Emerging treatments in heart failure

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Disclosures

Honoraria, sponsorship, or advisory boards (listed)

- AstraZeneca: Hyperkalaemia advisory board
- Bayer
- Boehringer Ingelheim: Diabetes advisory board
- Bristol-Myers Squibb
- Eli Lilly: Diabetes advisory board
- Menarini
- Novartis: Heart failure advisory board
- Otsuka: Tolvaptan advisory board
- Servier
- Vifor Pharma: Hyperkalaemia medical advisory board

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Emerging treatments in heart failure

- Acute heart failure
- Chronic heart failure with reduced LVEF
- Chronic heart failure with preserved LVEF
- Valvular heart disease

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MEDICAL INTELLIGENCE

Cardiac decompensation: Current concepts

General principles of treatment

ALBERTO RAMÍREZ, M.D., AND
WALTER H. ABELMANN, M.D.

- Identify and treat correctable causes
- Improve oxygenation (sitting position, oxygen ± positive pressure, furosemide)
- Increase myocardial contractility
- Nitroglycerin, nitroprusside

ciples in mind: reduction of circulatory demands and improvement of tissue oxygenation; increase of

ty. In the presence of acute pulmonary edema, morphine sulfate is the drug of choice; 10 to 15 mg subcutaneously or 5 to 8 mg intravenously is well tolerated

common-pathway result of most heart disease and re-

identify the causes of cardiac decompensation at the

administered through a well fitted mask; nasal cathe-

ration of oxy-

e inspired air

ances, oxygen

ve pressure is

rendered more

uniform, and alveolar pressure is increased, reducing

m alveolar capillaries as well

ngs, resulting in a fall in pul-

lung stiffness and hence the

duced. Endotracheal intuba-

sitive pressure is reserved for

the most desperately ill patient when routine measures have failed and examination of arterial-blood gases in-

Treatment of patients with acute cardiac decompen-

Supported in part by grants (10539 and 5244) from the National Heart and Lung Institute, U.S. Public Health Service.

NEJM 1974 290:499

Phase 3 RCT's	Year	Intervention	Outcome
OPTIME	2002	Milrinone	Neutral. Increased AE's.
VMAC	2002	Nesiritide	Greater decrease PCWP (vs. placebo/ GTN) and symptoms (vs. placebo).
VERITAS	2007	Tezosentan	Neutral. Increased AE's.
SURVIVE	2007	Levosimendan	Neutral (vs. dobutamine).
EVEREST	2007	Tolvaptan	Improved symptoms. No effect on mort./ hosp.
PROTECT	2010	Rolofylline	Neutral. Increased seizures.
DOSE	2011	Frusemide	Neutral (Continuous vs. bolus; HD vs. LD).
ASCEND-HF	2011	Nesiritide	Neutral (symptoms, mort./ hosp.).
CARESS	2012	Ultrafiltration	Inferior (vs. stepped drug therapy).
RELAX-AHF	2013	Serelaxin	Positive (VAS AUC). Reduced 180d mort.
ASTRONAUT	2013	Aliskiren	Neutral.
REVIVE	2013	Levosimendan	Improved clinical status. Increased AE's.
ROSE	2013	LD dopamine/ nesiritide	Neutral.
TRUE-AHF	2016	Ularitide	Neutral
RELAX-AHF-2	2017	Serelaxin	Neutral

* comparisons are vs. placebo unless otherwise stated

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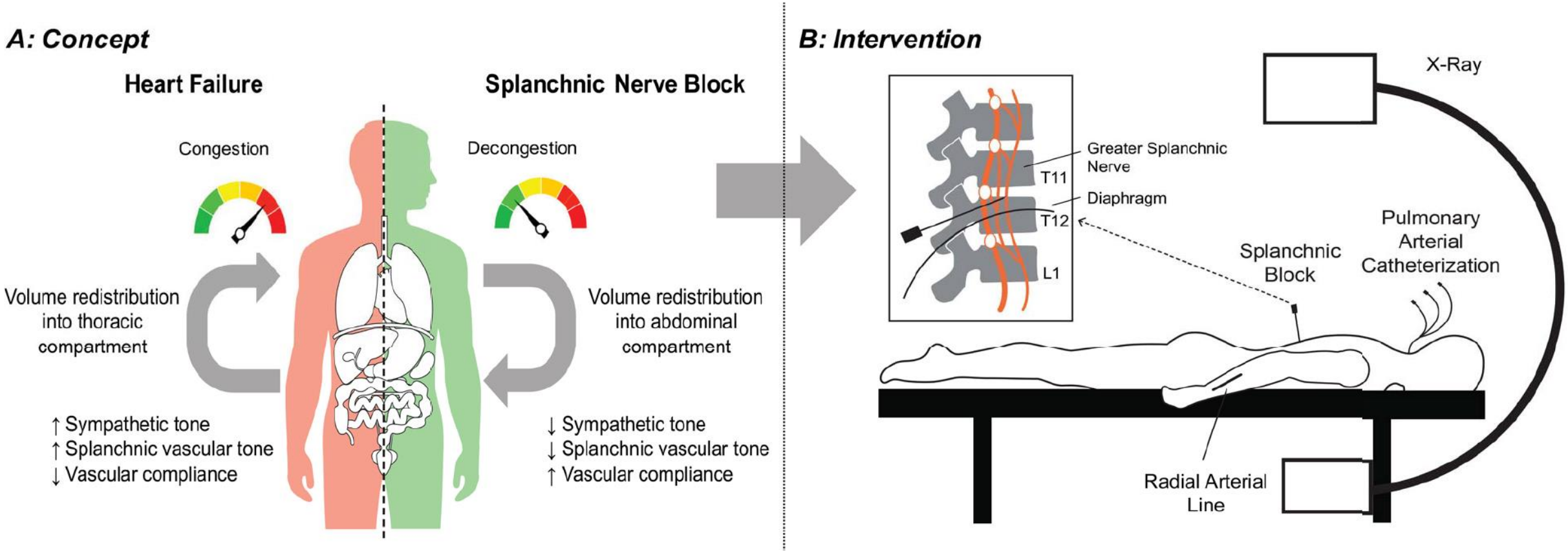
Splanchnic nerve block for AHF?



Fudim M et al. Circulation 2018

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- Chronic heart failure with reduced LVEF
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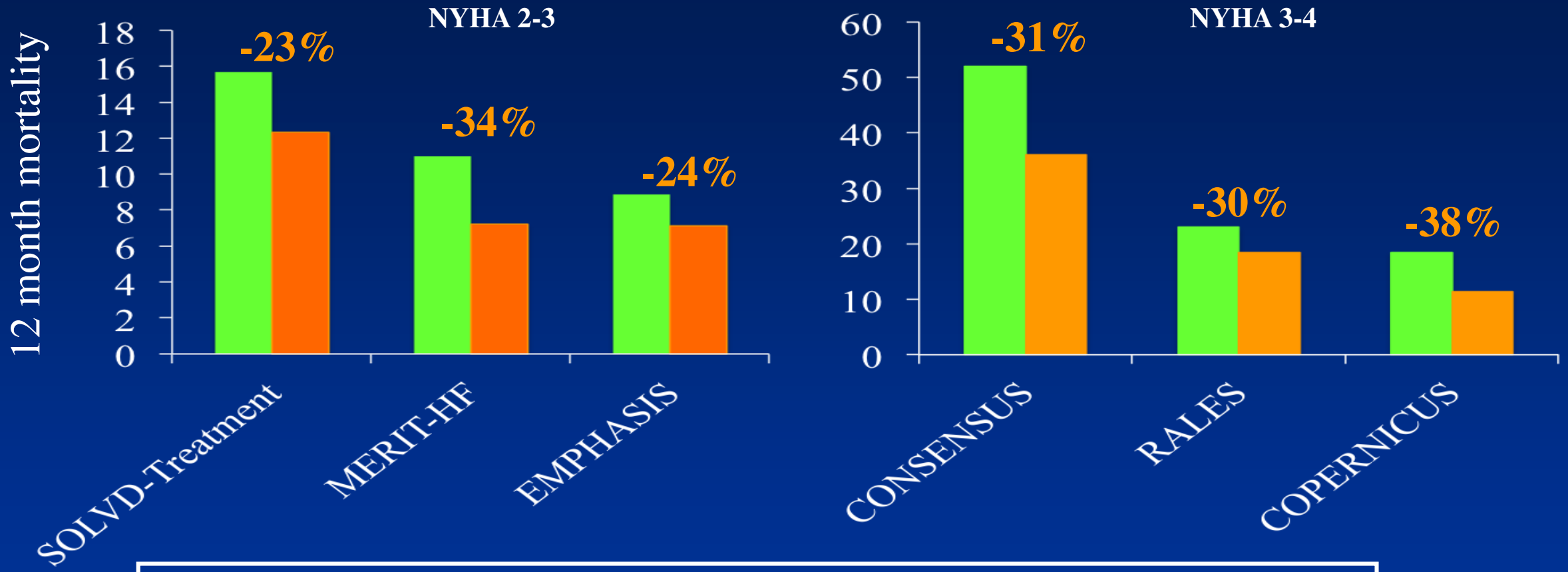
ACEI + Beta blocker + MRA



60-70% RRR mortality in HFrEF

Hayman S and Atherton JJ. Cardiac Failure Review 2016;2:47-50.

ACEi+BB+MRA in HF with LVEF ≤35-40%

What next?
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Add ivabradine
Intravenous iron
Add ICD
Add CRT
AF ablation

