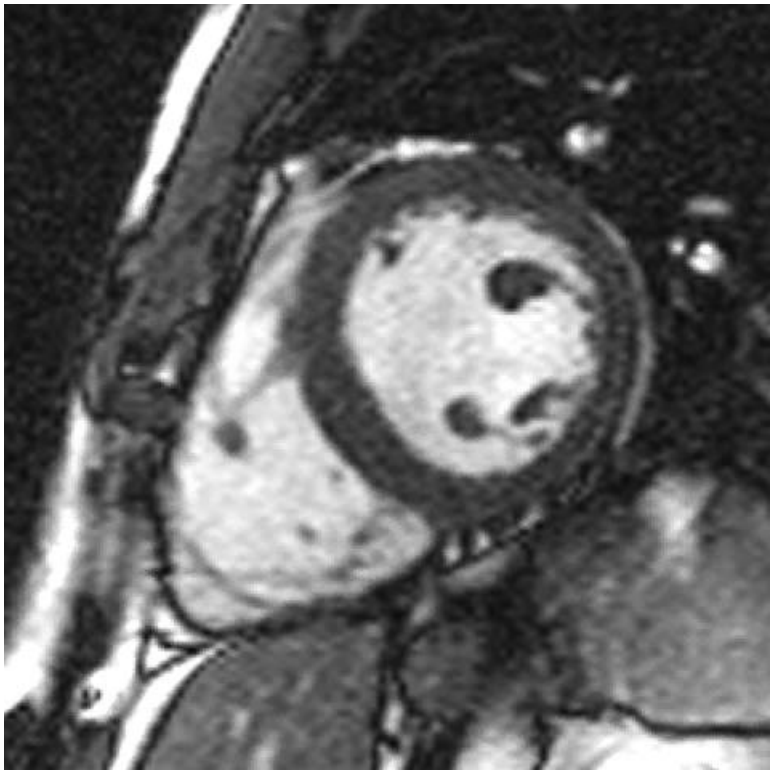
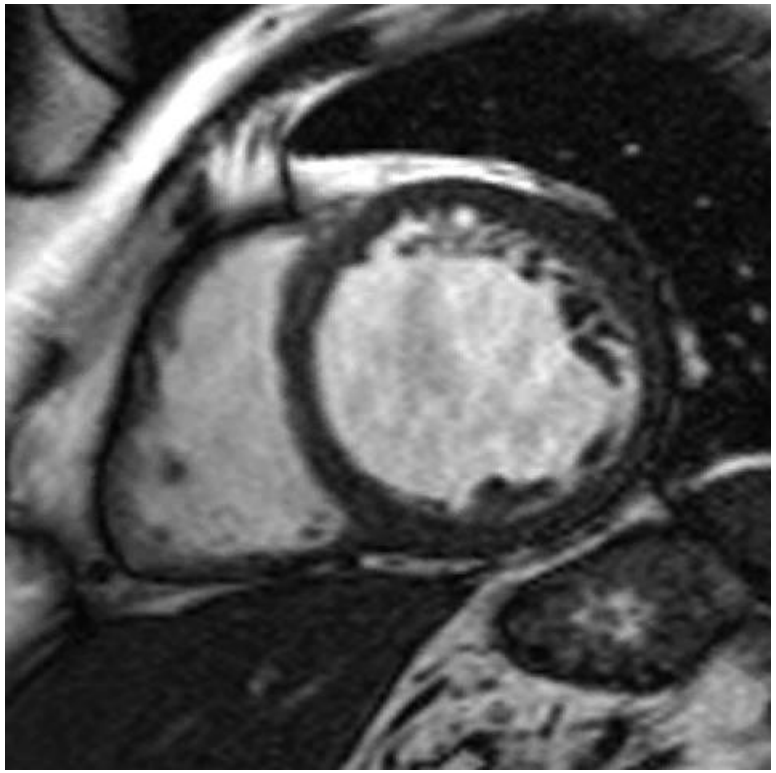
Treatment of heart failure: past, present and future

John McMurray

Eugene Braunwald Scholar in Cardiovascular Diseases, Brigham and Women's Hospital, Boston & Visiting Professor, Harvard Medical School

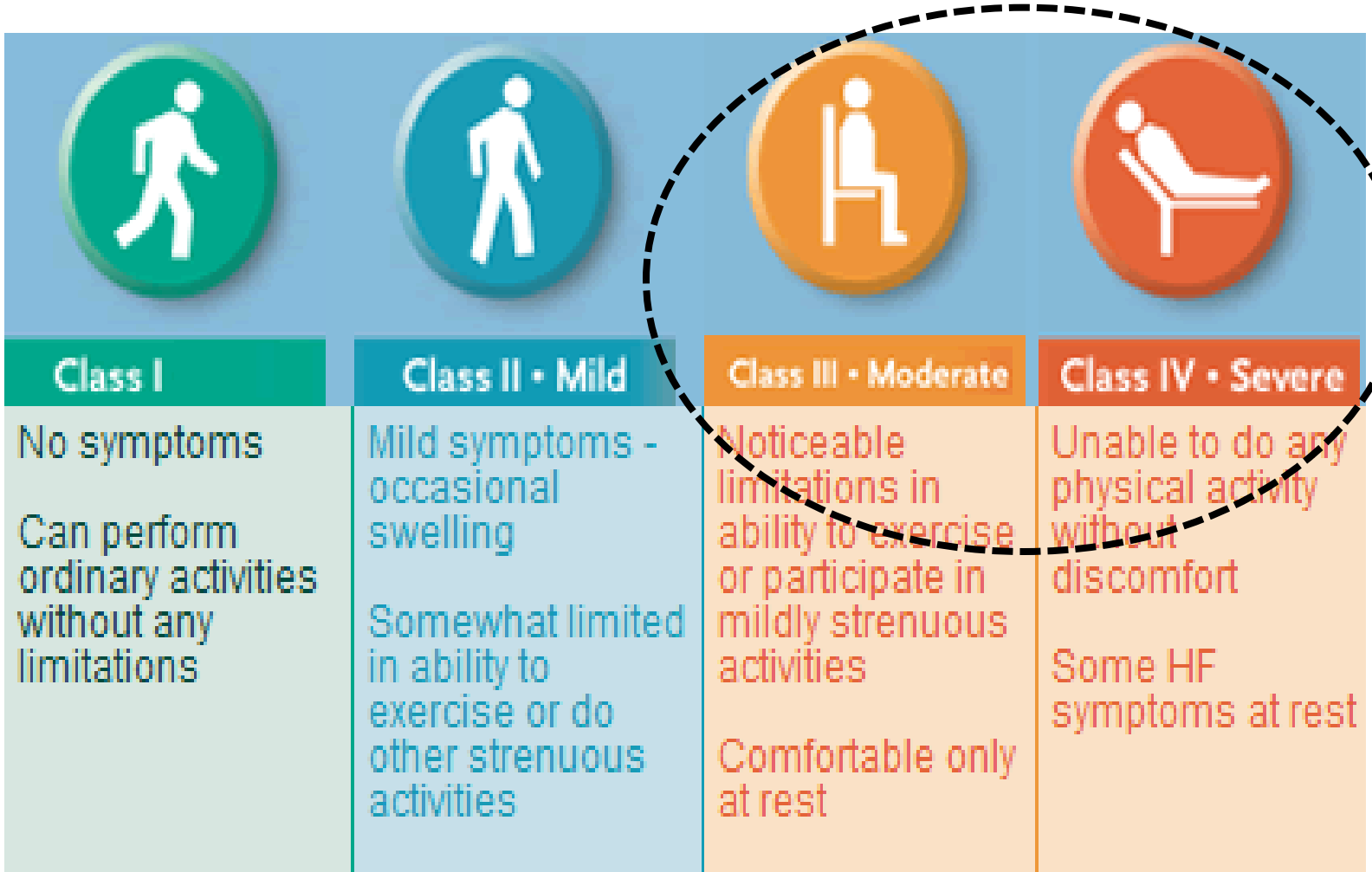
Treatment of low LVEF CHF





Evidence-based treatment of systolic heart failure

NYHA class III-IV: Moderate-severe symptoms

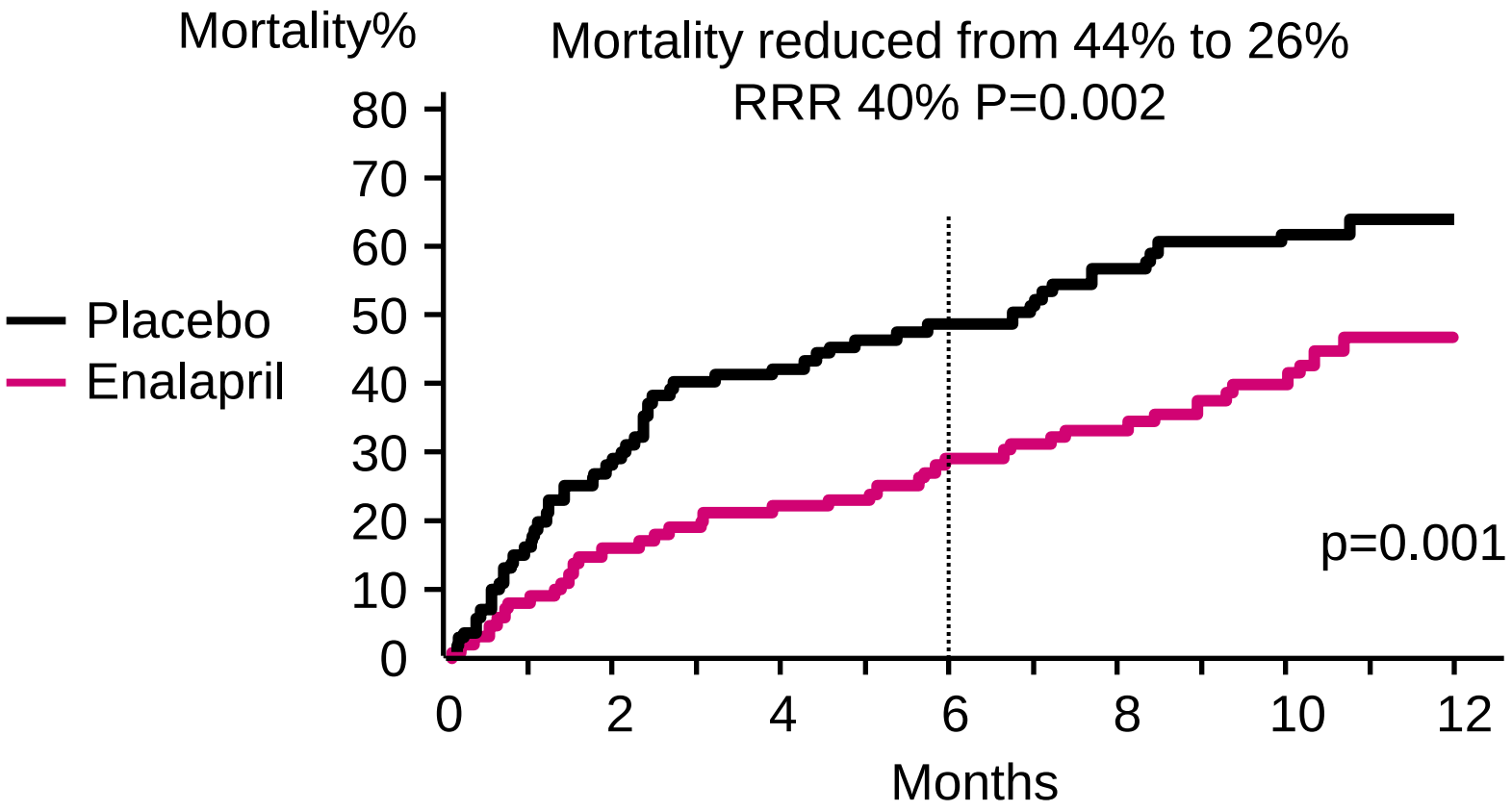


Class I	Class II • Mild	Class III • Moderate	Class IV • Severe
No symptoms Can perform ordinary activities without any limitations	Mild symptoms - occasional swelling Somewhat limited in ability to exercise or do other strenuous activities	Noticeable limitations in ability to exercise or participate in mildly strenuous activities Comfortable only at rest	Unable to do any physical activity without discomfort Some HF symptoms at rest

CONSENSUS

Co-operative North Scandinavian Survival Trial

253 patients, NYHA class IV only (no LVEF entry requirement). Furosemide 98% (mean dose 205mg), digoxin 93% and spironolactone 53% (mean dose 80mg). Mean follow-up 6.3 months.

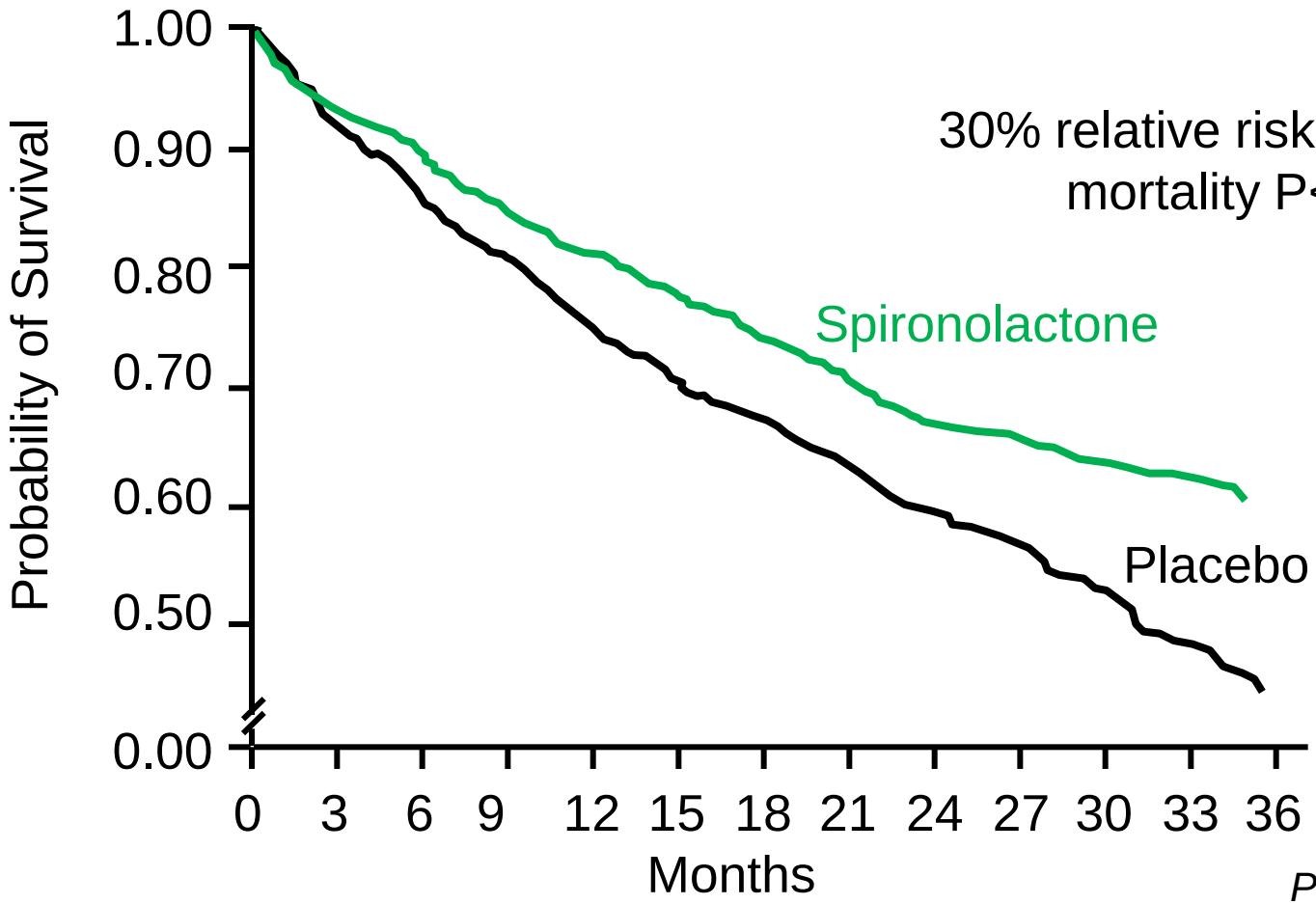


Swedberg et al NEJM 1987

RALES

Randomized ALdactone Evaluation Study

1663 patients, NYHA class III-IV, LVEF ≤0.35. ACE-i 95%, digoxin 73% and beta blockers 10.5%. Mean follow-up 24 months.



