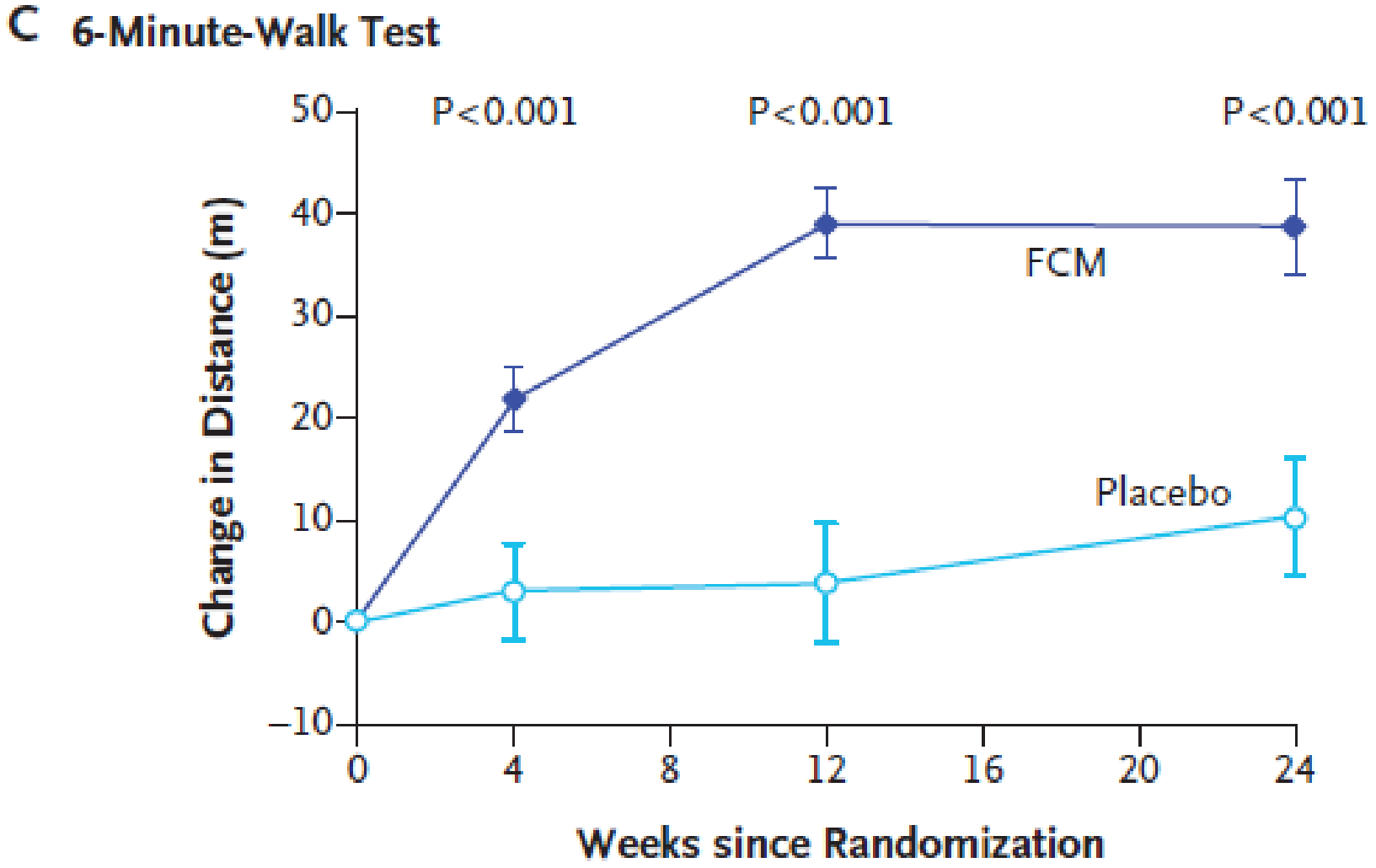
Jankowska et al. Eur Heart J 2010

Iron Deficiency and Symptoms

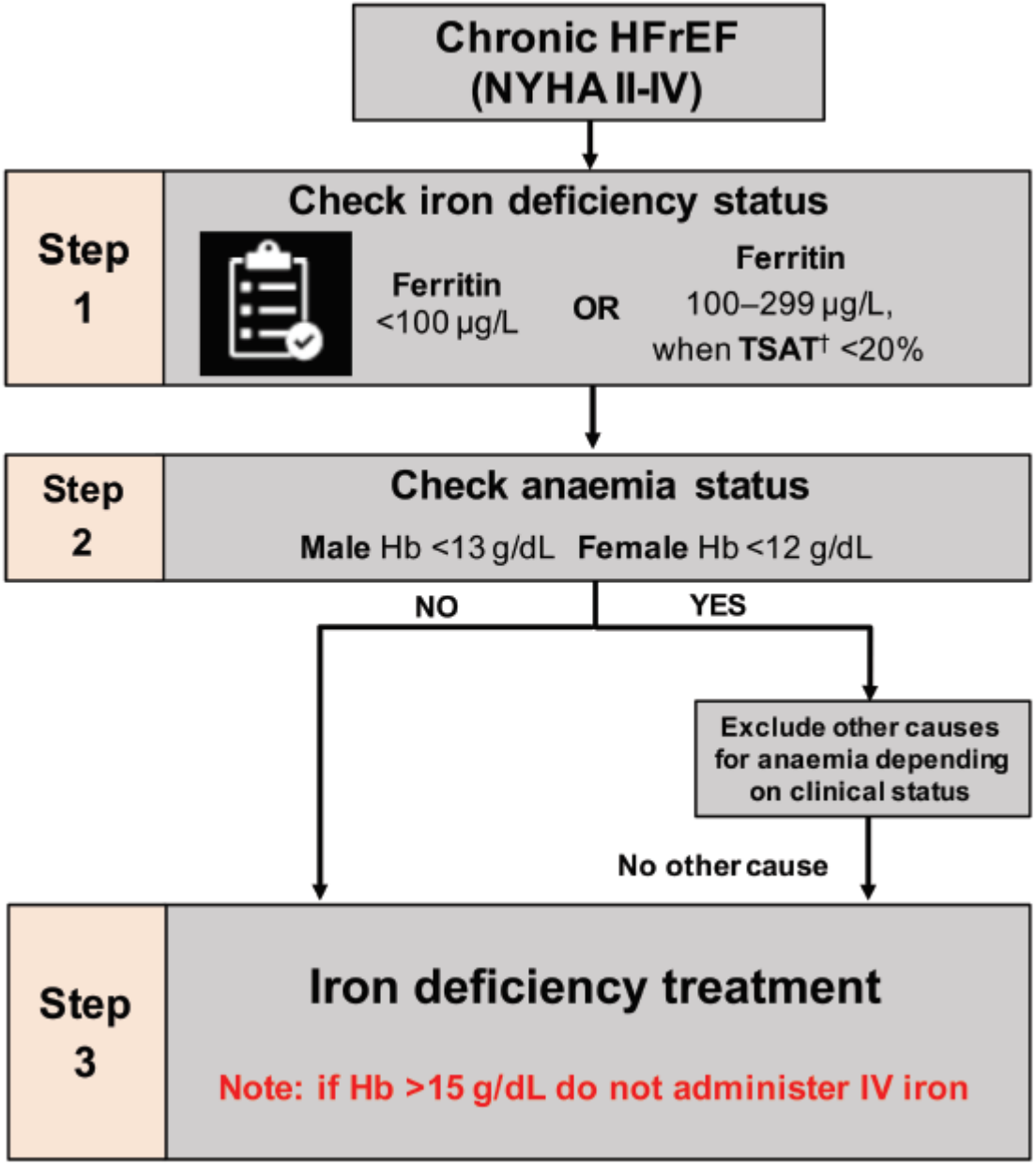


Klip IT et al. Am Heart J 2013

Treatment of iron deficiency in HFrEF

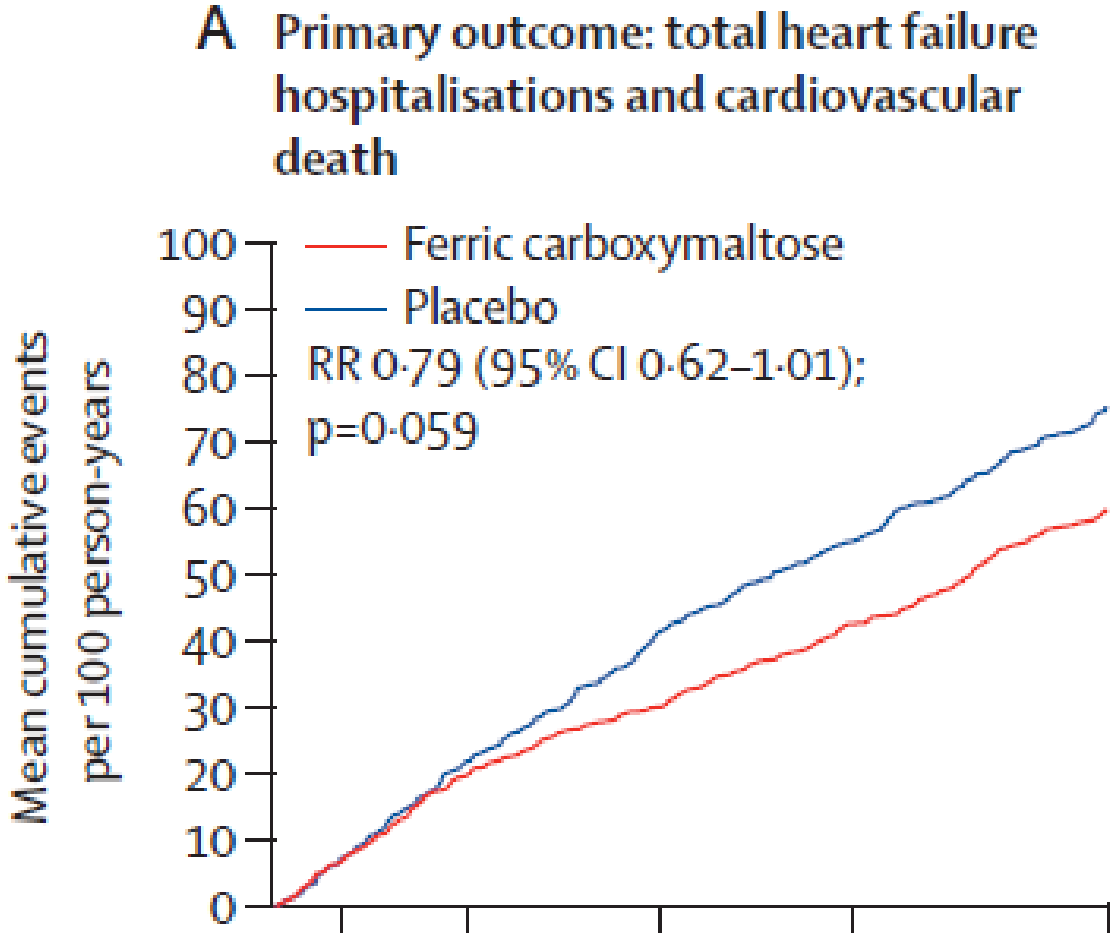


Anker S et al. NEJM 2009



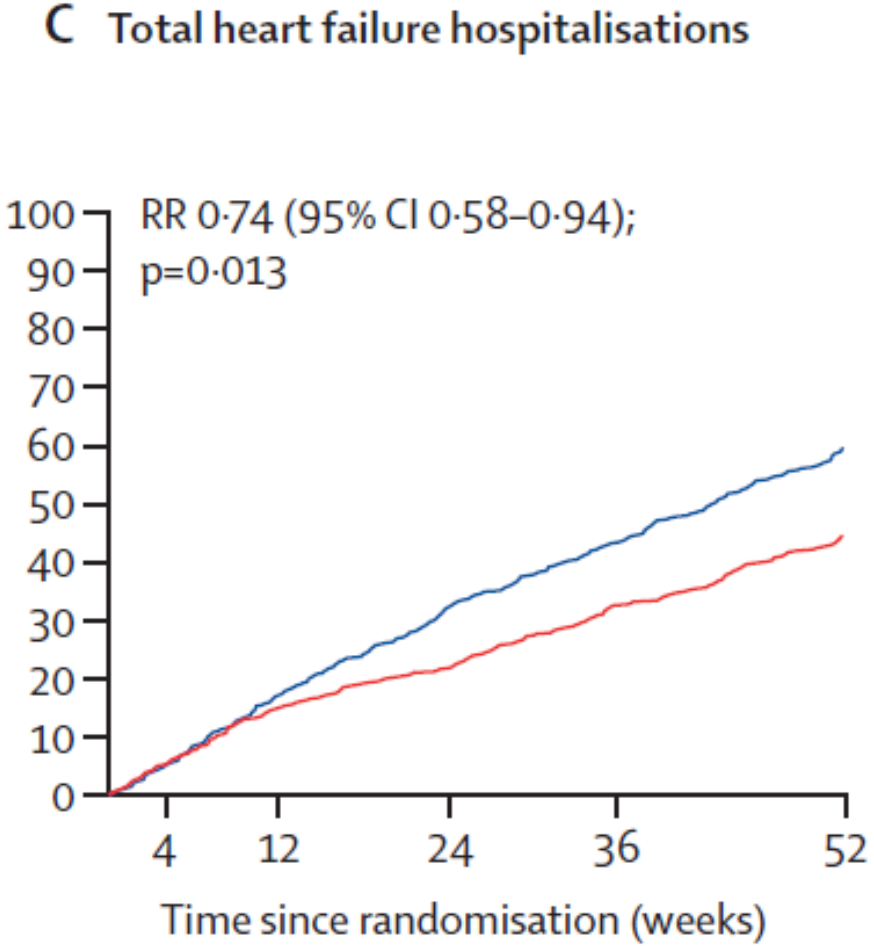
McDonagh T et al. Eur J Heart Fail 2018

Ferric carboxymaltose in acute decompensated HF (LVEF <50%)



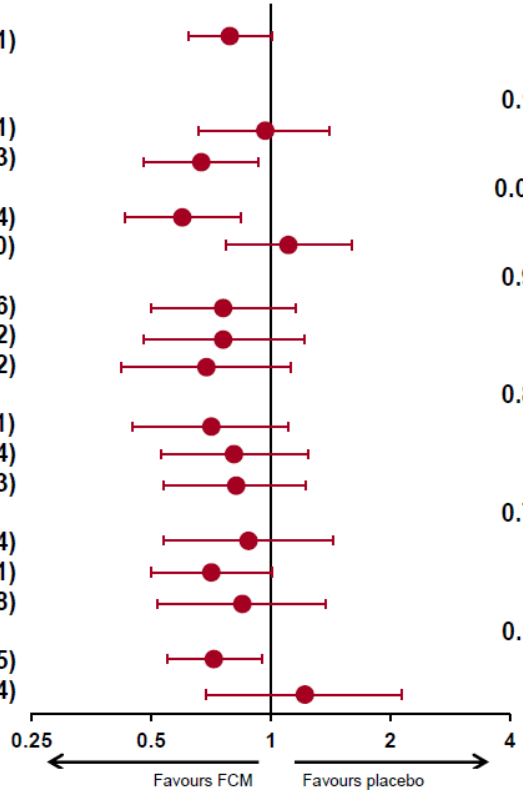
Ponikowski P et al. Lancet 2020

	Ferric carboxymaltose (n=558)	Placebo (n=550)
(Continued from previous column)		
Heart failure history		
Newly diagnosed at index hospitalisation	153 (27%)	165 (30%)
Hospitalisation for heart failure in previous 12 months	152 (27%)	153 (28%)
Hospitalisation for heart failure >12 months before index hospitalisation	253 (45%)	232 (42%)
Pharmacotherapy		
Angiotensin converting enzyme inhibitor	293 (53%)	283 (51%)
Angiotensin receptor blocker	97 (17%)	100 (18%)
