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New Classes of Therapy in Heart Failure: How Strong is the Evidence?

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Neprilysin as a Therapeutic Target in Heart Failure

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Endogenous vasoactive peptides

(natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide, amyloid-β peptide)

- Neurohormonal activation
- Vascular tone
- Cardiac fibrosis, hypertrophy
- Sodium retention

Neprilysin

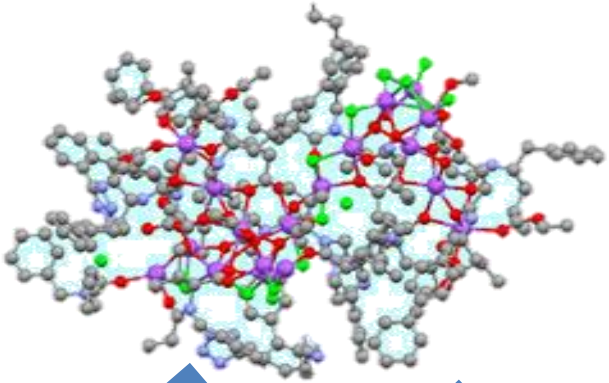
Inactive metabolites

Neprilysin inhibition

RAAS Activation

NEP inhibition alone not effective

Sacubitril/Valsartan (LCZ696): A first-in-class angiotensin/neprilysin inhibitor (ARNi)



LCZ696 is a novel crystalline complex consisting of the molecular moieties of valsartan and sacubitril in an equimolar ratio

Dissociates at low pH

Sacubitril
↓
LBQ657

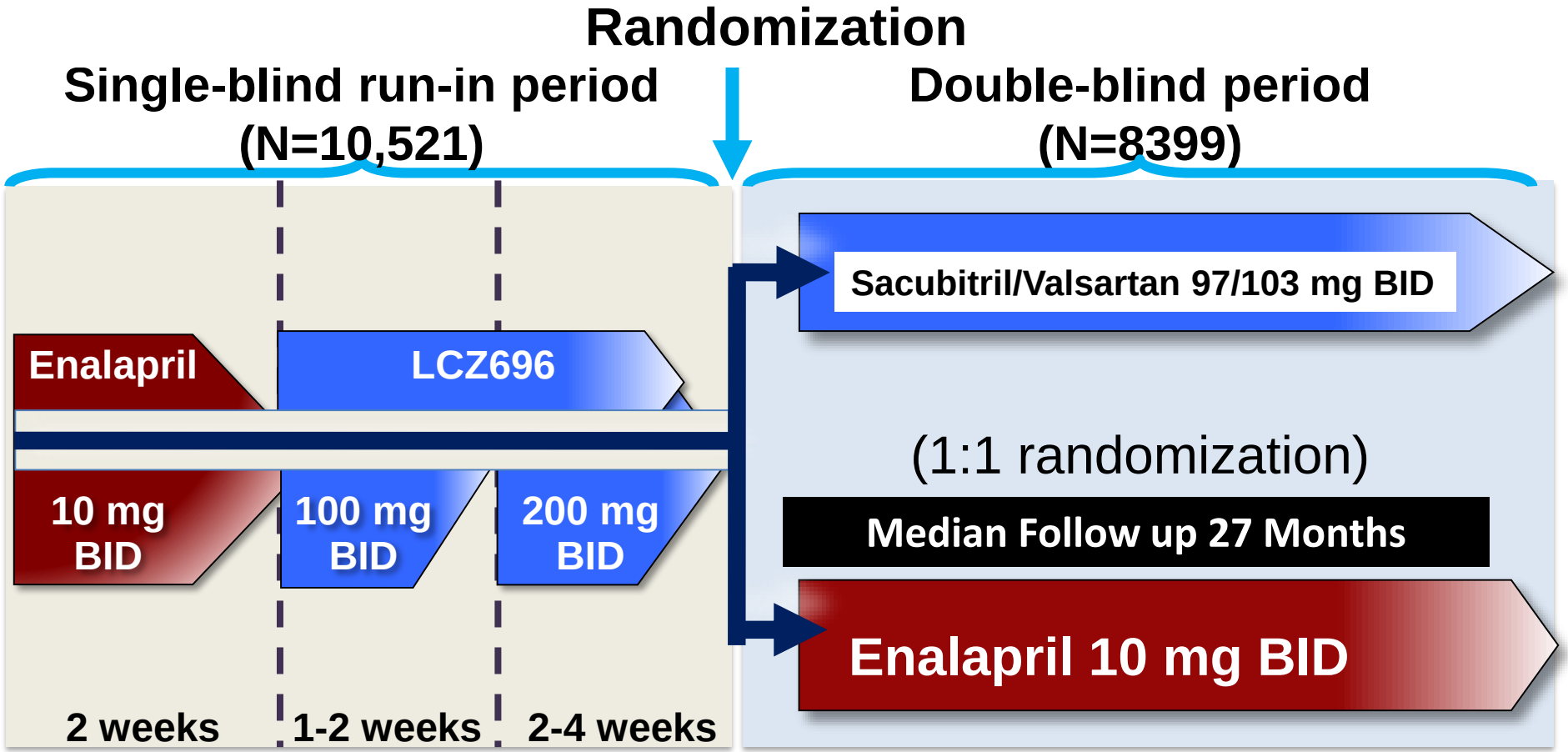
Neprilysin Inhibitor

+

Valsartan

ARB

PARADIGM-HF Study Design



Choice of Comparator

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- Enalapril is regulatory 'gold standard' ACE-inhibitor
- Dosing chosen to match doses achieved in pivotal trials
- In CONSENSUS, only 22% achieved target dose

Trial	N	Target dose, mg	Mean daily dose, mg
CONSENSUS (1987)	127	20 bid	18.4
SOLVD-T (1991) *	1284	10 bid	16.6
SOLVD-P (1992)	2111	10 bid	16.7
V-HeFT II (1991)	403	10 bid	15.0
OVERTURE (2002)	2884	10 bid	17.7

PARADIGM-HF: Who was eligible?