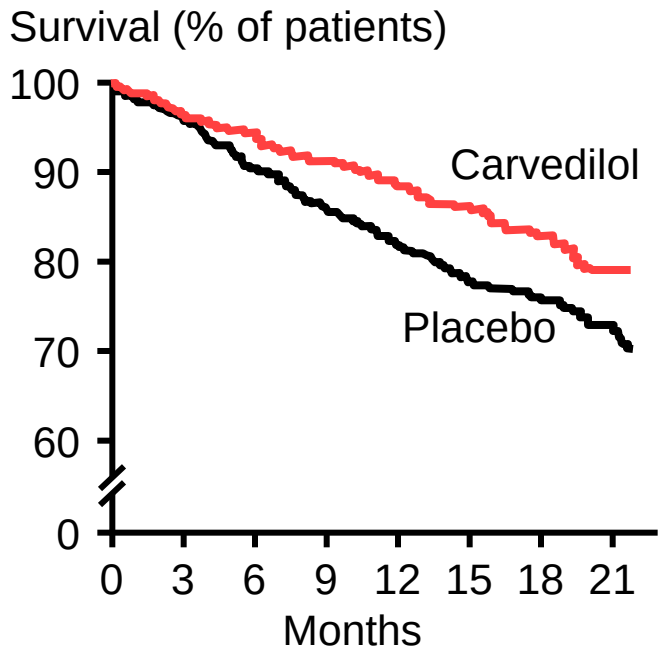
Pitt et al. NEJM 1999

COPERNICUS

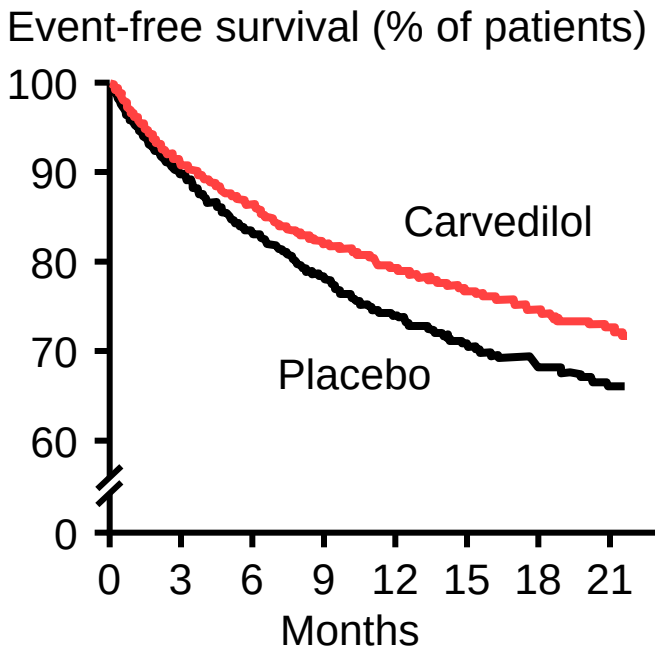
Carvedilol Prospective Randomized Cumulative Survival

2289 patients, NYHA class III-IV, LVEF ≤0.25. ACE-i/ARB 97%, digoxin 66% and spironolactone 20%. Mean follow-up 10.4 months

Death from all causes
35 % risk reduction

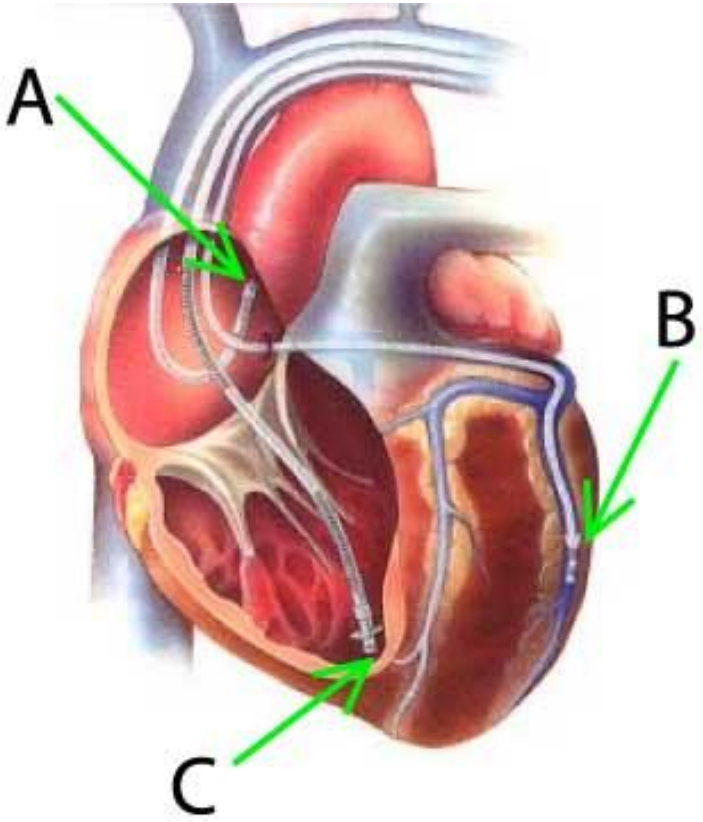


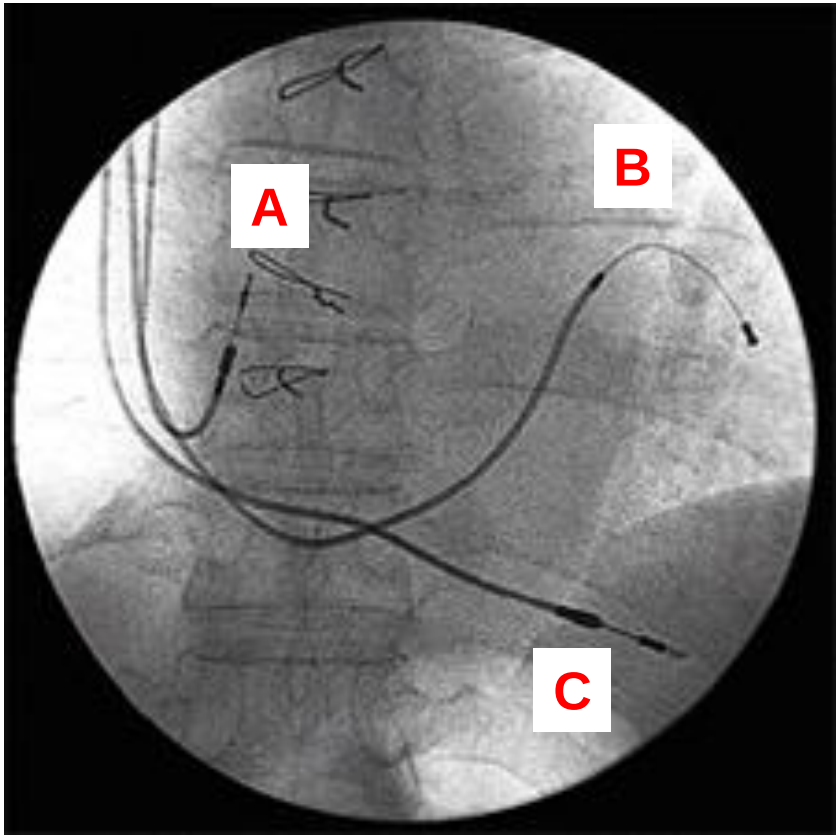
Death or hosp. from all causes
24 % risk reduction