Angiotensin receptor neprilysin inhibitor	35 (6%)	36 (7%)
Mineralocorticoid receptor antagonist	376 (67%)	352 (64%)
β blocker	453 (81%)	461 (84%)
Digitalis glycosides	83 (15%)	101 (18%)
Loop diuretic	483 (87%)	465 (85%)
Laboratory test results		
NT-proBNP, pg/mL	4743 (2781–8128)	4684 (2785–8695)



Ponikowski et al. Lancet 2020

	FCM Events / Patients	Placebo Events / Patients	Rate Ratio (95% CI)	P for interaction
Overall	293 / 558	372 / 550	**0.79 (0.62–1.01)**	
Hb level at baseline				**0.15**
<12 g/dL	136 / 228	171 / 236	**0.97 (0.66–1.41)**	
≥12 g/dL	156 / 329	201 / 314	**0.67 (0.48–0.93)**	
Heart Failure aetiology				**0.015**
Ischaemic	149 / 265	236 / 257	**0.60 (0.43–0.84)**	
Non-ischaemic	140 / 282	128 / 275	**1.11 (0.77–1.60)**	
eGFR tertiles (mL/min per 1.73 m^2) at baseline				**0.94**
<42.96	115 /157	152 / 165	**0.76 (0.50–1.16)**	
≥42.96 to <64.32	76 /166	83 / 156	**0.76 (0.48–1.22)**	
