Whats New in the Treatment of Heart Failure?

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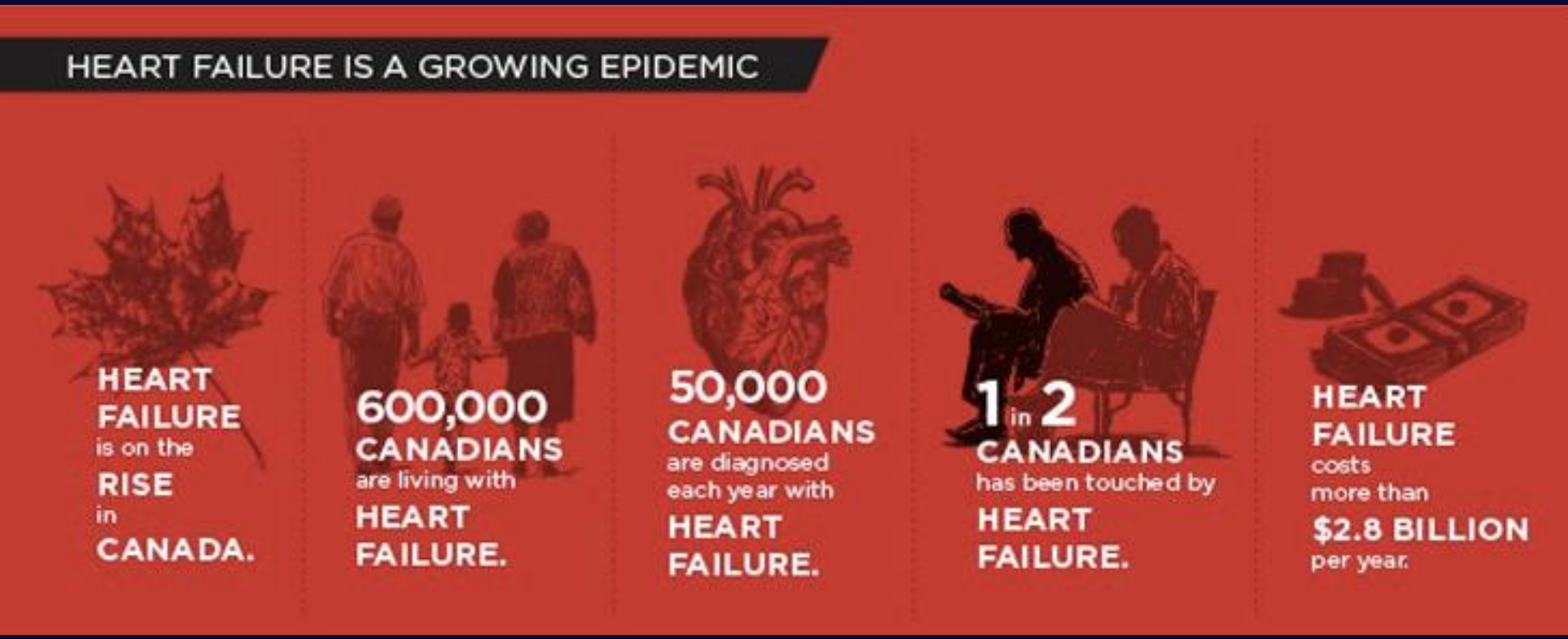
Objectives

- Epidemiology of Heart Failure in Canada
- Traditional Triple Therapy for Heart Failure
- Novel Therapies in Heart Failure
  - Ivabradine
  - Entresto
- Conclusions

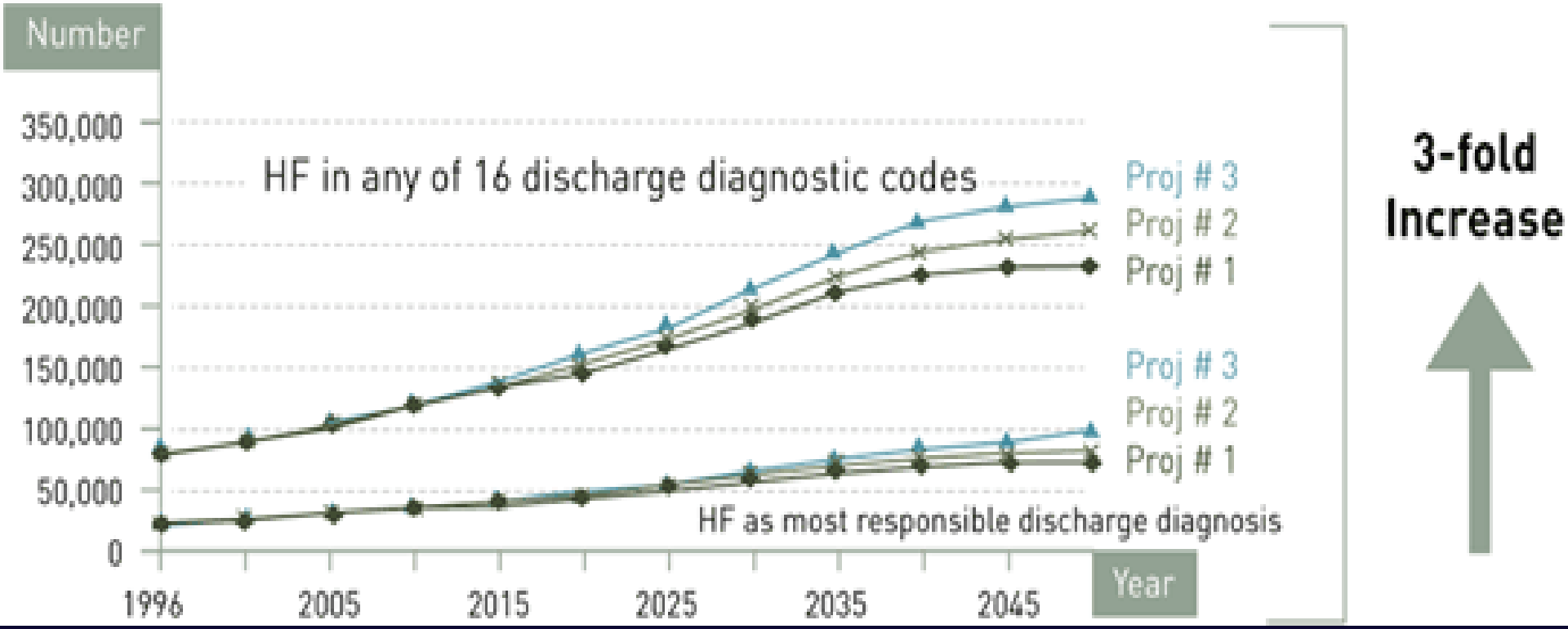
HF is a Growing Epidemic



Heart and Stroke 2016

HF Cases on the Rise

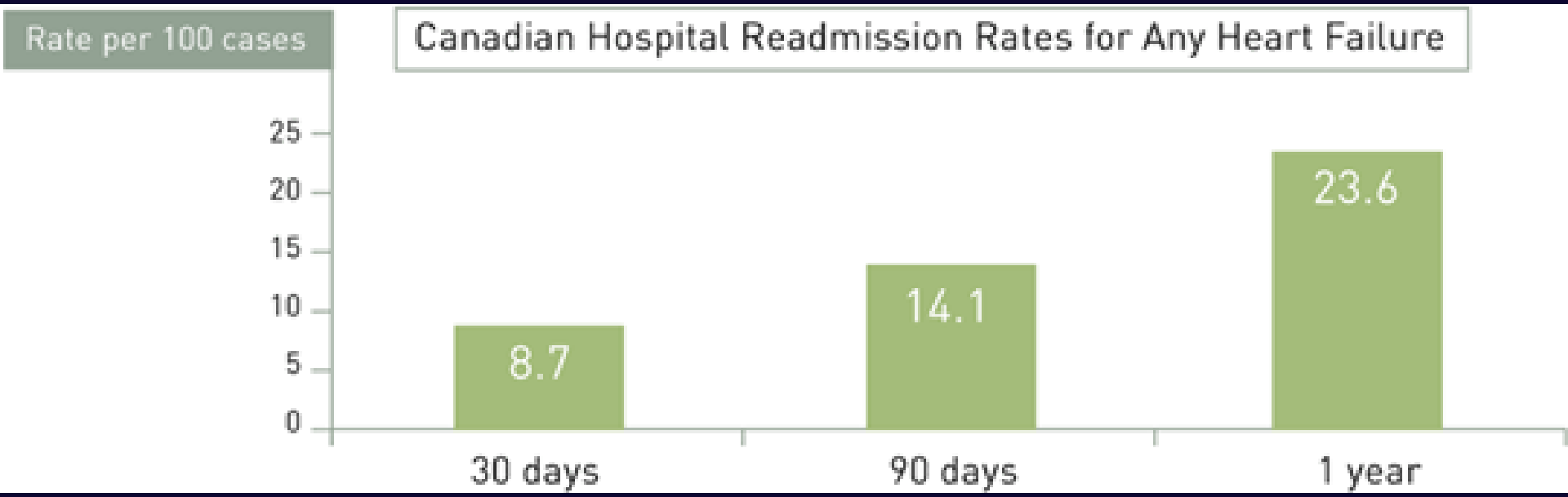
- Projected number of incident hospitalizations for CHF patients, using high, medium and low population growth projections in Canada 1996-2050



Johansen et al. Can J Cardiol 2003

HF Readmissions

- Hospital readmission rates are high, and mainly due to recurrent heart failure



Lee DS et al. Can J Cardiol 2004

Heart Failure Mortality

- Canada's average annual in-hospital mortality rate
  - 9.5 deaths/100 hospitalized patients >65yo
  - 12.5 deaths/100 hospitalized patients >75yo