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Inclusion Criteria

- Chronic HF with LVEF ≤40%
- NYHA II-IV symptoms
- Elevated natriuretic peptides
- On guideline-directed medical therapy for > 4 weeks including:
  - ACEi or ARB (enalapril 10 mg daily or equivalent)
  - β-blocker (unless intolerant)
  - MRA if appropriate

Exclusion Criteria

- History of angioedema
- eGFR <30 mL/min/1.73 m^2 (or reduction of > 35% from screening)
- Serum potassium >5.2 mmol/L at screening or > 5.4 mmol/L at randomization
- SBP <100 mmHg (screening) or <95 mm Hg (randomization) or symptomatic hypotension
- Current Acute Decompensated HF

McMurray et al. NEJM 2014

PARADIGM-HF: Baseline Characteristics

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	LCZ696 (n=4187)	Enalapril (n=4212)
Age (years)	63.8 ± 11.5	63.8 ± 11.3
Women (%)	21.0%	22.6%
Ischemic cardiomyopathy (%)	59.9%	60.1%
LV ejection fraction (%)	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class II / III (%)	71.6% / 23.1%	69.4% / 24.9%
Systolic blood pressure (mm Hg)	122 ± 15	121 ± 15
Heart rate (beats/min)	72 ± 12	73 ± 12
N-terminal pro-BNP (pg/ml)	1631 (885-3154)	1594 (886-3305)
B-type natriuretic peptide (pg/ml)	255 (155-474)	251 (153-465)
History of diabetes	35%	35%
Digitalis	29.3%	31.2%
Beta-adrenergic blockers	93.1%	92.9%
Mineralocorticoid antagonists	54.2%	57.0%
ICD and/or CRT	16.5%	16.3%

McMurray et al. NEJM 2014

PARADIGM-HF: CV Death or HF Hospitalization (Primary Endpoint)

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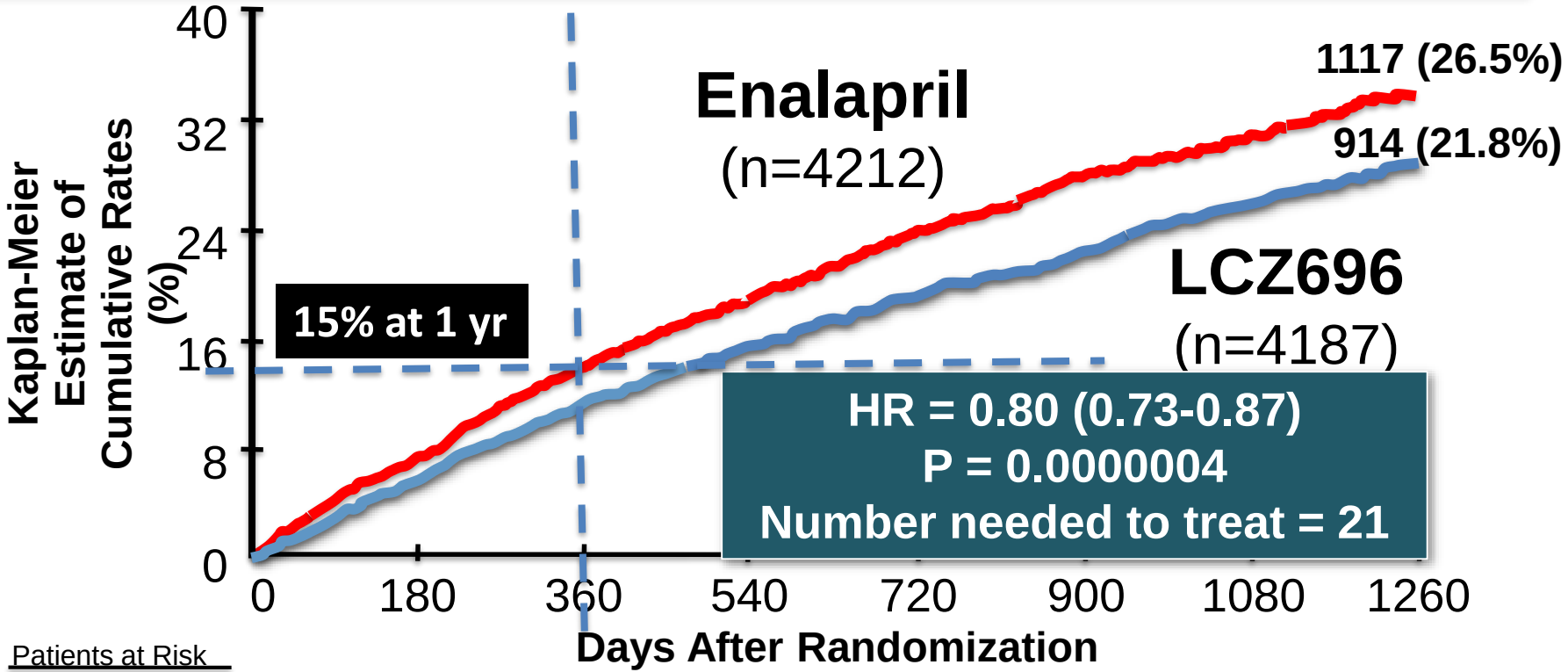

Patients at Risk

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

McMurray et al. NEJM 2014

Other Key Endpoints

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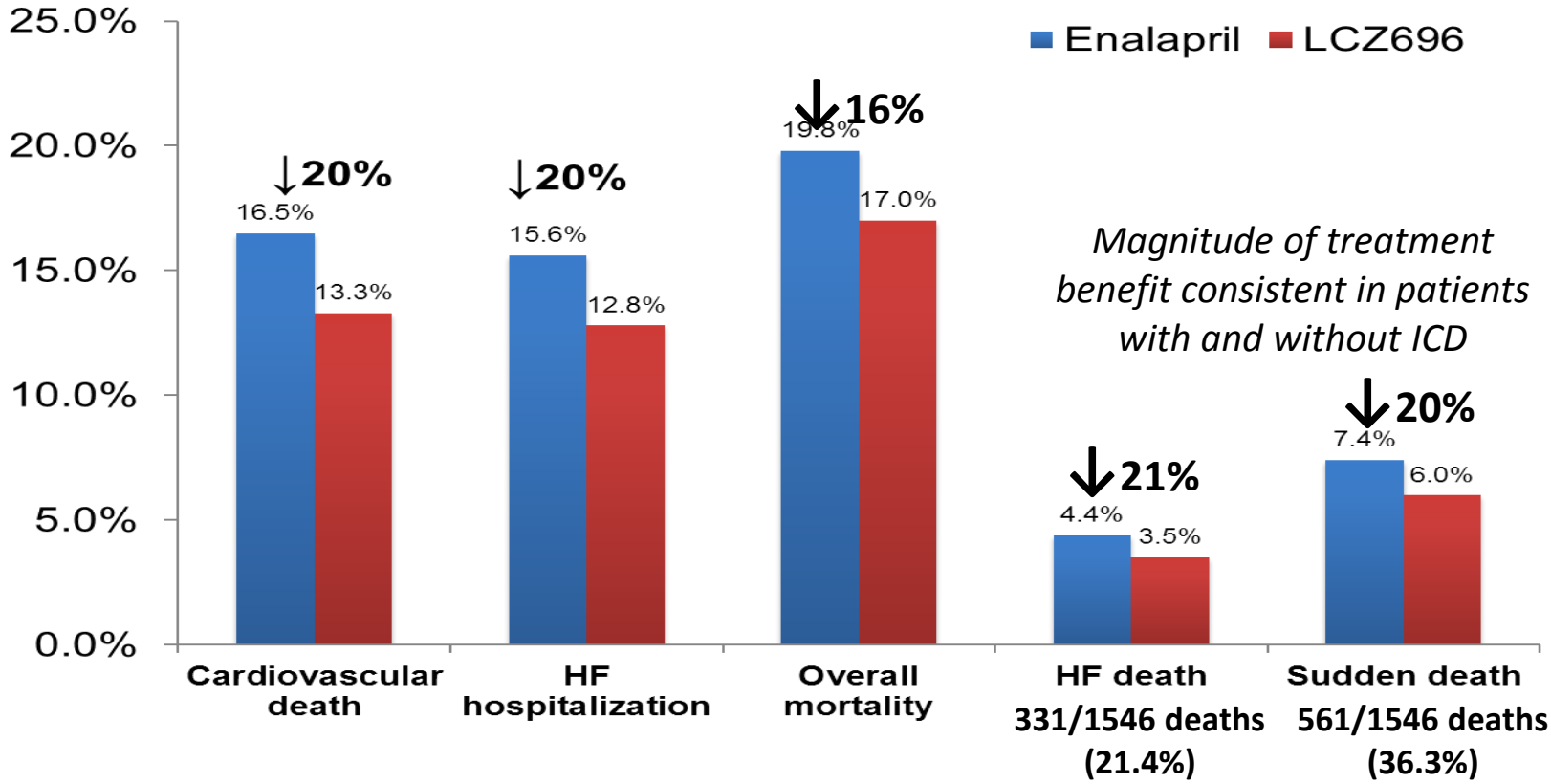