≥64.32	56 /164	79 / 159	**0.69 (0.42–1.12)**	
NT-pro BNP (pg/mL) or BNP (pg/mL) at baseline				**0.88**
Lower tertile	69 / 187	105 / 177	**0.71 (0.45–1.11)**	
Middle tertile	99 / 191	115 / 183	**0.81 (0.53–1.24)**	
Upper tertile	125 / 179	152 / 189	**0.82 (0.54–1.23)**	
Left ventricular ejection fraction at baseline				**0.74**
<25%	84 / 104	113 / 122	**0.88 (0.54–1.44)**	
25% to <40%	144 / 288	178 / 243	**0.71 (0.50–1.01)**	
40% to <50%	65 / 166	80 / 184	**0.85 (0.52–1.38)**	
Diagnosis of HF				**0.11**
Documented HF prior to index hospitalisation	249 / 405	336 / 385	**0.72 (0.55–0.95)**	
Newly diagnosed at index hospitalisation	44 / 153	36 / 165	**1.22 (0.69–2.14)**	



MED-HQ-FCM-2000056
Date of preparation: 13 November 2020

Ponikowski P, et al. *The Lancet*. 2020. https://doi.org/10.1016/S0140-6736(20)32339-4

Ponikowski et al. Lancet 2020

30 day readmission

- Edema
- Lower systolic blood pressure
- Higher creatinine
- Anemia
- Angina
- Dry cough