Packer et al NEJM 2001

Biventricular/multi-site pacing or "cardiac resynchronization" therapy

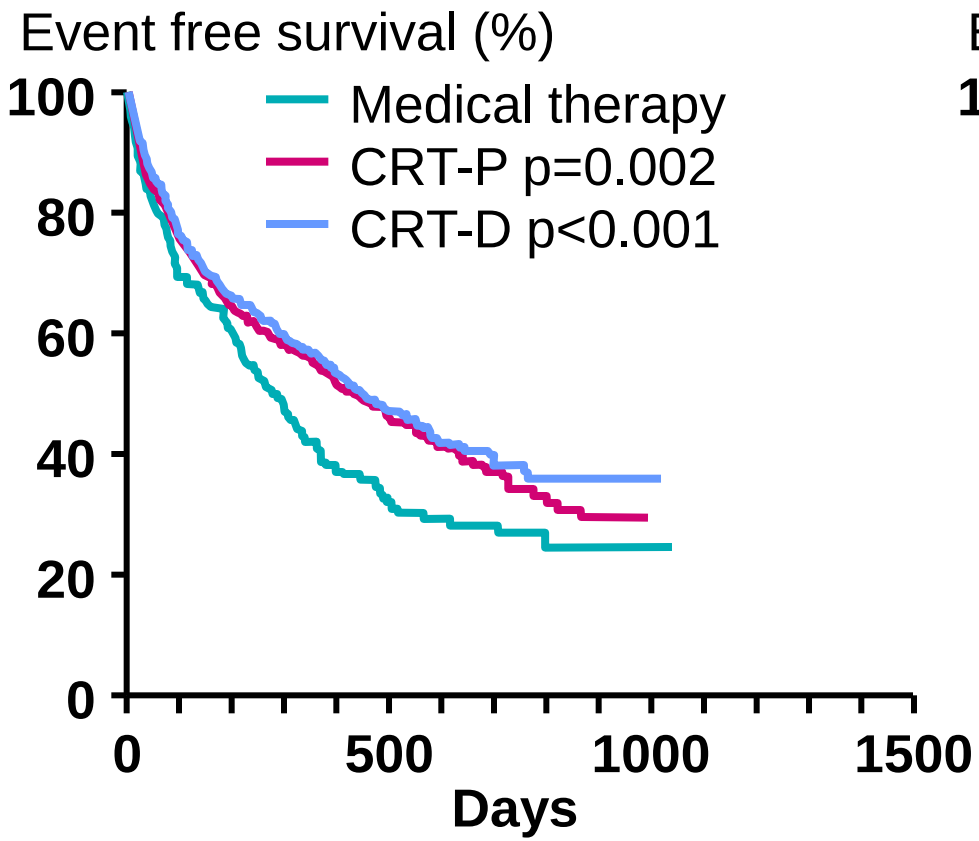




CRT for severe HF: two pivotal trials

COMPANION

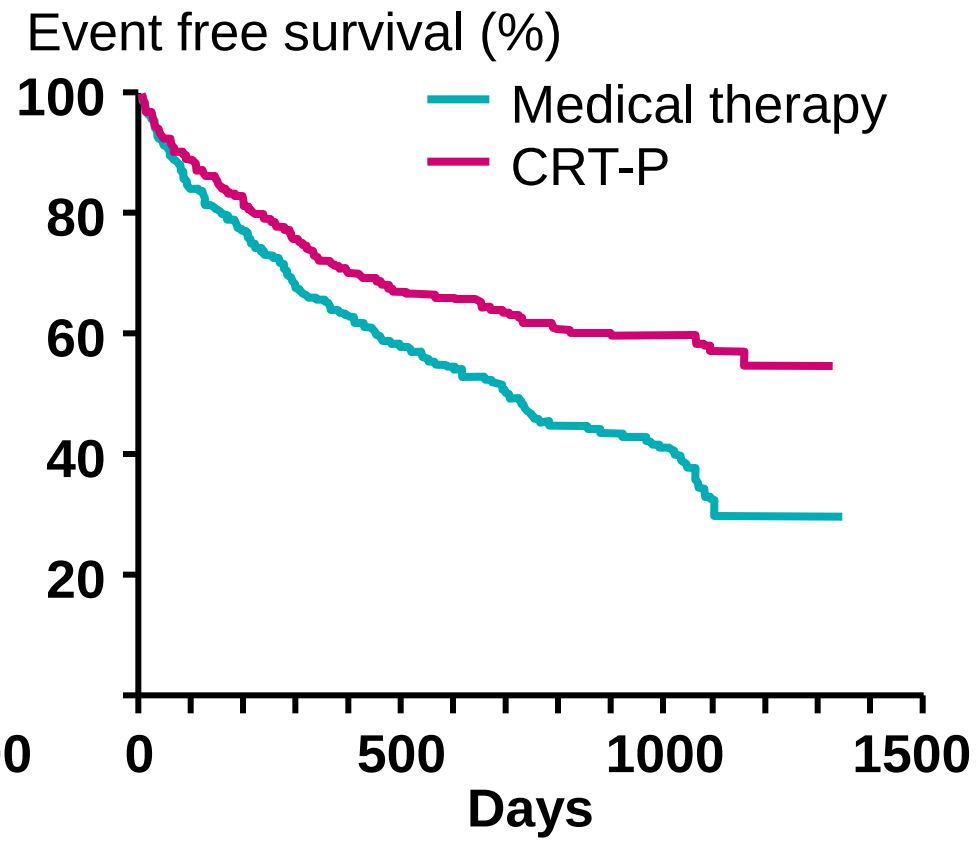
CV death or CV hospitalization



Bristow et al. Engl J Med 2004;350:2140-50

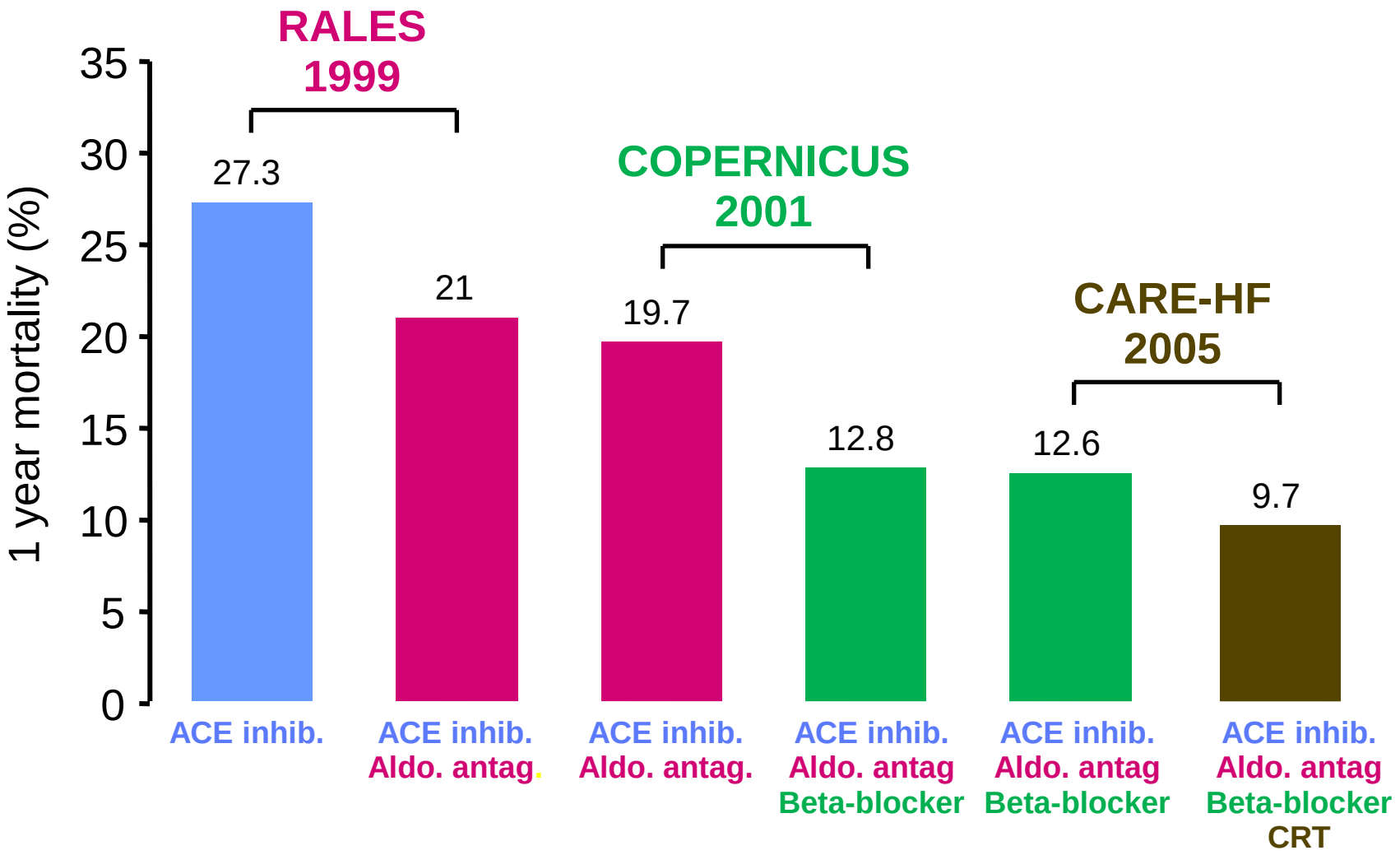
CARE-HF

Death or CV hospitalization

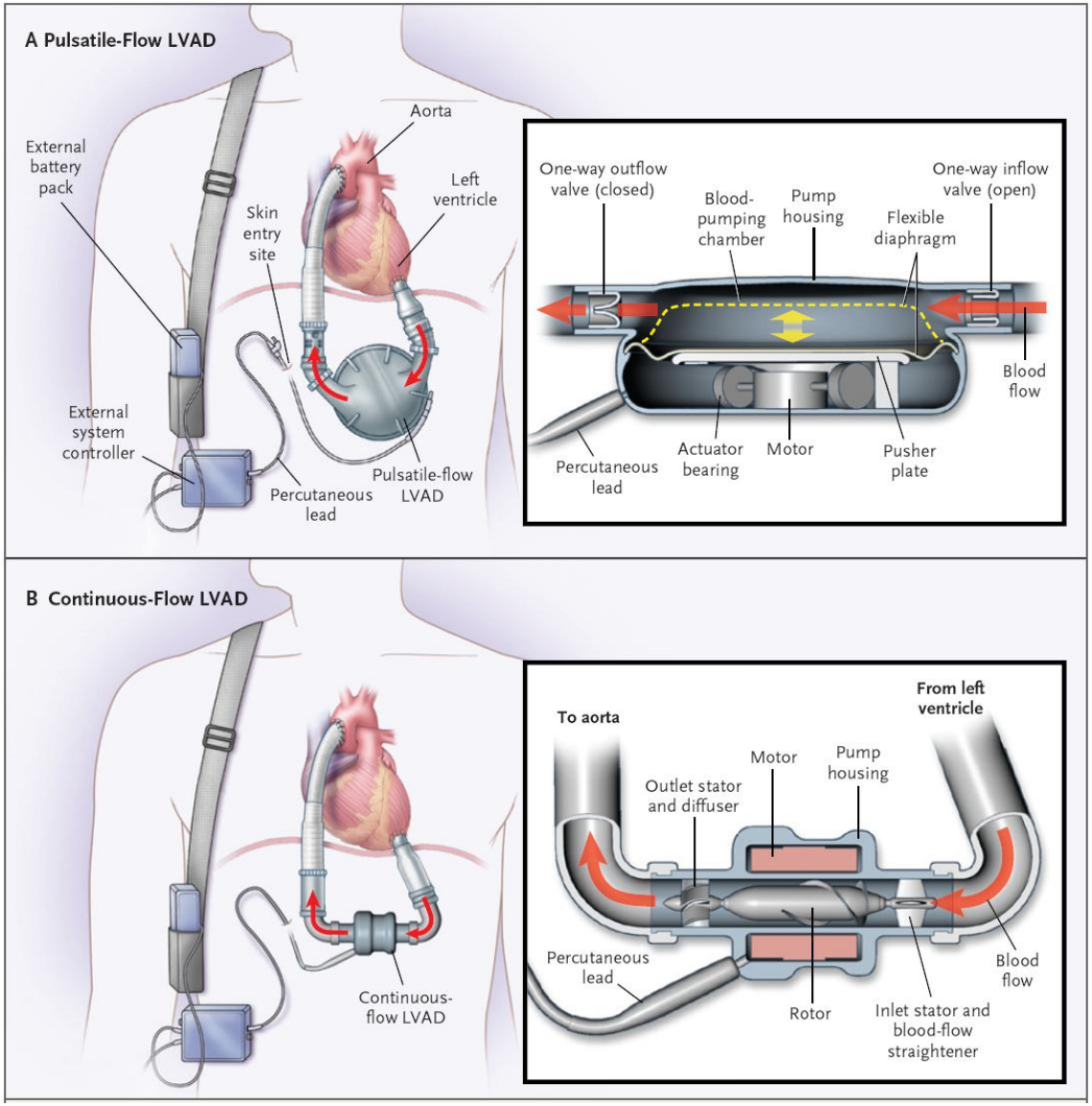


Cleland et al. NEJM 2005

Cumulative benefit of poly-pharmacy (and CRT) in severe HF

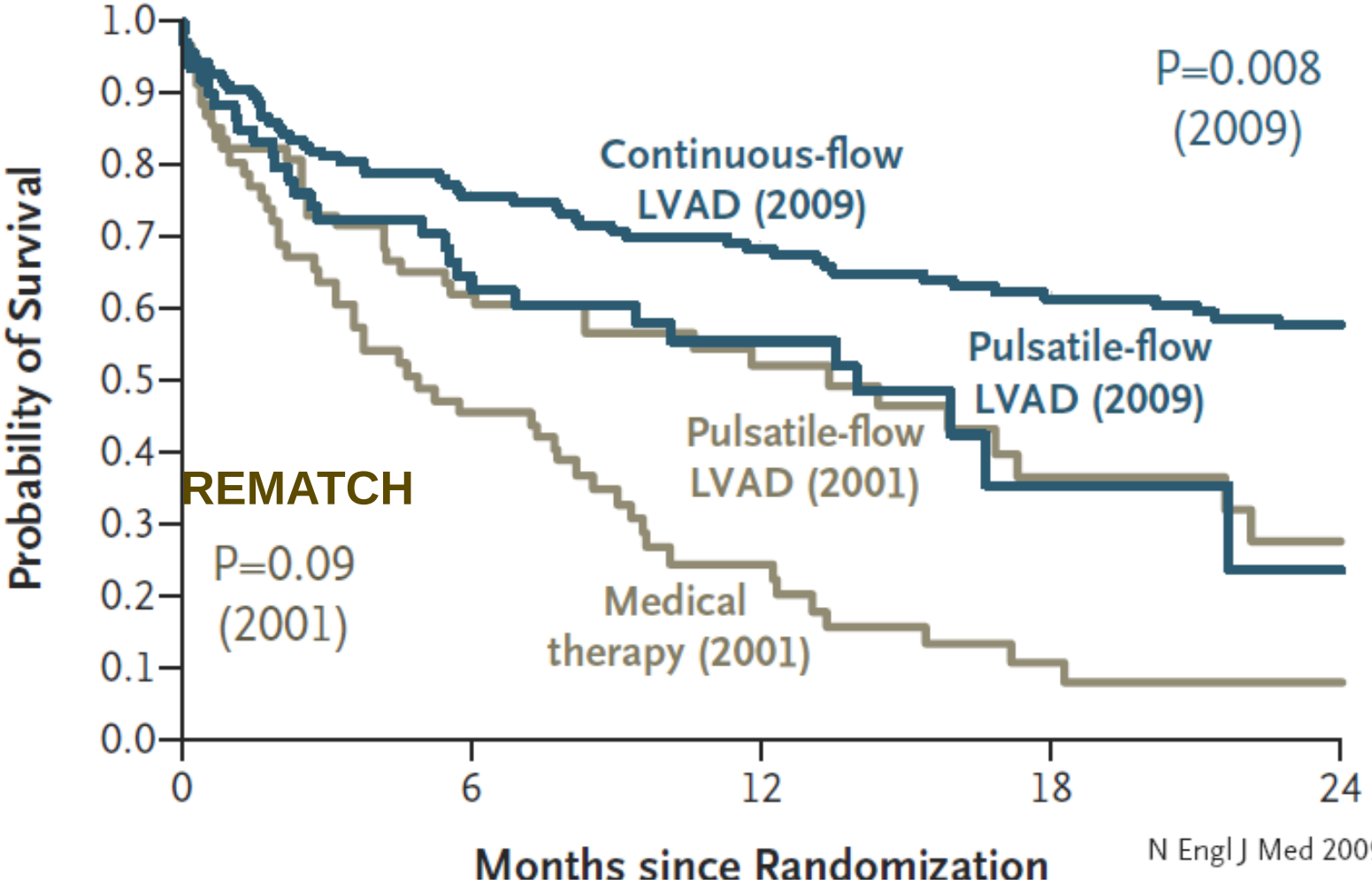


Ventricular assist devices



HeartMate II trial

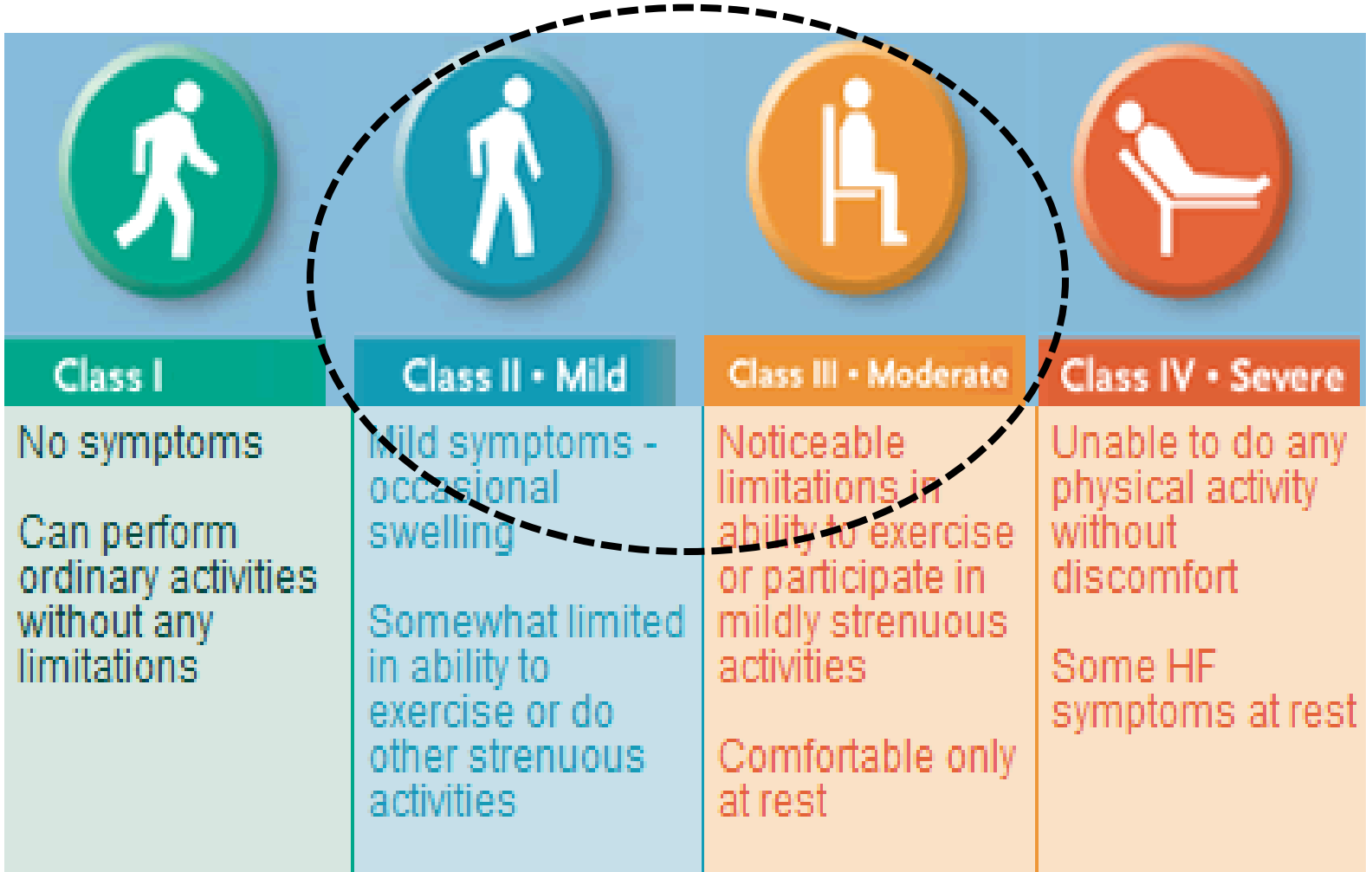
200 patients, ineligible for transplantation. Randomized 2:1 continuous- *vs.* pulsatile-flow device. Mean age 64 years and mean LVEF 17%.



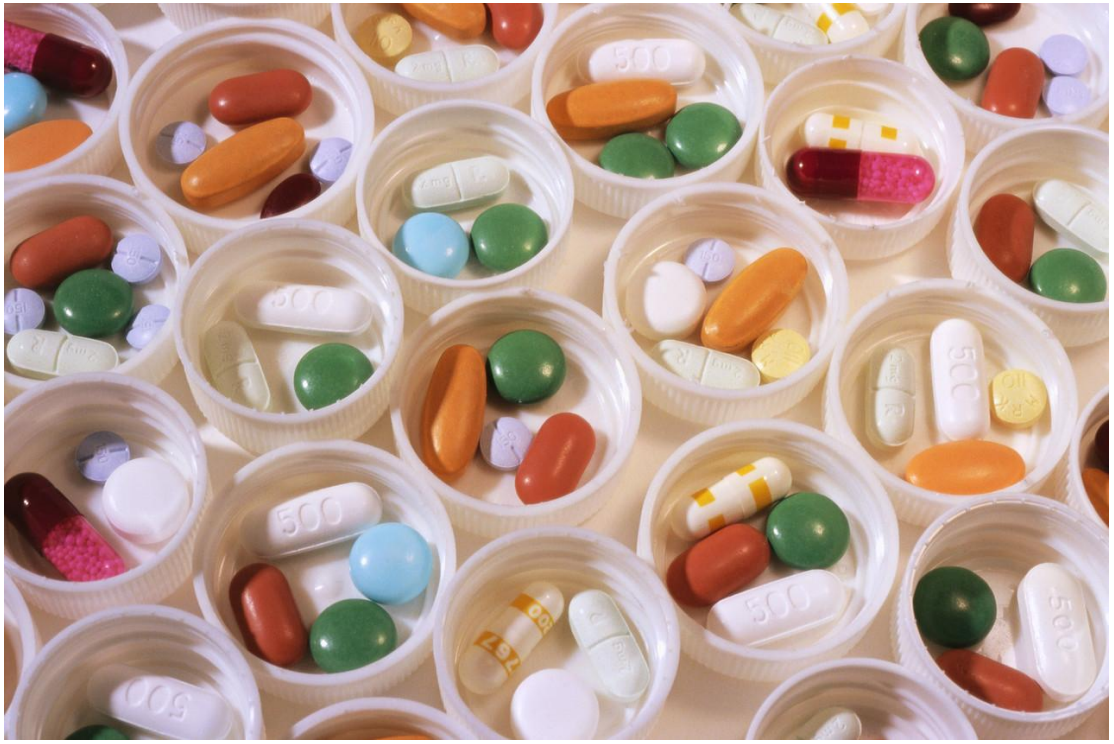
N Engl J Med 2009;361:2241-51.

Evidence-based treatment of systolic heart failure

NYHA class II-III: Mild-moderate symptoms



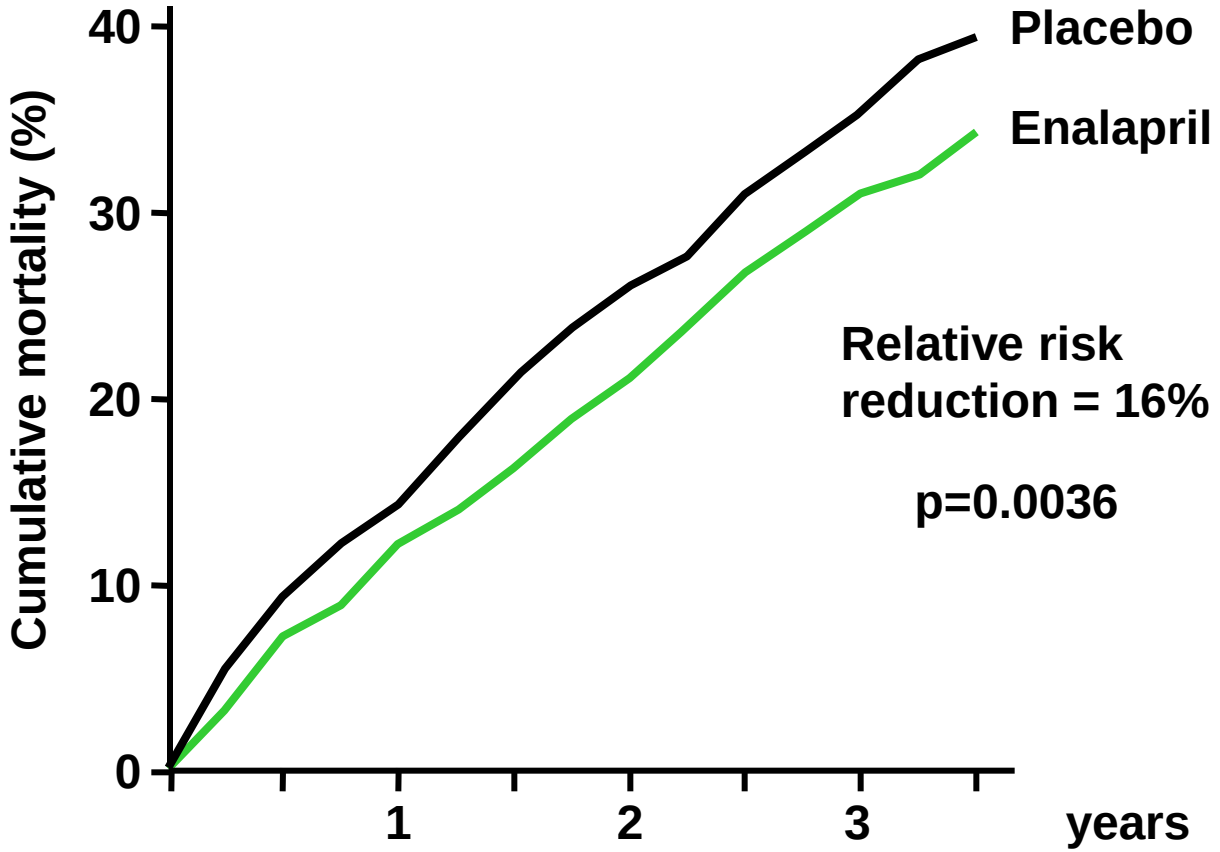
Pharmacotherapy



SOLVD Treatment Trial

Studies of Left Ventricular Dysfunction

2569 patients, NYHA class II-IV, LVEF ≤0.35. Diuretic 85%, digoxin 67%.
Followed for a mean of 41 months

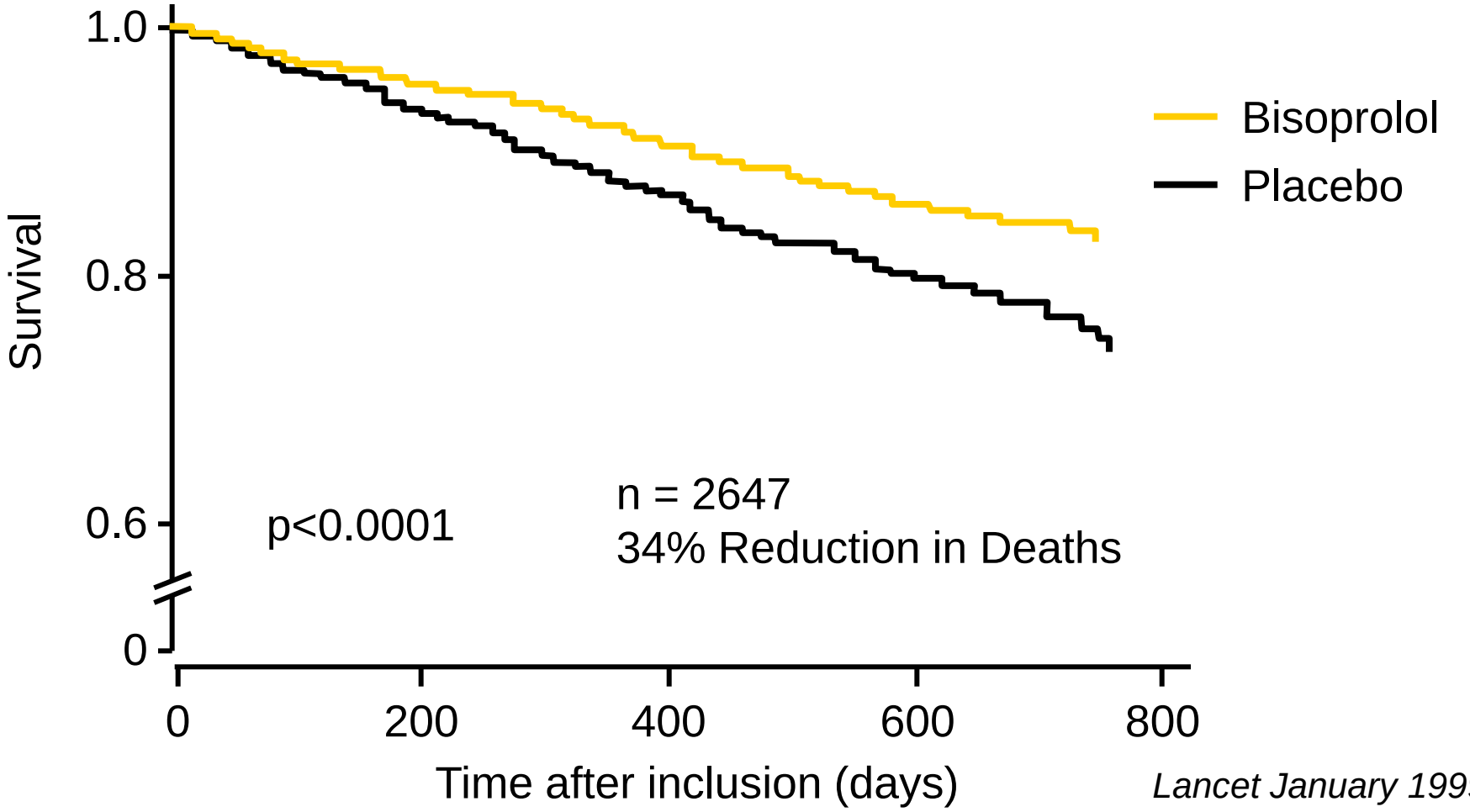


SOLVD Investigators NEJM 1991

CIBIS 2

Cardiac Insufficiency Bisoprolol Study 2

2647 patients, NYHA class III/IV, LVEF ≤0.35. Diuretic 99%, digoxin 52%, ACEi 96%. Followed for a mean of 1.3 years.