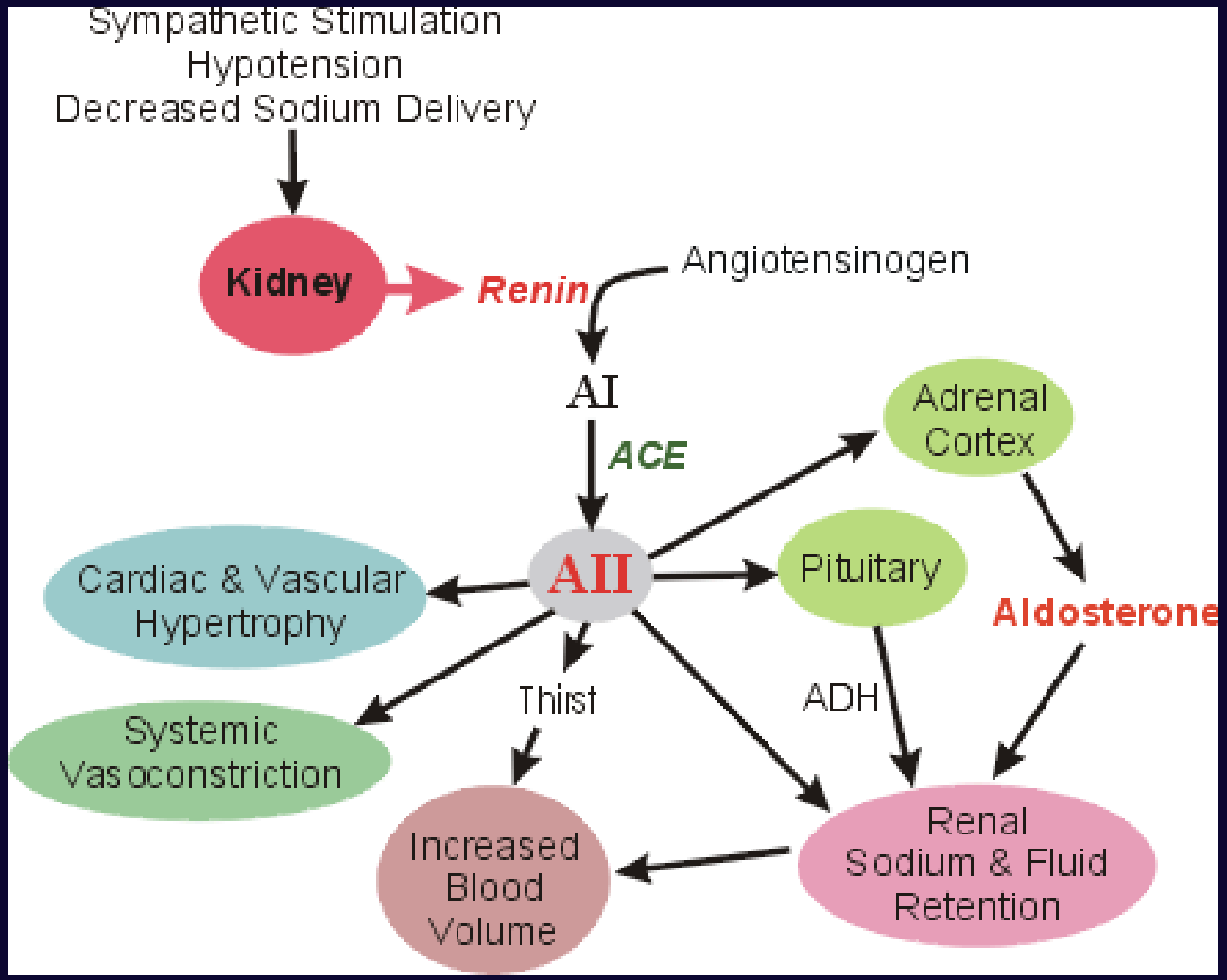
- HF patients have a poor prognosis, with an average 1-year mortality rate of 33%

Lee DS et al. Can J Cardiol 2004

Traditional Triple Therapy

ACEi/ARB B-blocker MRA

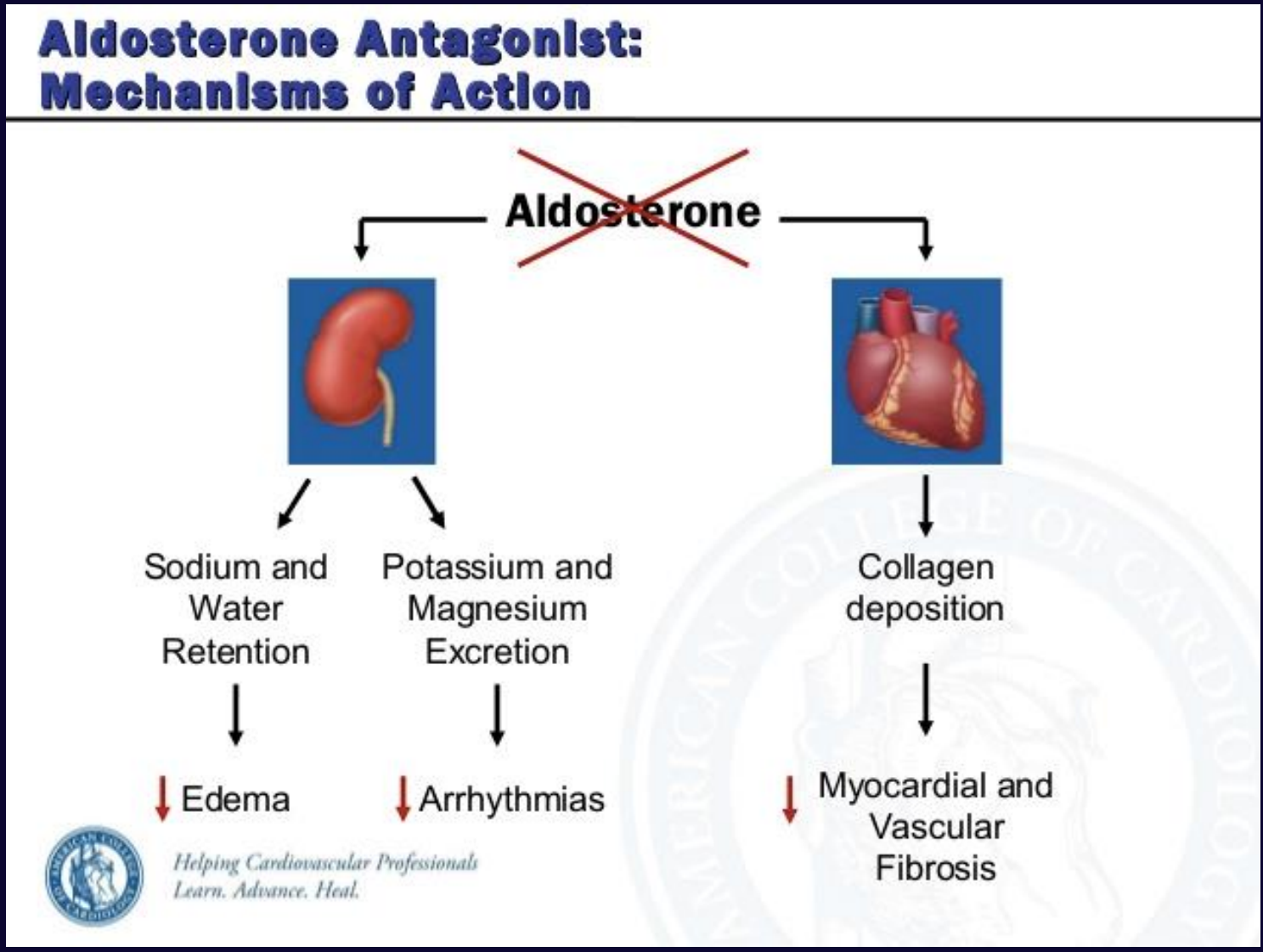
ACE Inhibition



ACEi + ARB in HF

ACEIs Goal: Target dose or maximal dose tolerated			
Captopril (generic)	12.5mg TID	25-50mg TID	12.5, 25, 50, 100
Enalapril (Vasotec®, generic)	2.5mg BID	10mg BID	2.5, 5, 10, 20
Lisinopril (Prinivil®, Zestril®, generic)	2.5mg daily	20-35mg daily	5, 10, 20, 40
Perindopril (Coversyl®)	2mg daily	4-8mg daily	2, 4, 8
Ramipril (Altace®, generic)	1.25-2.5mg BID	5mg BID	1.25, 2.5, 5, 10, 15
Trandoapril (Mavik®, Tarka®)	1-2mg daily	4mg daily	0.5, 1, 2, 4
ARBs Goal: Target dose or maximal dose tolerated			
Candesartan (Atacand®, generic)	4mg daily	32mg daily	4, 8, 16, 32
Valsartan (Diovan®, generic)	40mg bid	160mg bid	40, 80, 160, 320

MRAs in Heart Failure

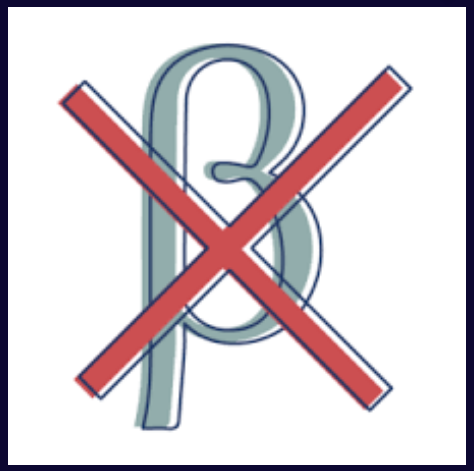


Smith et al. JACC 2007

Beta Blockade

CATECHOLAMINES
-pre/afterload
-HR/ARRHYTHMIA

OTHER VASOCONSTRICTORS
-RENIN, ENDOTHELIN



IMPROVED CONTRACTILE FUNCTION
-UPREGULATION OF B-RECEPTORS
-DECREASED 02 DEMAND
-INCREASED DIASTOLIC PERFUSION→HIBERNATING TISSUE

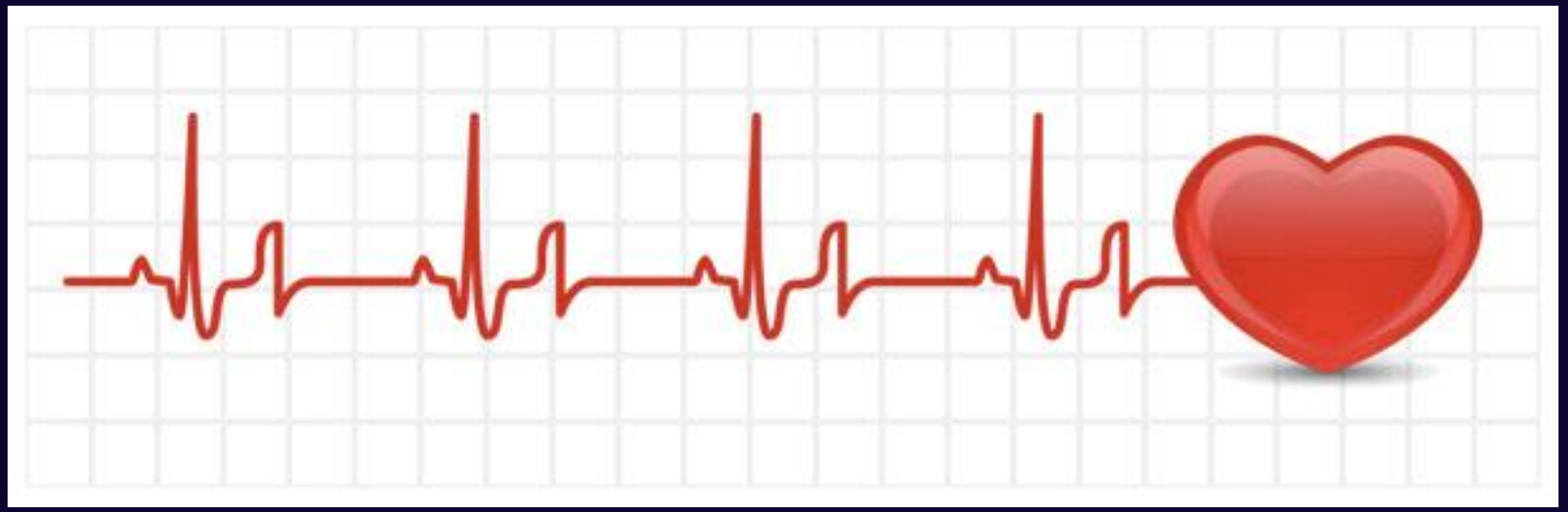
IMPROVES OVERALL LV REMODELING
-METOPROLOL AND CARVEDILOL HAVE BOTH BEEN SHOWN BENEFICIAL IN LV REMODELLING AND REDUCTION OF MR