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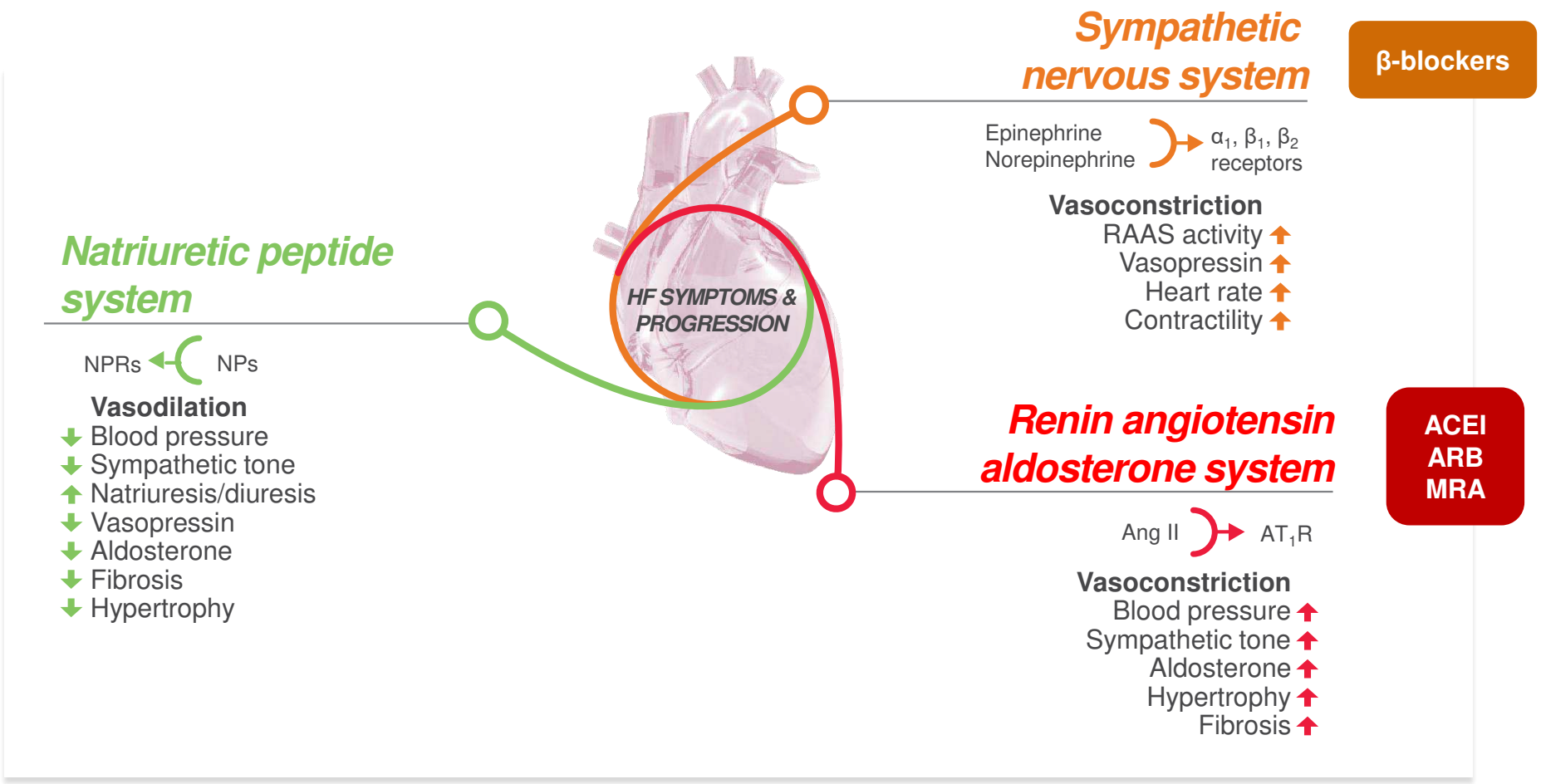
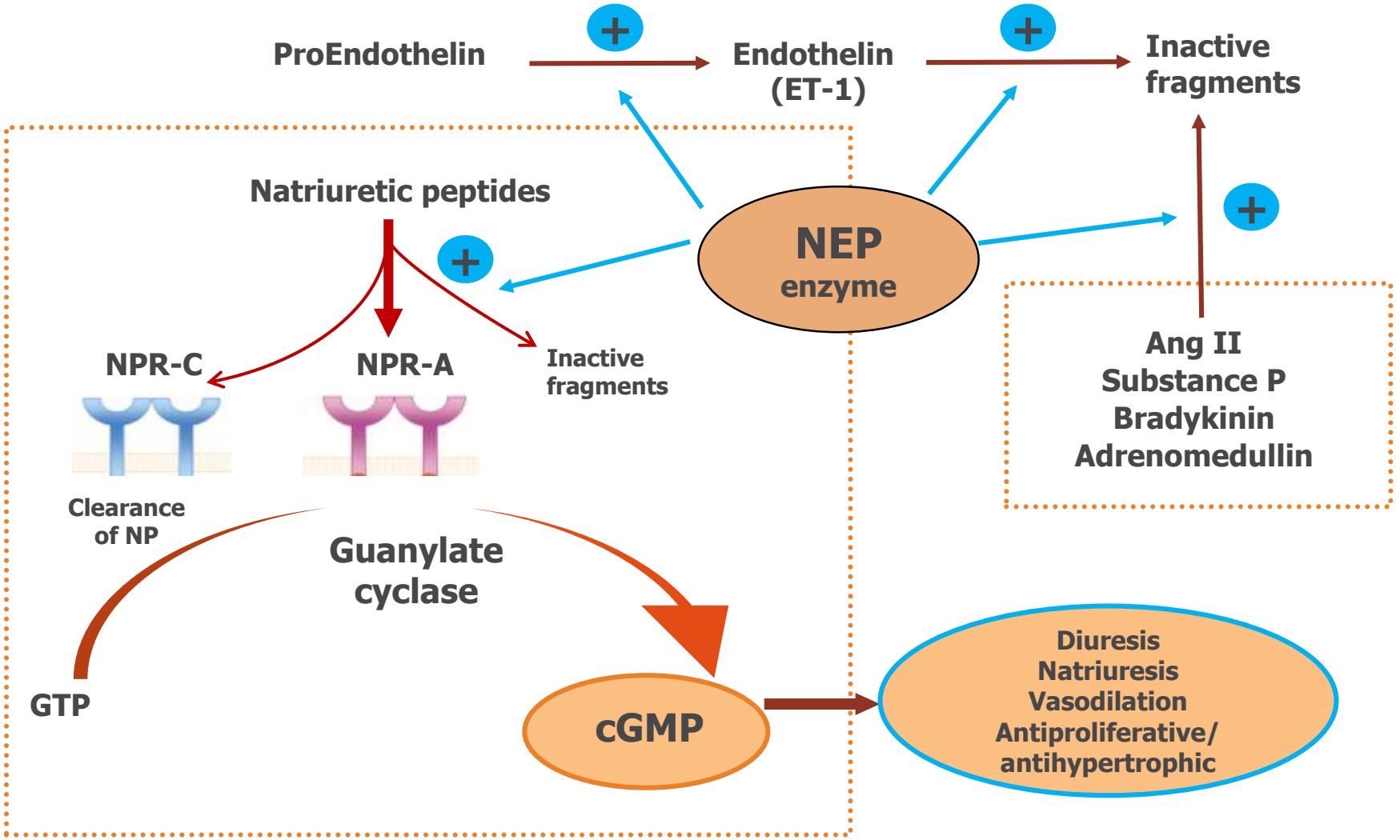
Neurohormonal modulation vs. antagonism in CHF



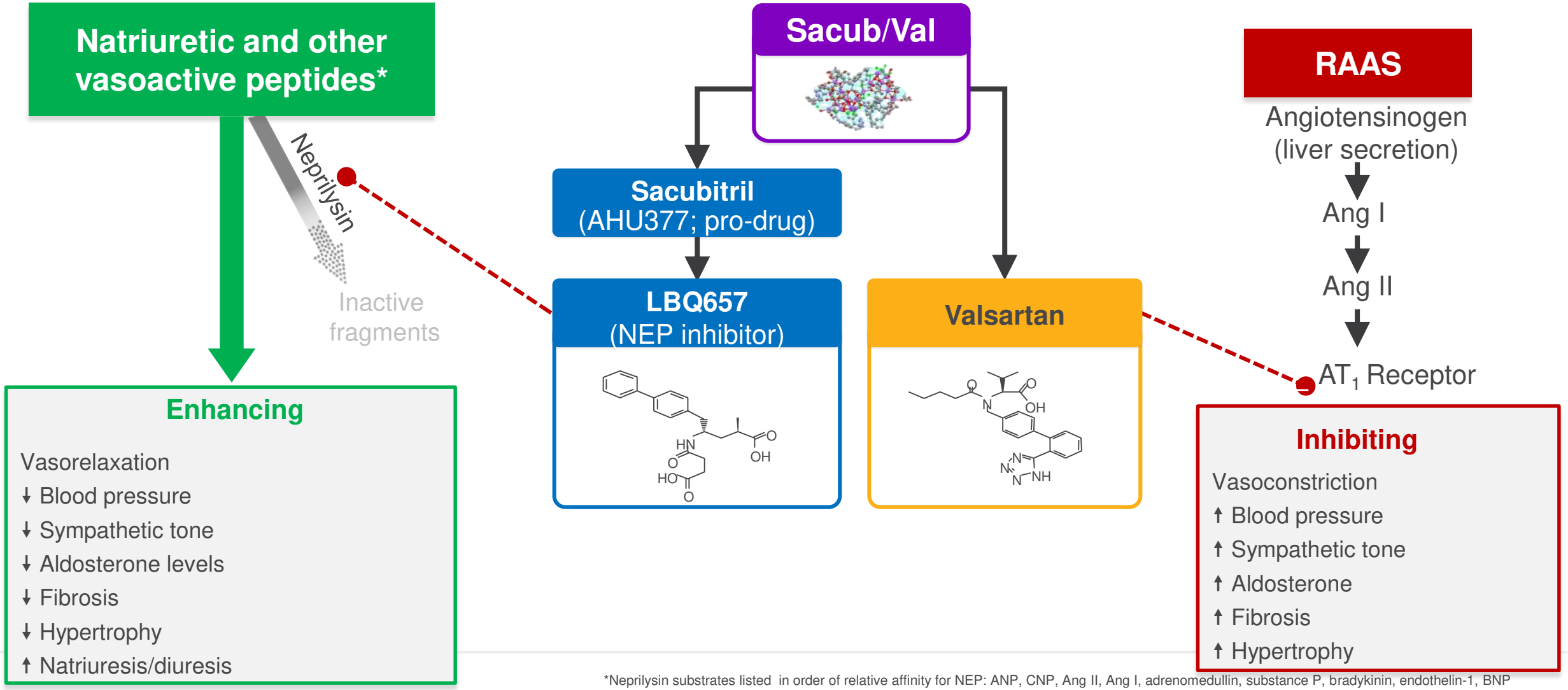
Levin et al. N Engl J Med 1998;339:321–8;
Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42;
Kemp & Conte. Cardiovascular Pathology 2012;365–371;
Schrier & Abraham. N Engl J Med 2009;341:577–85

Clearance of Natriuretic Peptides



1. Erdos, Skidgel. FASEB J 1989;3:145–51; 2. Levin et al. N Engl J Med 1998;339;321–8;
3. Murphy et al. Br J Pharmacol 1994;113:137–42; 4. Jiang et al. Hypertens Res 2004;27:109–17;
5. Ferro et al. Circulation 1998;97:2323–30; 6. Martinez-Rumayor et al. Am J Cardiol 2008;101[suppl]:3A-8A;
7. Richards et al. J Hypertens 1993;11:407–16

Sacubitril/ Valsartan simultaneously inhibits NEP (via LBQ657) and blocks the AT_1 receptor (via valsartan)



*Neprilysin substrates listed in order of relative affinity for NEP: ANP, CNP, Ang II, Ang I, adrenomedullin, substance P, bradykinin, endothelin-1, BNP

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

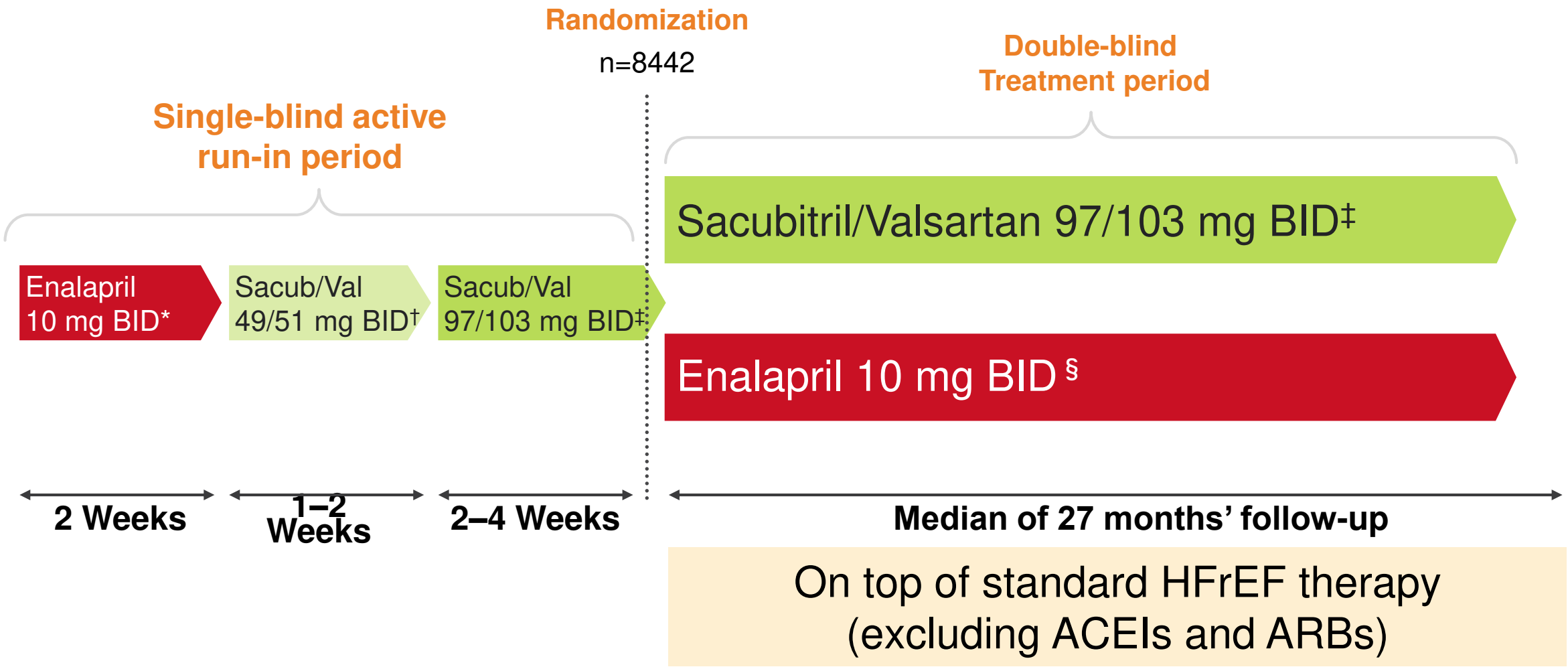
PARADIGM-HF: Key inclusion criteria

- Chronic HF NYHA FC II–IV with LVEF ≤40%*
- BNP (or NT-proBNP) levels as follows:
  - ≥150 (or ≥600 pg/mL), or
  - ≥100 (or ≥400 pg/mL) and a hospitalization for HFrEF within the last 12 months
- ≥4 weeks' stable treatment with an ACEI or an ARB#, and a β-blocker
- Aldosterone antagonist should be considered for all patients (with treatment with a stable dose for ≥4 weeks, if given)