McMurray, *NEJM* 2014; Desai et al. *European Heart Journal* 2015

Doubling of Survival over ACE/ARB

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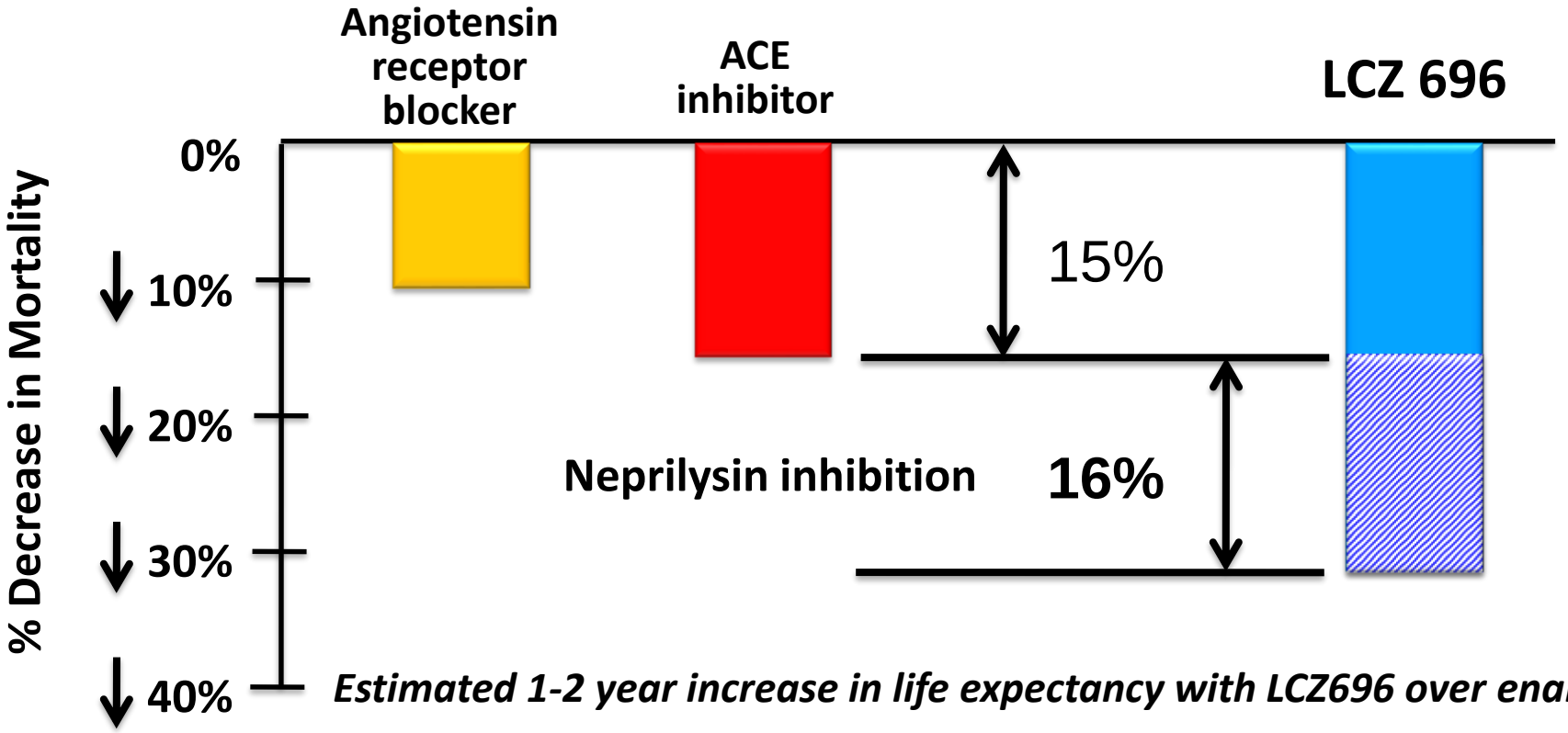

Estimated 1-2 year increase in life expectancy with LCZ696 over enalapril

McMurray et al. EHJ 2015; Claggett, et al NEJM 2015

Heart Failure Progression

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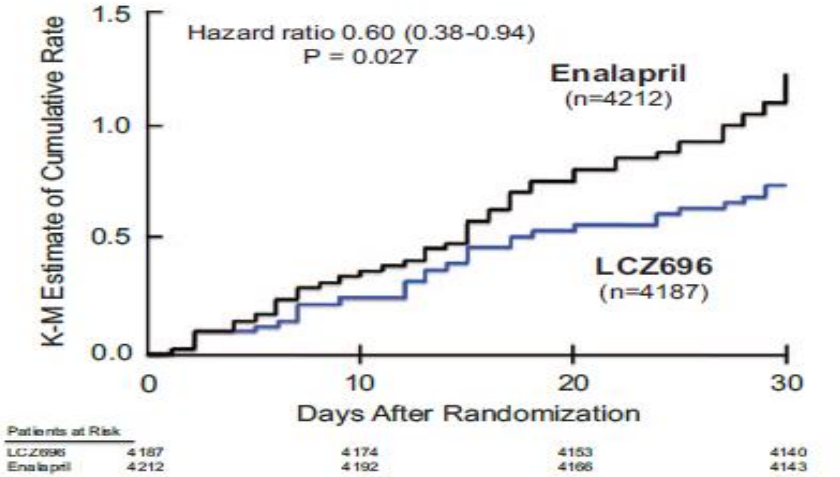
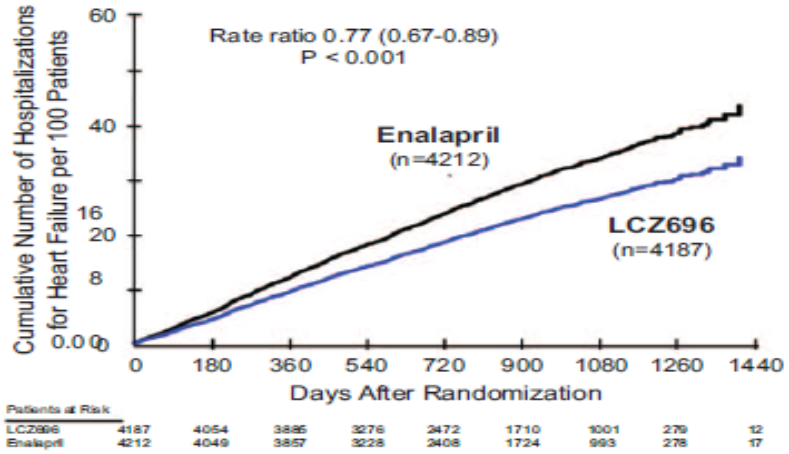
Time to First HF Hospitalization (first 30 days)