B-Blockers in HF

Beta-Blockers Goal: Target dose or maximal dose tolerated			
Bisoprolol (generic)	1.25mg daily	10mg daily	5, 10
Carvedilol (generic)	3.125mg BID	25mg BID >85kg:50mg BID	3.125, 6.25, 12.5, 25
Metoprolol tartrate (Lopressor®, generic)	6.25-12.5mg BID	100mg BID	25, 50, 100 SR:100, 200

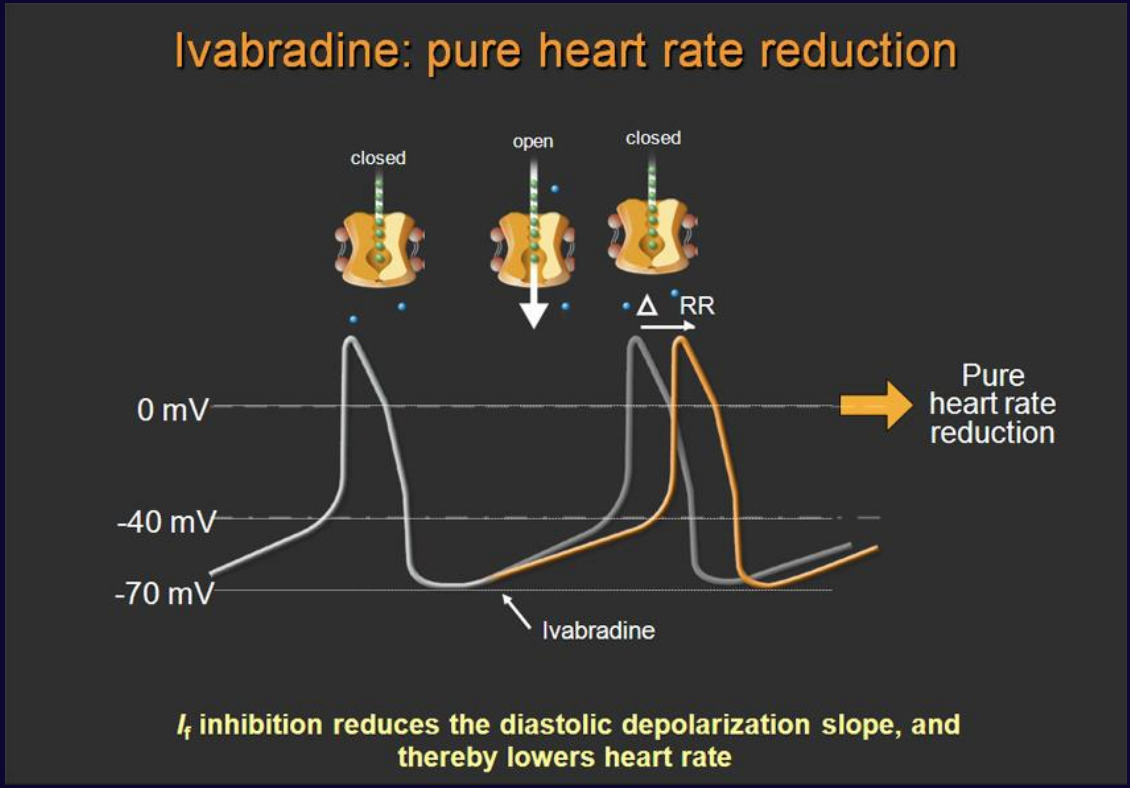
Novel Therapy in Heart Failure

Ivabradine



Ivabradine

- Inhibits the f-current (I_f)
  - Sinoatrial pacemaker modulating current



Ivabradine vs. B-blockers

Does not alter:

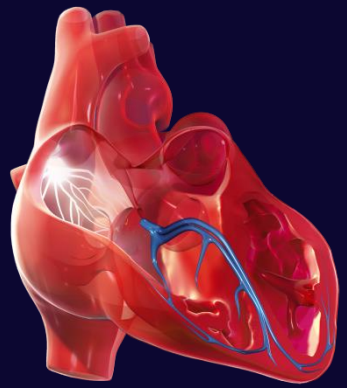
1. Ventricular repolarisation

2. Myocardial Contractility

3. Blood Pressure

The Role of HR in CV Disease

Elevated heart rate



Atherosclerosis

Endothelial dysfunction↑

Oxidative stress↑

Plaque stability↓

Arterial stiffness↑

Chronic heart failure

Oxygen demand↑

Ventricular efficiency ↓

Ventricular relaxation↑

Ischemia

Oxygen consumption↑

Duration of diastole↓

Coronary perfusion↓

Remodeling

Cardiac hypertrophy↑

Heart Rate and CV Death

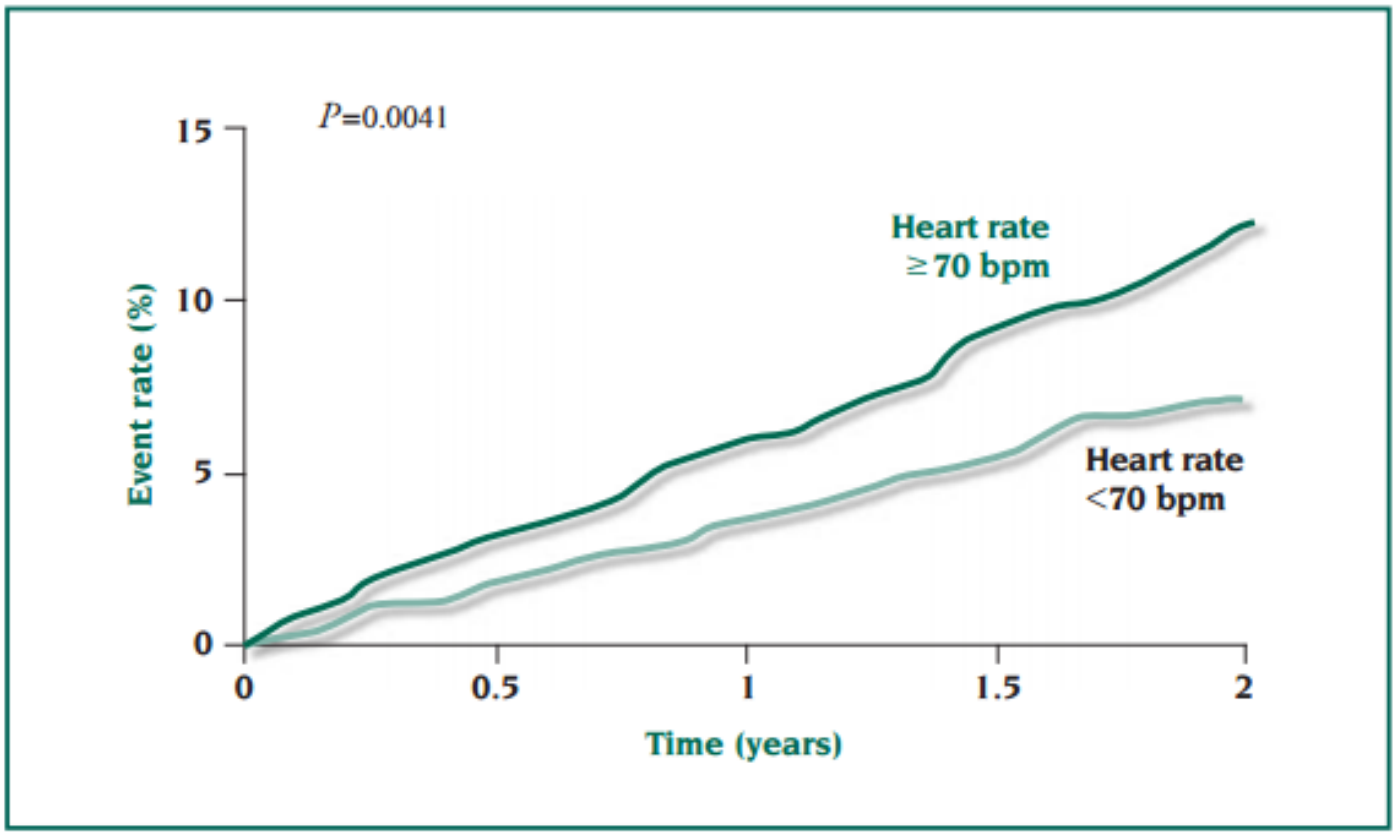
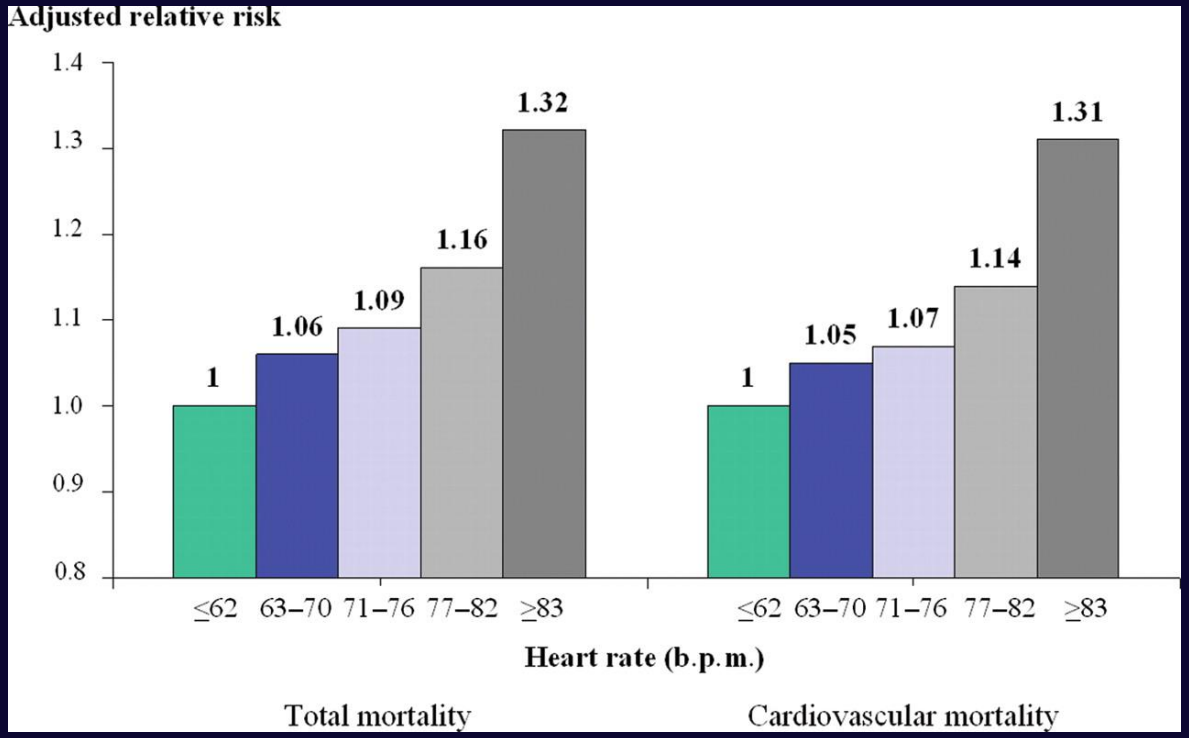


Figure 3. Elevated heart rate (≥70 bpm) as a predictor of cardiovascular death in a population with stable CAD and left ventricular dysfunction.
Kaplan-Meier curves for cardiovascular death in the placebo arm of the BEAUTIFUL study.