*The ejection fraction entry criteria was lowered to ≤35% in a protocol amendment
#Dosage equivalent to enalapril ≥10 mg/day

McMurray et al. Eur J Heart Fail. 2013;15:1062–73

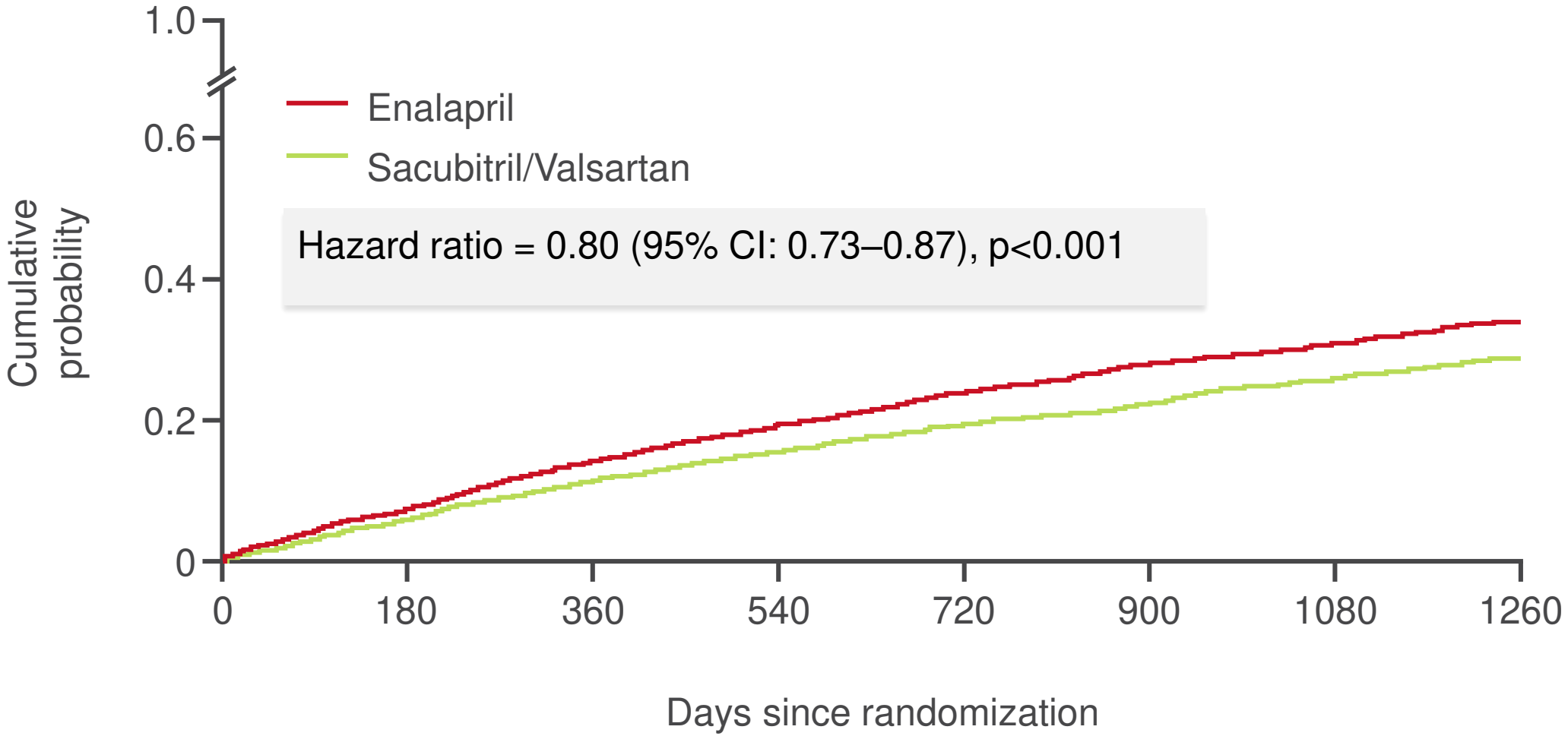
PARADIGM-HF: Study design



*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; Primary endpoint: CV death or first hospitalization for HF



- McMurray et al. N Engl J Med 2014;371:993–1004

Prospectively defined safety events

Event, n (%)	Sacub/Val (n=4187)	Enalapril (n=4212)	p-value‡
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with SBP <90 mmHg	112 (2.7)	59 (1.4)	<0.001
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
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema (adjudicated by a blinded expert committee)			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalized without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	---

- Fewer patients in the Sacubitril/Valsartan group than in the enalapril group stopped their study medication because of an AE (10.7 vs 12.3%, p=0.03)

- McMurray et al. N Engl J Med 2014;371:993–1004

ACEi+BB+MRA in HF with LVEF ≤35-40%

What next?	
Switch ACEi to ARNI	Morbidity and mortality benefit
Add ivabradine	
Intravenous iron	
Add ICD	
Add CRT	
AF ablation	

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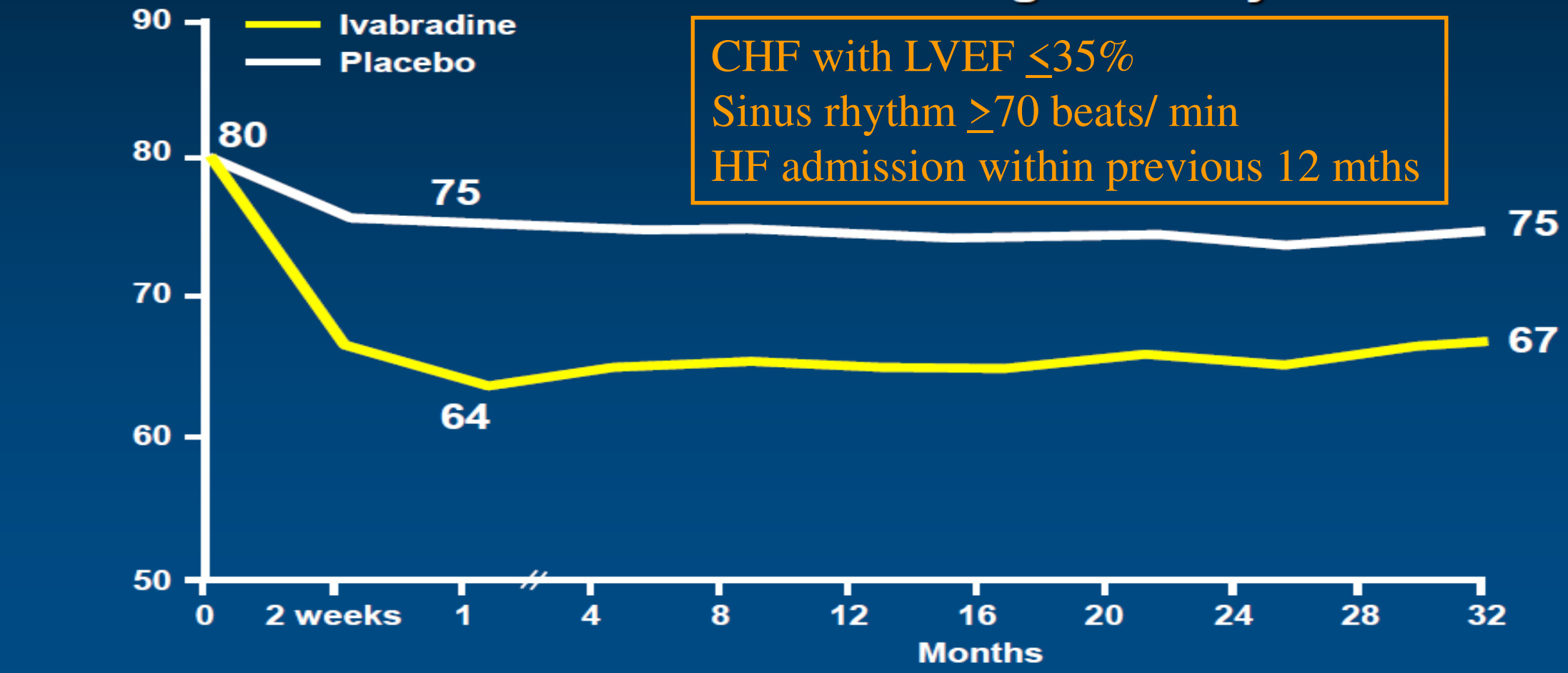
Mean heart rate reduction

Mean ivabradine dose: 6.4 mg bid at 1 month
6.5 mg bid at 1 year



CHF with LVEF ≤35%
Sinus rhythm ≥70 beats/ min
HF admission within previous 12 mths

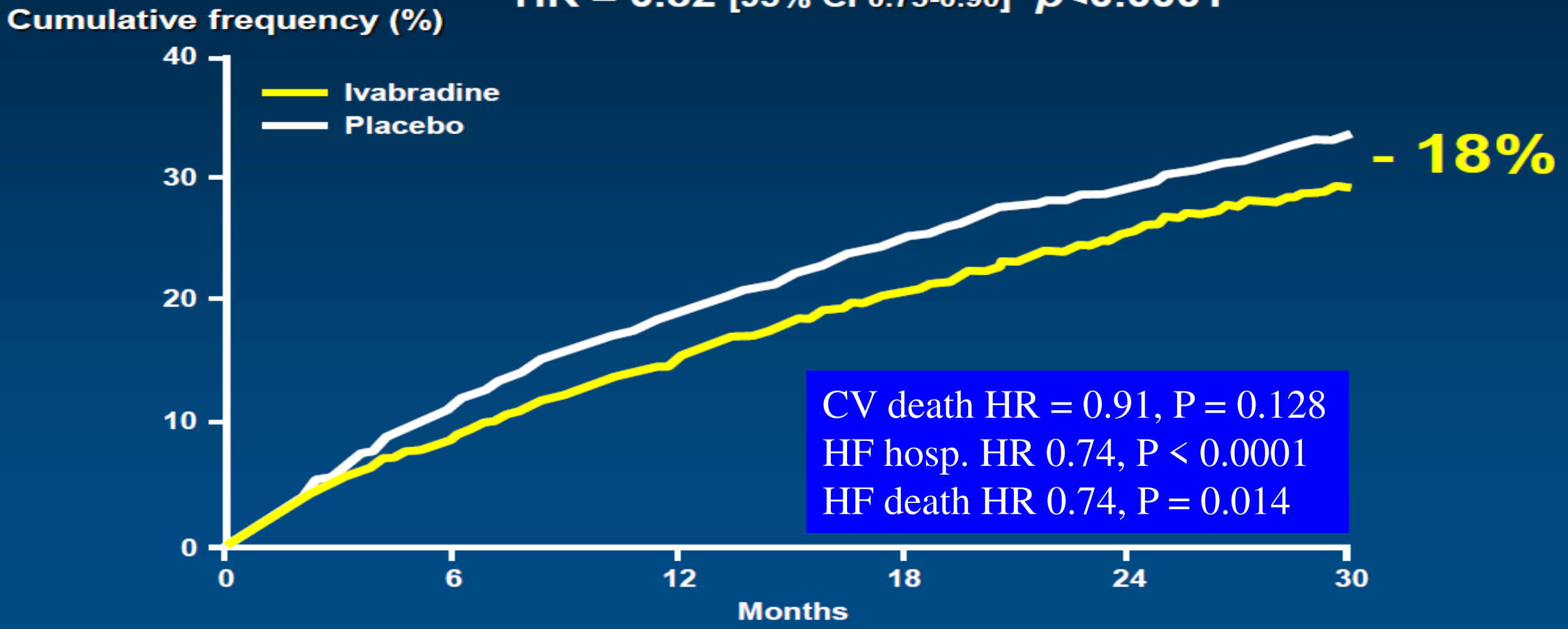
Swedberg et al. Lancet 2010

Primary composite endpoint

Cardiovascular death or heart failure hospitalisation

Ivabradine n=793 (14.5%PY) Placebo n=937 (17.7%PY)

HR = 0.82 [95% CI 0.75-0.90] $p<0.0001$



CV death HR = 0.91, P = 0.128
HF hosp. HR 0.74, P < 0.0001
HF death HR 0.74, P = 0.014