Cumulative HF Hospitalizations



Fewer LCZ696-treated patients experienced worsening HF symptoms or required intensification of medical treatment, emergency department evaluation, intensive care, or inotropic support for HF

Packer M, et al. Circulation 2015

Consistent Benefits Across a Spectrum of HF Severity

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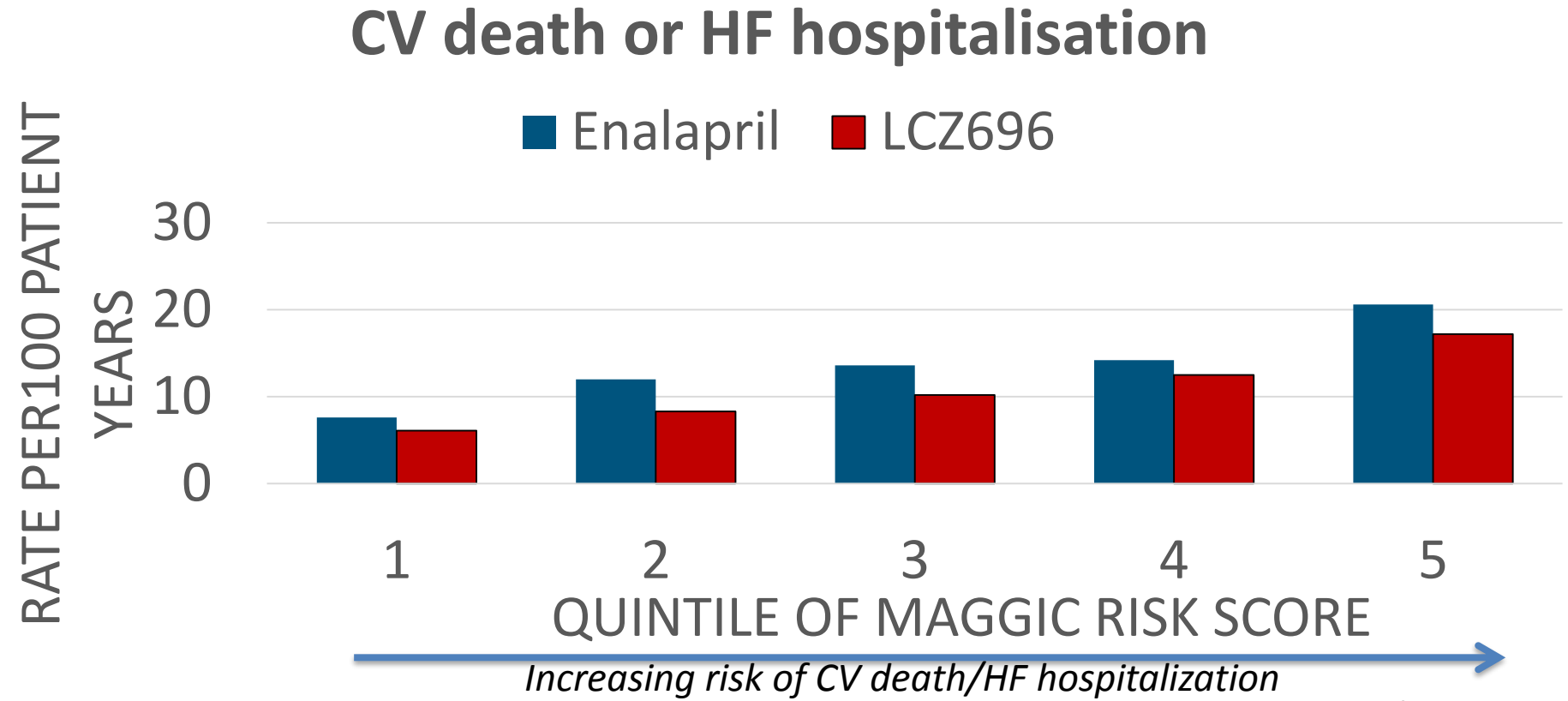

Simpson J, et al. JACC 2015

PARADIGM-HF: Safety

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	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Prospectively identified adverse events			
Symptomatic hypotension	588 (14%)	388 (9.2%)	< 0.001
Serum potassium > 6.0 mmol/l	181 (4.3%)	236 (5.6%)	0.007
Serum creatinine ≥ 2.5 mg/dl	139 (3.3%)	188 (4.5%)	0.007
Cough	474 (11.3%)	601 (14.3%)	< 0.001
Discontinuation for adverse event	**449**	**516**	**0.02**
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001
Angioedema (adjudicated)			
Medications, no hospitalization	16 (0.3%)	9 (0.2%)	NS
Hospitalized; no airway compromise	3 (0.1%)	1 (<0.1%)	NS
Airway compromise	0	0	----

Guideline Update

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2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure

COR	LOE	Recommendations
I	B-R	ACEi OR ARB OR ARNI in conjunction with beta-blockers + MRA (where appropriate) is recommended for patients with chronic HFrEF to reduce morbidity and mortality.
I	B-R	In patients with chronic, symptomatic HFrEF NYHA class II or III who tolerate and ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality
III	B-R	ARNI should NOT be administered concomitantly with ACEi or within 36 hours of last ACEi dose
III	C=EO	ARNI should NOT be administered to patients with a history of angioedema