Fox et al. Lancet 2008

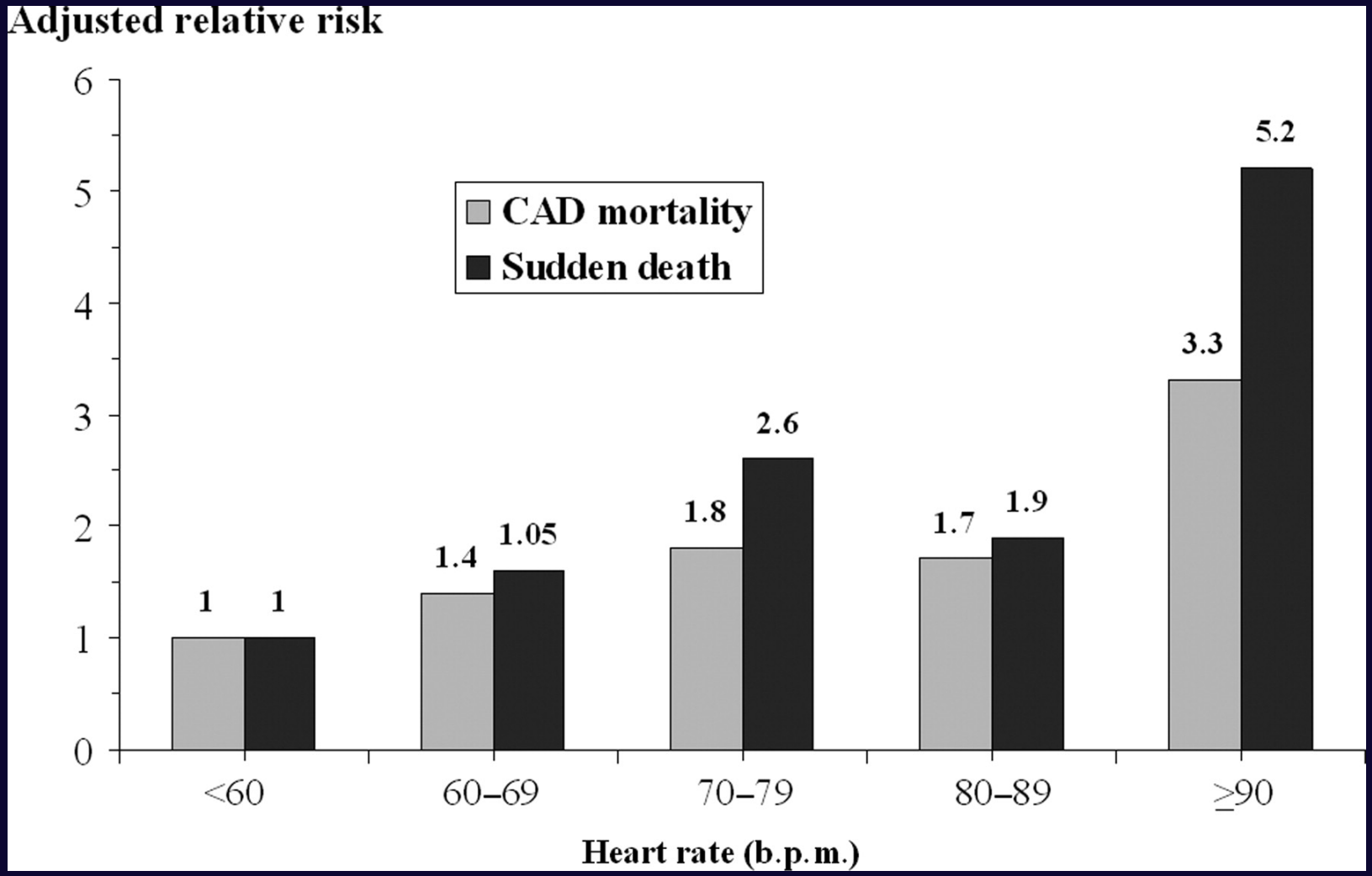
HR and Mortality in Patients with Known CAD



Total and cardiovascular mortality according to resting heart rate: multivariate Cox regression survival analysis for 24 913 patients with suspected or proven coronary artery disease in the Coronary Artery Surgery Study (CASS)

Ferrari et al. **Eur Heart J Suppl 2009**

HR and Mortality Without Known CAD



Ferrari et al. Eur Heart J Suppl 2009

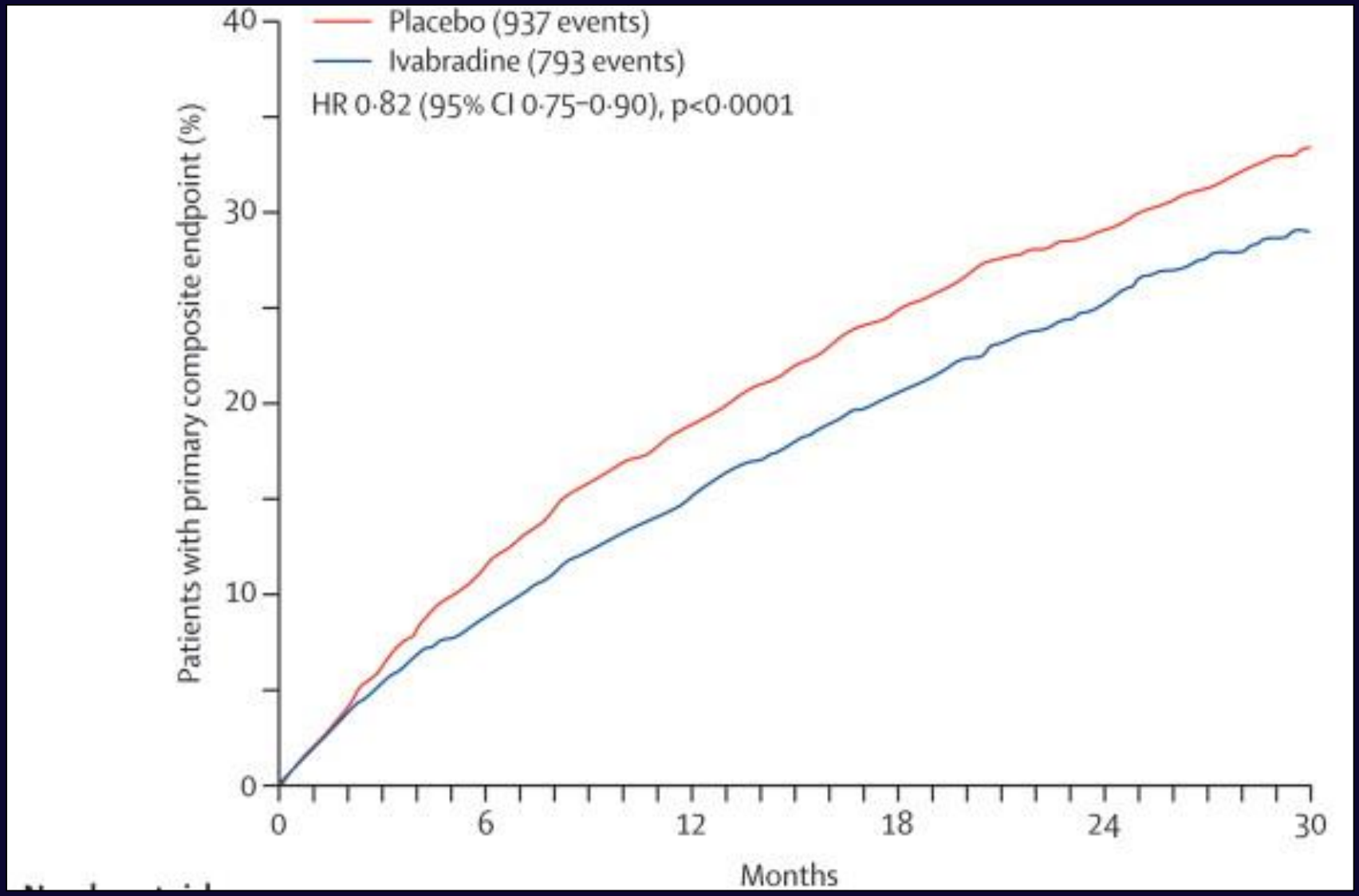
- RCT investigating patients stable symptomatic HF of ≥4 weeks, LVEF ≤35% with an admission over the last 12mos

- Sinus rhythm with HR >70bpm on OMT(including BB) for at least 4 weeks
  - 90% on BB, 84% on ACE/ARBs, 60% Aldo antagonists

- Randomized to Ivabradine vs. Placebo (n=6558)