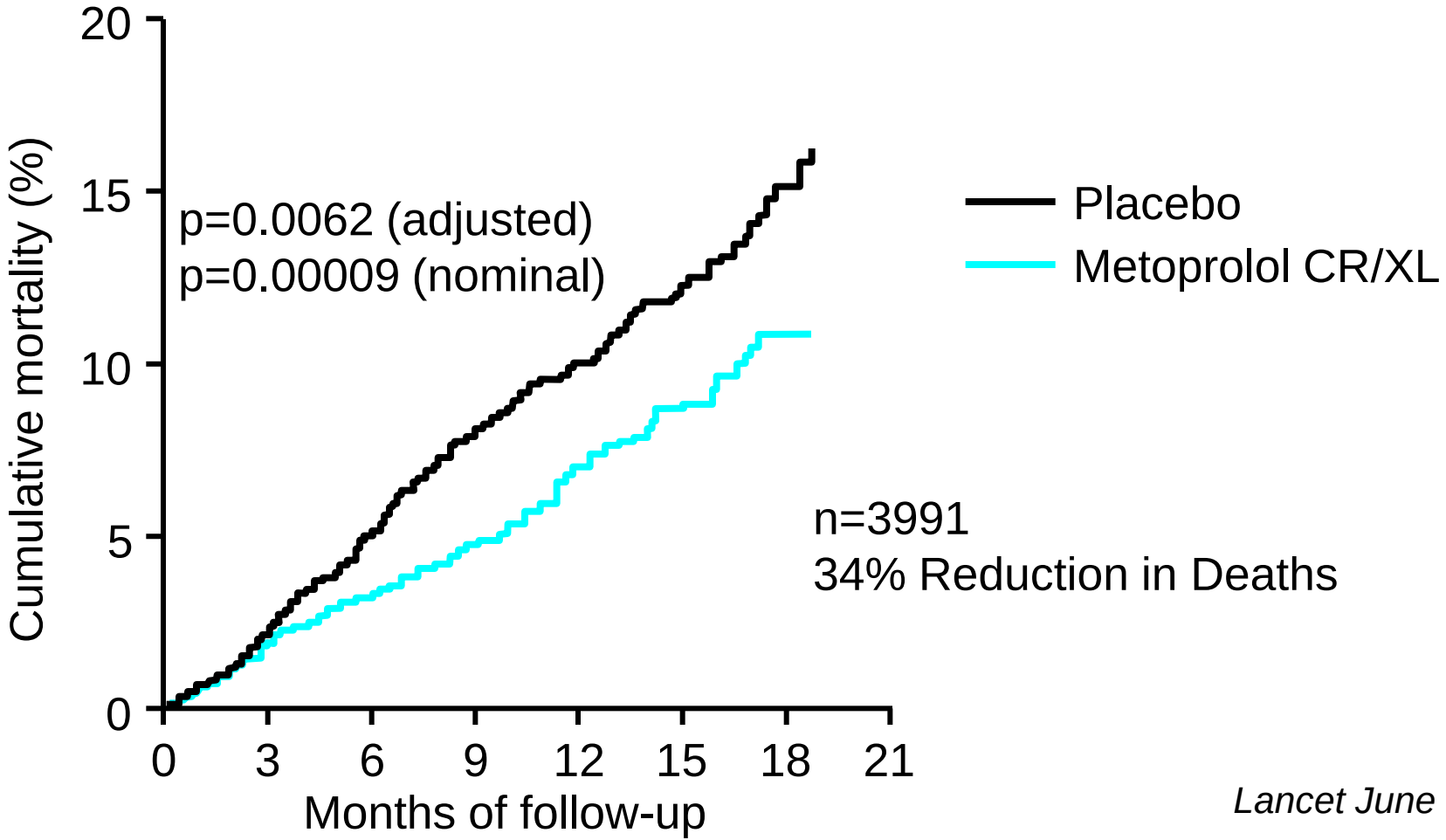


Lancet January 1999

MERIT HF

Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure

3991 patients, NYHA class II-IV, LVEF ≤0.40. Diuretic 91%, digoxin 64%, ACEi/ARB 96%. Followed for a mean of 12 months

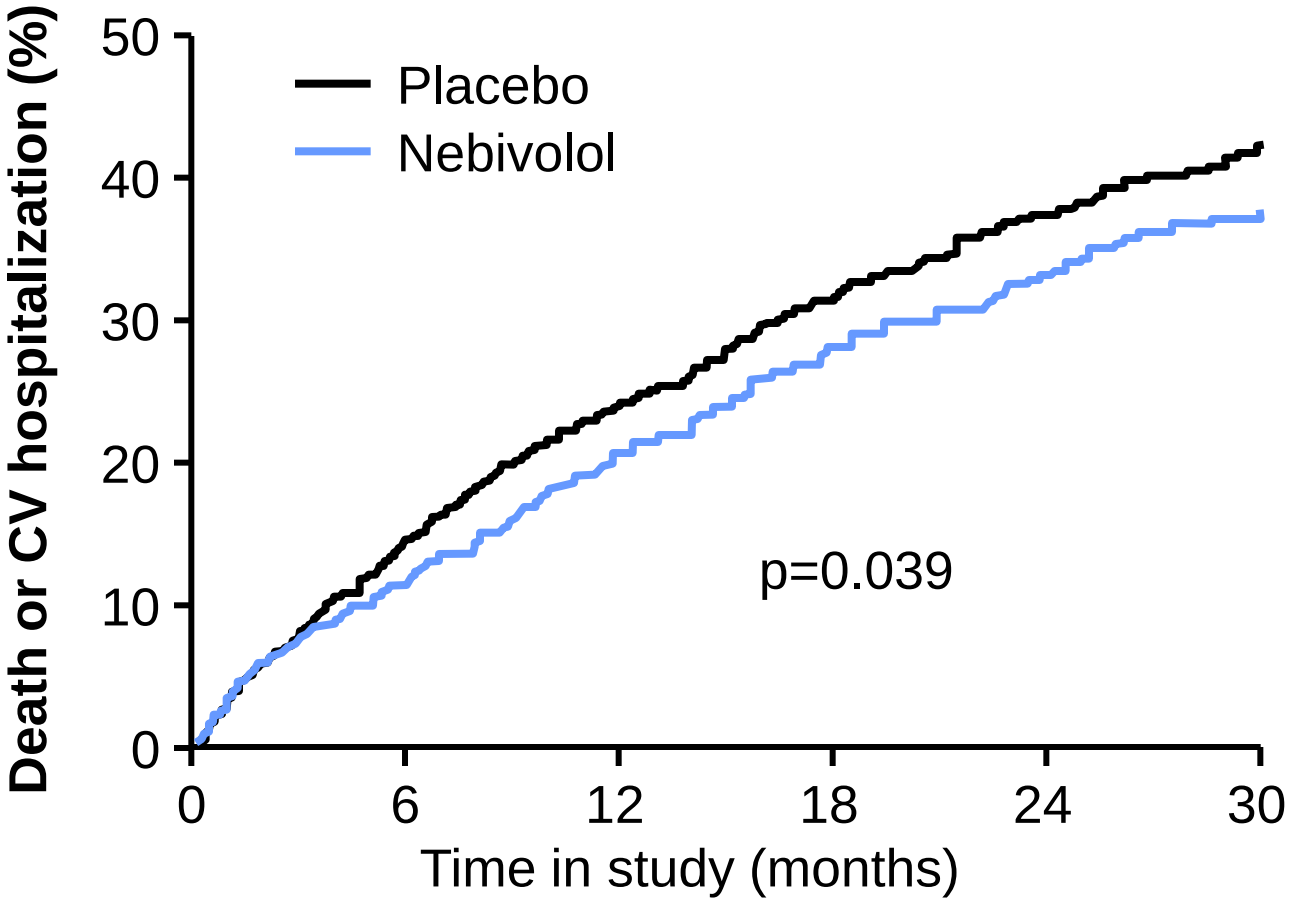


Lancet June 1999

SENIORS

Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure

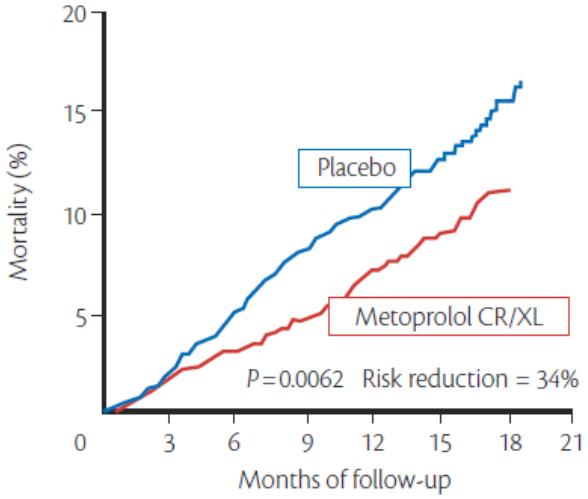
2128 patients ≥70 yrs with prior HF hospitalization or LVEF ≤0.35
Followed for a mean of 21 months



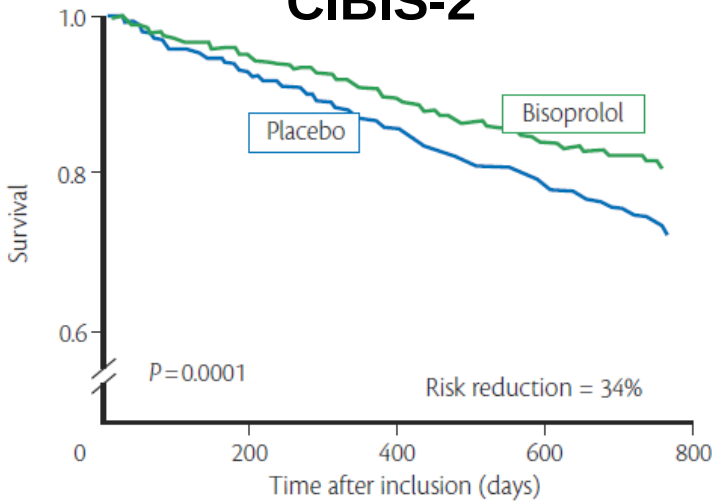
Flather et al. Eur Heart J 2005;26:215-25

Beta-blockers are the most evidence-based therapy in heart failure

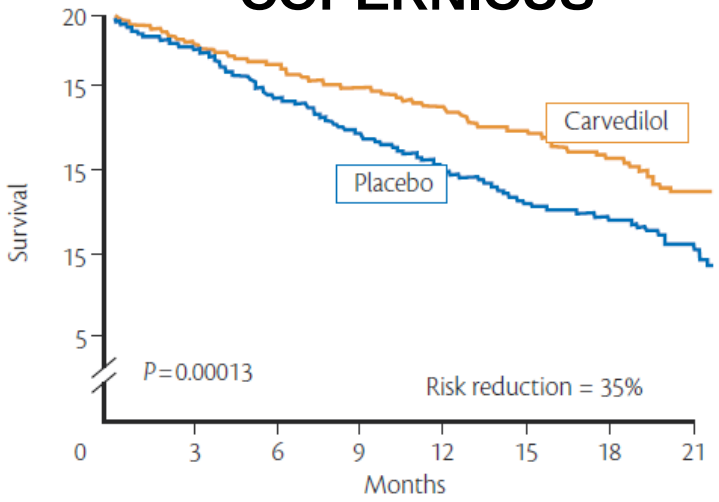
MERIT-HF



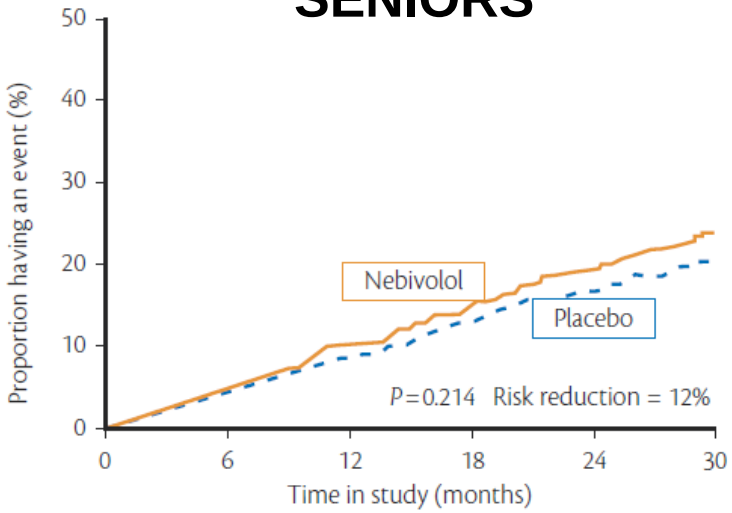
CIBIS-2



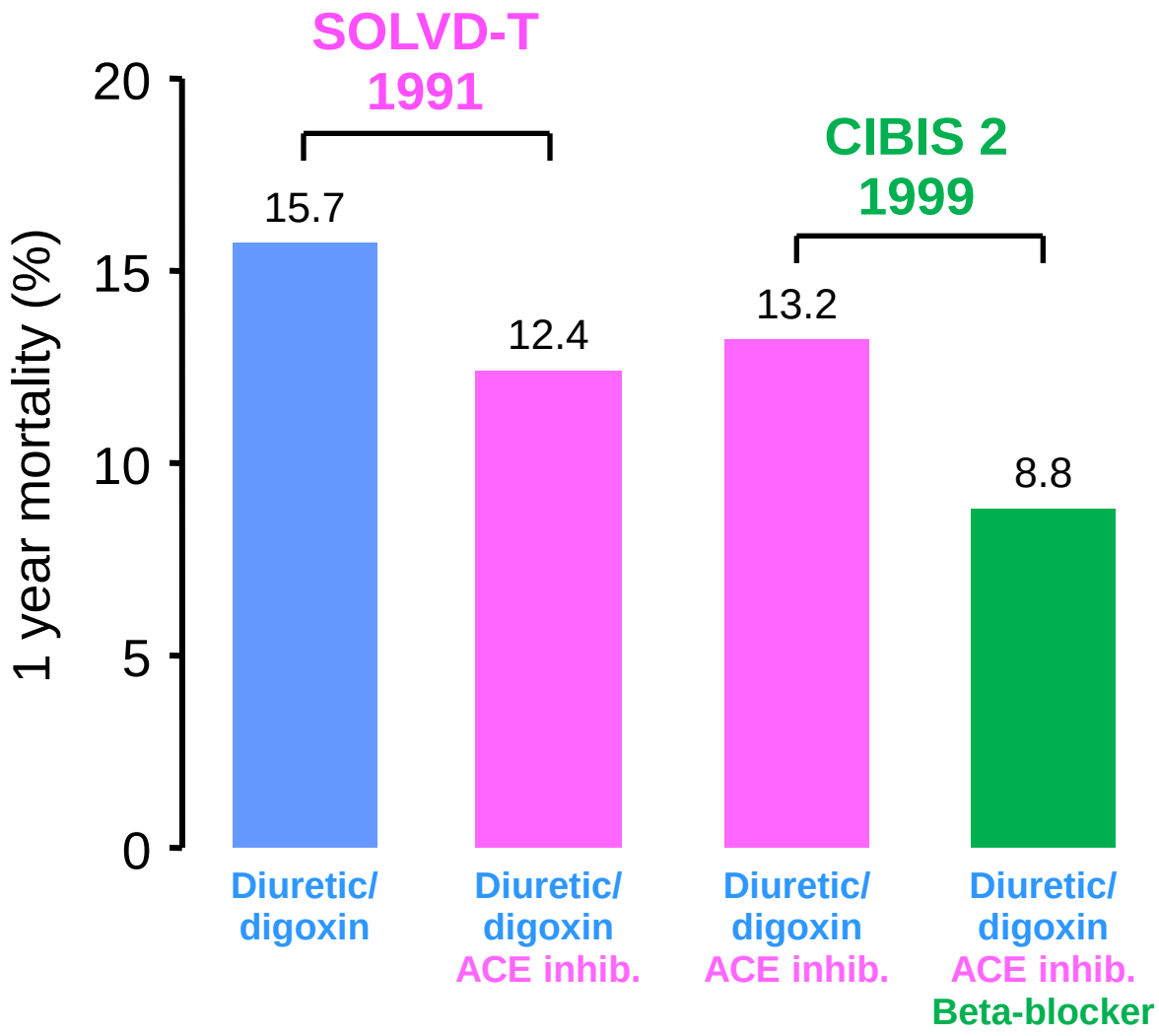
COPERNICUS



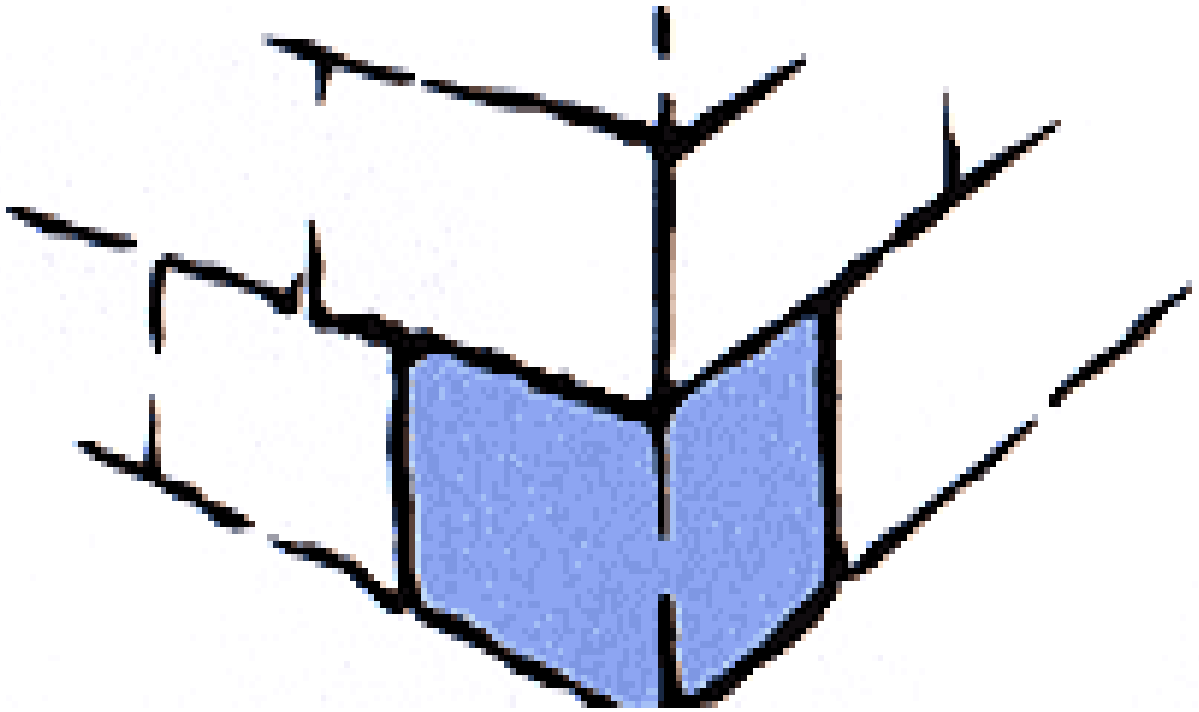
SENIORS



The stunning success of ACE inhibitors and beta blockers in mild-moderate HF



The cornerstone of therapy



ACE inhibitor (or ARB)
Beta-blocker

Can we do even better?