Swedberg et al. Lancet 2010

Krum and Sindone CSANZ 2013	Baseline HR≥77 bpm Subgroup (Hazard Ratio [95% CI])	p value	All SHIFT Patients (Hazard Ratio [95% CI])	p value
Primary composite endpoint	0.75 [0.67; 0.85]	<0.0001	0.82 [0.75; 0.90]	<0.0001
CV death	0.81 [0.69; 0.96]	0.0137	0.91 [0.80; 1.03]	0.128
Hospitalisation for worsening CHF	0.69 [0.59; 0.80]	<0.0001	0.74 [0.66; 0.83]	<0.0001
All-cause death	0.81 [0.69; 0.94]	0.0074	0.90 [0.80; 1.02]	0.092
Death from CHF	0.61 [0.45; 0.83]	0.0017	0.74 [0.58; 0.94]	0.014
Hospitalisation for any cause	0.82 [0.74; 0.91]	0.0002	0.89 [0.82; 0.96]	0.003
Hospitalisation for CV reason	0.79 [0.71; 0.89]	<0.0001	0.85 [0.78; 0.92]	0.0002

ACEi+BB+MRA in HF with LVEF ≤35-40%

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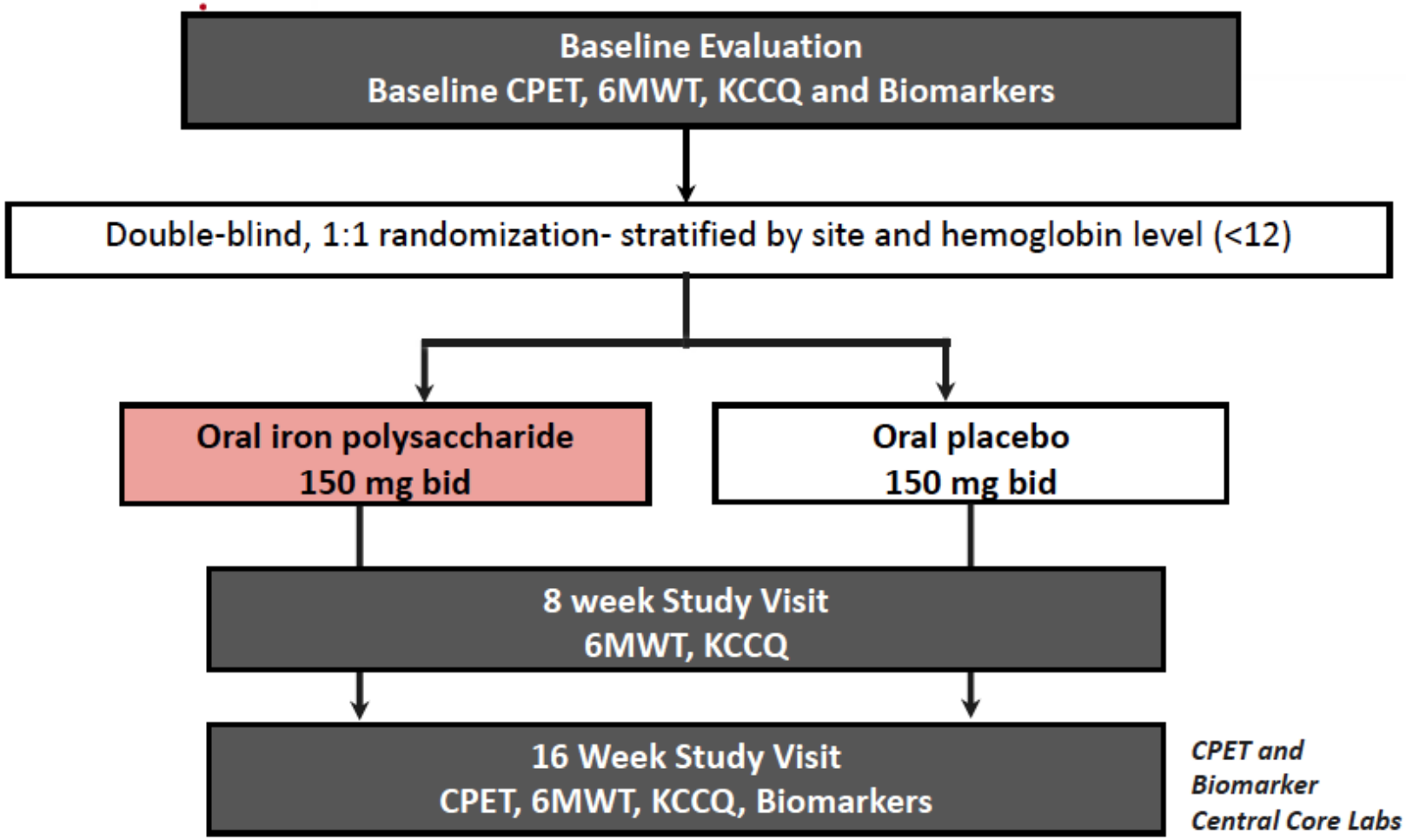
Efficacy of intravenous iron in HFrEF

	n	Design	Inclusion	Treatment	F/U	Outcome
Bolger 2006	16	Open, pre-post	Ferritin≤400	Iron sucrose	92 days	↑Hb, ↑HRQoL, ↑6MWT, ↓NYHA
Toblli 2007	40	DB, PC, RCT	Ferritin<100 and/or TSAT≤20%	Iron sucrose	6 mths	↑Hb, ↑HRQoL, ↑6MWT, ↑LVEF, ↓NYHA, ↑CrCl, ↓NT-proBNP, ↓Hosp.
Okonko 2008	35	SB, RCT	Ferritin<100 or 100–300 + TSAT <20%	Iron sucrose	18 wks	↓HF symp. (PGA, NYHA), ↑peak VO_2/kg, ↓Fatigue
Usmanov 2008	32	Open, pre-post	Ferritin not specified	Iron sucrose	26 wks	↓NYHA (in NYHA class III) ↑Hb, Reverse remodelling
Anker 2009	459	DB, PC, RCT	Ferritin<100 or 100–300 + TSAT <20%	Ferric carboxymaltose	24 wks	↓HF symp. (PGA, NYHA), ↑6MWT, ↑HRQoL, , ↑eGFR
Gaber 2012	40	Open, pre-post	Ferritin<100, TSAT<20%	Iron dextran	12 wks	↓NYHA , ↑6MWT, Tissue Doppler/ strain improved
Beck-da-Silva 2013	16	DB, PC, RCT	Ferritin<500, TSAT<20%	Iron sucrose	3 mths	Underpowered
Ponikowski 2015	304	DB, PC, RCT	Ferritin<100 or 100–300 + TSAT <20%	Ferric carboxymaltose	52 wks	↑6MWT, ↓HF symp. (PGA, NYHA), ↑HRQoL, ↓Fatigue, ↓HF hosp.
van Velduisen 2017	174	Open, RCT	Ferritin<100 or 100–300 + TSAT <20%	Ferric carboxymaltose	24 wks	↑peak VO2, ↓HF symp (PGA, NYHA)

IRONOUT HF

HEART FAILURE NETWORK

Study Design

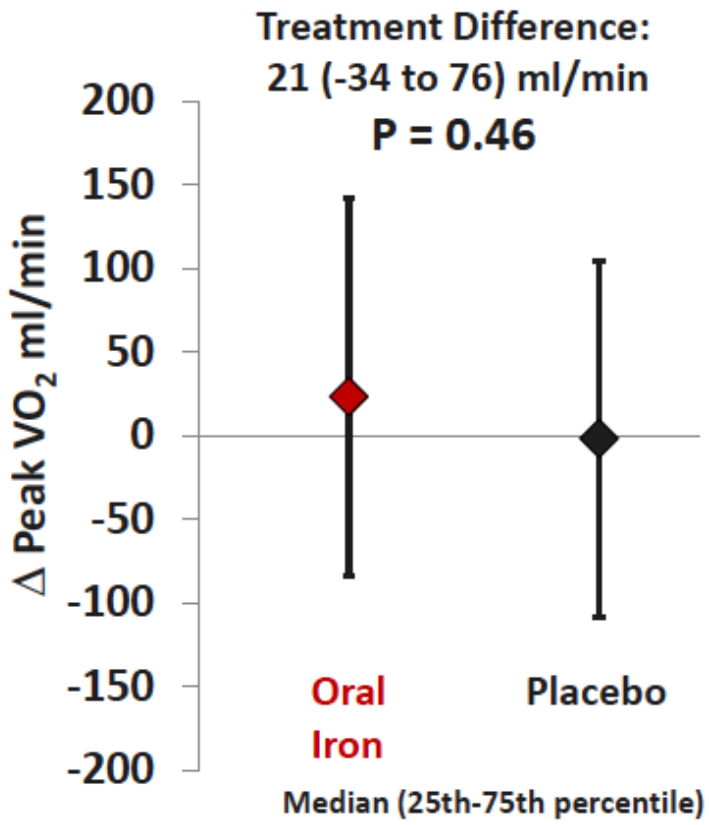


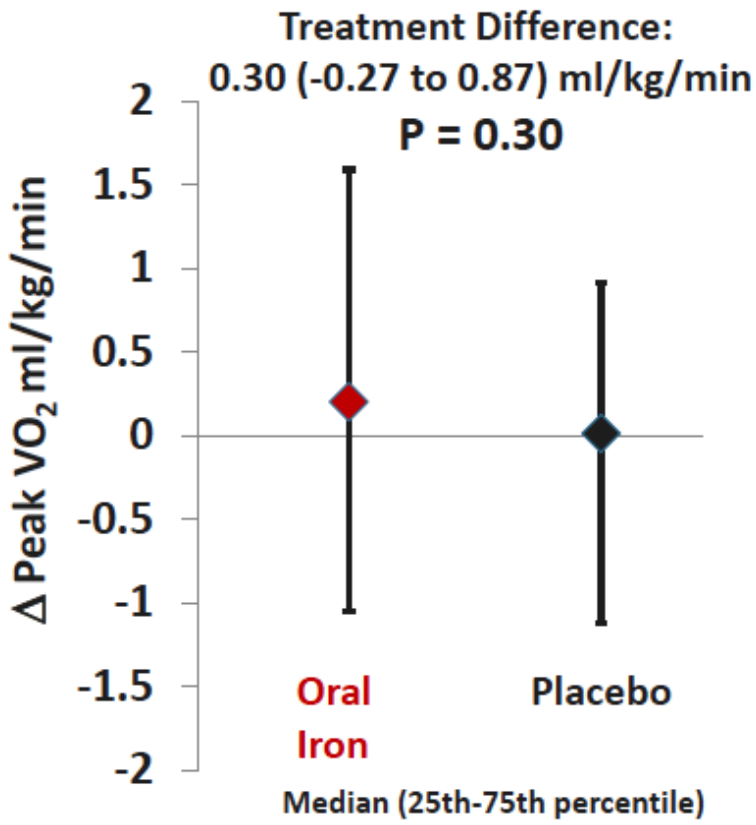
Lewis GD et al.
JAMA 2017;
317:1958-66.

American Heart Association Scientific Sessions 2016

IRONOUT HF

Primary Endpoint





Lewis GD et al.
JAMA 2017;
317:1958-66.