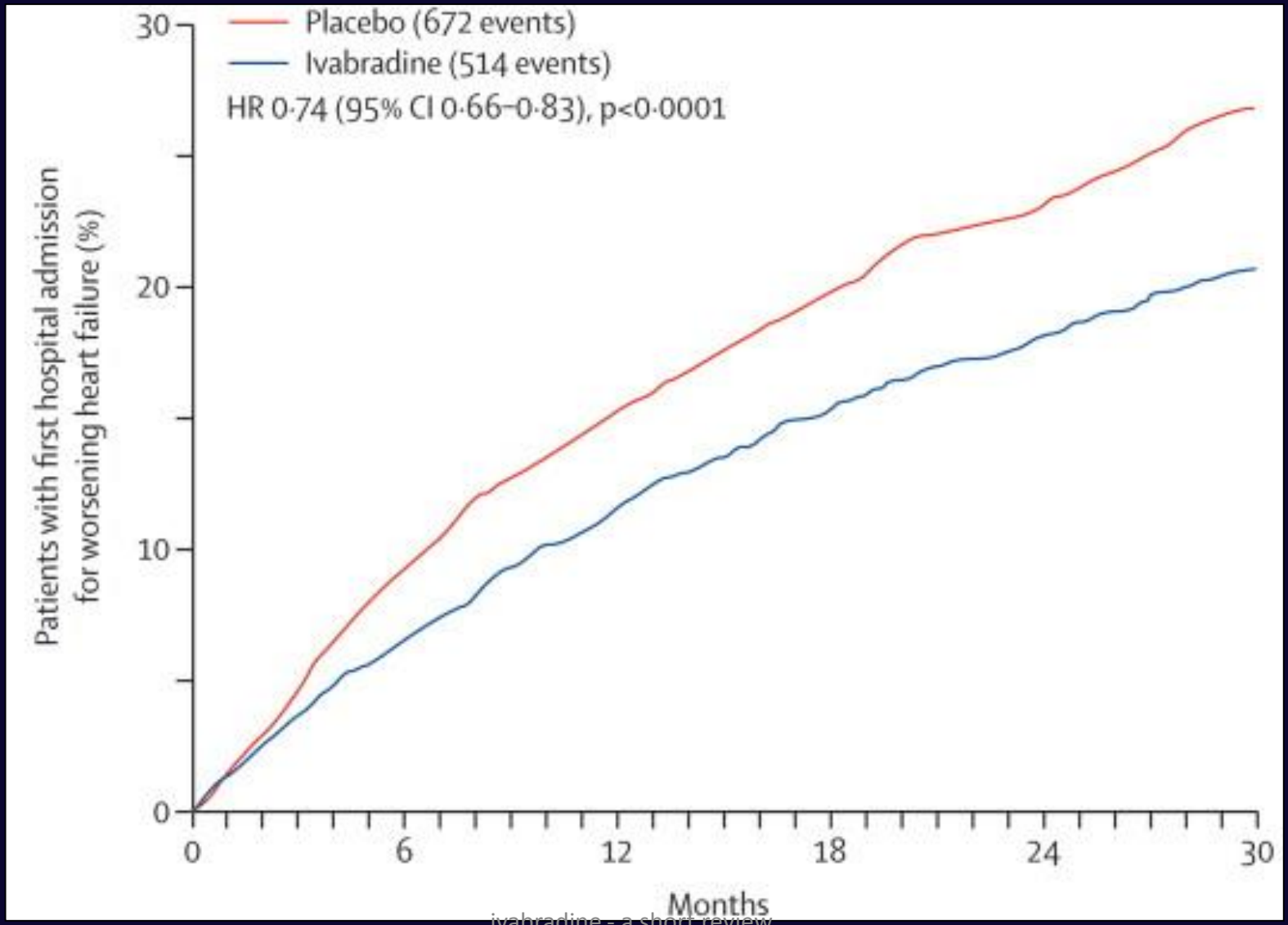
Swedberg et al. Lancet 2010

Cardiovascular Death and Heart Failure Admissions



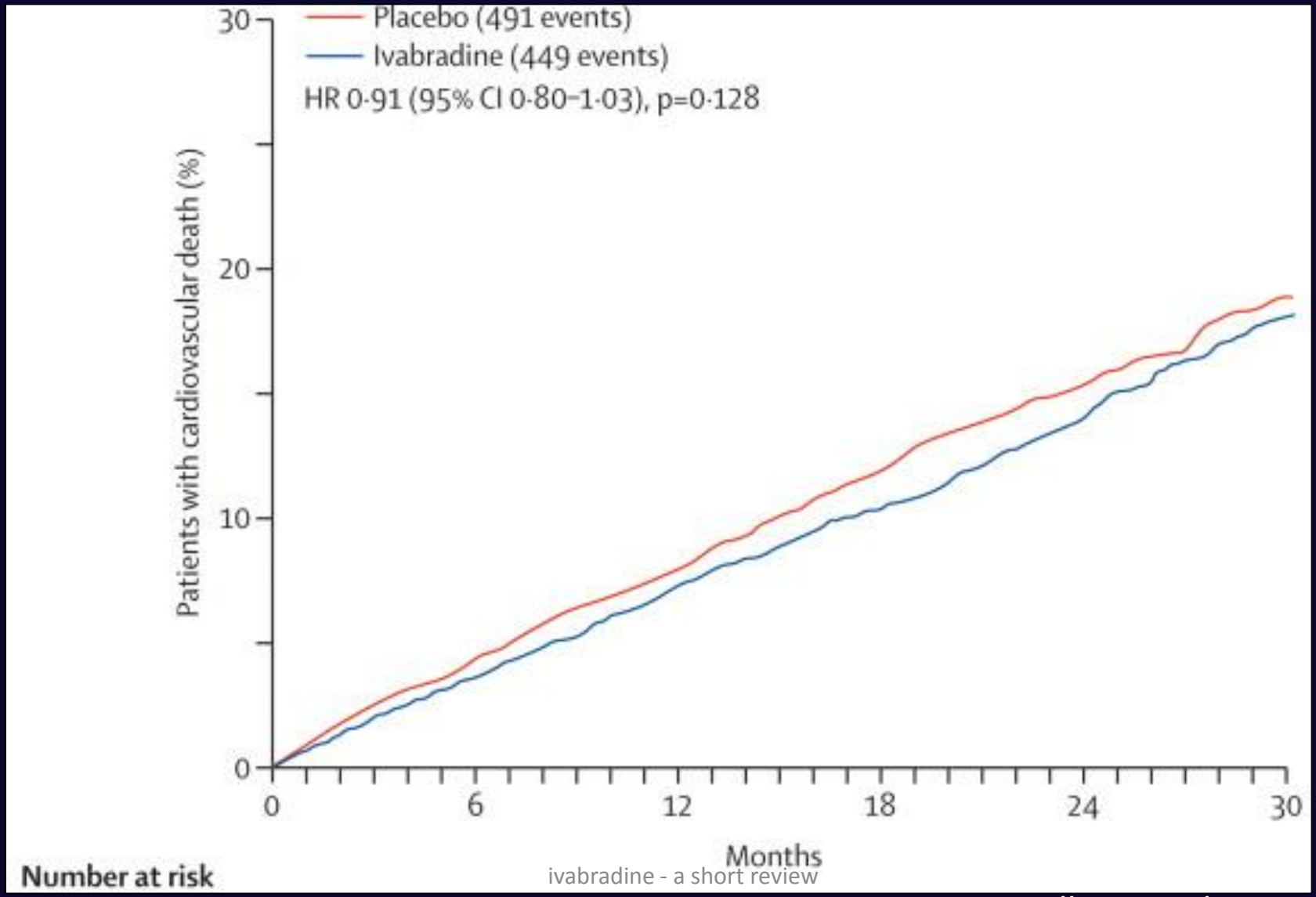
Swedberg et al. Lancet 2010

Heart Failure Admissions



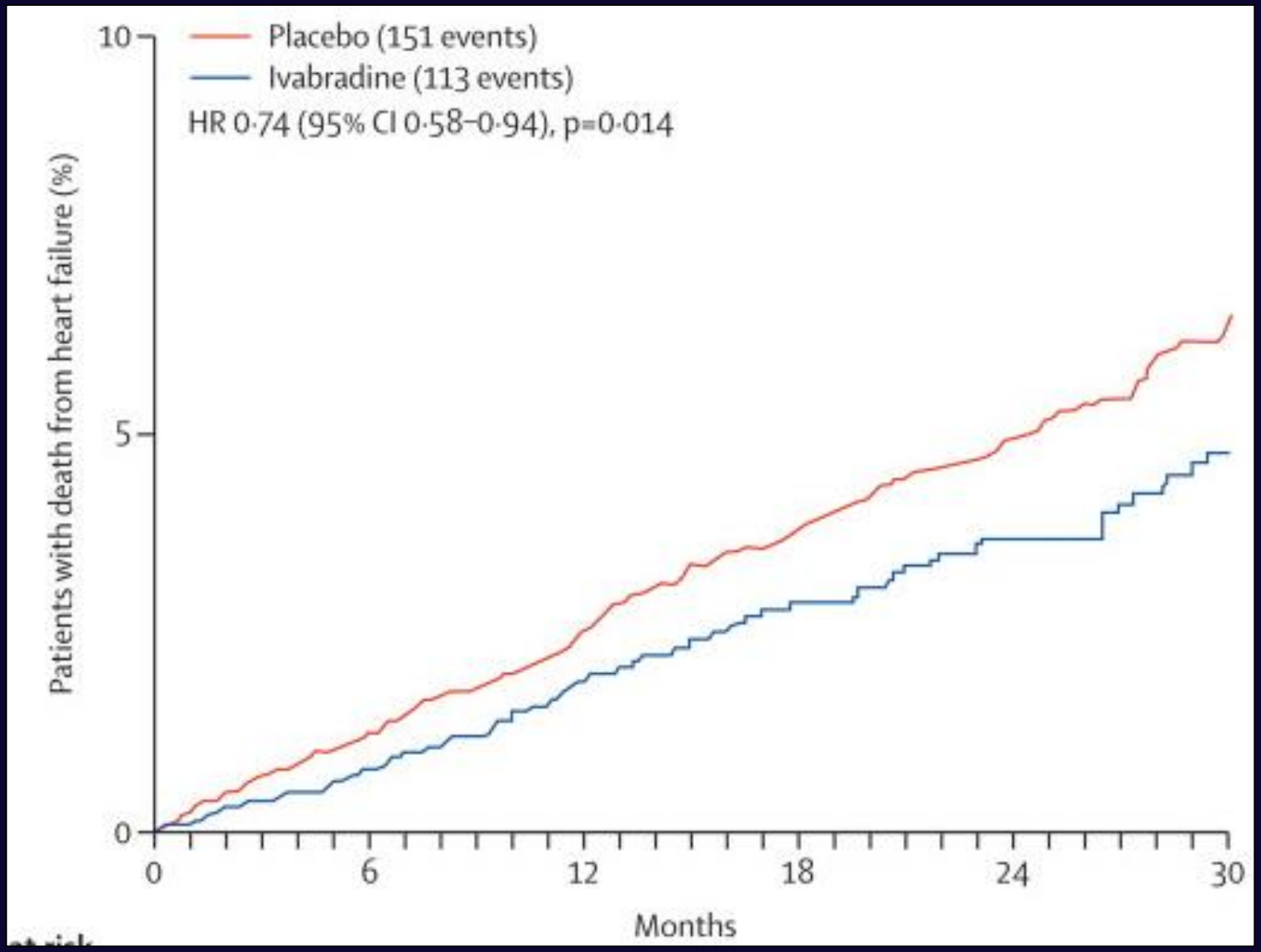
Swedberg et al. Lancet 2010

Cardiovascular Mortality



Swedberg et al. Lancet 2010

Deaths due to Heart Failure



Swedberg et al. Lancet 2010

Contraindications to Ivabradine

- Acute decompensated HF
- Blood pressure less than 90/50
- Sick sinus syndrome, sinoatrial block or third degree atrioventricular block, unless a functioning demand pacemaker is present
- Pacemaker dependence
- Severe hepatic impairment
- In combination with strong cytochrome CYP34A inhibitors
  - would increase ivabradine plasma concentrations

Ivabradine Review

- In patients on optimal medical management in sinus rhythm with HR >70BPM
  - Reduced Cardiovascular Death and Heart Failure Admissions
  - Reduced HF admissions
  - Reduced Deaths due to Heart Failure