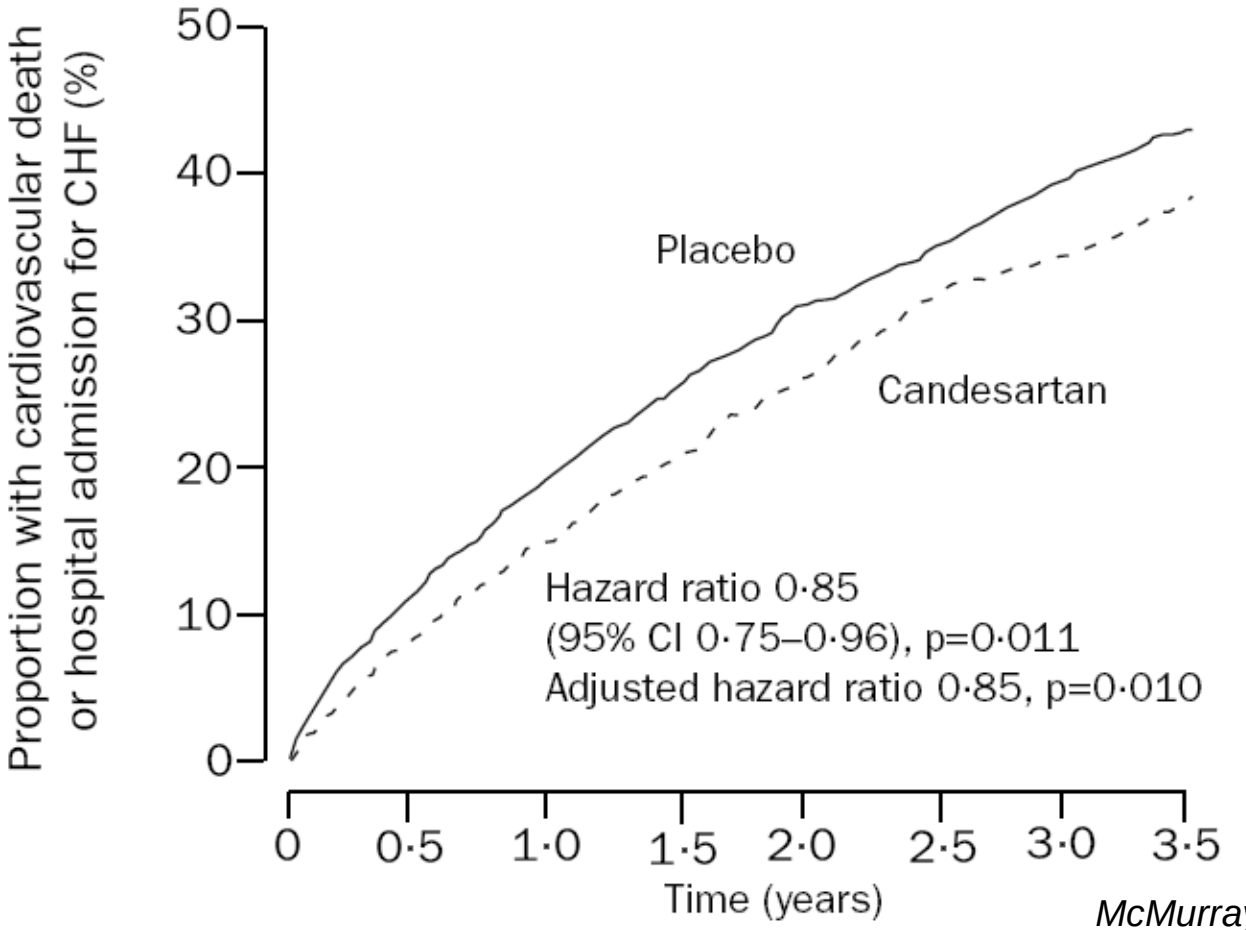
Adding to an ACE inhibitor:

- **Angiotensin receptor blocker?**
- **Sinus node inhibitor?**
- **Aldosterone antagonist?**

CHARM-Added

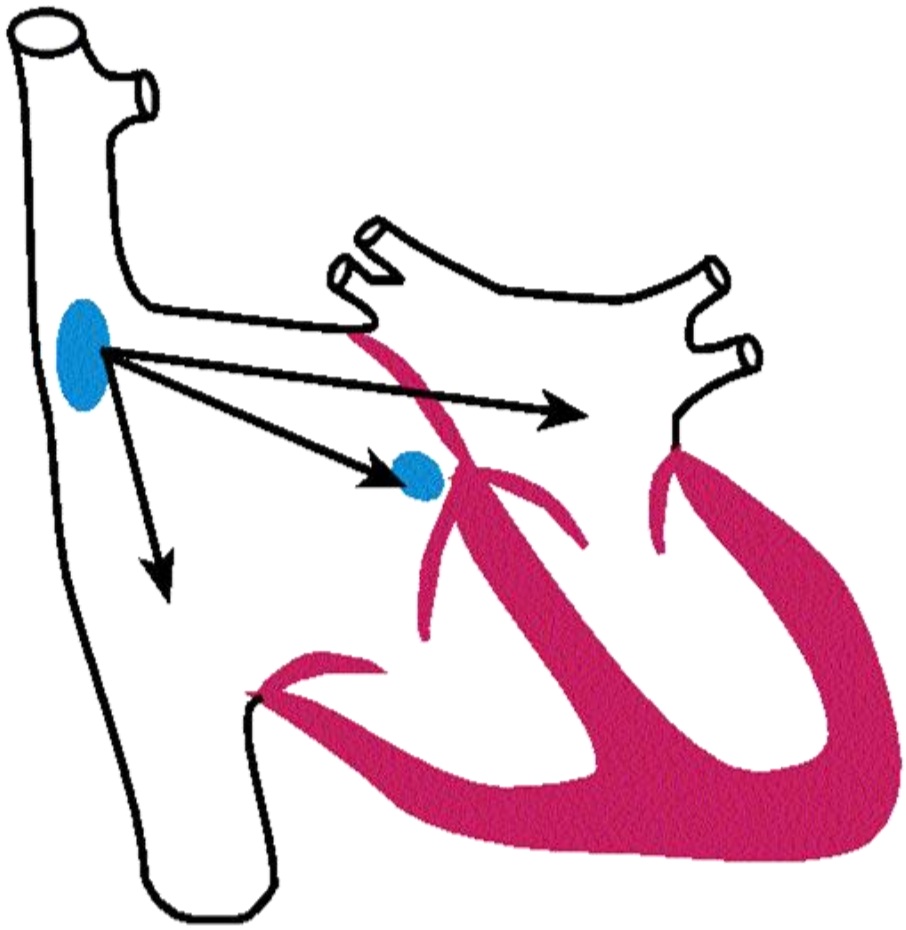
Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity

2548 patients, NYHA class II-IV, LVEF ≤0.40. Diuretic 90%, digoxin 59%, ACEi 100%; β-blocker 56%, spironolactone 17%.Followed a median of 41 months.



McMurray et al Lancet 2003

Sinus node inhibition

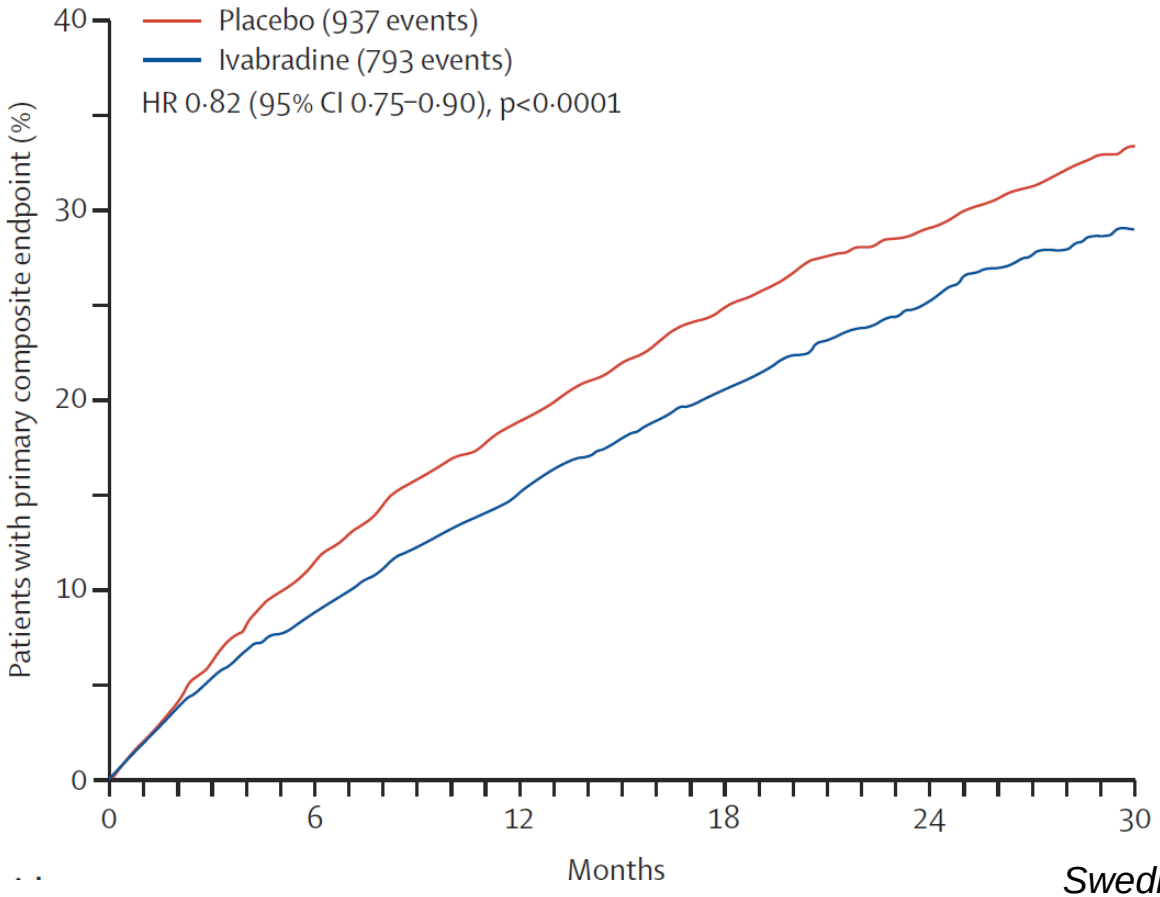


I_f current inhibition with ivabradine

SHIFT

Systolic Heart failure treatment with the *If* inhibitor ivabradine Trial

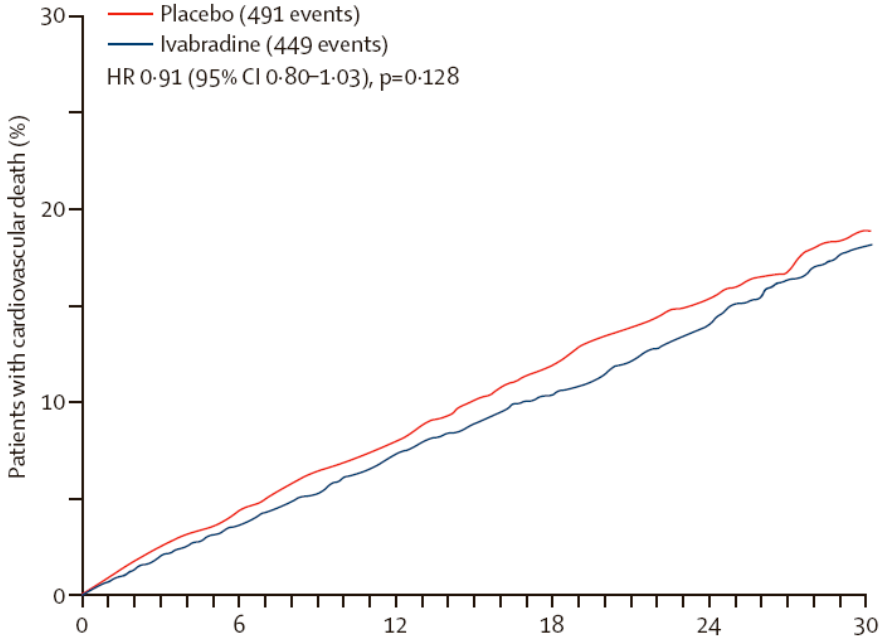
6558 patients, NYHA class II-IV, LVEF ≤0.35, HF hosp. within 1 year, sinus rhythm, HR ≥70/min. Diuretic 84%, digoxin 22%, ACEi 79%/ARB 14%, β-blocker 90%, aldo. antagonist 60%. Followed for a median of 23 months



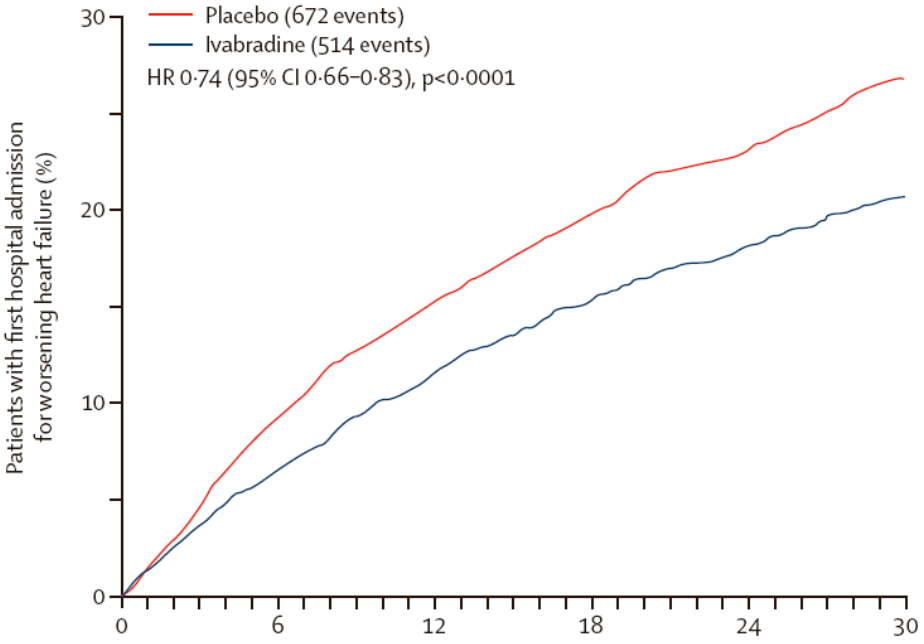
Swedberg et al Lancet 2010

SHIFT: Components of primary endpoint

Cardiovascular death



HF hospitalization



Months of follow-up

SHIFT: The problem in interpretation

	Ivabradine group (n=3241)	Placebo group (n=3264)
Mean daily dosage of β blocker (mg)		
Carvedilol	25.0	25.0
Bisoprolol	6.2	6.2
Metoprolol succinate	90.2	89.5
Metoprolol tartrate	66.8	71.2
Nebivolol	5.9	5.9
Patients at target dose of β blocker	26%	26%
Patients at ≥ 50% target dose of β blocker	56%	56%

What effect will SHIFT have on clinical practice?