American Heart Association Scientific Sessions 2016

ACEi+BB+MRA in HF with LVEF ≤35-40%

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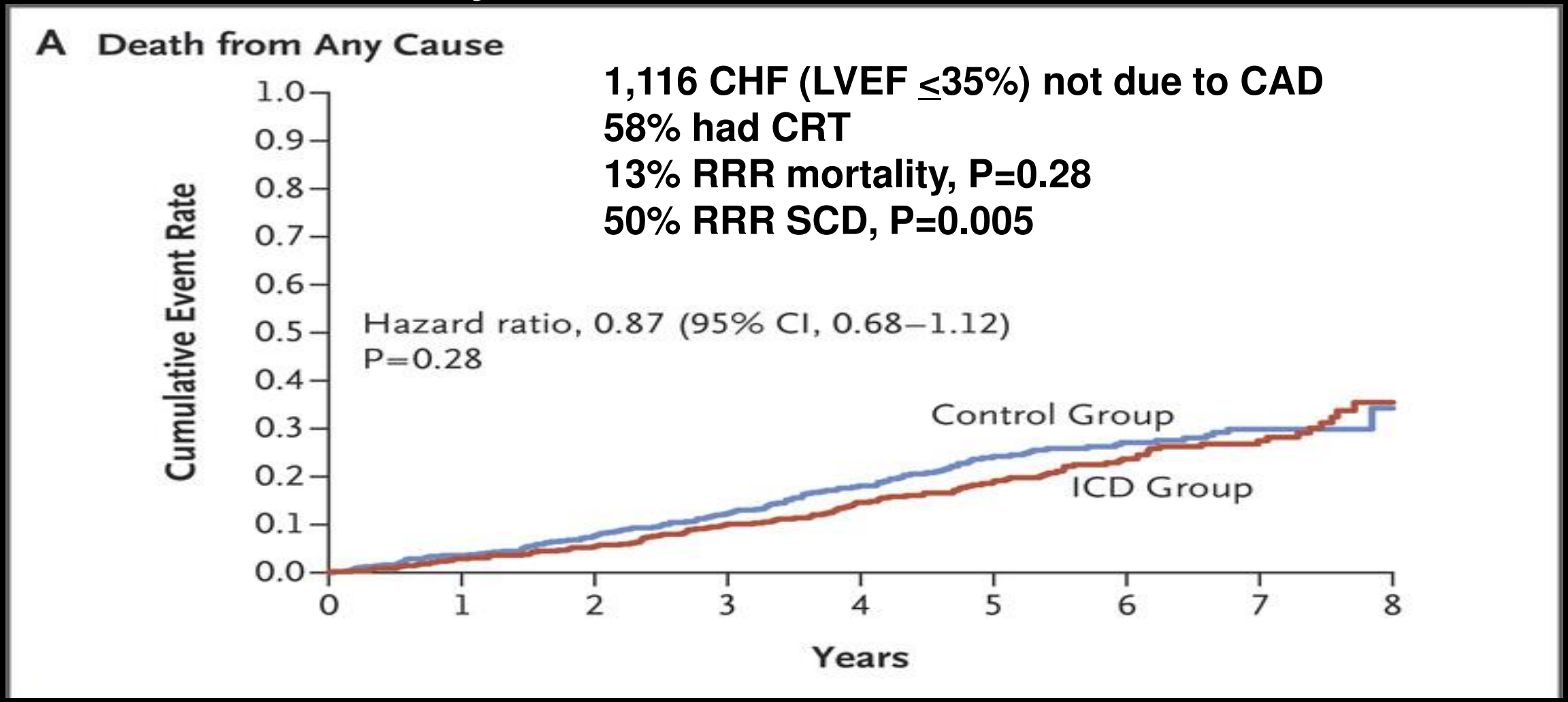
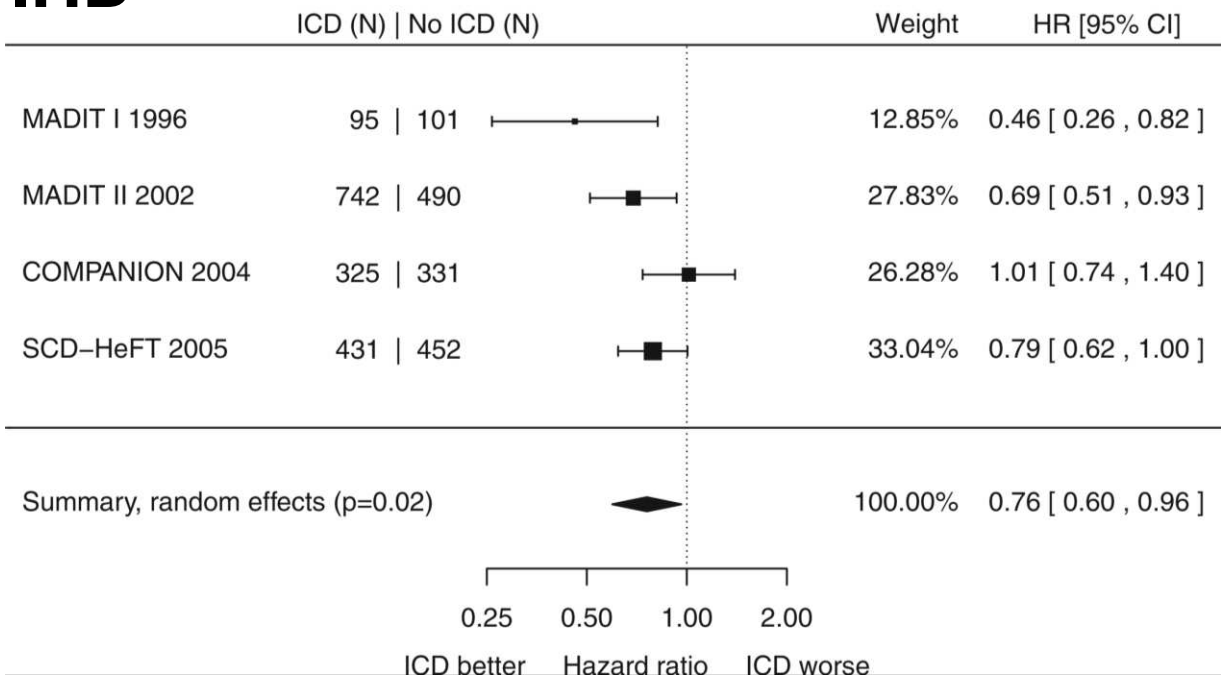
DANISH: Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure

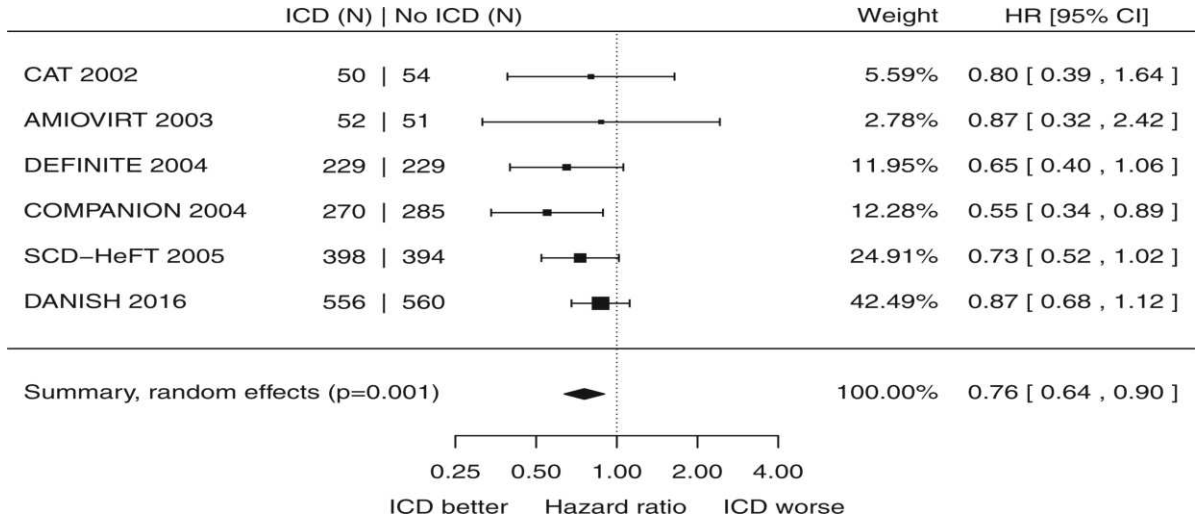


Køber L et al. N Engl J Med 2016;375:1221-30.

IHD



No IHD



Meta-analysis of ICDs for primary prevention of death in LV dysfunction (8567 patients in 11 trials)

Similar mortality relative risk reduction with or without IHD

Shun-Shin MJ et al.
Eur Heart 2017;38:1738-46.

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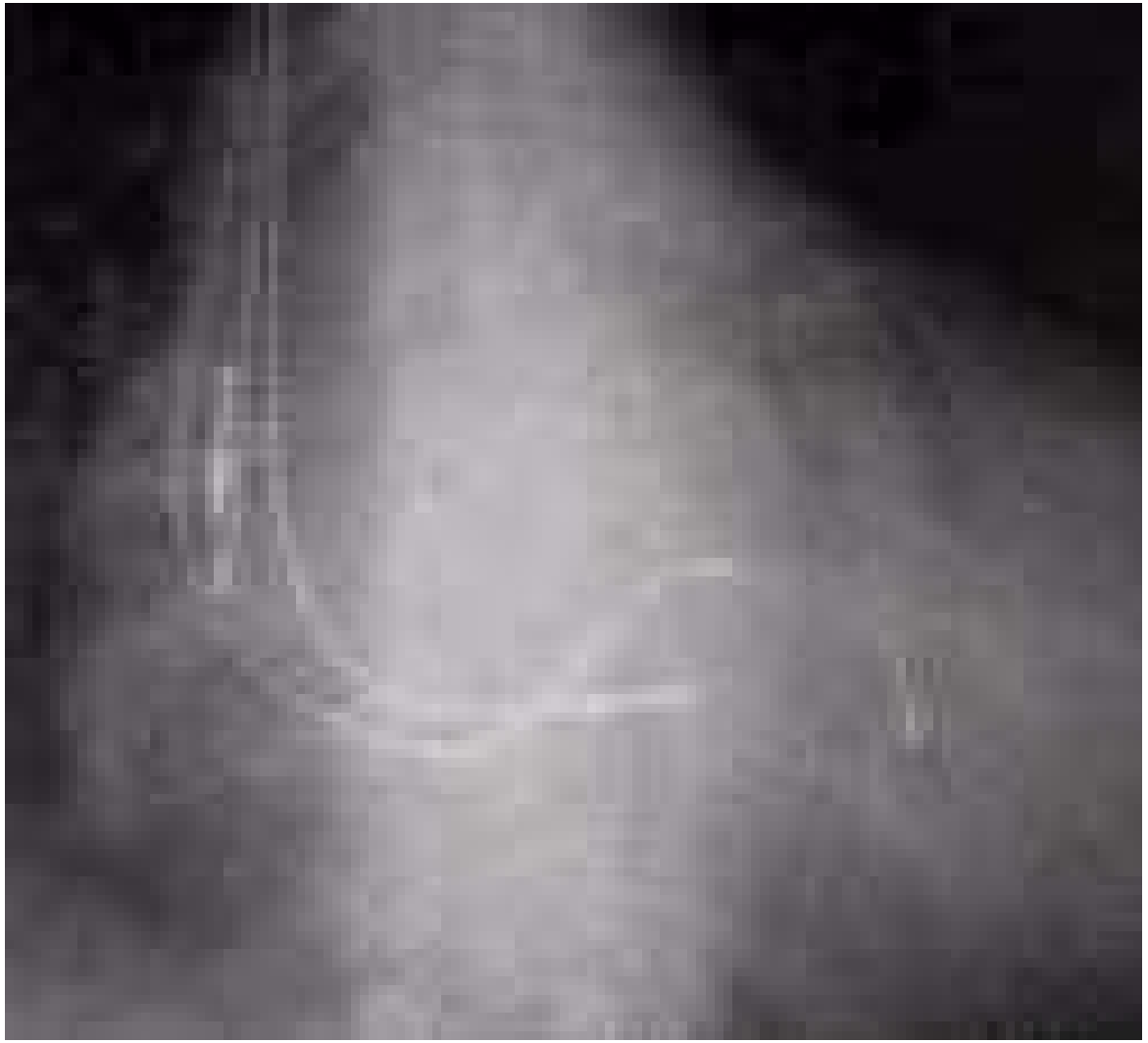
Cardiac Resynchronisation (CRT)



CHF patients
NYHA Class 2-4 symptoms
QRS ≥130ms (esp. LBBB?)
LVEF ≤30-35%
Optimal drug therapy