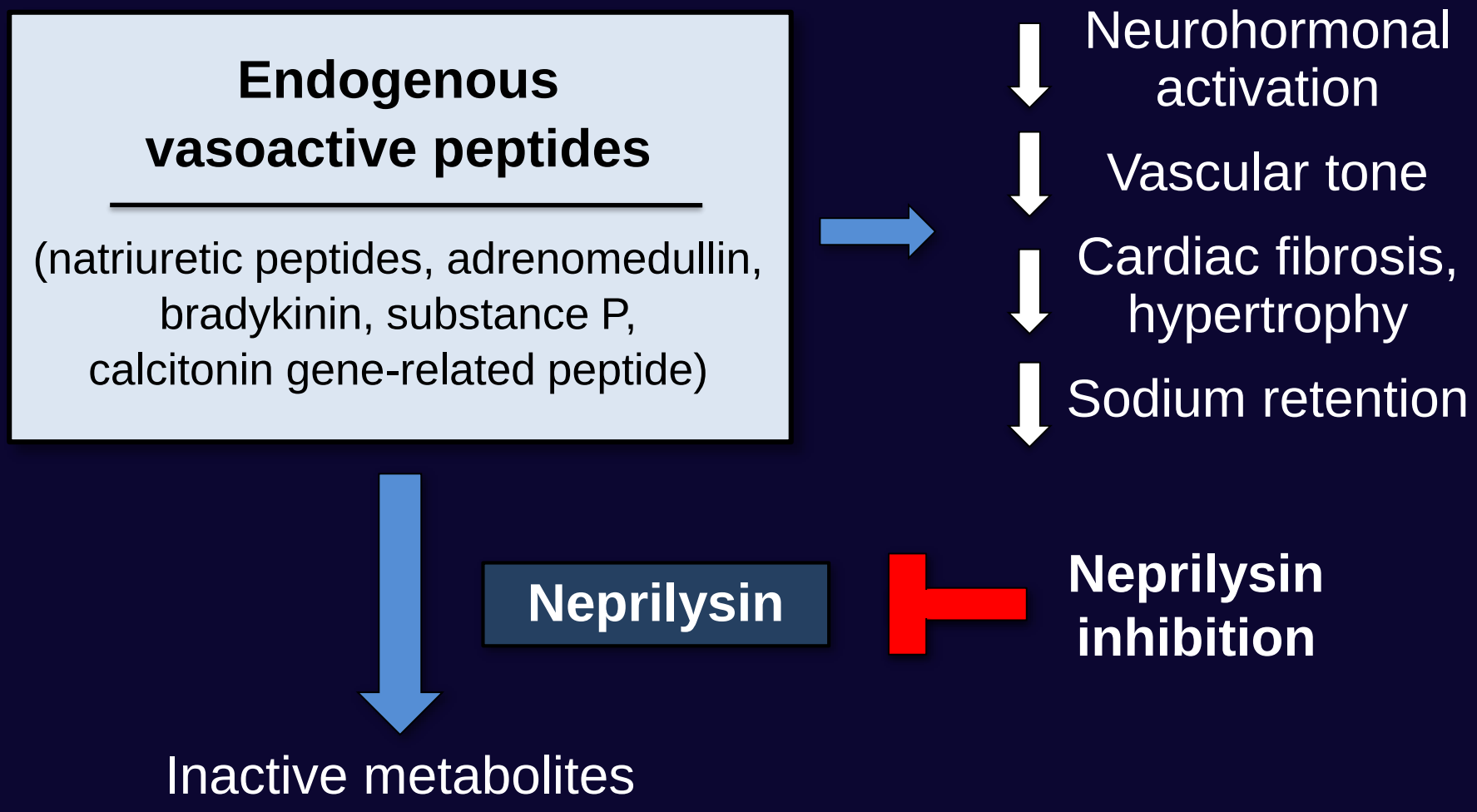
Angiotensin Receptor-Neprilysin Inhibition (ARNIs)

Angiotensin Receptor-Neprilysin Inhibition (ARNIs)

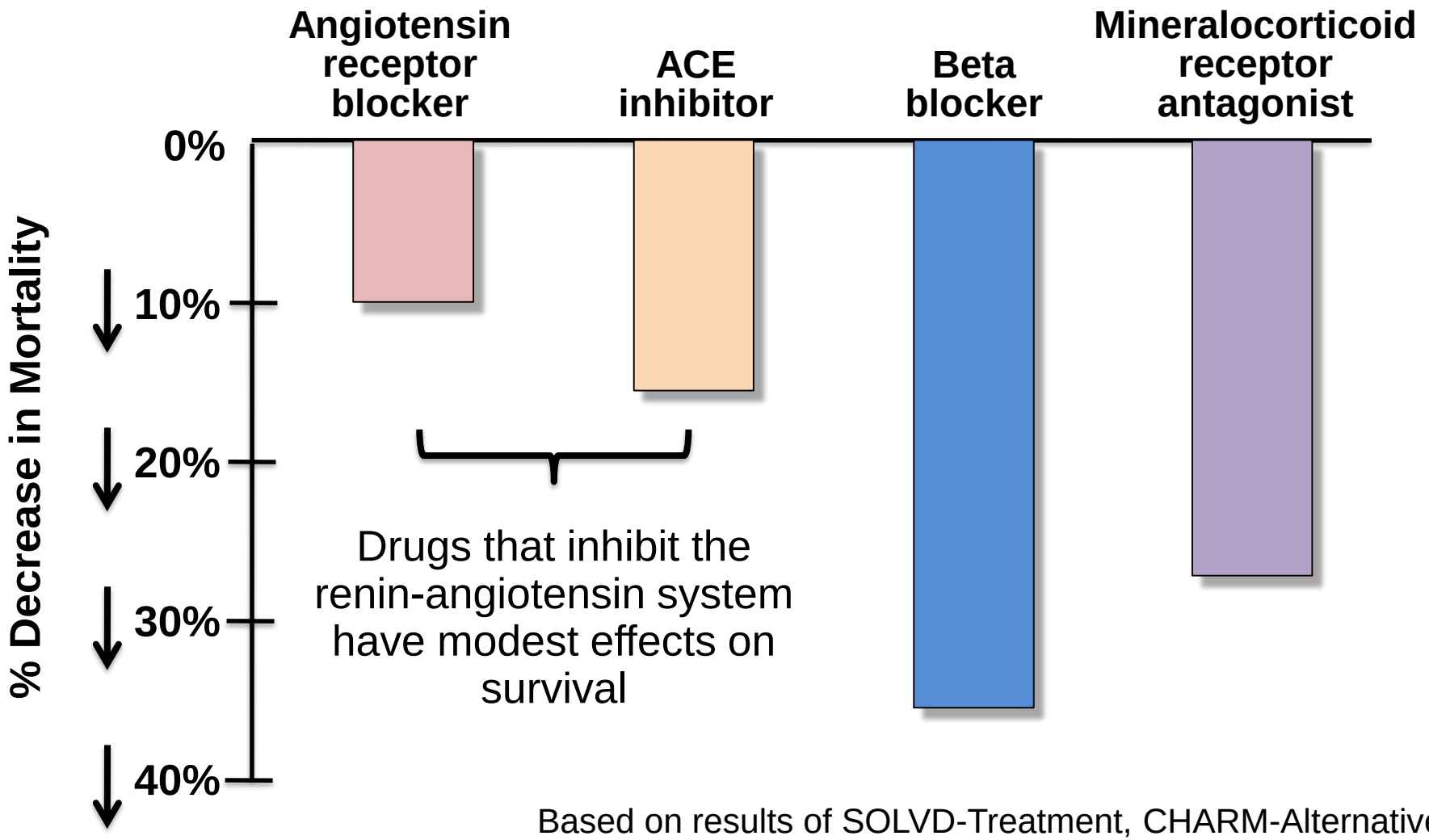
- RAAS blockade has been known to be beneficial in hard endpoint outcomes for HFrEF patients for nearly 25 years

- Neprilysin
  - Neutral endopeptidase which degrades several endogenous vasoactive peptides
  - Raises levels of natriuretic peptides, bradykinin, and adrenomedullin and may thus have beneficial hemodynamic effects in HF patients

Angiotensin Receptor-Neprilysin Inhibitors (ARNI) Maladaptive Mechanisms in Heart Failure



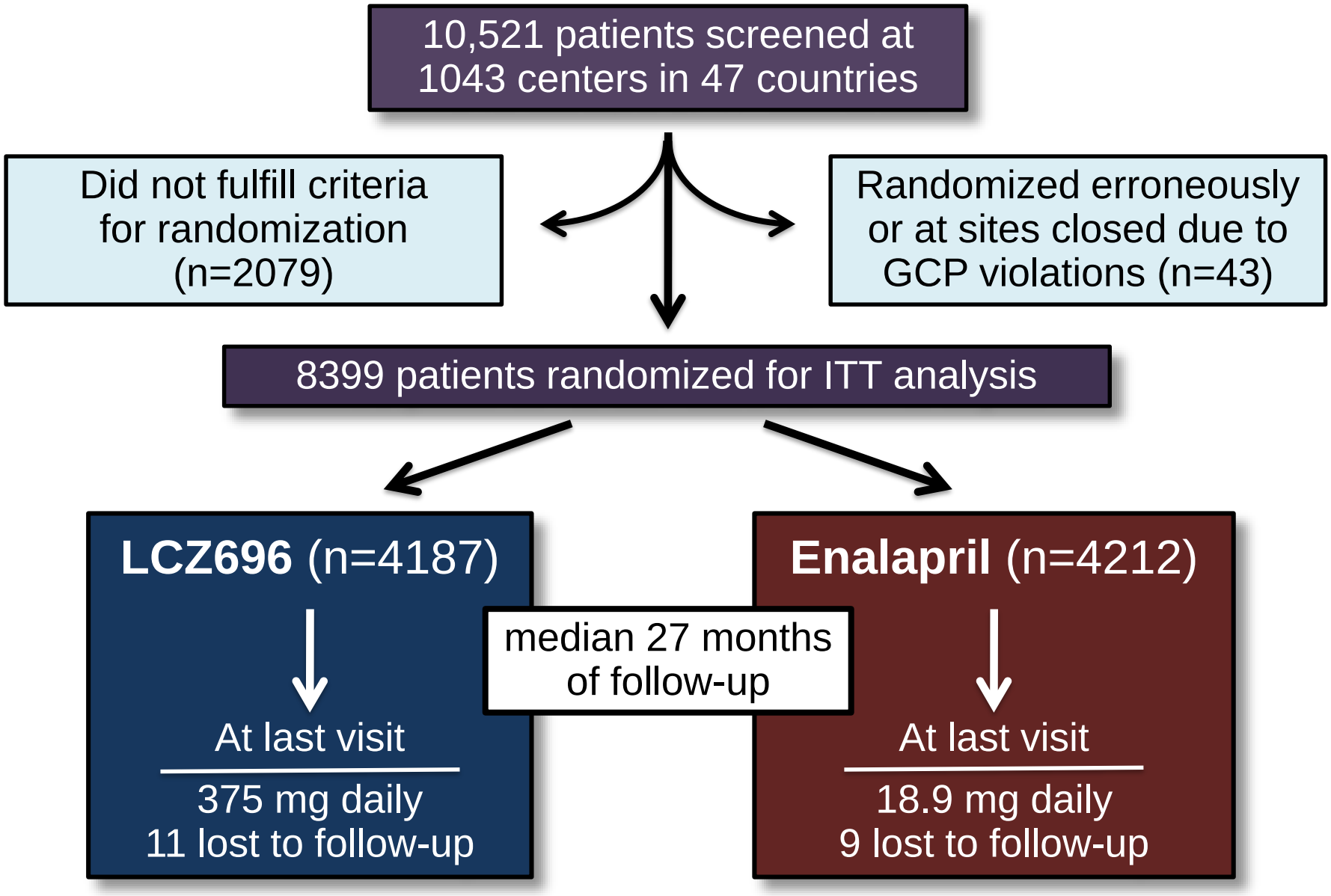
Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction



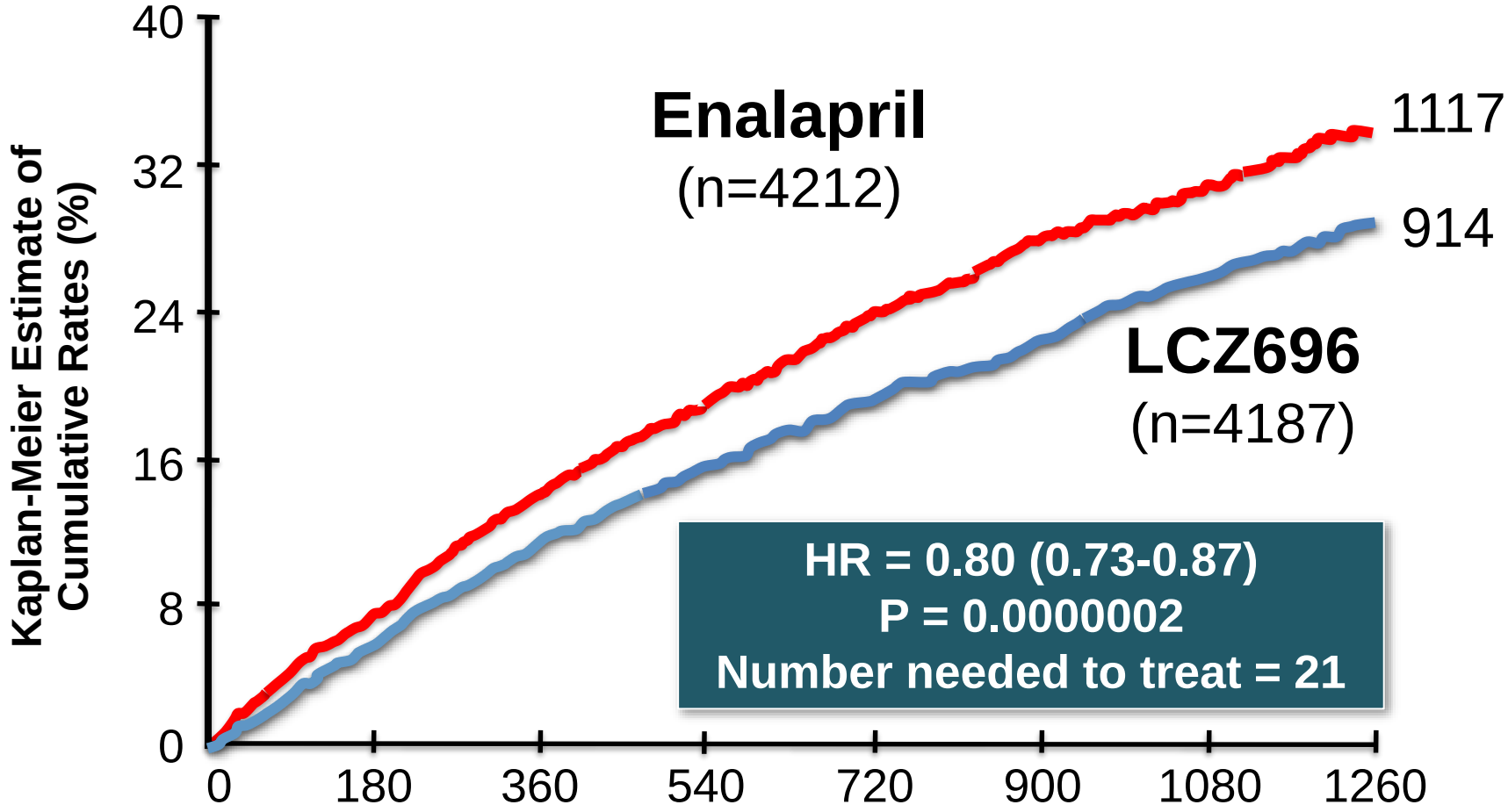
Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF

- Multicentre RCT comparing LCZ696 vs enalapril in adults with NYHA II-IV HF with LVEF<35% (changed from LVEF<40%)
  - N= 10, 521
- Required to have BNP>150 pg/ml or NT-proBNP >600 pg/ml
  - Or hospitalization within 1-year+ BNP 100 pg/ml/NT-proBNP >400
- Patients should have been on ACEi/ARB equivalent to Enalapril 10mg OD for at least 4 weeks prior to enrollment with stable dose of beta-blocker

PARADIGM-HF: Patient Disposition



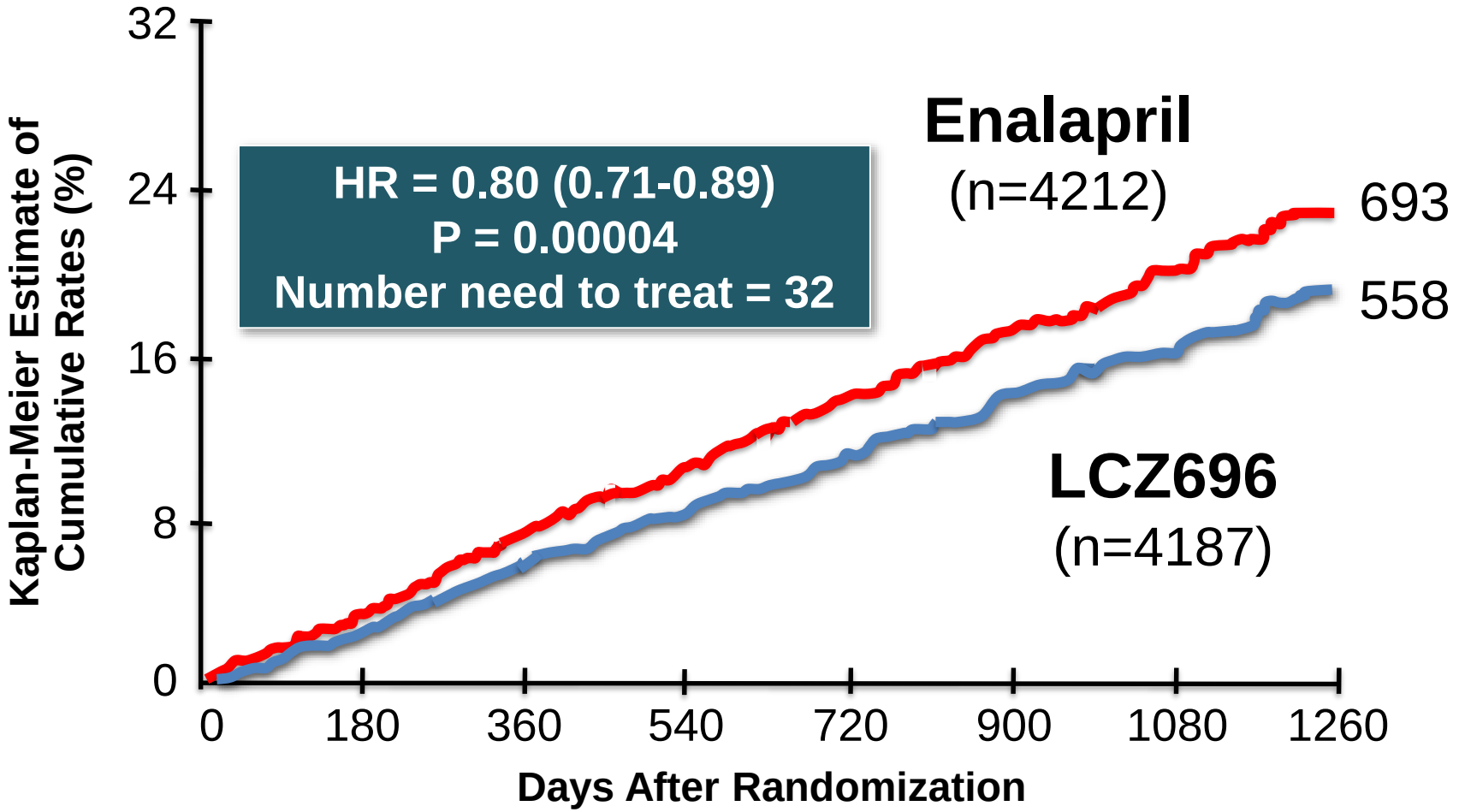
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)



Patients at Risk

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

PARADIGM-HF: Cardiovascular Death



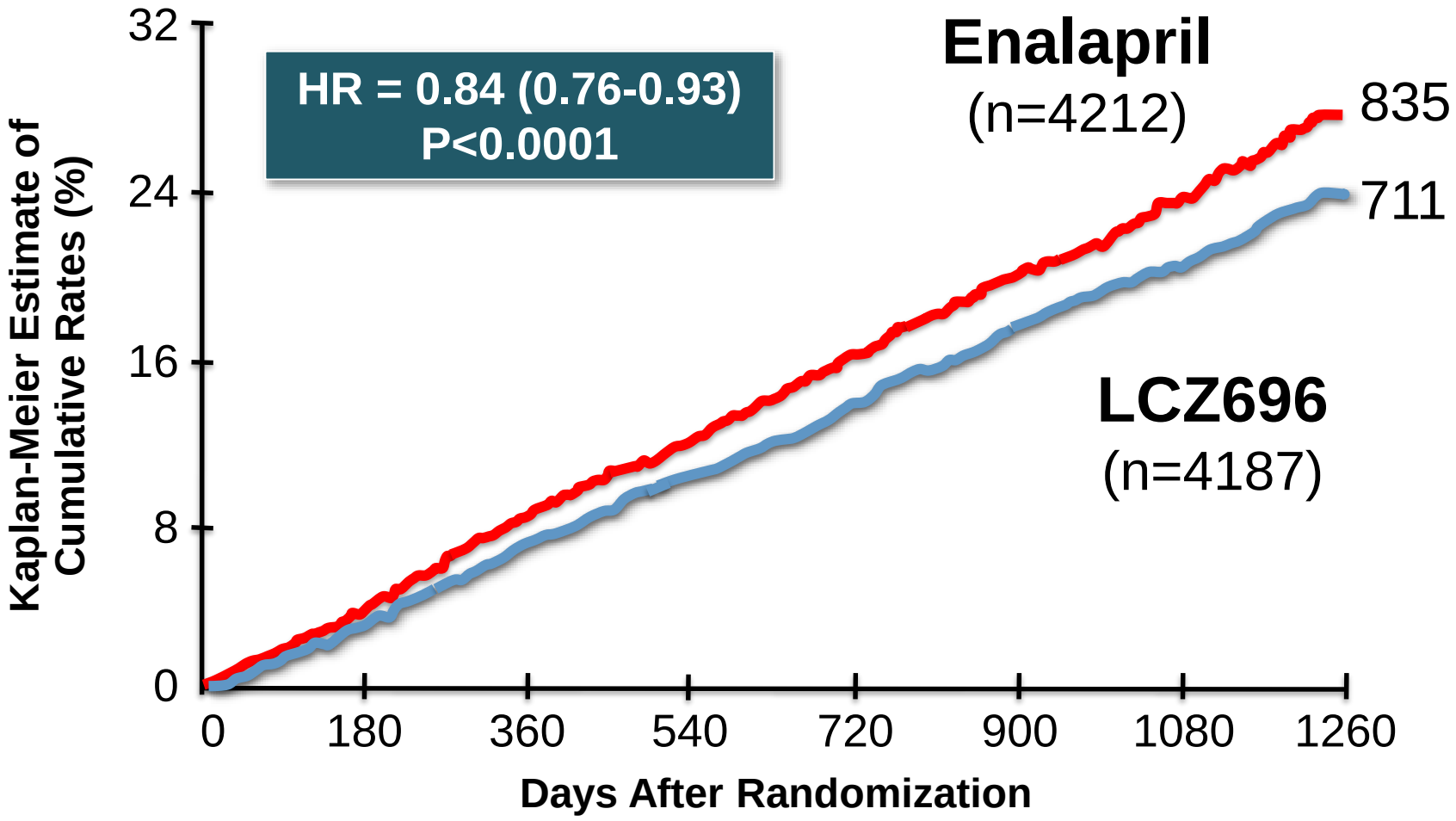
Patients at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