THE LANCET

Comment

Ivabradine in heart failure—no paradigm SHIFT...yet

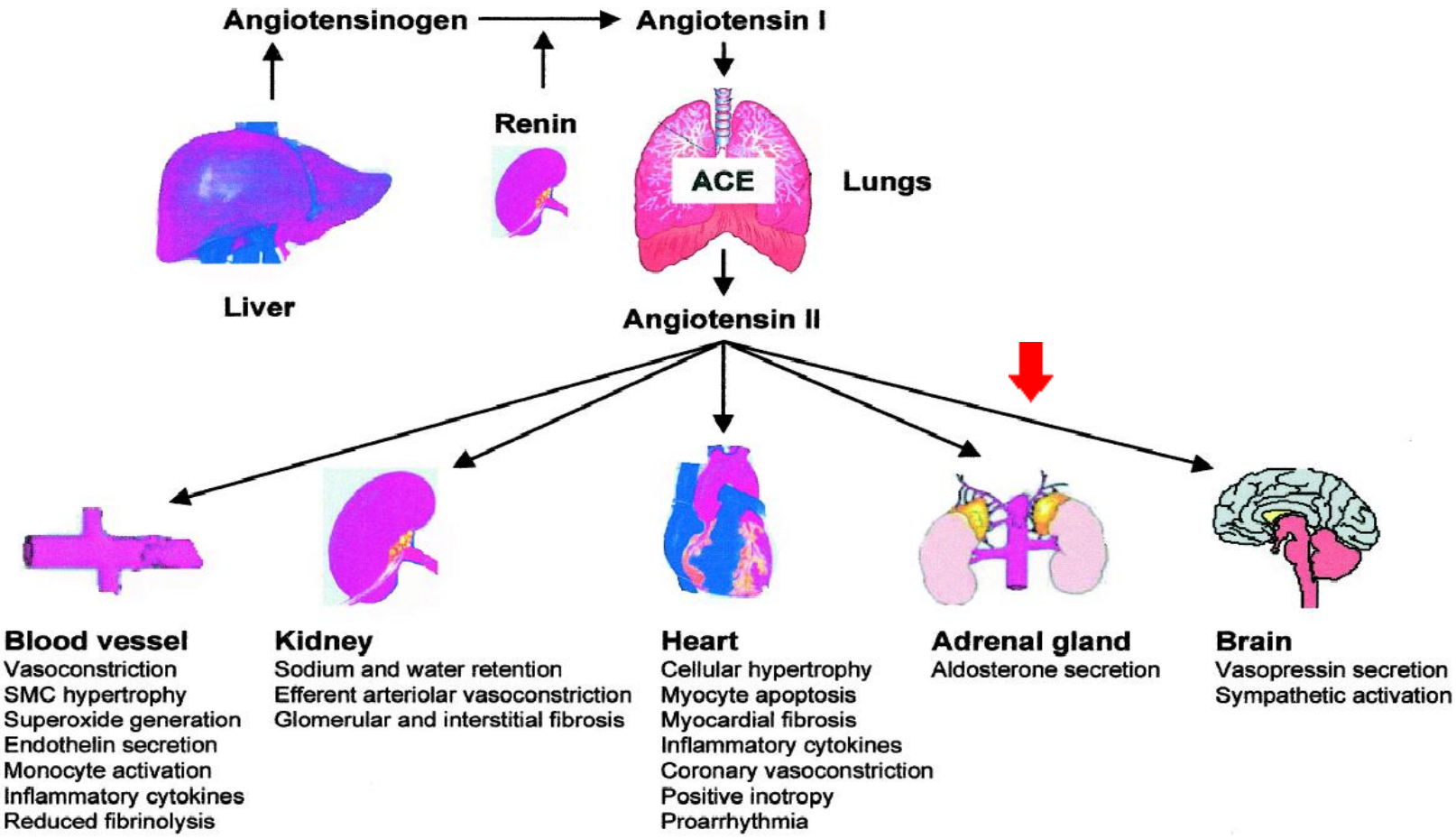
Wisely and slowly, they stumble that run fast

William Shakespeare (Romeo and Juliet, Act II, Scene iii)

In *The Lancet* today, investigators provide support for Shakespeare's admonishment, in two articles from the Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT).[1,2] The investigators randomised baseline heart rates (<77 beats per min). Ivabradine was well tolerated with relatively few, although statistically significant, mechanism-related adverse events, such as bradycardia, atrial fibrillation, and visual disturbances. The accompanying analyses from the second SHIFT report[2] showed a proportional relation between baseline heart rate and subsequent outcomes in the placebo-

John Teerlink

Is aldosterone antagonism beneficial in mild HF?

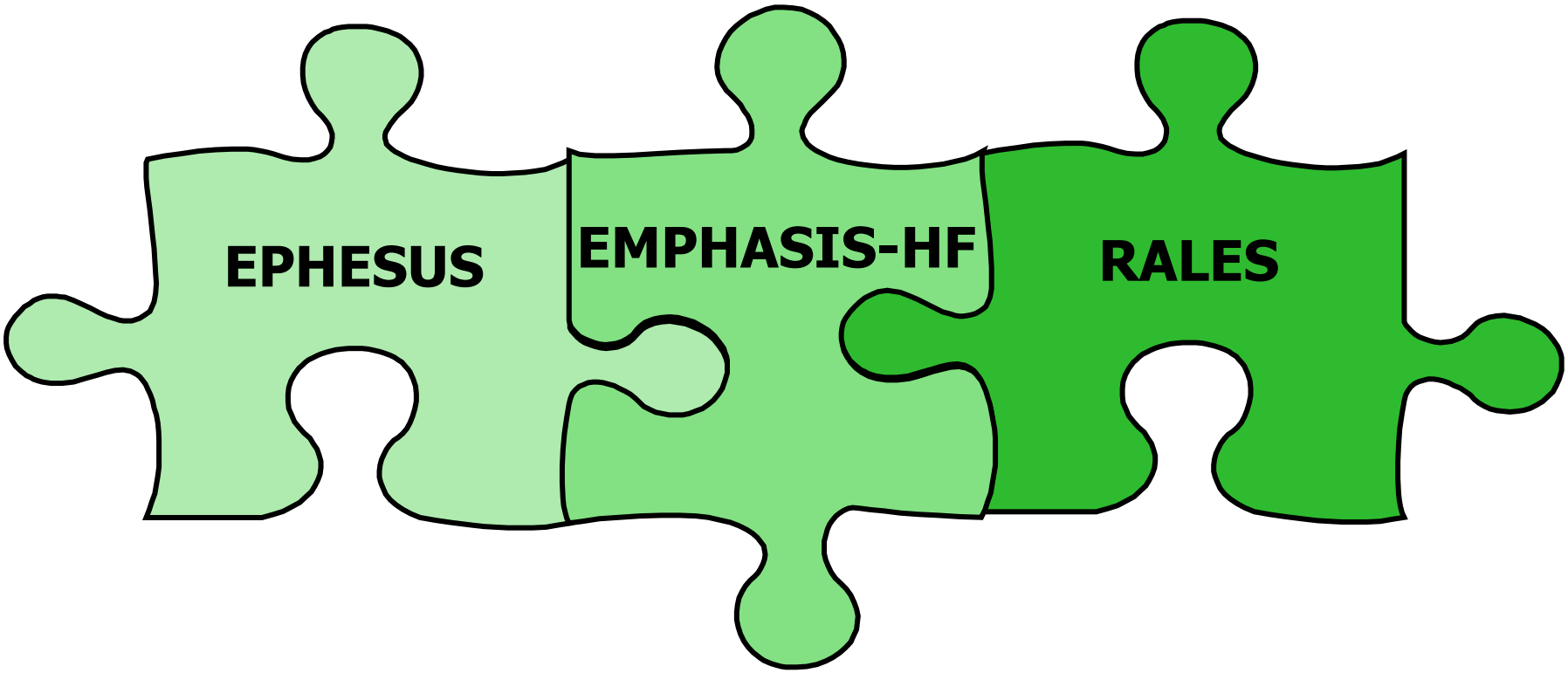


The missing piece of the aldosterone-antagonist jigsaw

LVSD and HF/ diabetes after AMI

Mild HF symptoms (NYHA class II)

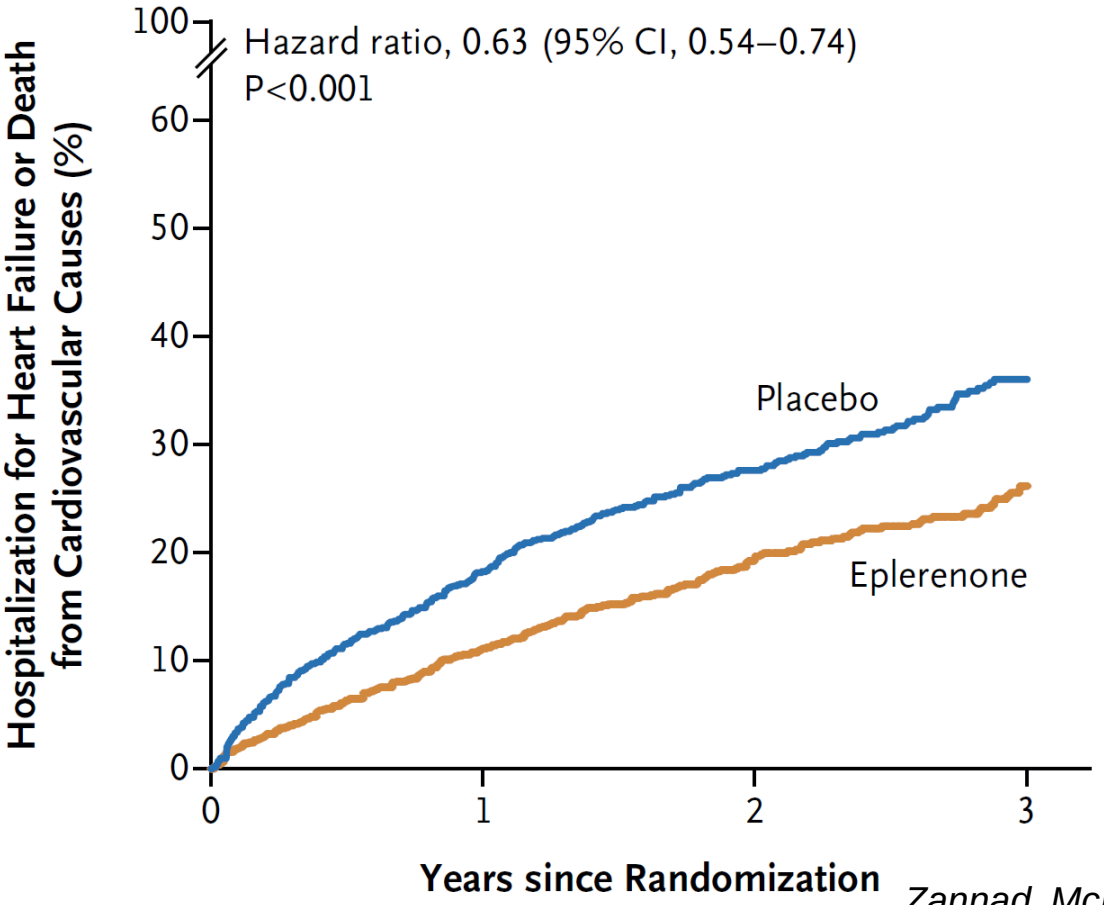
Severe HF symptoms (NYHA class III/IV)



EMPHASIS-HF

Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure

2737 patients, ≥55 years, NYHA class II, with CV hospitalization within 6 months (or elevated BNP/NT pro BNP) and LVEF ≤0.30 (or ≤0.35 if QRS duration >130msec. Followed for a median of 21 months

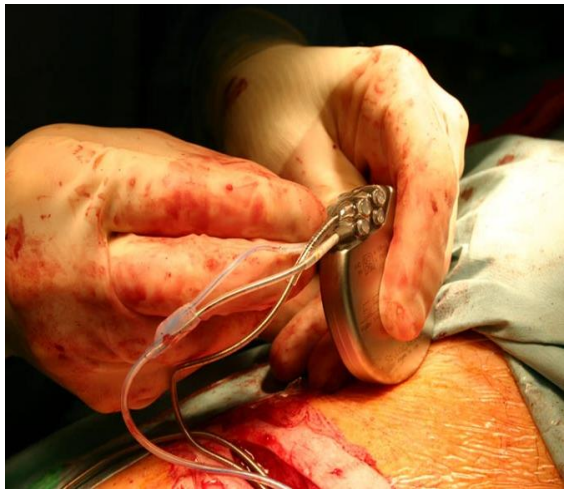


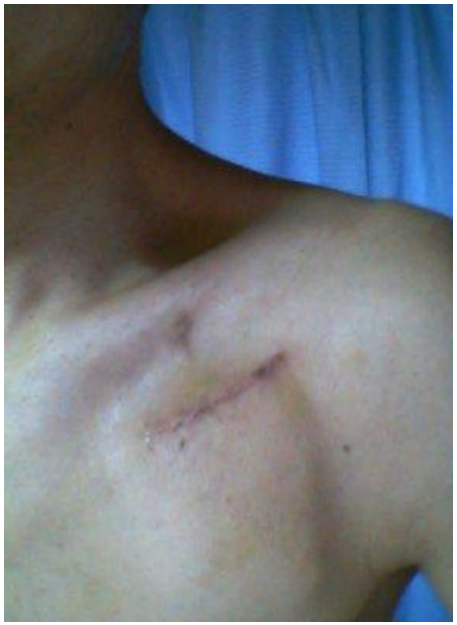
Zannad, McMurray et al NEJM 2011

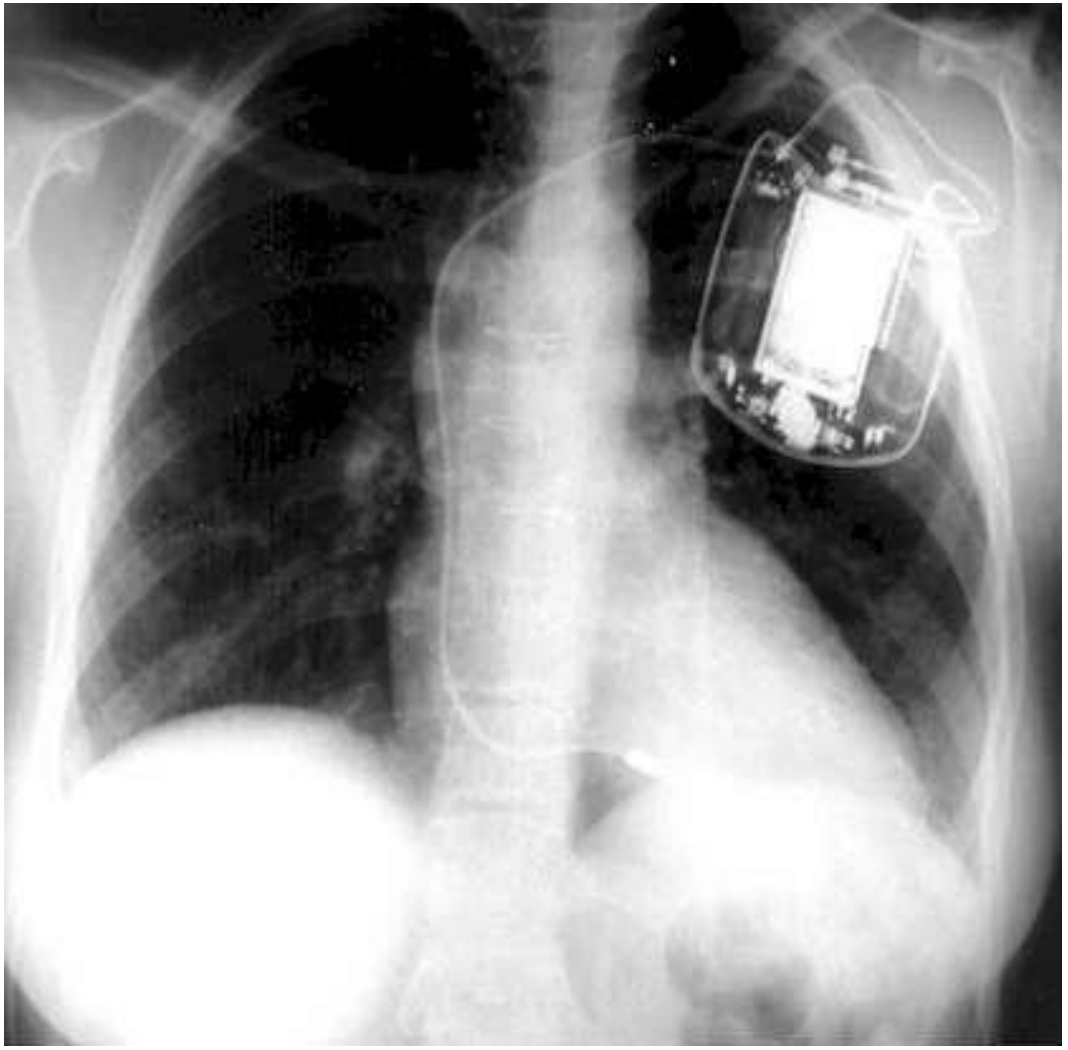
EMPHASIS-HF: Other outcomes

Endpoint	Hazard ratio (95% CI)	P value
All-cause death	0.76 (0.62-0.93)	0.008
Cardiovascular death	0.76 (0.61-0.94)	0.01
All-cause death or HF hospitalization	0.65 (0.55-0.76)	<0.001
All-cause death or all-cause hospitalization	0.75 (0.66-0.85)	<0.001
HF hospitalization	0.58 (0.47-0.70)	<0.001

Devices



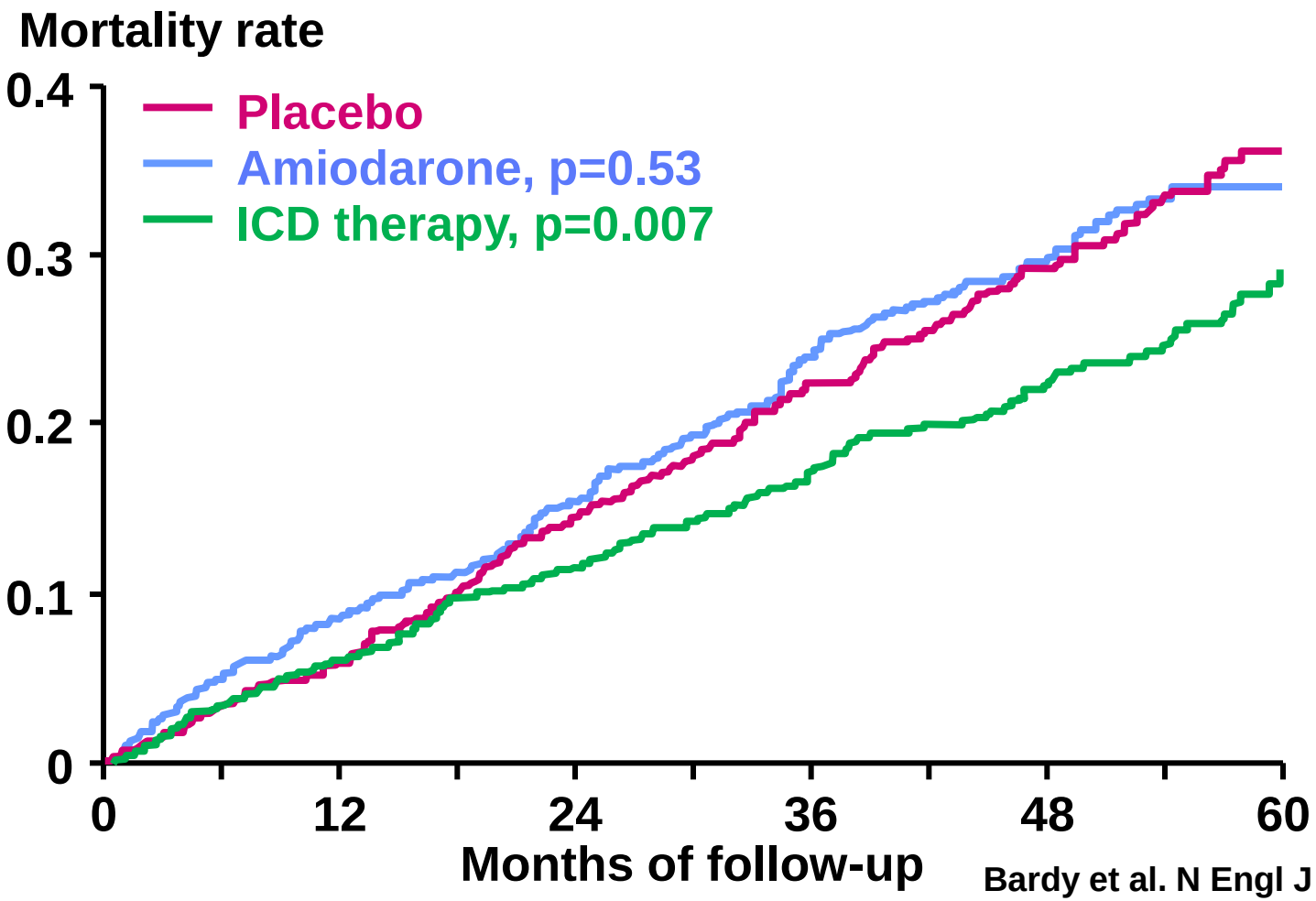




SCD-HeFT

Sudden Cardiac Death in Heart Failure Trial

2521 patients with LVEF ≤0.35 and NYHA class II-III HF
Followed for a median of 45.5 months



Bardy et al. N Engl J Med 2005;352:225-37

Can we do even better than optimal medical therapy and an ICD?