Yancy, et al. Circulation 2016

ESC HF Guideline Update

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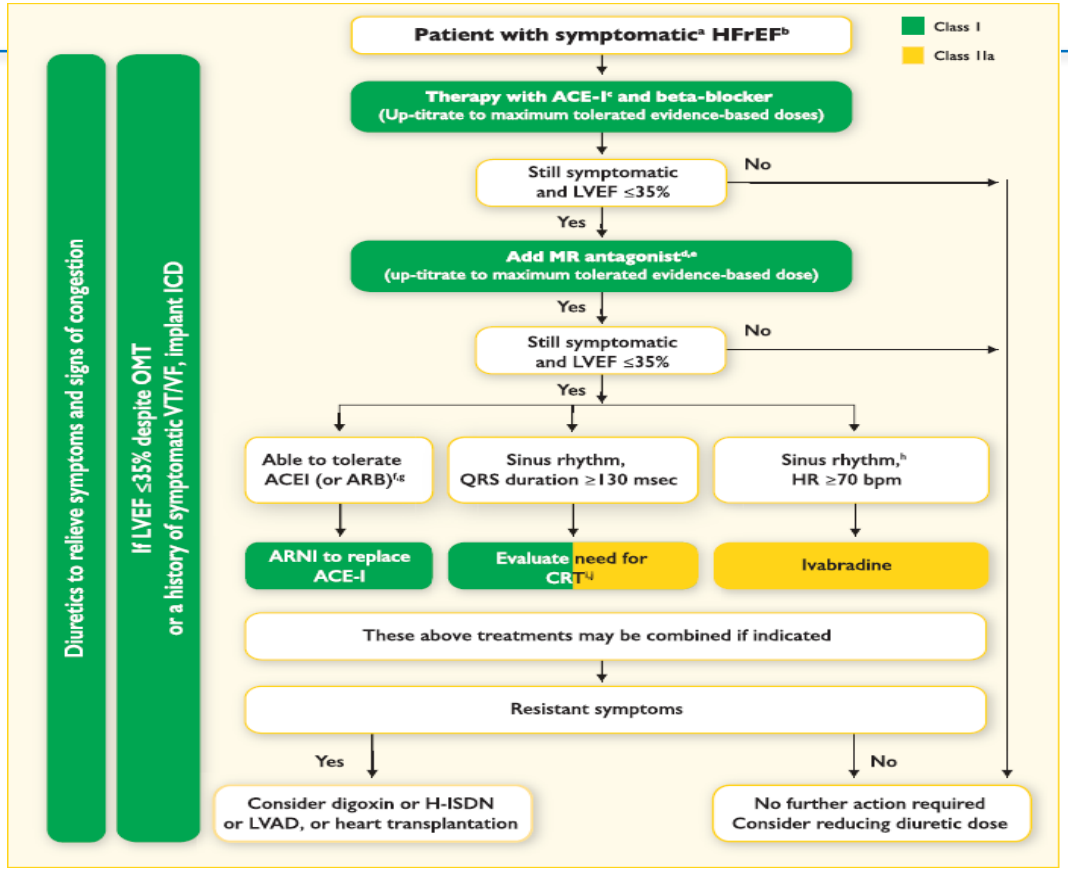

Ponikowski, et al. Eur Heart J 2016

Impact of Heart Rate on Outcomes in HF

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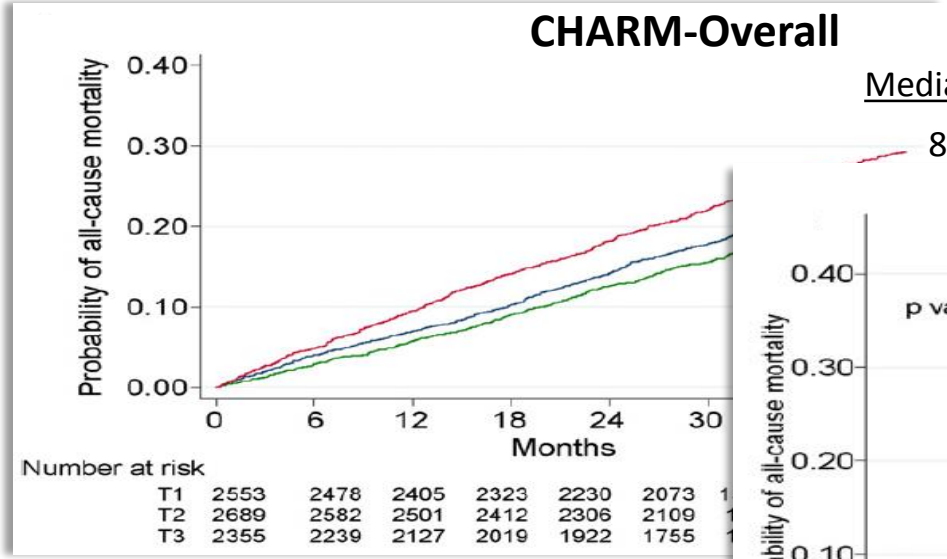
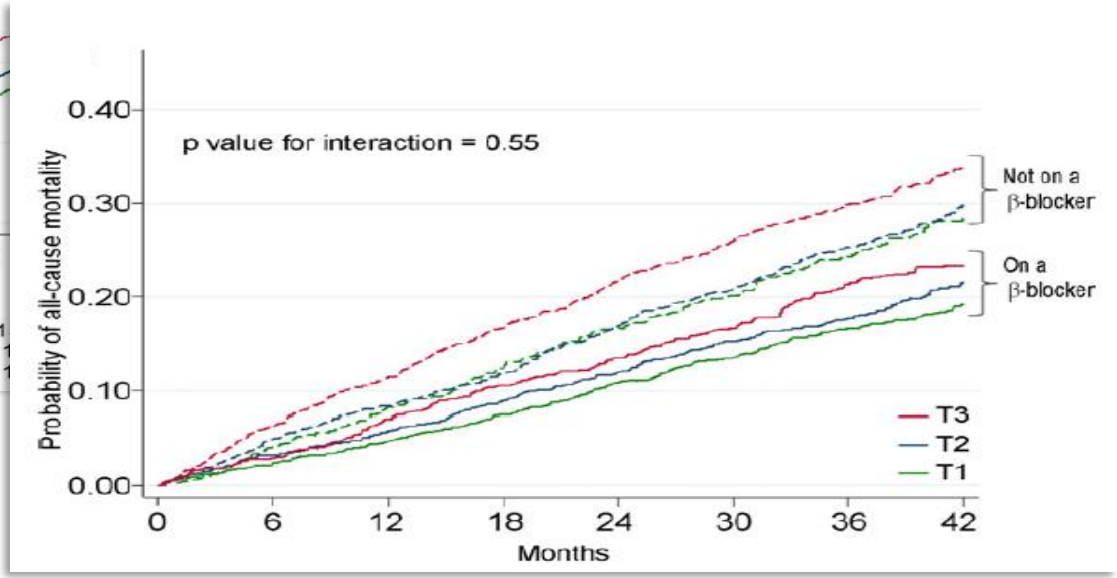


Median HR (IQR)

85 (80-91)