Muzzarelli S et al. Am Heart J 2010

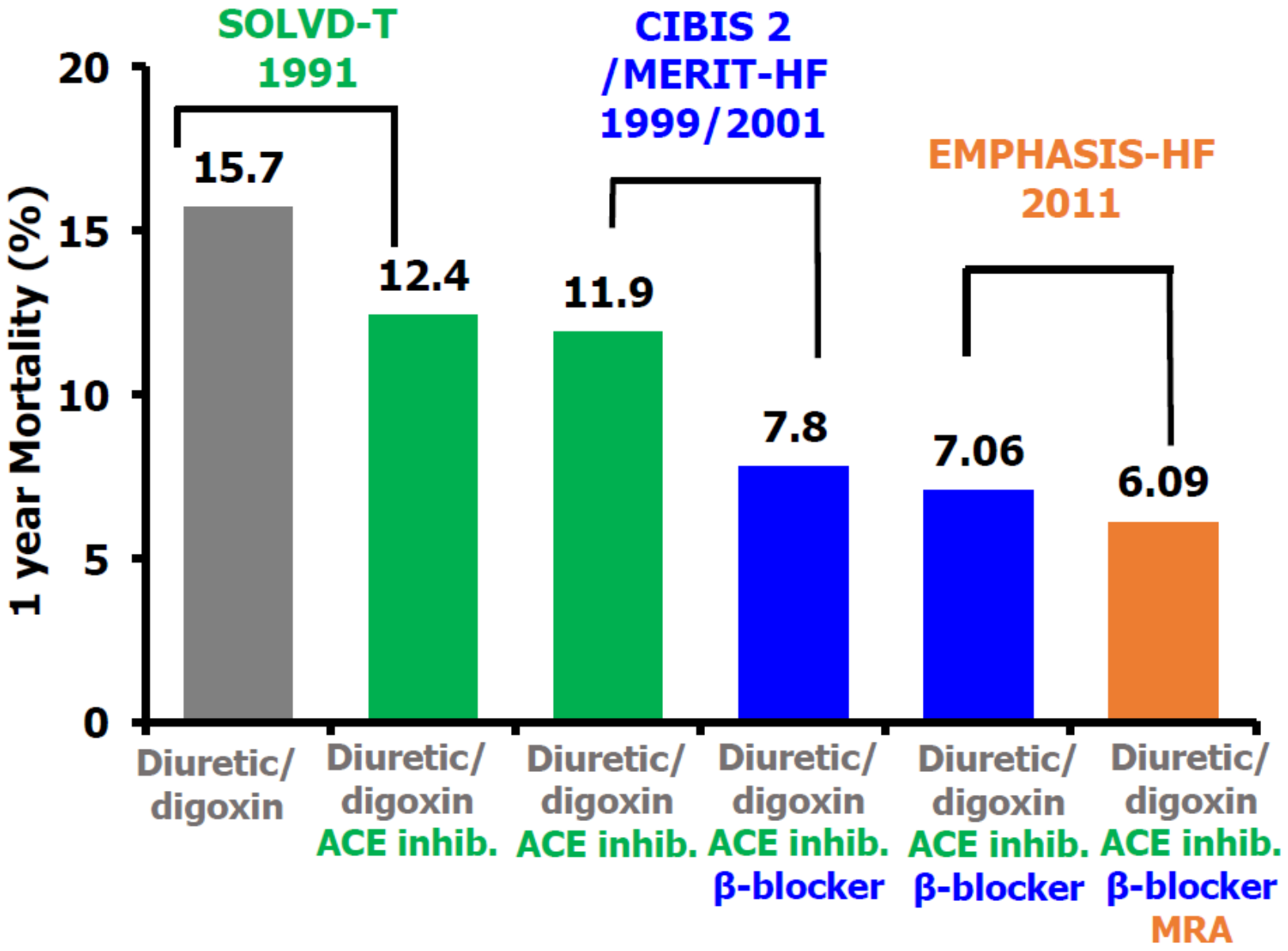
Angina/CAD

- Ischemic HF etiology: higher risk of death, sudden death
- CAD is a key driver of worsening LVEF
- CAD work-up may be required
  - Viability/ischemia
  - Revascularization?
  - Prevention of sudden death?

30 day readmission

- Edema
- Lower systolic blood pressure
- Higher creatinine
- Anemia
- Angina
- Dry cough