Improves symptoms
Decreased hospitalisation
Decreased mortality

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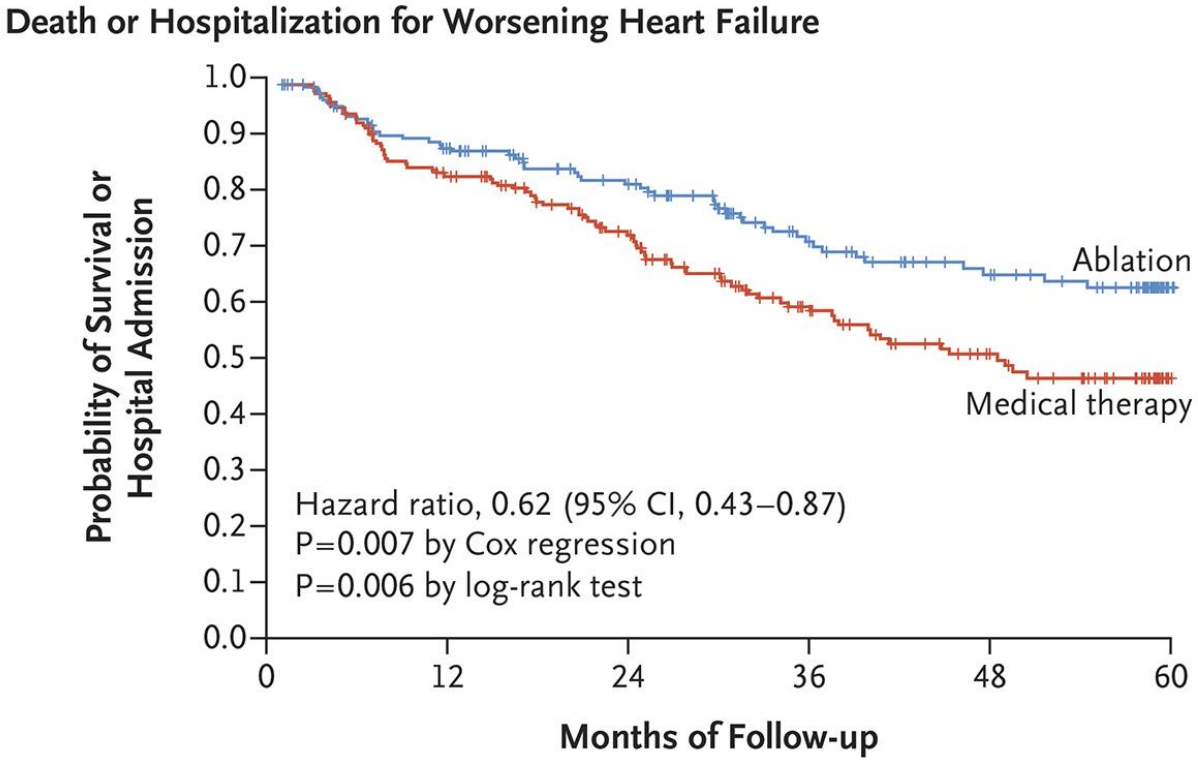
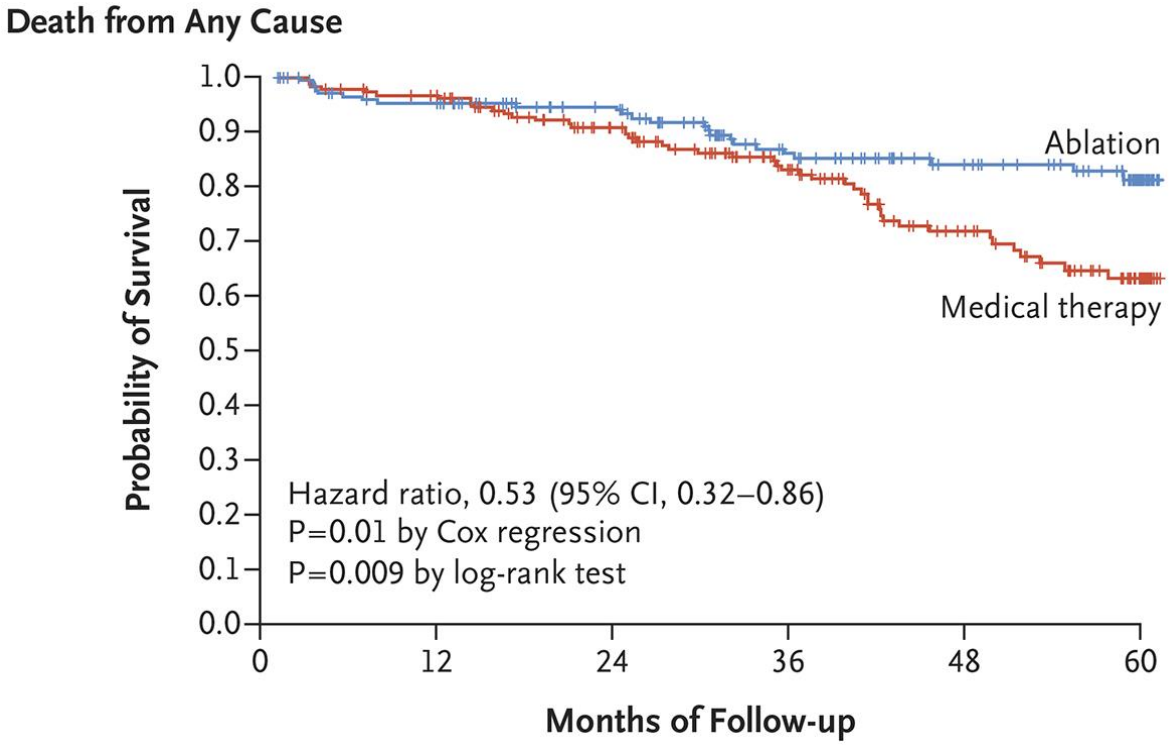
CASTLE-AF

AF catheter ablation

- Symptomatic paroxysmal or persistent AF
- Failure/ intolerance ≥1 AAD (or unwilling)
- HFrEF with LVEF ≤0.35
- NYHA class ≥2
- ICD or CRT-D with home monitoring





NF Marrouche et al. N Engl J Med 2018;378:417-27.

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Add ICD	Mortality benefit
Add CRT	Morbidity and mortality benefit for QRS ≥130ms
AF ablation	Morbidity and mortality benefit for recurrent AF

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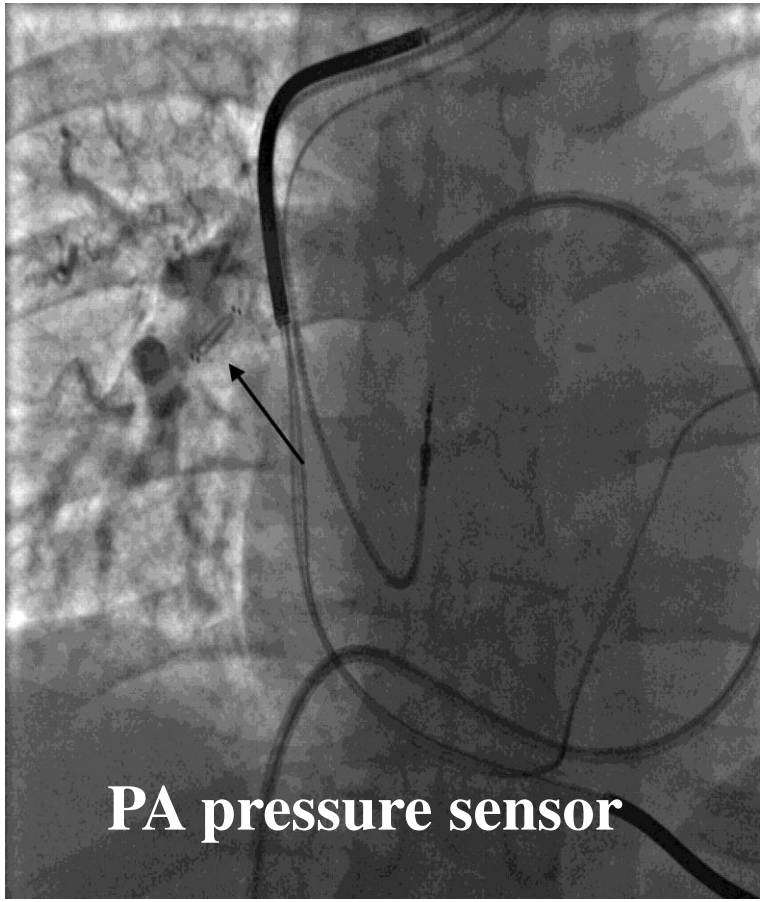
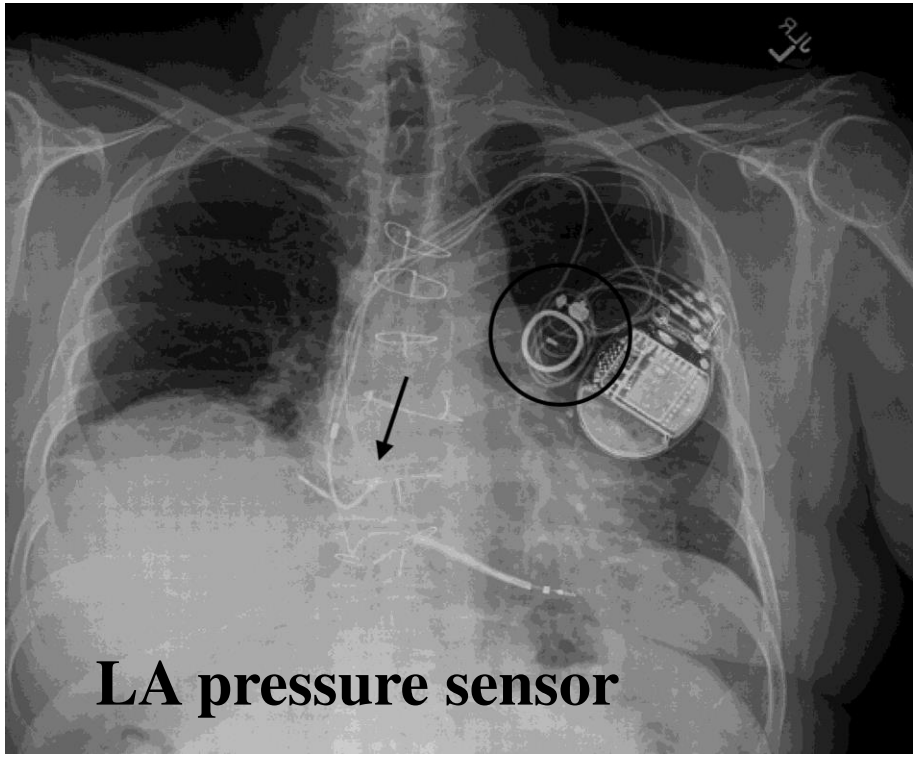
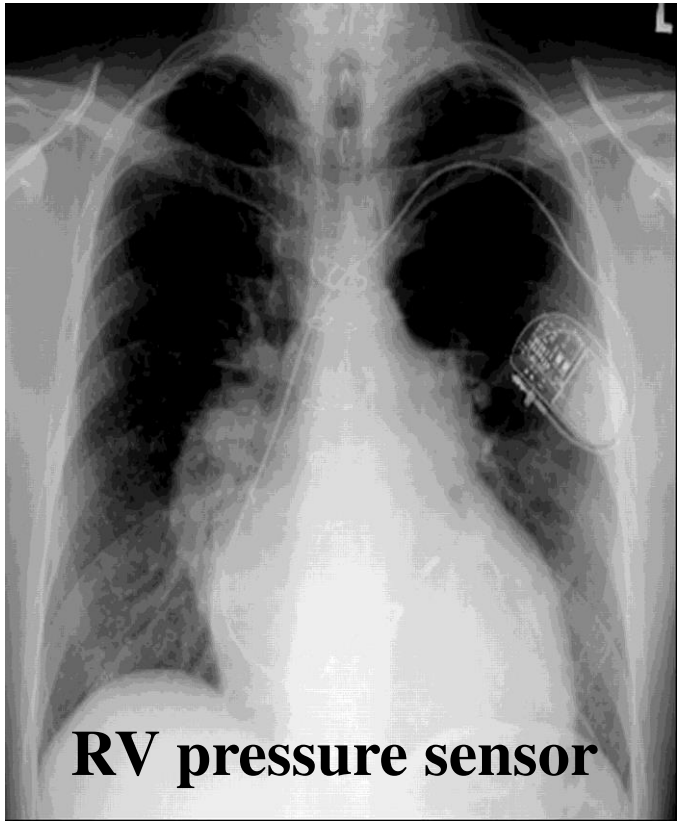
QUT Queensland University of Technology
University of the Sunshine Coast Queensland, Australia