Castagno D, et al. J Am Coll Cardiol 2012; 59: 1785-92

Heart Rate Reduction and Mortality in HF Trials

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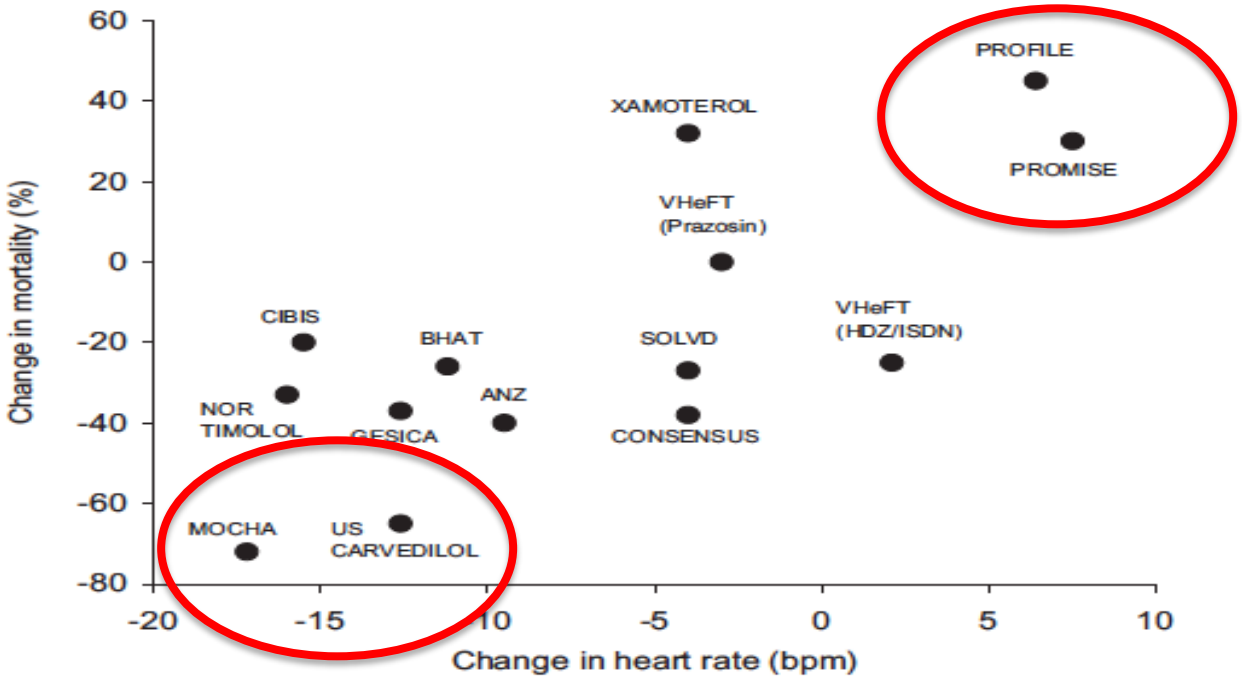

Fox K, et al. J Am Coll Cardiol 2007; 50: 823-30

Ivabradine: A selective I_f Inhibitor

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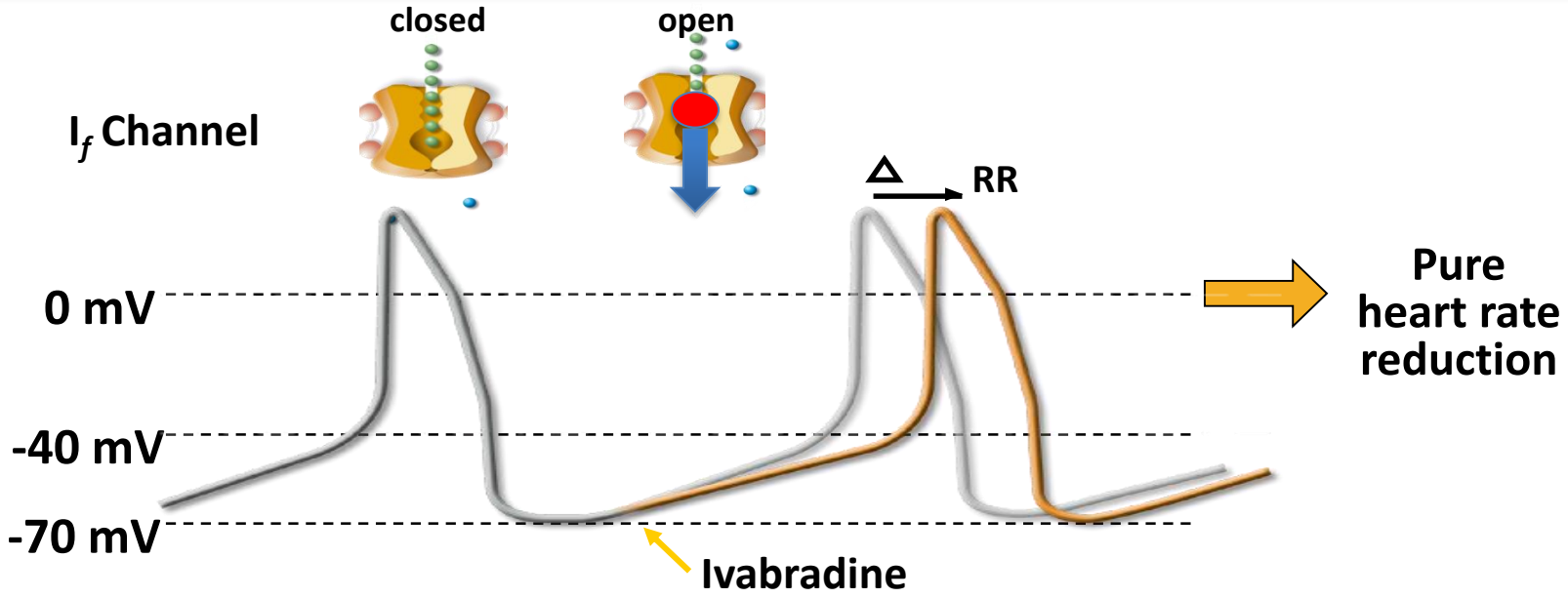

I_f inhibition reduces the diastolic depolarization slope, thereby lowering heart rate

No effect on myocardial contractility or relaxation

Use-dependent block = low risk of bradycardia

Thollon et al. *Br J Pharmacol*. 1994;112:37-42.

Study design

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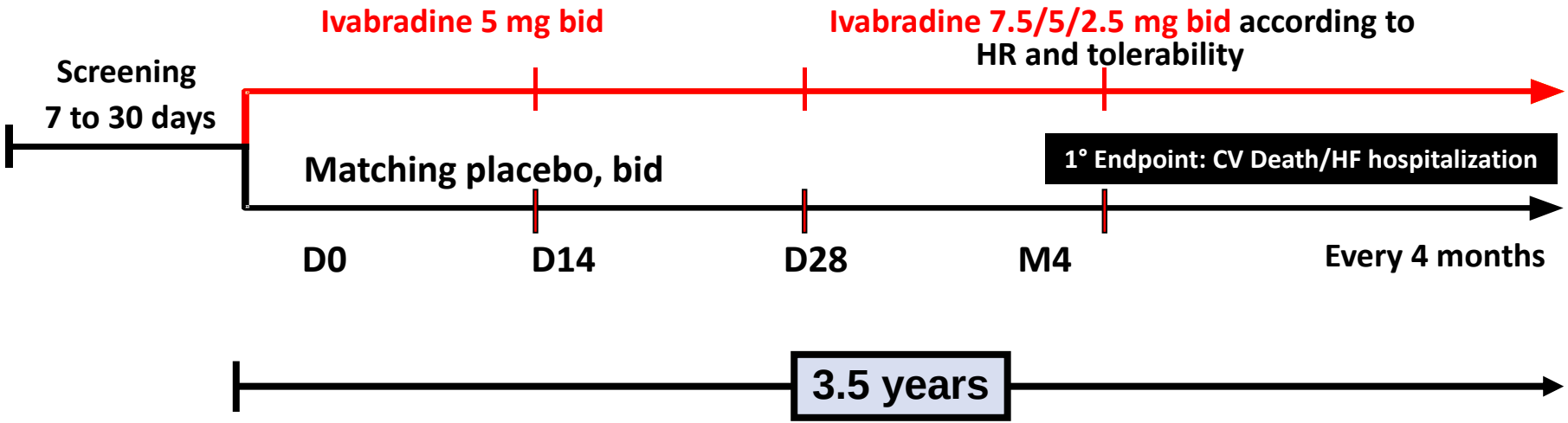
6558 patients with NYHA II-IV HF, LVEF≤35%, prior HF hospitalization (within 12 months) and HR≥70 bpm in sinus rhythm