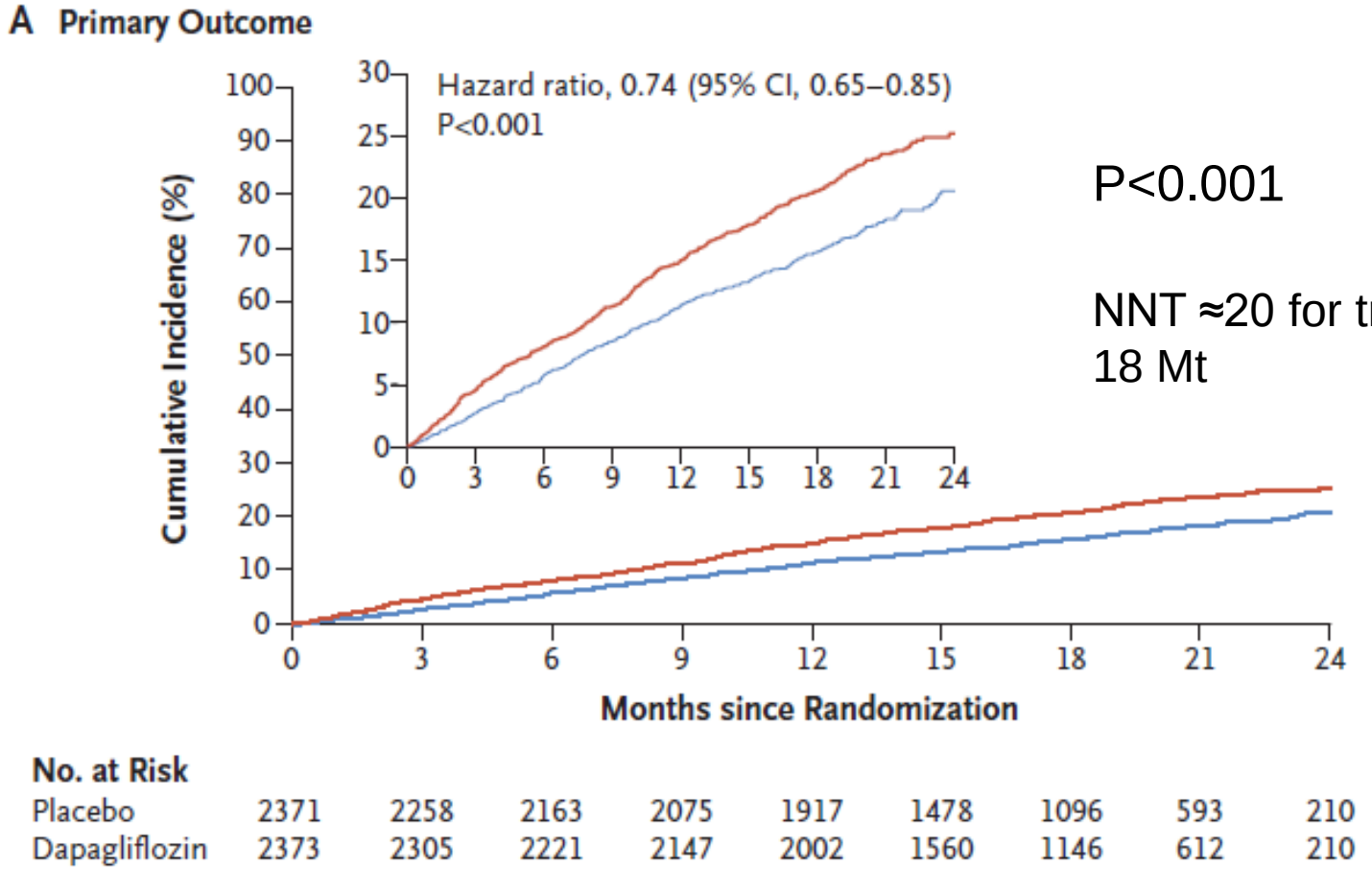
Muzzarelli S et al. Am Heart J 2010



McMurray JJV. Talk ESC 2020

Dapagliflozin

1 EP: «worsening HF» (HF Hosp oder dringliche Visite mit nachfolgend IV Diuretika-Therapie) oder CV Tod



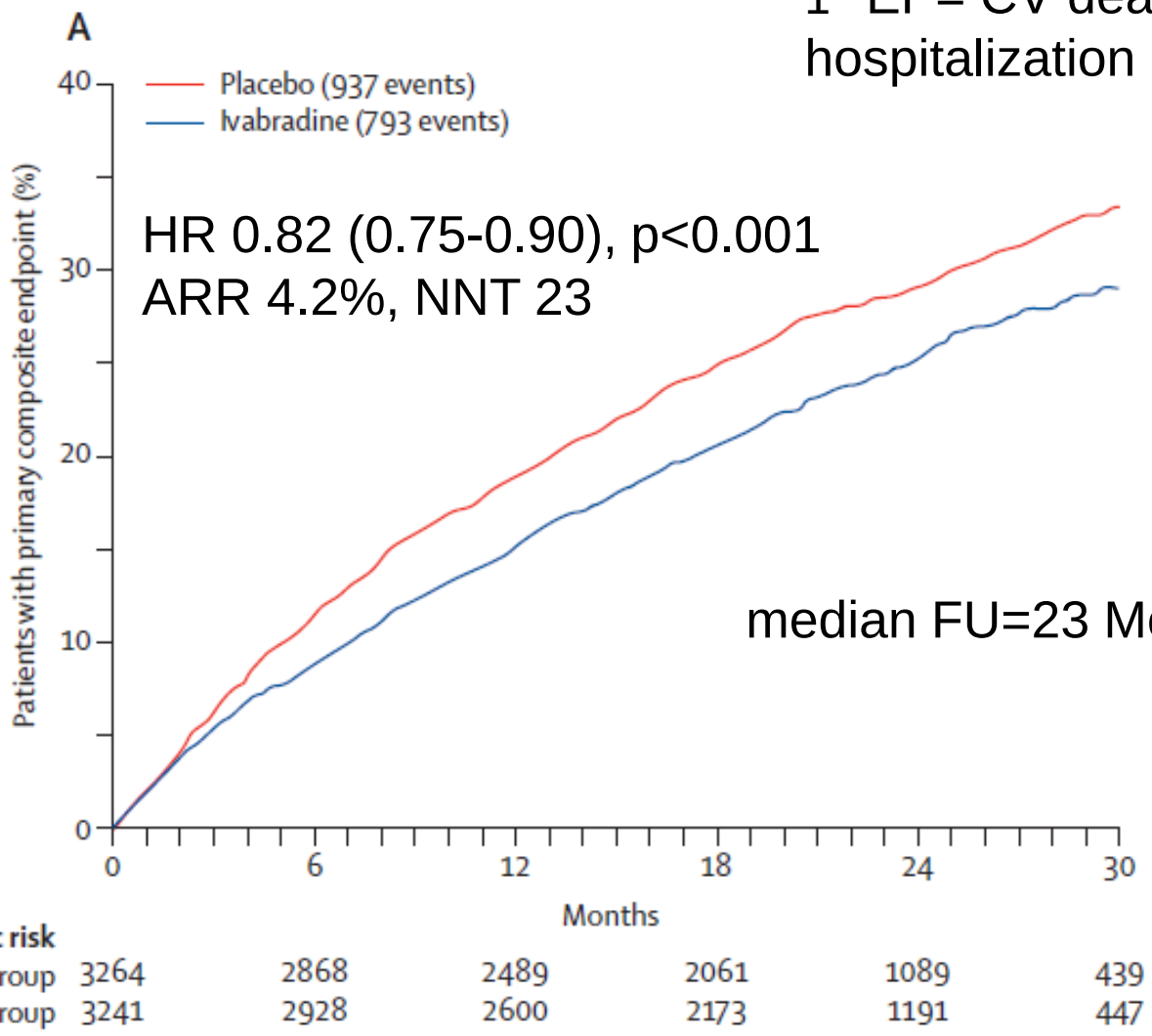
P<0.001

NNT ≈20 for treatment for 18 Mt

McMurray JJV et al. NEJM 2019

Ivabradin

1° EP= CV death or HF hospitalization

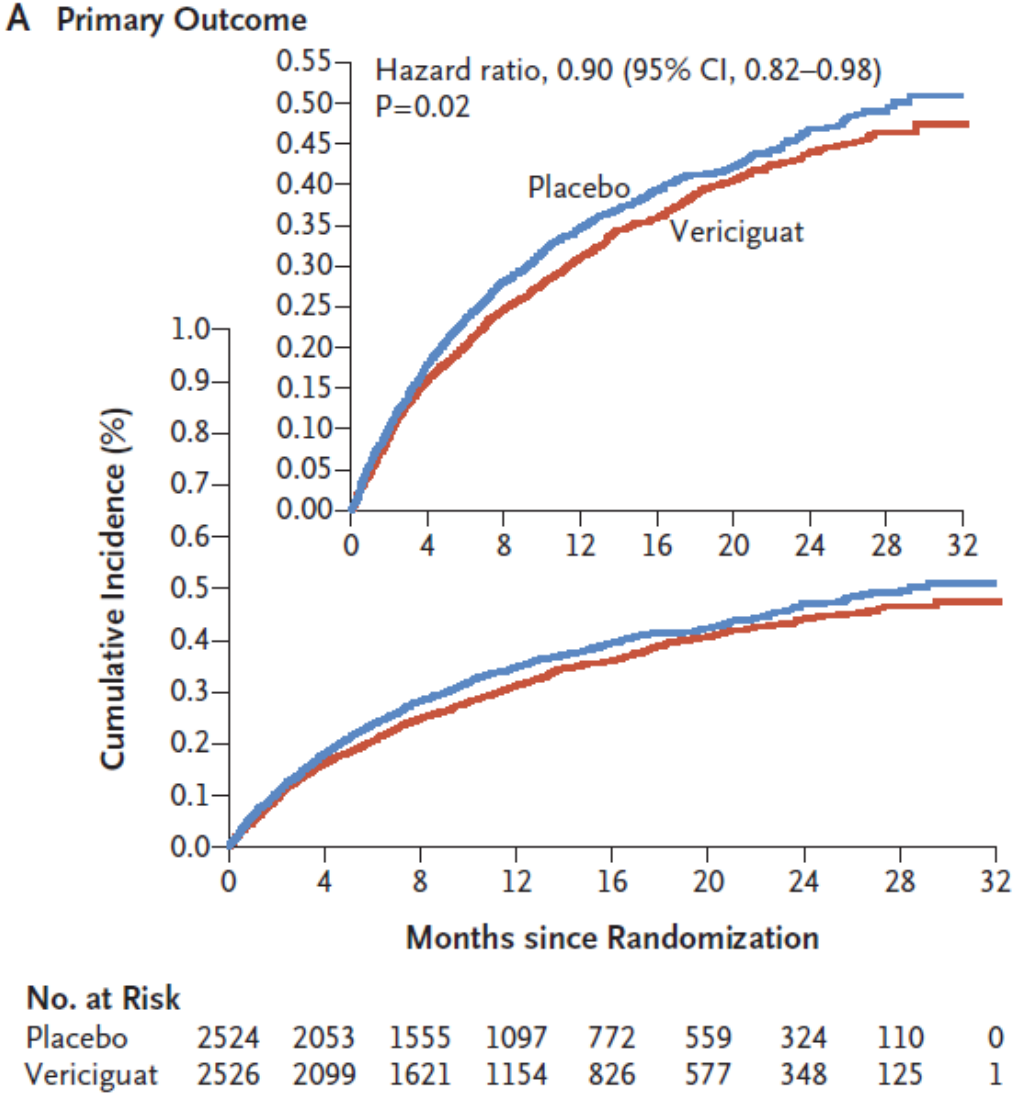


HR 0.82 (0.75-0.90), p<0.001