Implantable haemodynamic sensors

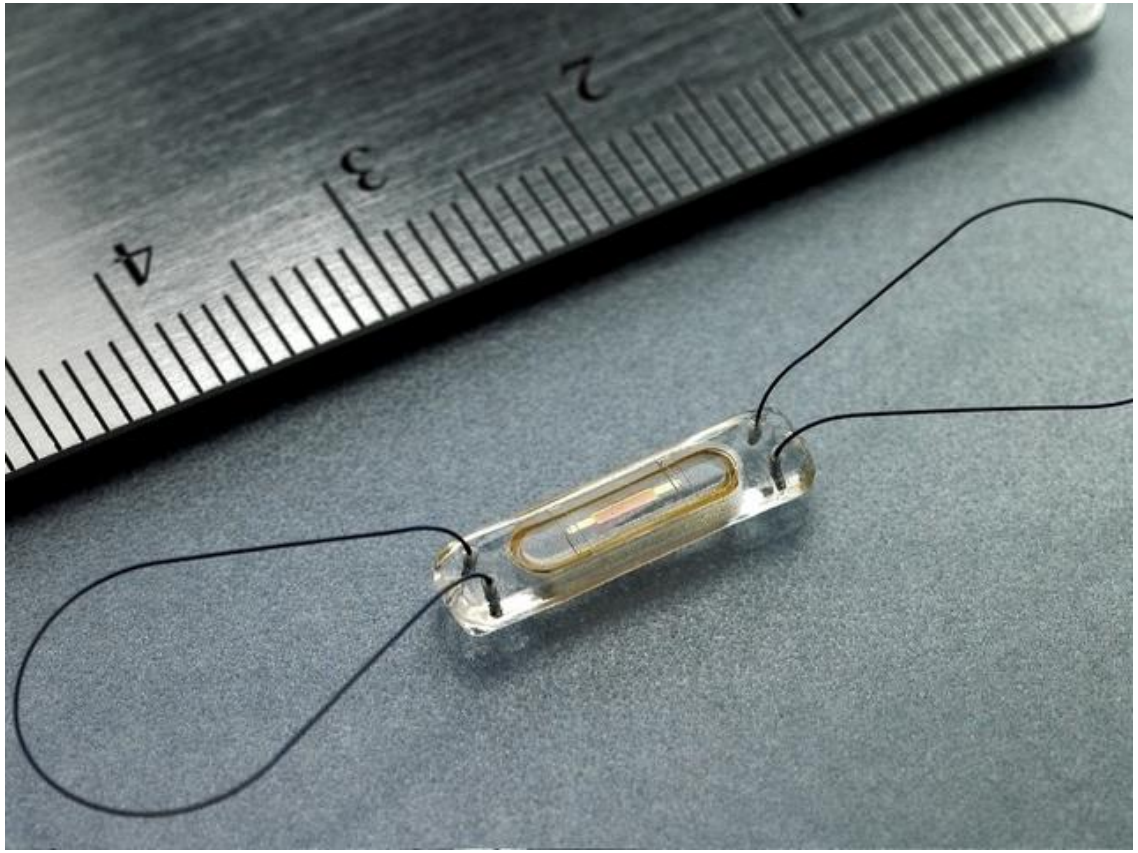






Hasan and Paul. Eur Heart J 2011;32:1457

CHAMPION: PA pressure monitoring in CHF



- 550 NYHA III CHF pts
- Single blind RCT
- Implanted PA sensor (wireless)
- 30% RRR HF hosp. 6 mths, P<0.001 (Prim. EP) and 15 mths
- 30% RRR any hosp., P=0.02
- Improved QOL
- Lower PAP
- Benefit in reduced and preserved systolic LVEF

Abraham et al. Lancet 2011;377:658-66.

Emerging treatments in heart failure

- Acute heart failure
- Chronic heart failure with reduced LVEF
- Chronic heart failure with preserved LVEF

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Drug class	HFrEF major RCT's		HFpEF major RCT's	
ACEi	CONSENSUS SOLVD-T	Positive Positive	PEP-CHF	Neutral
Beta blockers	CIBIS-II MERIT-HF COPERNICUS BEST	Positive Positive Positive Neutral	J-DHF	Neutral
MRA	RALES EMPHASIS-HF	Positive Positive	TOPCAT	Neutral
ARNI	PARADIGM-HF	Positive	PARAGON	Ongoing
ARB	CHARM-Alternative CHARM-Added Val-HeFT	Positive Positive Positive	CHARM-Preserved I-Preserve	Neutral Neutral
Ivabradine	SHIFT	Positive		
n3-PUFA	GISSI-HF	Positive		

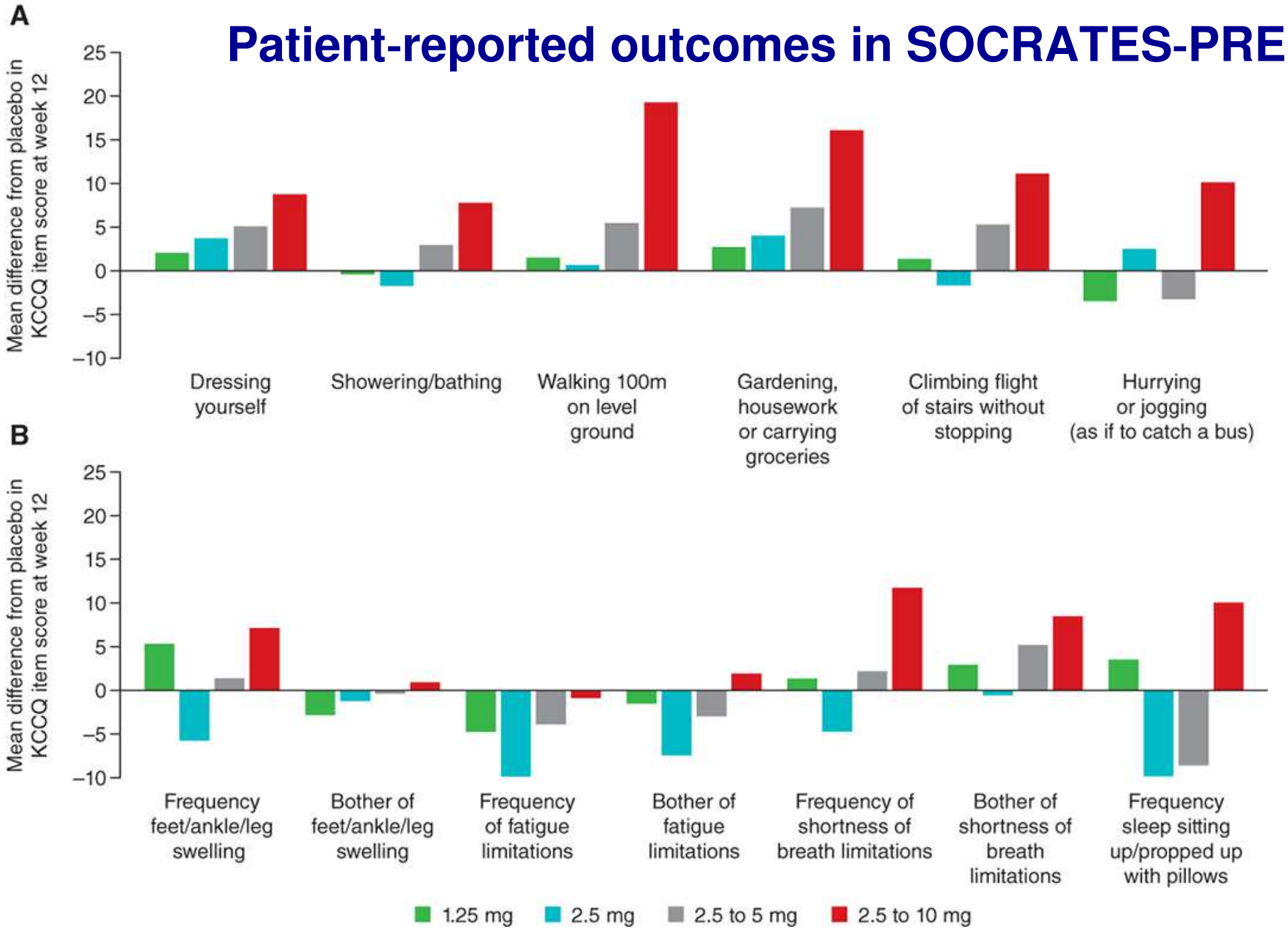
Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED EF (SOCRATES-PRESERVED) study

Pieske B et al. Eur Heart J 2017;38:1119-27.

Aims To determine tolerability and the optimal dose regimen of the soluble guanylate cyclase stimulator vericiguat in patients with chronic heart failure and preserved ejection fraction (HFpEF).

Conclusion Vericiguat was well tolerated, did not change NT-proBNP and LAV at 12 weeks compared with placebo but was associated with improvements in quality of life in patients with HFpEF. Given the encouraging results on quality of life, the effects of vericiguat in patients with HFpEF warrant further study, possibly with higher doses, longer follow-up and additional endpoints.

Patient-reported outcomes in SOCRATES-PRESERVED



Filippatos G B et al.
Eur J Heart Fail
2017;19:782-91.

Sacubitril/Valsartan Outcomes Program

CHF and high-risk AMI

HFrEF
Chronic Heart Failure
with reduced ejection fraction

PARADIGMHF

- First-in-class (ARNI)
- Replace current SoC
- Superior to ACEI
- Reduced CV mortality and HF hospitalization

HFpEF
Chronic Heart Failure
with preserved ejection fraction

PARAGONHF

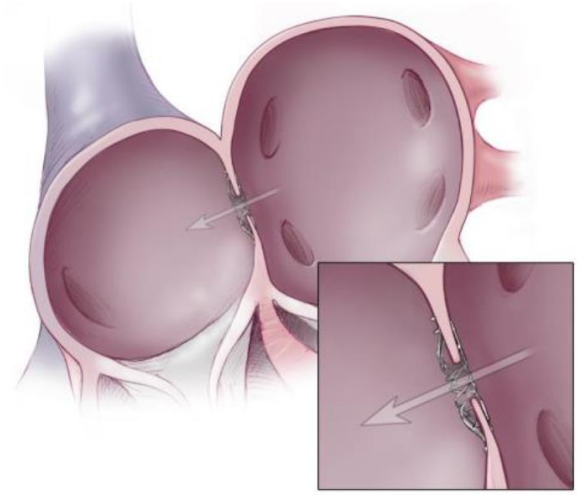
- No effective therapy today
- Establish SoC
- PARAMOUNT Phase 2: Positive Proof of Concept
- PARAGON-HF Phase 3 ongoing

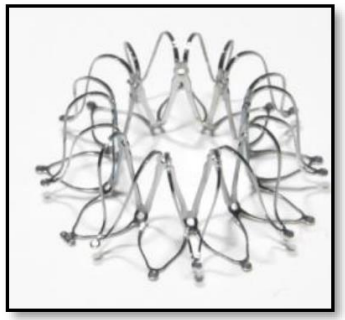
Post-AMI
Post-Acute Myocardial Infarction

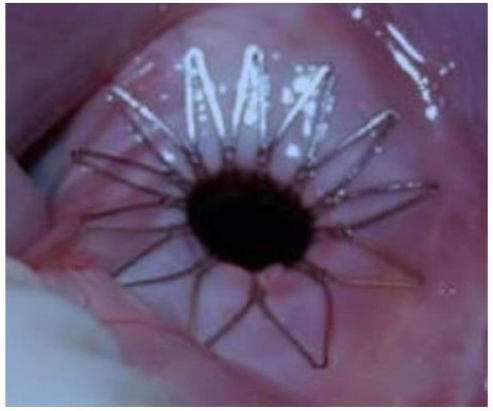
PARADISE-MI

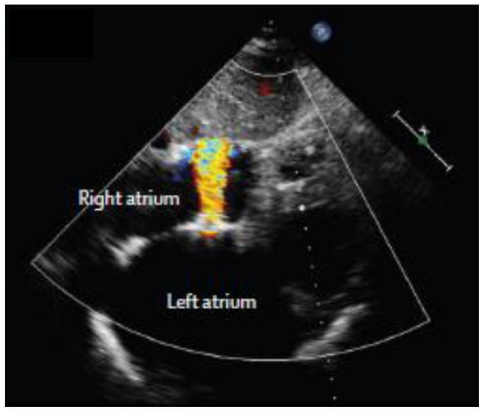
- Beyond chronic HF: HF prevention and reduction of CV mortality
- Front-loading event accrual enables shorter patient follow-up