Median study duration: 22.9 months; maximum: 41.7 months

Swedberg K, et al. *Eur J Heart Fail.* 2010;12:75-81

Baseline characteristics

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	Ivabradine N=3241	Placebo N=3264
Mean age, y	60.7	60.1
Male, %	76	77
Ischemic aetiology, %	68	67
NYHA II, %	49	49
NYHA III/IV, %	51	51
Previous MI, %	56	56
Diabetes, %	30	31
Hypertension, %	67	66

~90% on beta-blockers + ACE/ARB and ~60% on MRA

Swedberg K, et al. *Lancet*. 2010;376(9744):875-885

Primary composite endpoint
(CV death or hospital admission for worsening HF)

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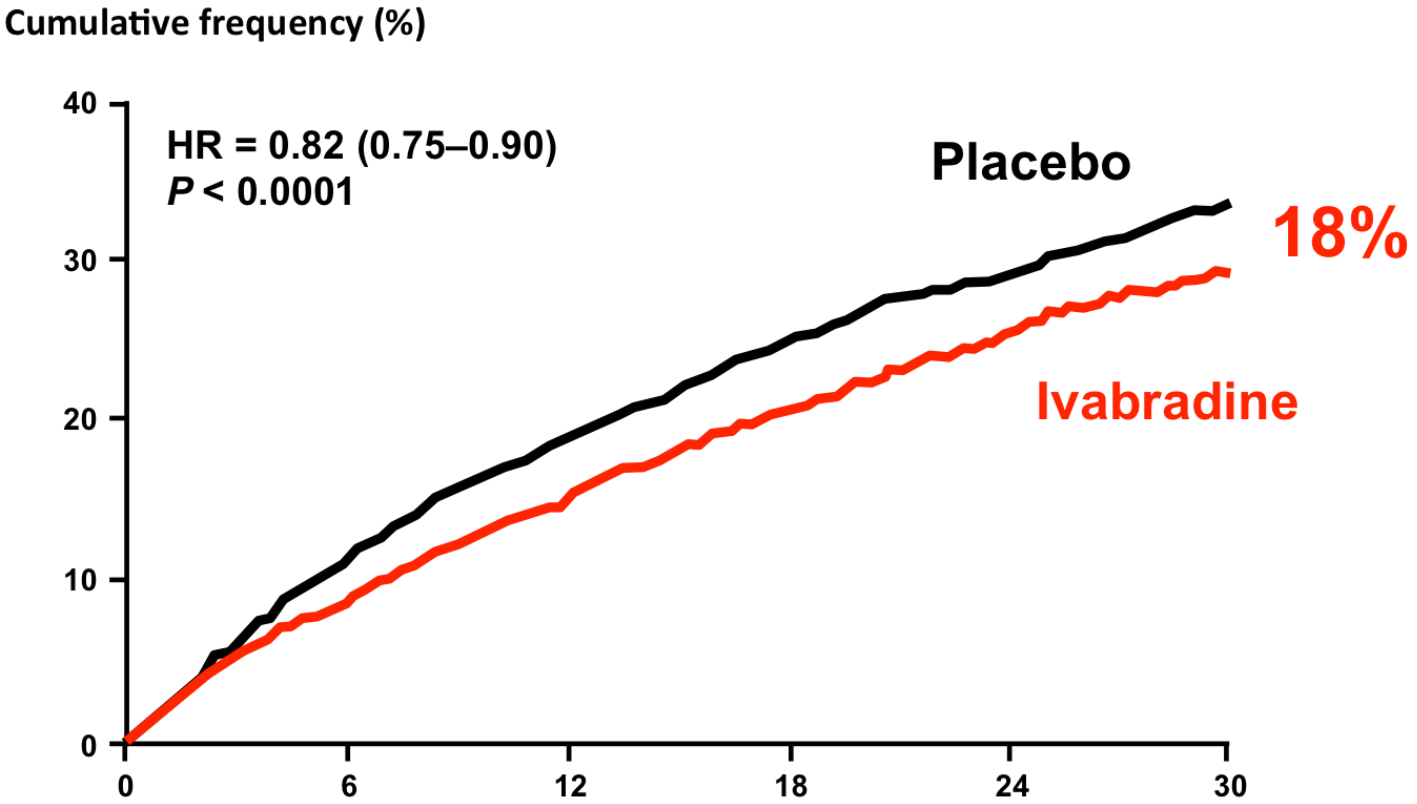