ARR 4.2%, NNT 23

median FU=23 Monate

Swedberg K, et al. Lancet 2010

Vericiguat

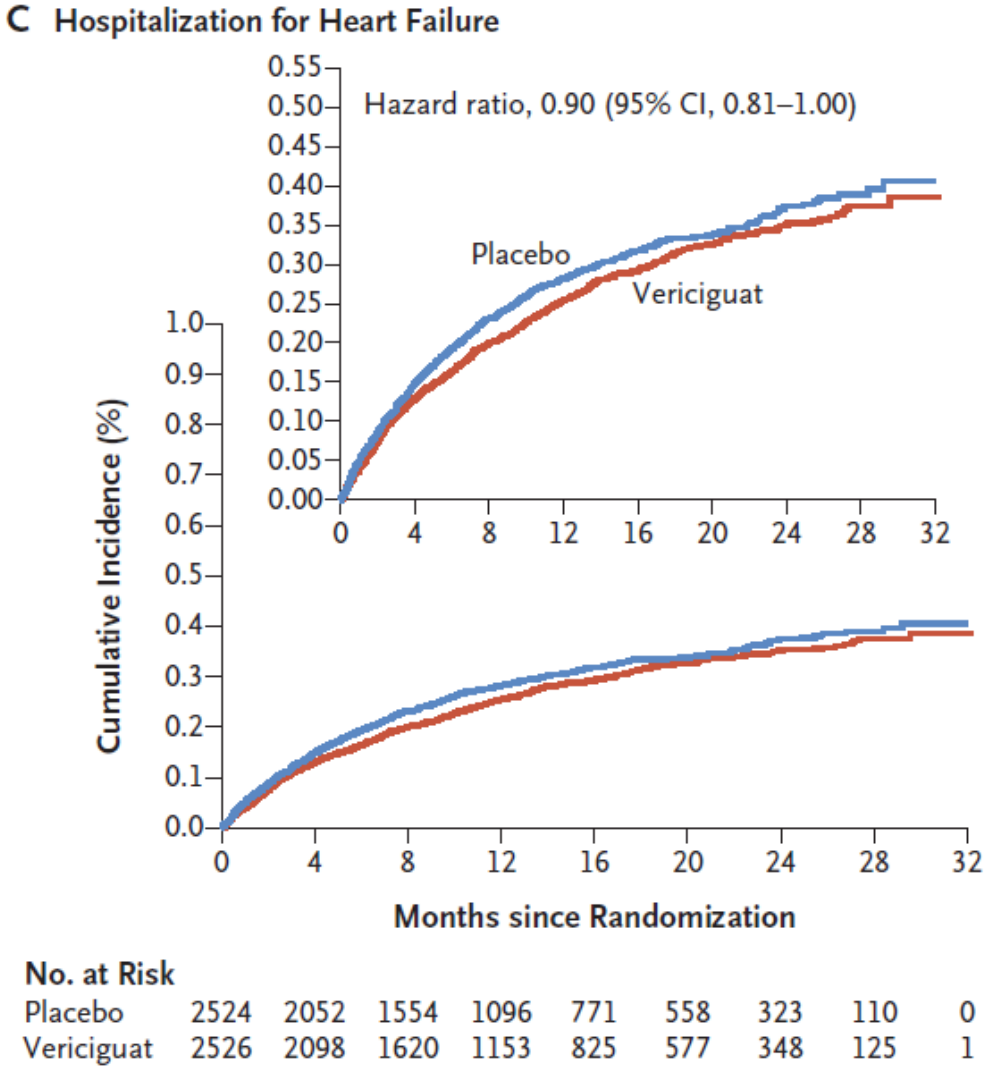


Vericiguat 1x2.5 mg/d versus Plazebo, up-titration to 1x10 mg/d

1 EP: CV death and first hospitalization for HF

Armstrong et al. NEJM 2020

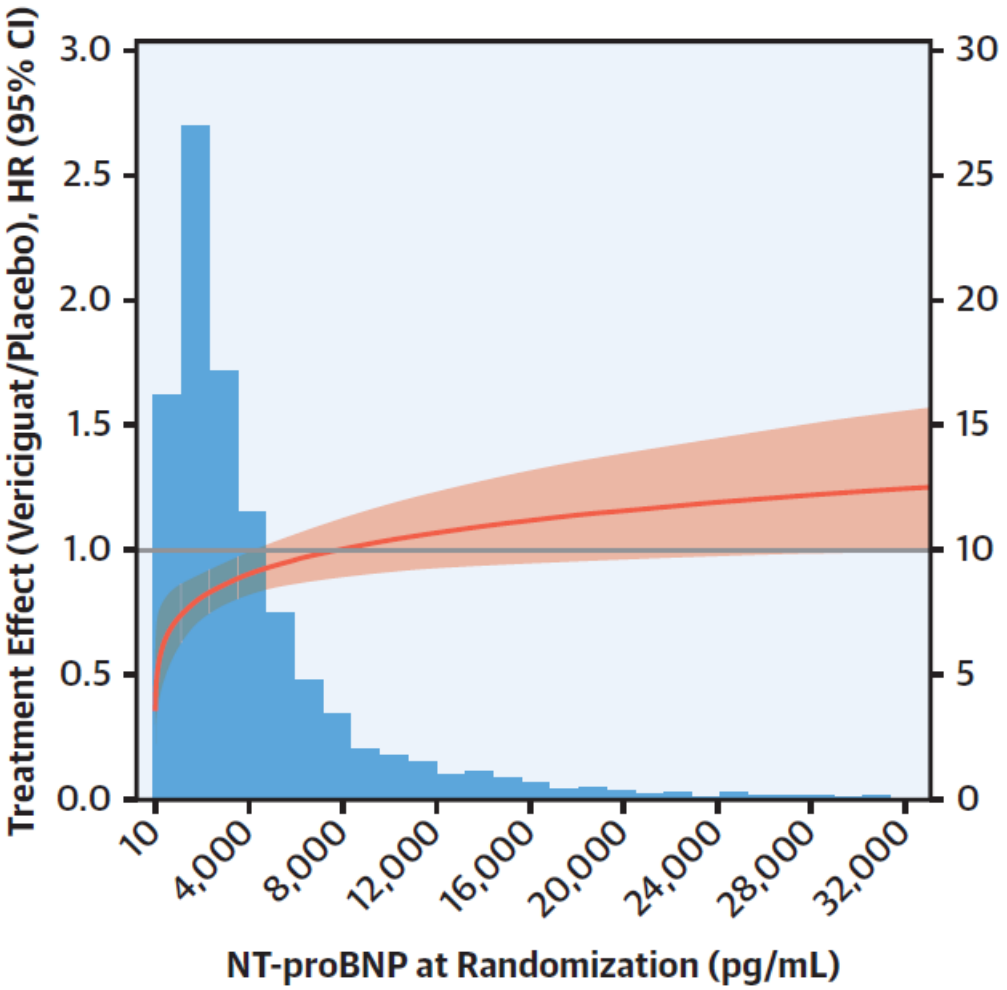
Vericiguat



HF Hospitalisationen

Armstrong et al. NEJM 2020

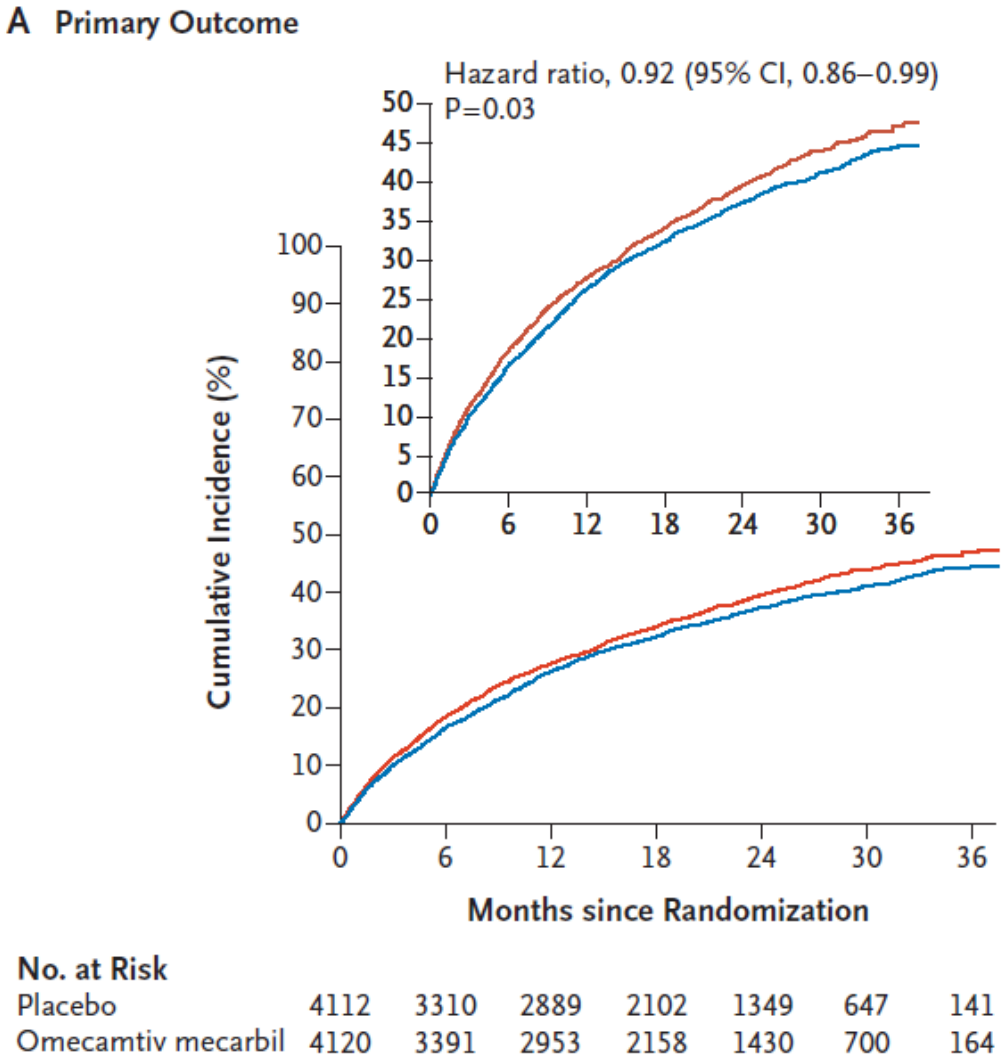
Effect of Vericiguat and NT-proBNP