PARADIGM-HF: Effect of LCZ696 vs Enalapril on Primary Endpoint and Its Components

	LCZ696 (n=4187)	Enalapril (n=4212)	Hazard Ratio (95% CI)	P Value
Primary endpoint	914 (21.8%)	1117 (26.5%)	0.80 (0.73-0.87)	0.0000002
Cardiovascular death	558 (13.3%)	693 (16.5%)	0.80 (0.71-0.89)	0.00004
Hospitalization for heart failure	537 (12.8%)	658 (15.6%)	0.79 (0.71- 0.89)	0.00004

PARADIGM-HF: All-Cause Mortality



Patients at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
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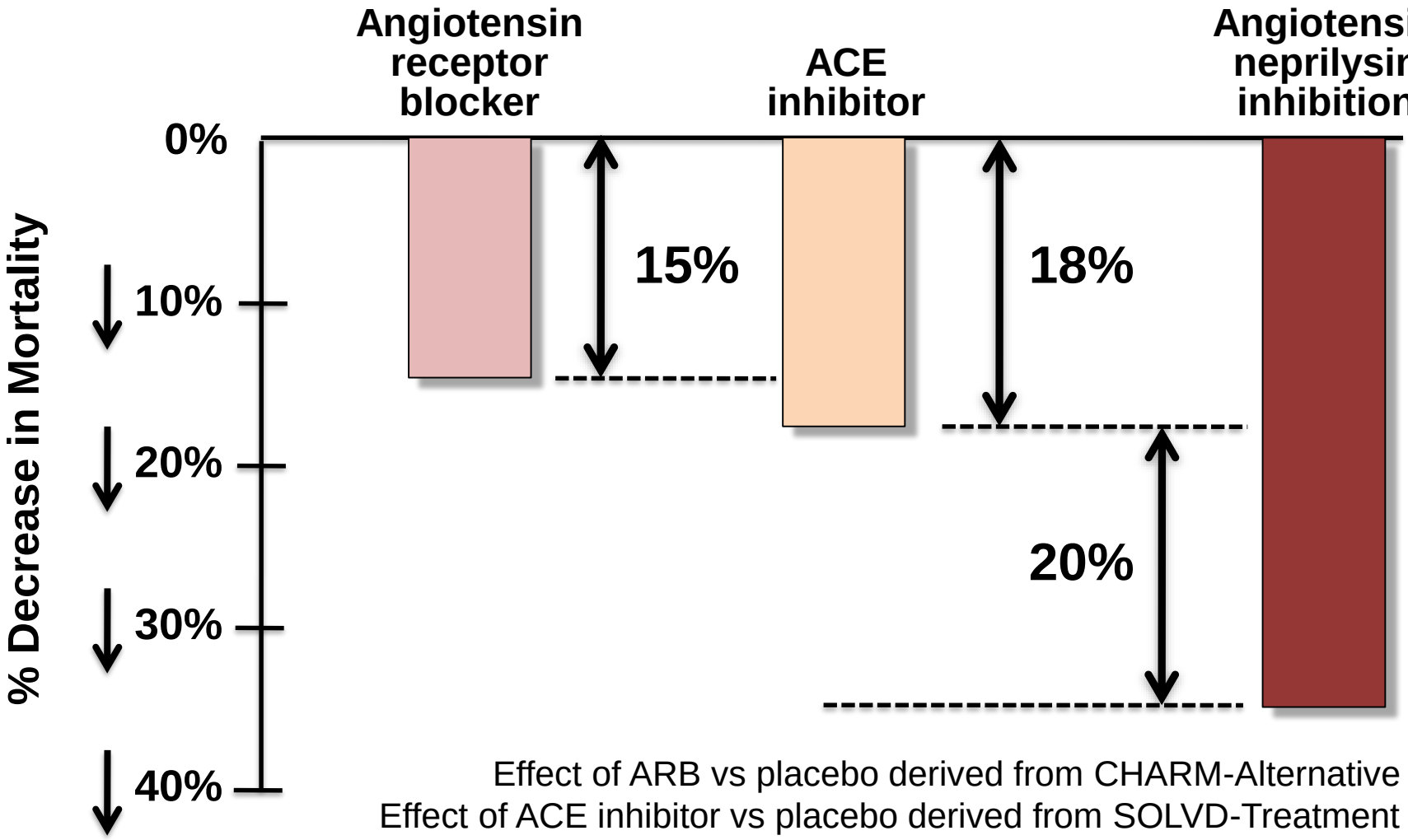
Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System



Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial

Contraindications to ARNIs

- Hypersensitivity to any component
- History of angioedema
  - whether resulting from ACE inhibition or not
- Pregnancy
- Should **not** be used concomitantly with :
  - ACE inhibitors (because of increased risk of angioedema)
    - Do **not** administer within 36 hours of switching to or from an ACE inhibitor
  - Aliskiren
  - Use of ARNIs with another angiotensin II receptor blocker (ARB) should be avoided (ie, avoid dual ARB therapy).

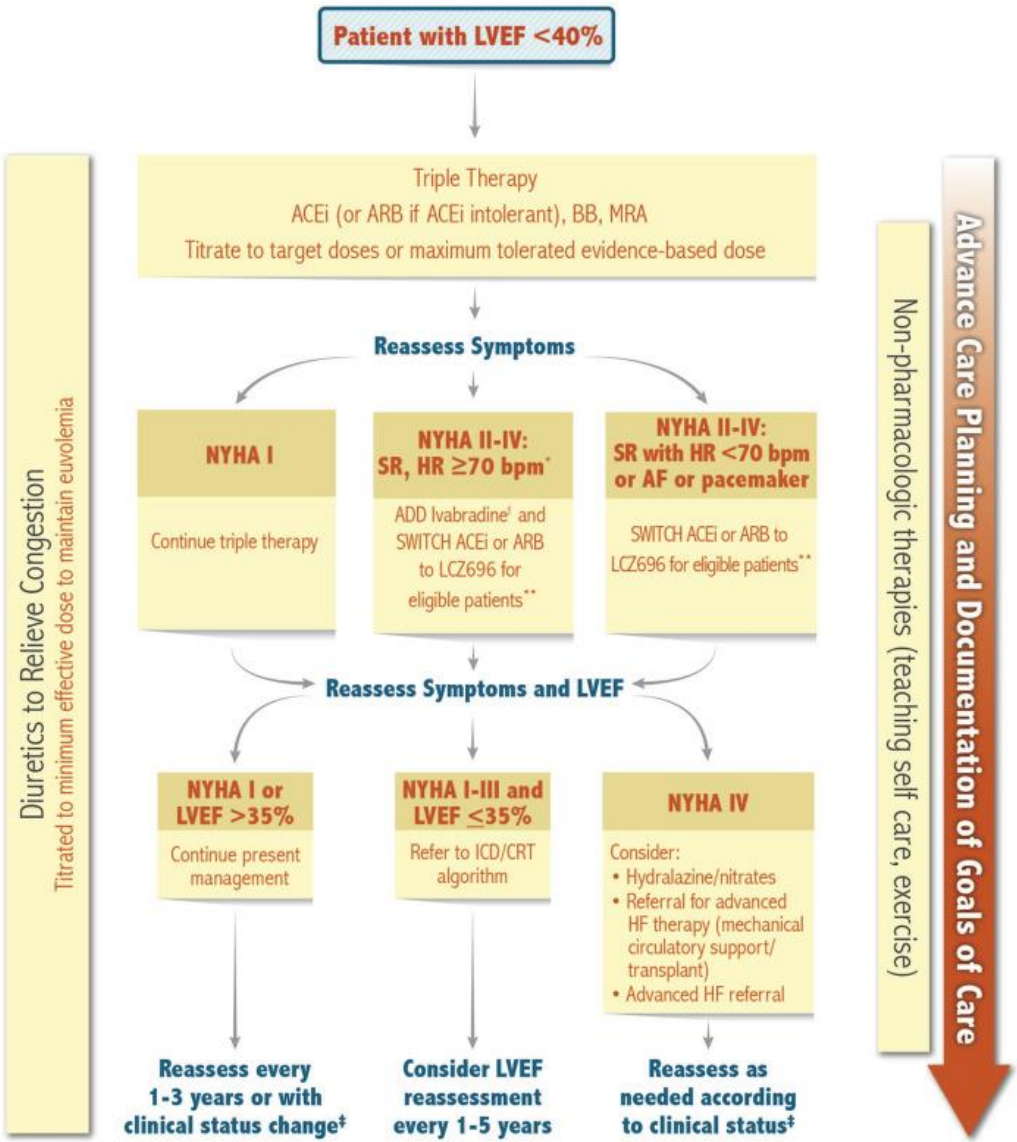
Entresto Review

- In patients with NYHA II-IV HF with LVEF<35% despite treatment with ACEi/ARB
  - Reduced Cardiovascular Death or Heart Failure Hospitalization
  - Reduced CV death
  - Reduced HF admissions
  - Reduced all cause mortality

Current CCS HF Guidelines

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

Therapeutic Approach to Patients with Heart Failure and Reduced Ejection Fraction



*Pending Health Canada approval
†Ivabradine may be added when available in Canada
**LCZ696, when available in Canada, will replace ACEi or ARB in patients with elevated NP or recent hospitalization (BNP >150pg/ml or NT-pro-BNP >600 pg/ml)
‡Refer to Table 4

Conclusions

- HF continues to be a growing epidemic worldwide
- The cornerstone of medical therapy for those with HFrEF continues to be triple therapy
  - ACEi/ARB, B-blockade, MRA
- For those who continue to be symptomatic (≥NYHA II), novel therapies such as Ivabradine and Entresto have been shown to be beneficial for symptom control, HF readmission and mortality

Questions