Swedberg K, et al. *Lancet*. 2010;376(9744):875-885

Effect of ivabradine on outcomes

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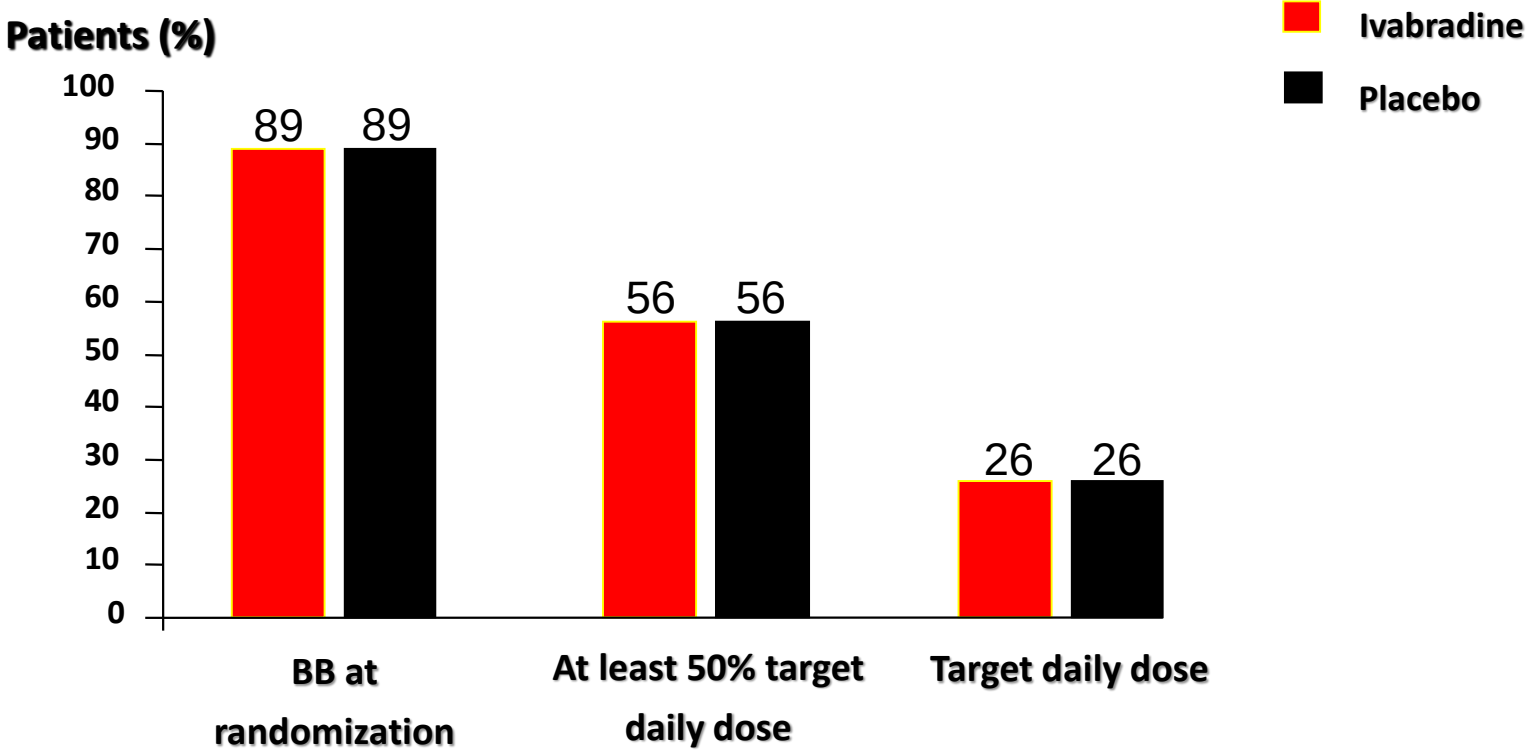
Endpoints	Hazard ratio	95% CI	*p* value
Primary composite endpoint (CV death or hospital admission for worsening HF)	0.82	[0.75;0.90]	*p*<0.0001
All-cause mortality	0.90	[0.80;1.02]	*p*=0.092
Death from heart failure	0.74	[0.58;0.94]	*p*=0.014
All-cause hospital admission	0.89	[0.82;0.96]	*p*=0.003
Any CV hospital admission	0.85	[0.78;0.92]	*p*=0.0002
CV death/hospital admission for HF or non-fatal MI	0.82	[0.74;0.89]	*p*<0.0001

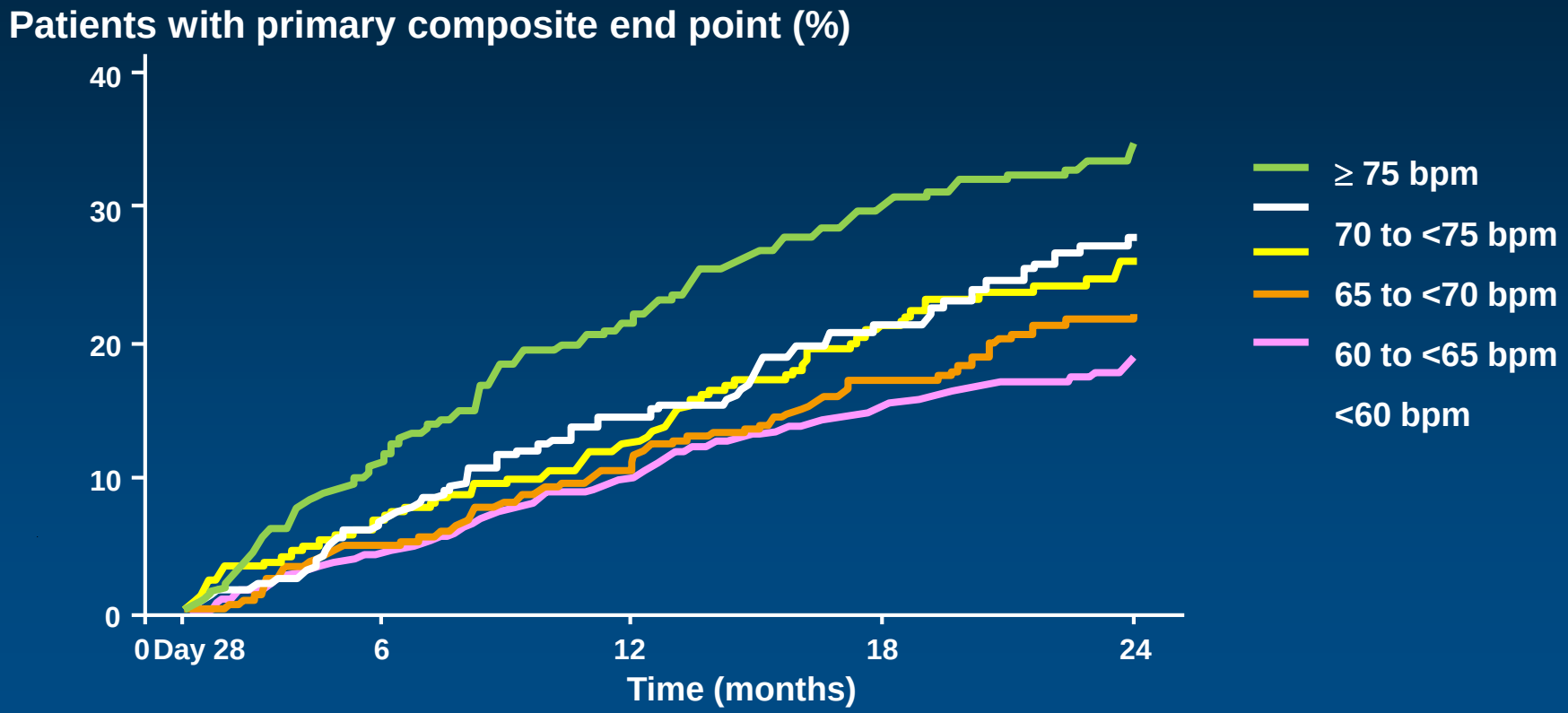
Swedberg K, et al. *Lancet*. 2010;376(9744):875-885

Background beta-blocker treatment



Swedberg K, et al. *Lancet*. 2010;376(9744):875-885

Effect of ivabradine on outcomes according to HR achieved at 28 days



Böhm M, Borer J, Ford I, et al. *Clin Res Cardiol*. 2013;102(1):11-22

Guideline Update

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COR	LOE	Recommendations
IIa	B-R	Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III), stable, chronic HFrEF (LVEF<=35%) who are receiving GDMT , including a beta-blocker at maximally tolerated dose, and who are in sinus rhythm with a HR>=70 bpm at rest

- The incremental benefits of ivabradine are more pronounced in patients with higher resting heart rates

- The magnitude of HR reduction achieved with ivabradine+ß-blockade is the principal determinant of subsequent outcome

Yancy, et al. Circulation 2016

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Thank You!

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