1 EP: CV death and first hospitalization for HF

Ezekowitz et al. JACC HF 2020

Omecamtiv Mecarbil



LVEF ≤35%, NYHA II-IV, current/previous hospitalization, NTproBNP ≥400 ng/l or BNP ≥125 ng/l (SR) or NT-proBNP ≥1200 ng/l or BNP ≥375 ng/l (AF)

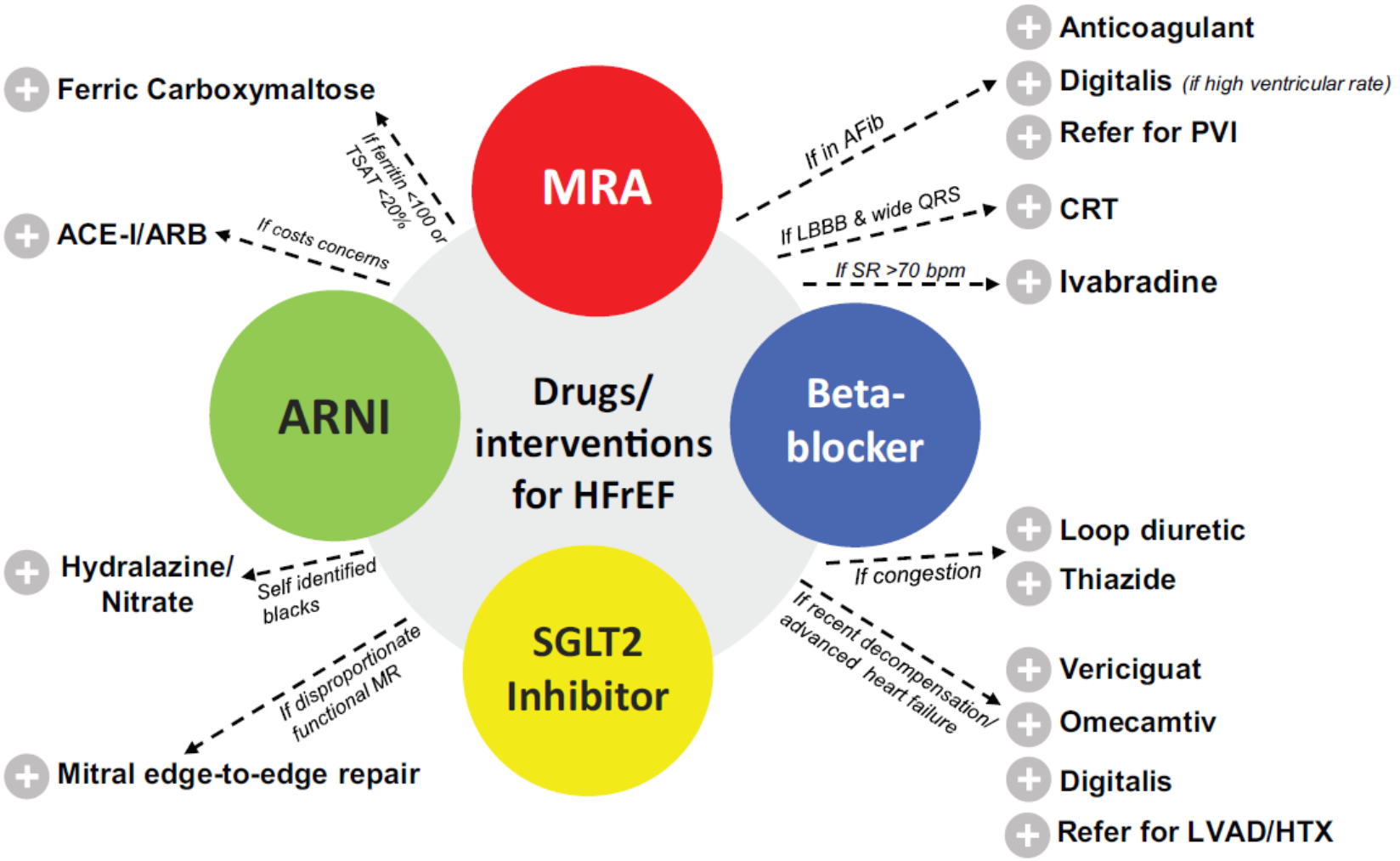
Randomized to OM 25-50 mg vs. placebo

Teerlink et al. NEJM 2020

Importance of NT-proBNP for treatment decisions

	PARADIGM-HF[1]	DAPA-HF[2]	EMPEROR-reduced[3]	GALACTIC-HF[4]	VICTORIA[5]
Median NT-proBNP (ng/l)	1608	1437	1907	2001	2816
NYHA III or IV (%)	25	32	25	47	41
HF Hosp < 6Mt	31	16			74
Mean/median eGFR (ml/min/1.73 m^2)	68	66	62	59	62
eGFR <60 ml/min/1.73 m^2	37	41	48	52	53
Median FU (months)	27	18	16	22	11
Event rate control group (events/100 py)	13.2	15.6	21.0	26.3	37.8

[1]McMurray et al. NEJM 2015, [2]McMurray et al. NEJM 2019, [3]Packer et al. NEJM 2020, [4]Teerlink et al. NEJM 2000. [5]Armstrong et al. NEJM 2000



Bauersachs J. EHJ 2021