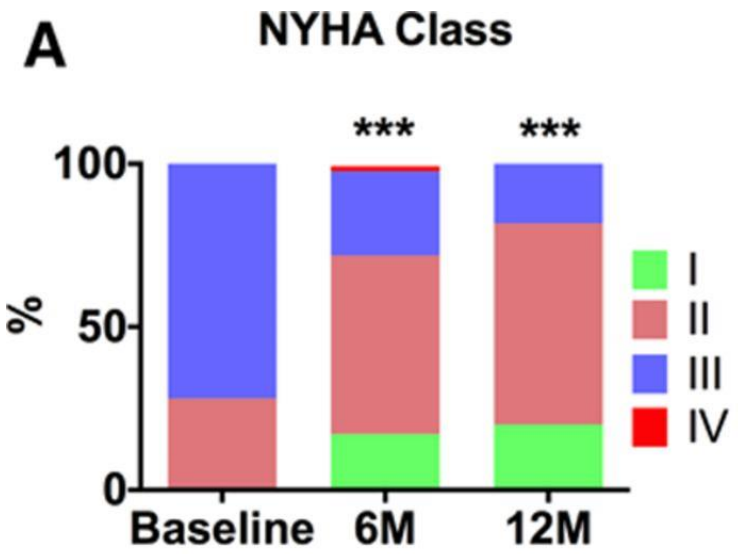
REDUCE LAP-HF

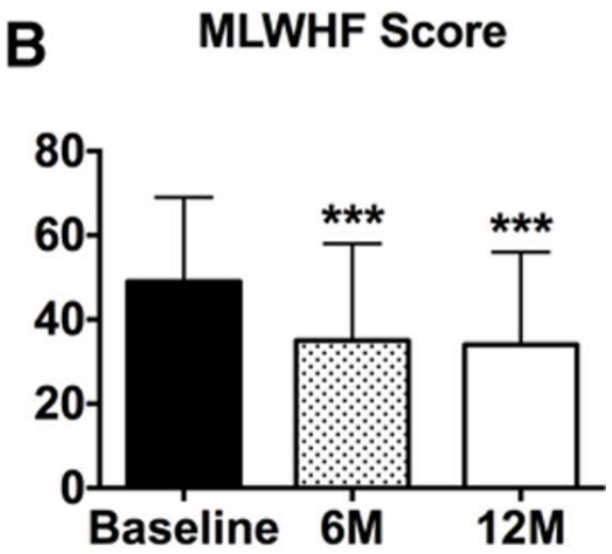


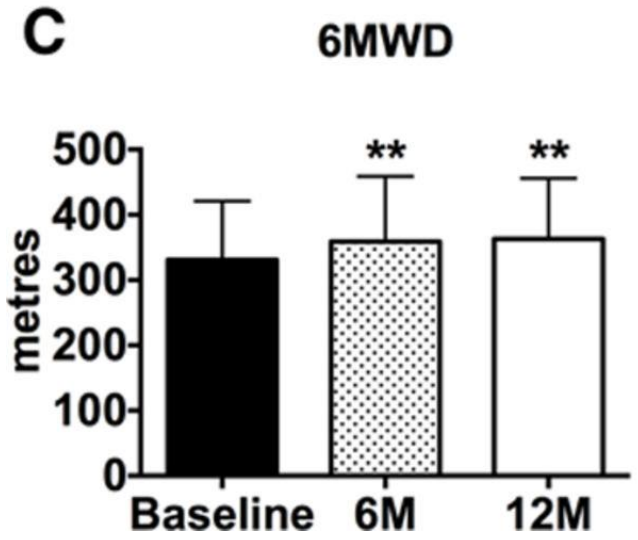


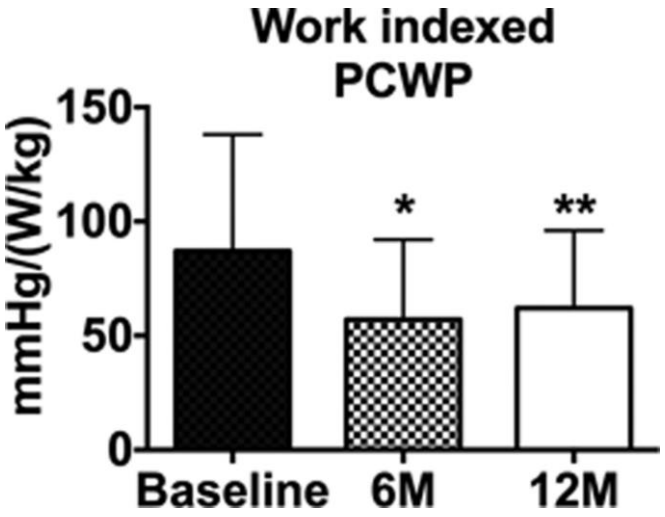






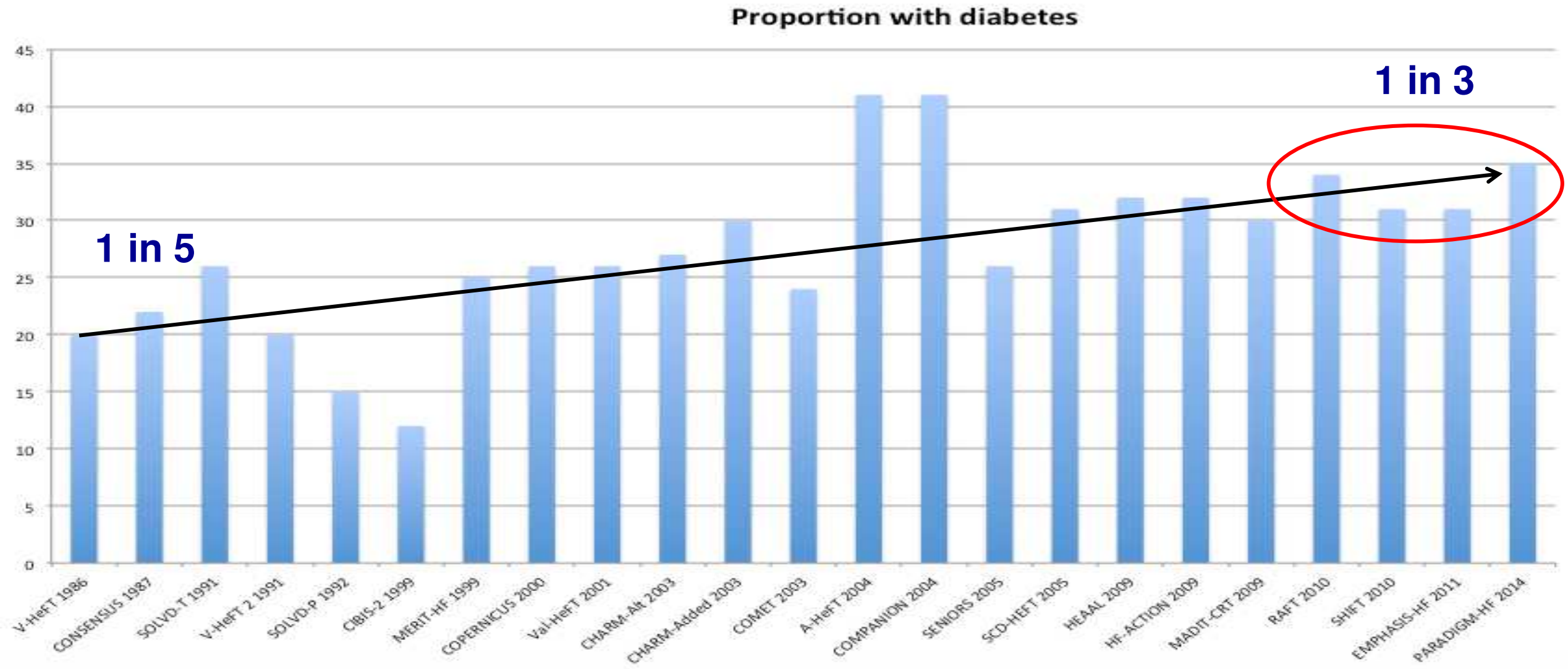




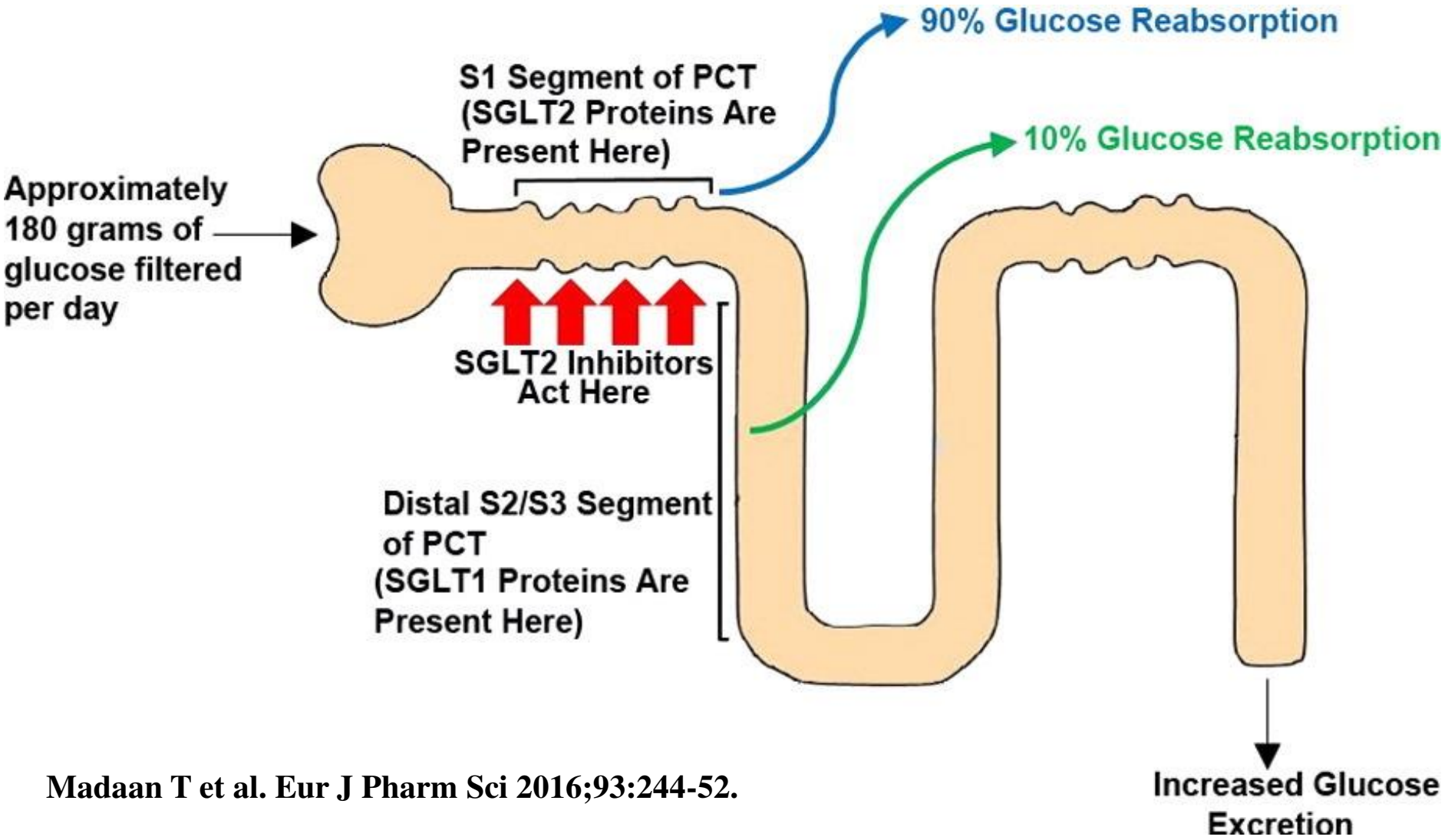


Hasenfuß G et al. Lancet 2016;387:1298–304. Kaye D et al. Circ HF 2016;9:e003662.

Diabetes in positive HFrEF trials



SGLT2 Inhibitors



Madaan T et al. Eur J Pharm Sci 2016;93:244-52.

SGLT2 Inhibitor Outcome RCTs

	EMPA-REG OUTCOME	CANVAS
CV death/ MI/ CVA	0.86 (0.74-0.99)	0.86 (0.75-0.97)
CV death	0.62 (0.49-0.77)	0.87 (0.72-1.06)
Nonfatal MI	0.87 (0.7-1.09)	0.85 (0.69-1.05)
Nonfatal CVA	1.24 (0.92-1.67)	0.90 (0.71-1.05)
Death	0.68 (0.57-0.82)	0.87 (0.74-1.01)
HF hospitalisation	0.65 (0.50-0.85)	0.67 (0.52-0.87)
CV death/ HF hosp.	0.66 (0.55-0.79)	0.78 (0.67-0.91)

Zinman B et al. N Engl J Med 2015. Neal B et al. N Engl J Med 2017.

Emerging treatments in heart failure

- AHF pharmacotherapy unchanged >30 years
- ACEi/BB/MRA decreases mortality by 60% in HFrEF
- Switch ACEi/ ARB to ARNI if persistent HF with LVEF ≤40%
- Further treatment options in selected patients with persistent HFrEF include ivabradine, ICD/ CRT, AF catheter ablation and intravenous iron
- HFpEF management remains empiric

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