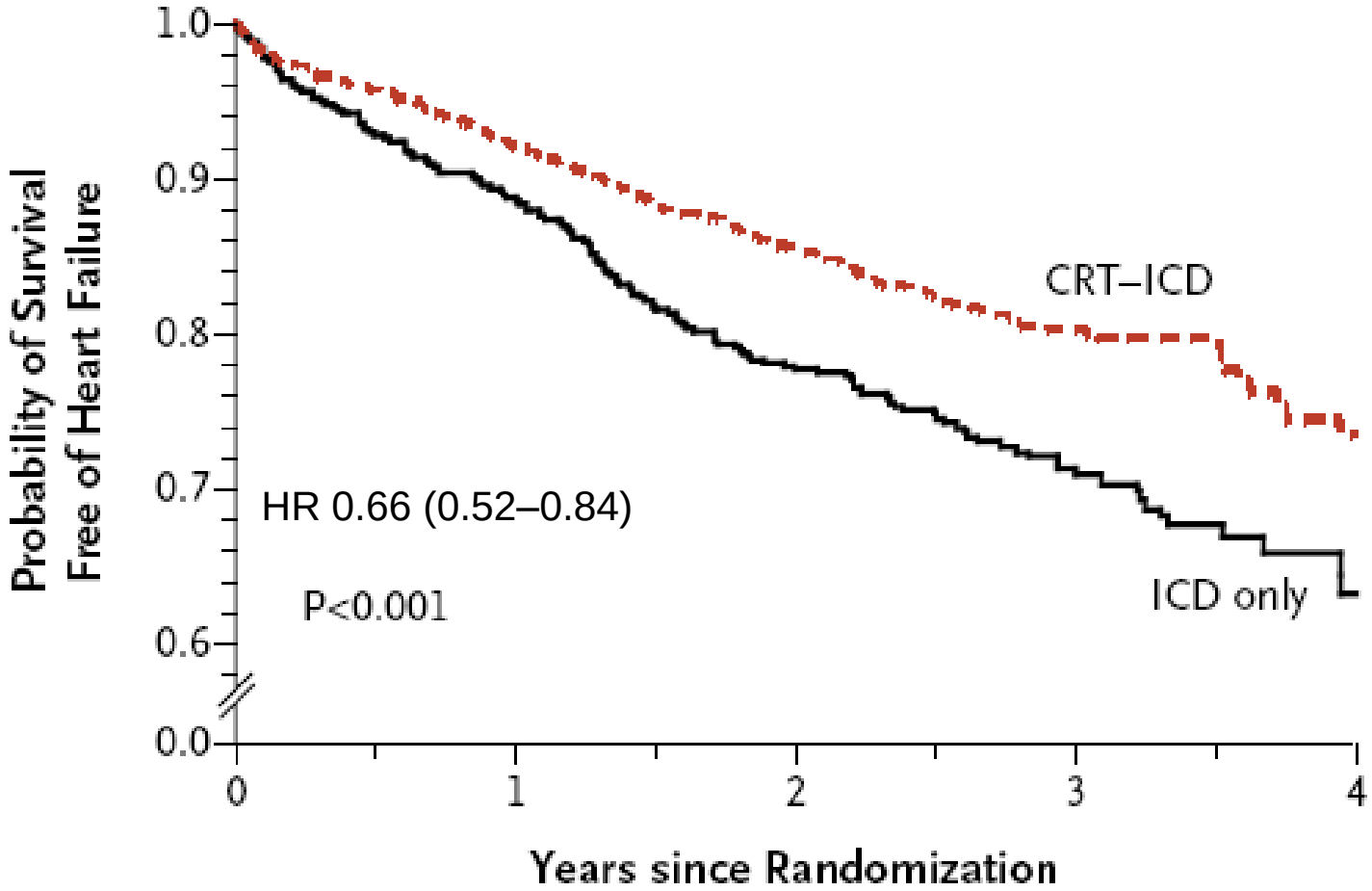
Adding CRT to OMT and an ICD:

- **MADIT-CRT**
- **RAFT**

MADIT-CRT

Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy

1820 patients with LVEF ≤0.30, NYHA class I-II HF, sinus rhythm and QRS duration ≥120 ms. Followed for a median of 2.4 yr (stopped early). Randomized 3:2 CRT+ICD vs ICD.



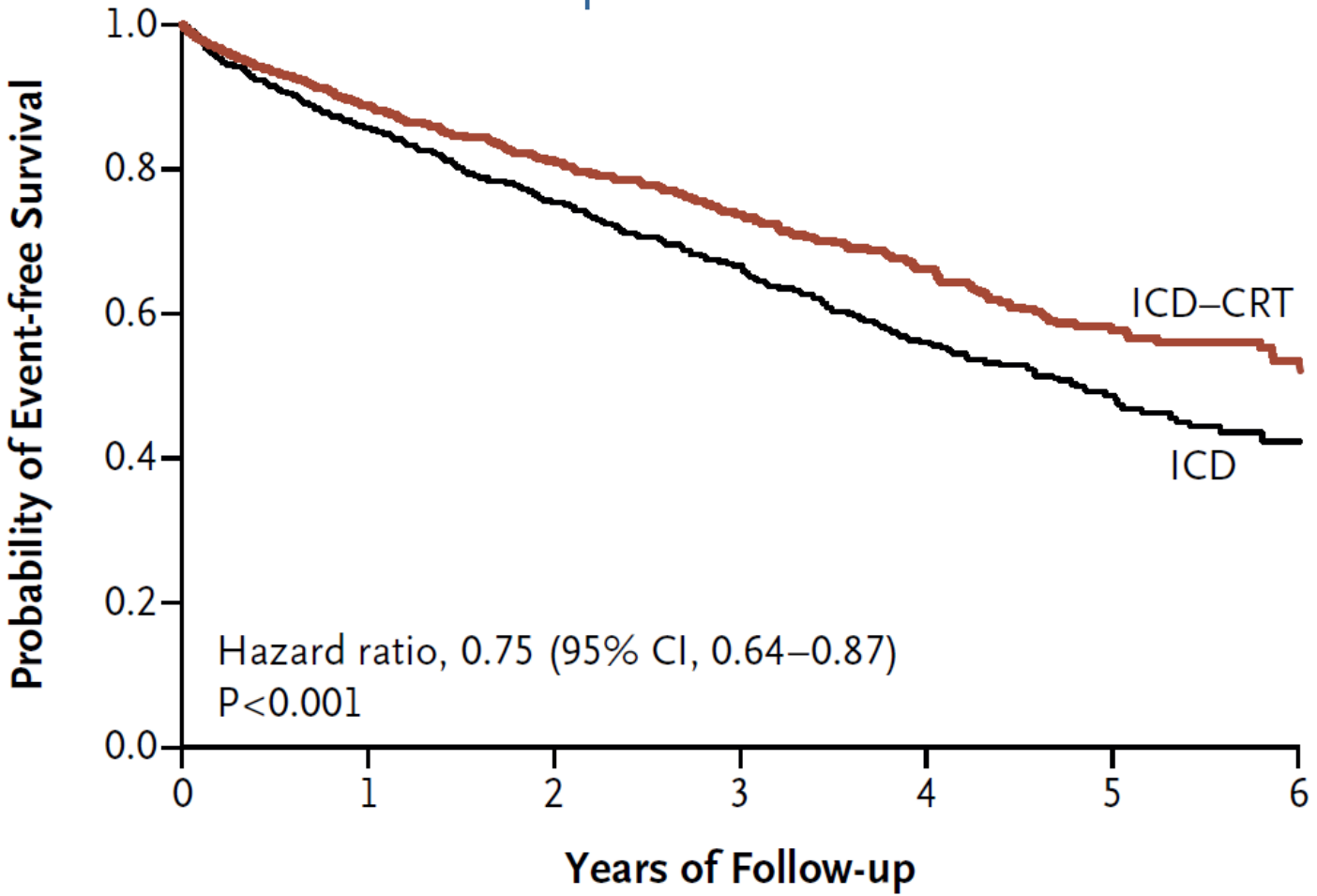
MADIT-CRT: components of primary endpoint

Endpoint	Hazard ratio (95% CI)	P value
Death or heart failure	0.66 (0.52-0.84)	0.001
Heart failure only	0.59 (0.47-0.74)	<0.001
Death at any time	1.00 (0.69-1.44)	0.99

RAFT

Resynchronization–Defibrillation for Ambulatory Heart Failure Trial

1798 patients with LVEF ≤0.30, NYHA class II-III HF, sinus rhythm and QRS duration ≥120 ms. Followed for median of 3.3 yr. Primary outcome death or HF hospitalization



RAFT: Secondary outcomes

Endpoint	Hazard ratio (95% CI)	P value
Death from any cause	0.75 (0.62-0.91)	0.003
Death from cardiovascular cause	0.76 (0.60-0.96)	0.02
Hospitalization for heart failure	0.68 (0.56-0.83)	<0.001

MADIT-CRT and RAFT: Sub-group analyses

- **Both trials showed an interaction between sex, QRS durationa and QRS morphology and effect of CRT**

- **More benefit in: women (vs. men), QRS ≥150 msec (vs. <150 msec) and LBBB (vs. RBBB)**

What's in the pipeline?

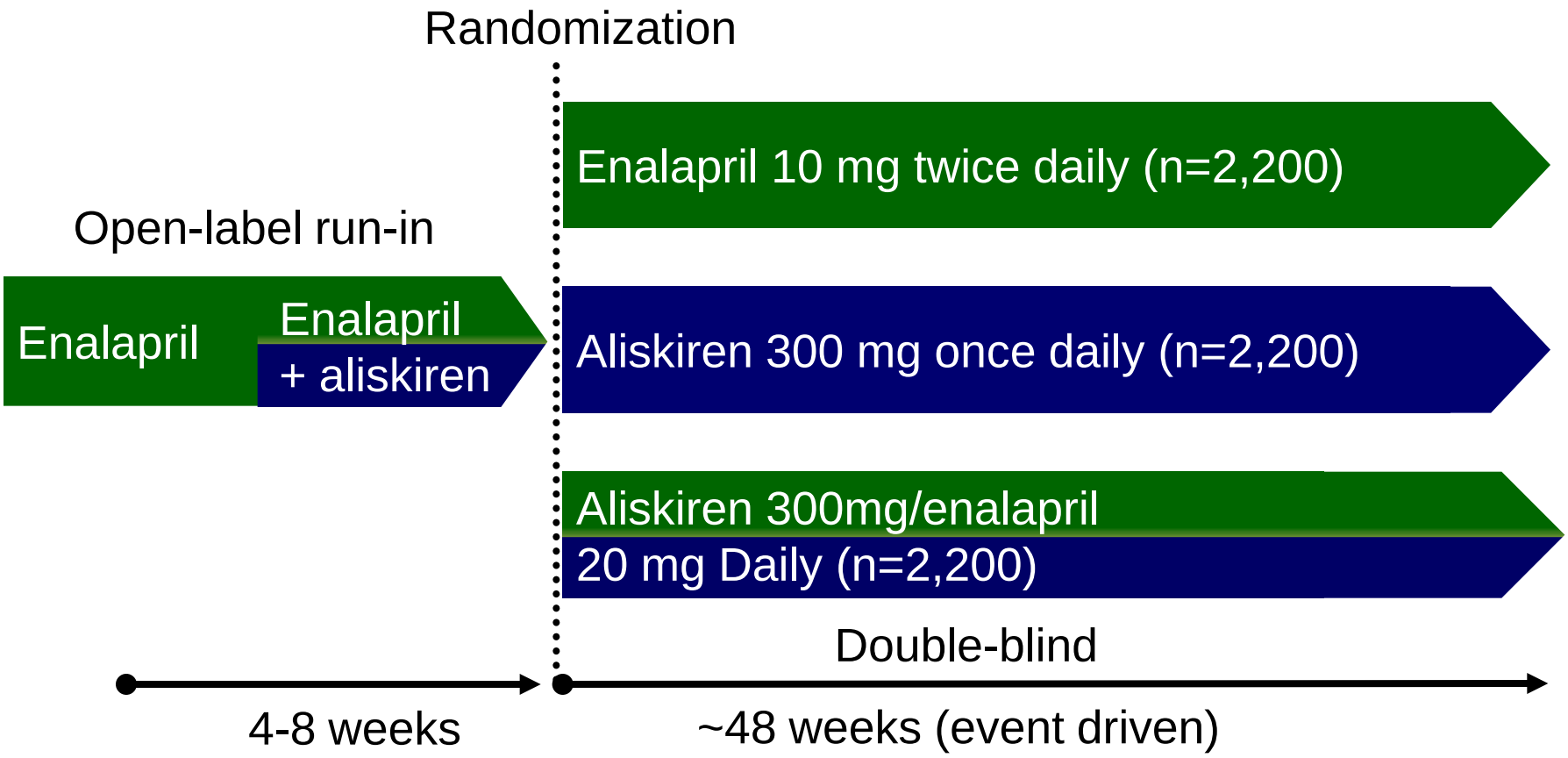
- Chronic HF with low LVEF
- Chronic HF with preserved LVEF (HF-PEF)
- Acute HF

Focus on ongoing large-scale mortality/morbidity outcome studies

Can we beat an ACE inhibitor? ATMOSPHERE: design overview

Primary outcome: CV death or heart failure hospitalization

(event driven: 2162 patients)



LCZ 696: an Angiotensin Receptor Neprilysin inhibitor (ARNi)

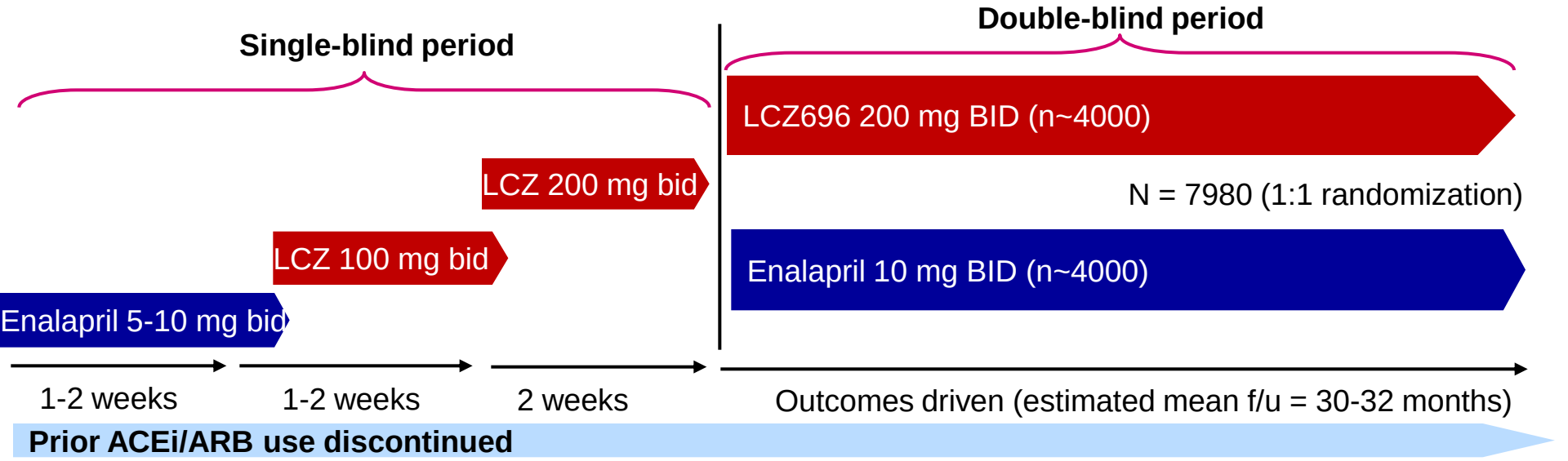
Molecular complex of:

- **An ARB - valsartan**
- **A NEP/neprilysin inhibitor – AHU 377**

NEP inhibition blocks breakdown of natriuretic peptides and augments plasma concentrations

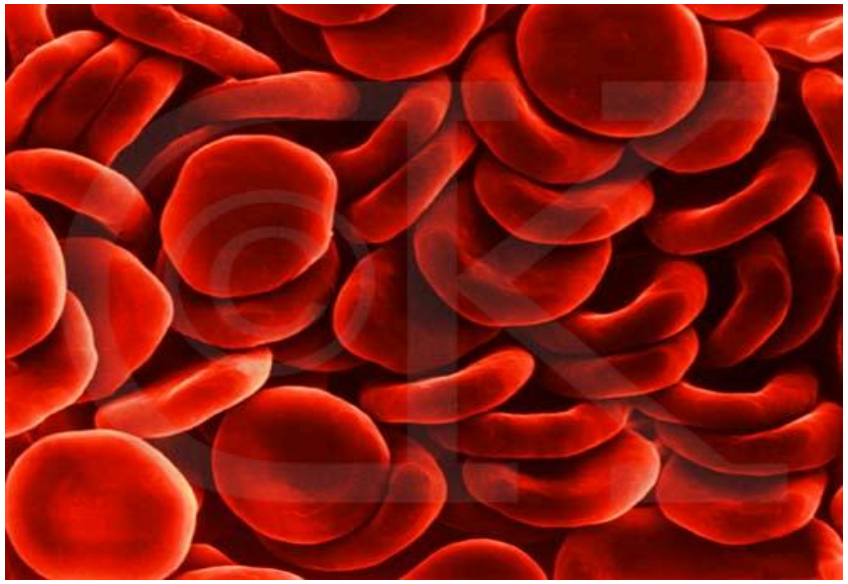
PARADIGM-HF

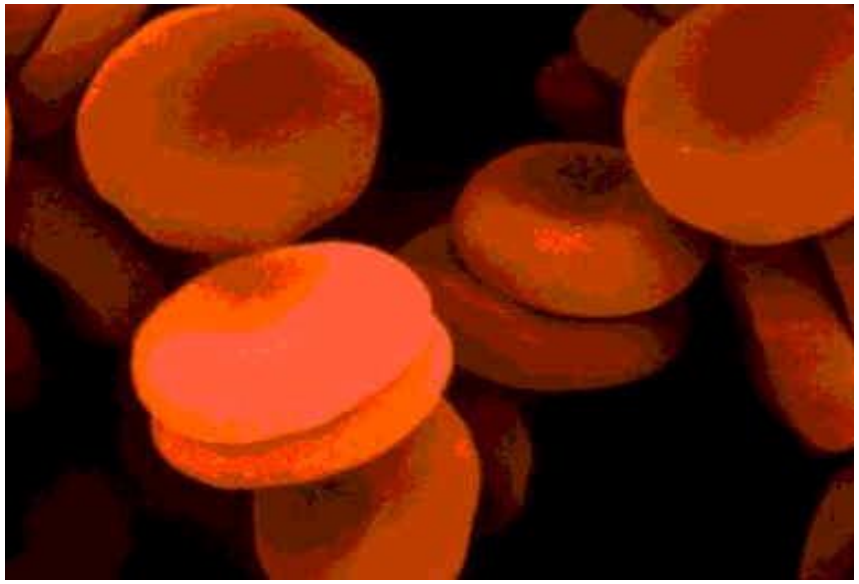
A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction



Primary objectives	Evaluate if LCZ696 is superior in delaying time to first occurrence of either **CV mortality or HF hospitalization** in CHF pts (NYHA Class II – IV) with reduced ejection fraction
Secondary objectives	▪ All cause mortality ▪ Renal progression (eGFR change) ▪ Clinical summary score (assessed by KCCQ)
Patient population	• 7980 patients with CHF NYHA class II – IV and reduced ejection fraction (LVEF < 40%) • BNP>150 pg/ml (NTproBNP > 600 pg/ml) or BNP > 100 pg/ml (NTproBNP > 400 pg/ml) and hospitalization within the last 12 months

RED-HF: Treating anaemia in HF





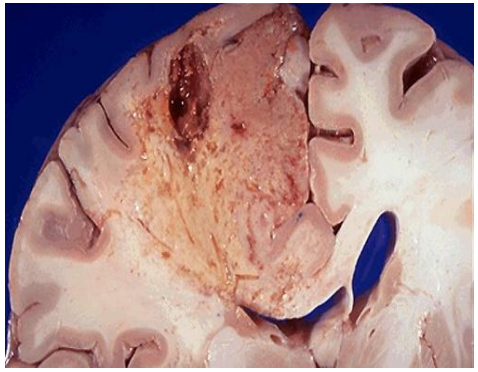
Treating anaemia in HF with an ESP (darbepoetin)?

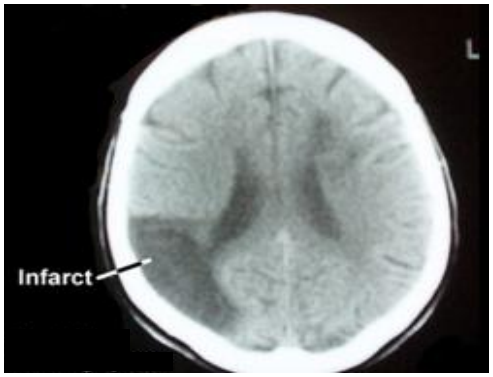
RED-HF

Reduction of Events with Darbepoetin alfa in Heart Failure

- **Hypothesis:** Darbepoetin will improve outcomes in patients with HF and anaemia
- **Population:** 3400 patients with LVEF ≤0.35 and NYHA class III-IV HF/class II and CV admission/ER visit within 12 months
- **Anaemia:** Hb ≥9.0 g/dL and ≤12.0 g/dL
- **Intervention:** Darbepoietin sc vs placebo; target Hb 13.0-14.5 g/dL
- **Primary endpoint:** Death or HF hospitalisation
- **Status:** Started summer 2006

WARCEF: HF and the risk of stroke



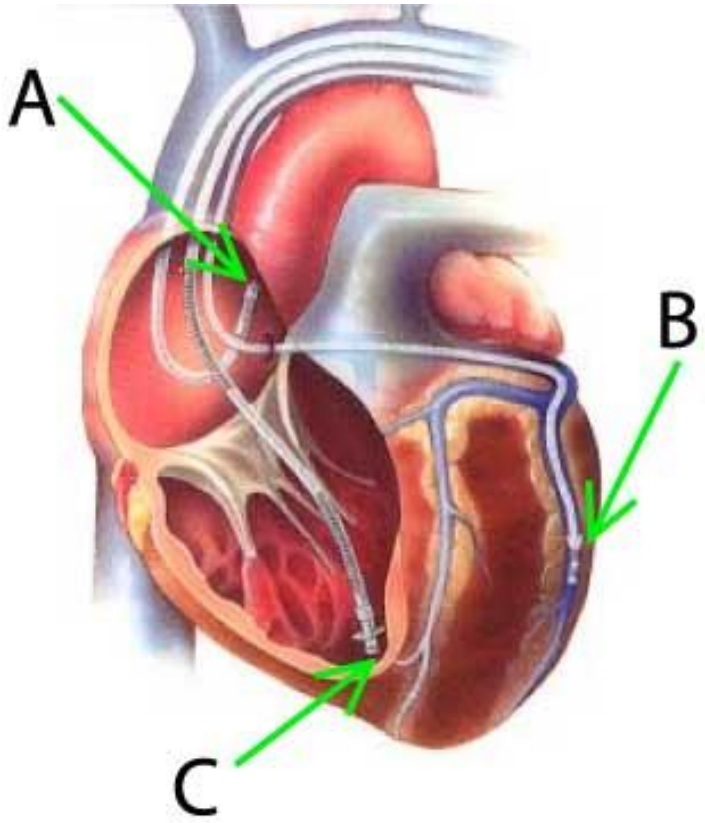


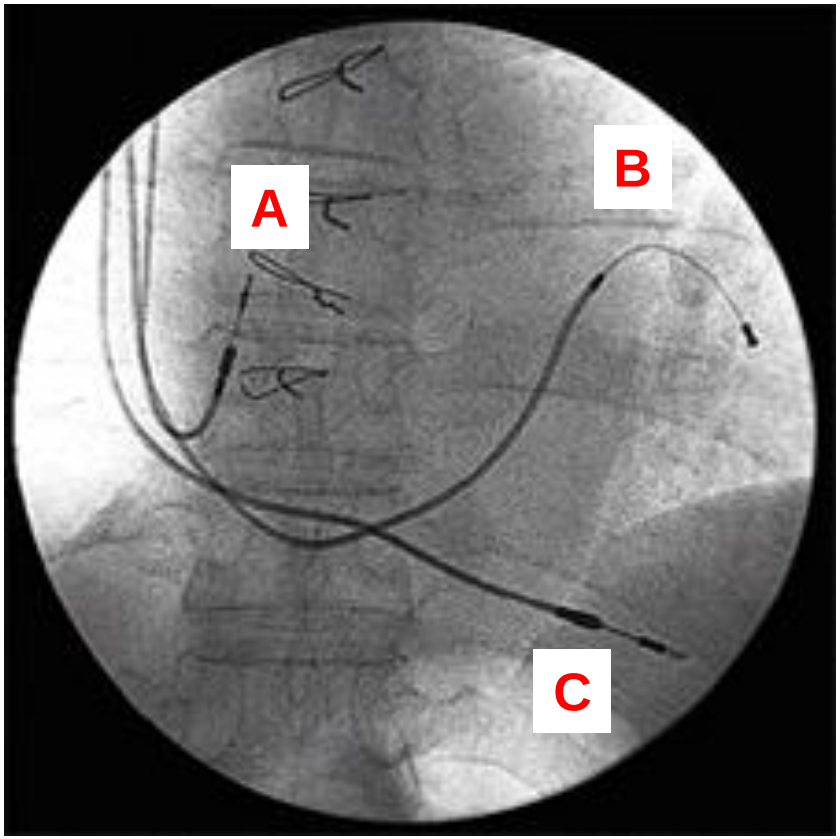
WARCEF

Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) Trial

- **Hypothesis: Which of two commonly used treatments warfarin or aspirin is better for preventing death and stroke in patients with low LVEF?**
- **Population: ~2860 patients NYHA I-IV with LVEF ≤35% and not in AF**
- **Intervention: Aspirin 325mg or warfarin (INR 2.5-3.0)**
- **Primary endpoint: Death or stroke**
- **Status: Recruitment started October 2002/estimated study completion 2012**

New CRT trials





BLOCK HF

- **Patients** — NYHA Class I-III, with advanced AV block, not currently indicated for CRT, LVEF ≤ 45%
- **Objective** — Assess whether biventricular pacing (BiV) will limit the clinical progression of heart failure when compared with atrial synchronous RV pacing
- **Primary endpoint** — Composite of mortality, morbidity & cardiac function
- **Size & Locations** — Up to 1,636 patients in up to 65 centers in North America
- **Study period** — Variable; Up to two interim analyses planned
- **Status** — Enrolling
- **Sponsor** — Medtronic

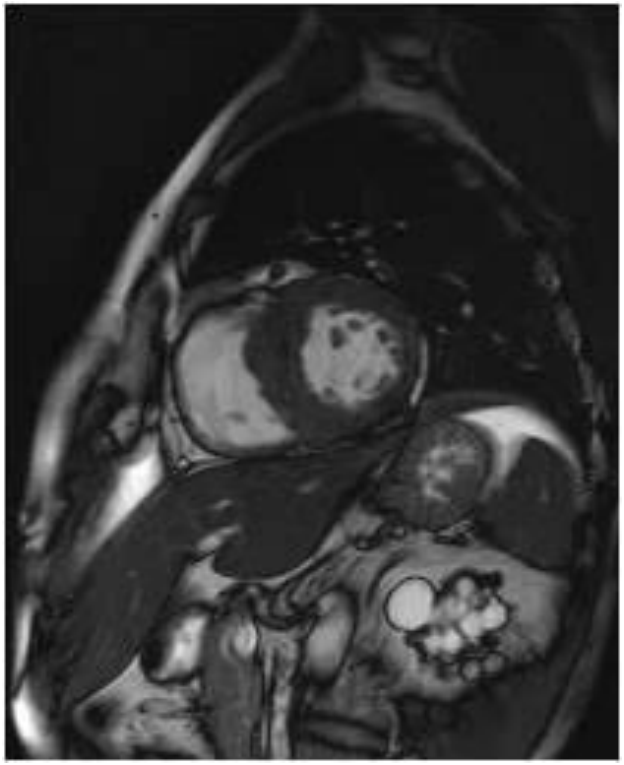
ECHO-CRT

Echocardiography guided **C**ardiac **R**esynchronization **T**herapy

- **Hypothesis:** **is CRT beneficial in patients with a narrow QRS with echo dyssynchrony?**
- **Population:** **2330 patients with LVEF ≤0.35 and LVEDD ≥55mm. NYHA class III-IV. Indication for ICD. QRS duration <130 ms. Optimal drug therapy.**
- **Echo dyssynchrony:** **TDI intra-LV dyssynchrony (opposing wall delay of ≥ 80 ms in the 4-C or apical LA view. Speckle-tracking radial strain septal - posterior wall delay ≥ 130 ms.**
- **Intervention:** **CRT-D on vs. CRT-D off**
- **Primary endpoint:** **Death or HF hospitalisation**
- **Status:** **Started summer 2008**

HF with preserved EF

We still do not have evidence-based treatment



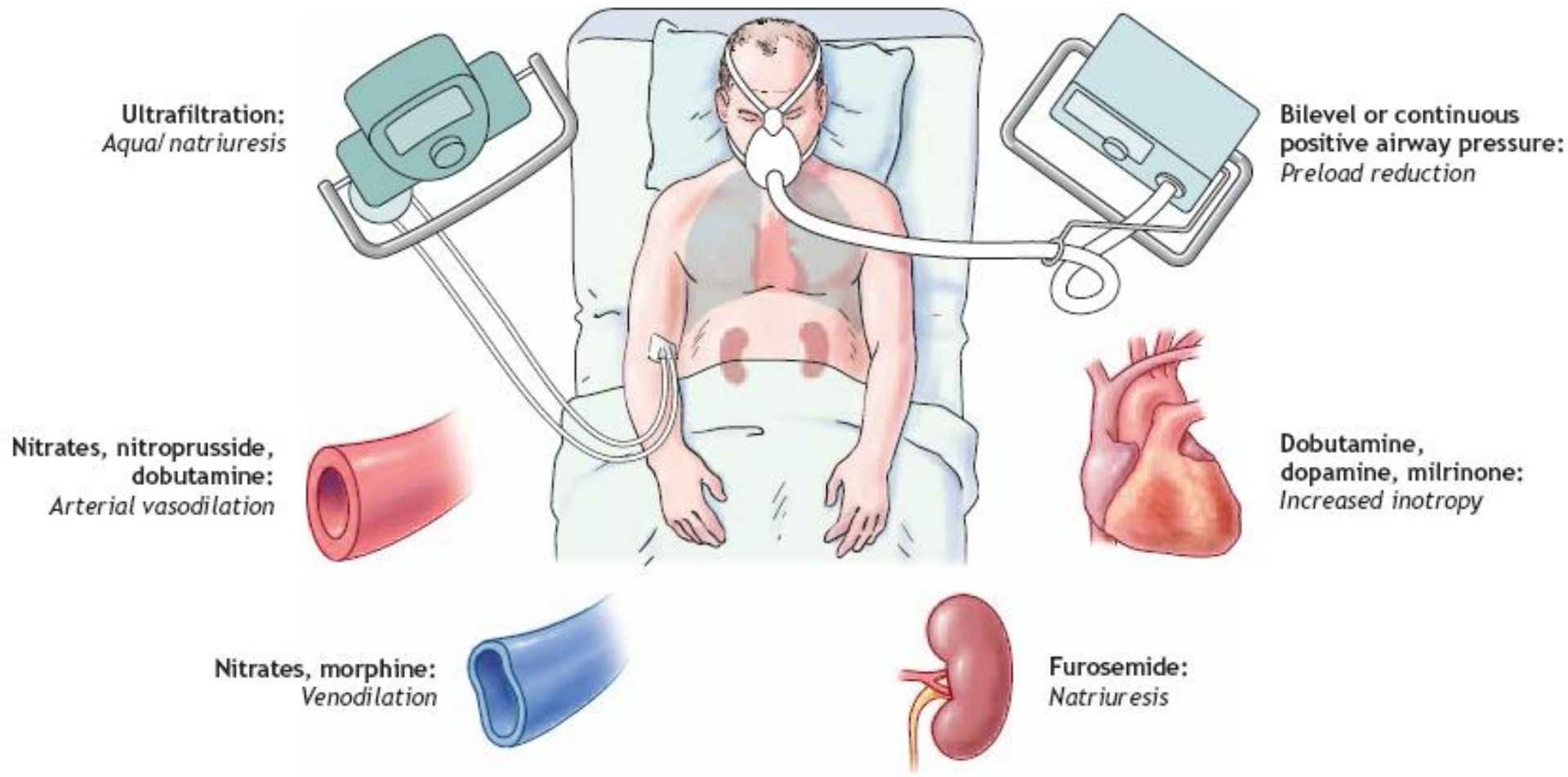
Funded by the NHLBI

Treatment Of Preserved Cardiac function heart failure with an Aldosterone anTagonist

TOPCAT

- **Hypothesis:** Spironolactone will reduce morbidity and mortality in mild HF and preserved LV function
- **Population:** 4500 patients >50 yrs with NYHA II HF (and admission or elevated BNP), EF ≥45%
- **Intervention:** Spironolactone (15-45 mg) vs placebo
- **Primary endpoint:** CV death, RCA, HF hospitalisation
- **Status:** Recruitment started 2008; slow; expected completion uncertain

Acute heart failure

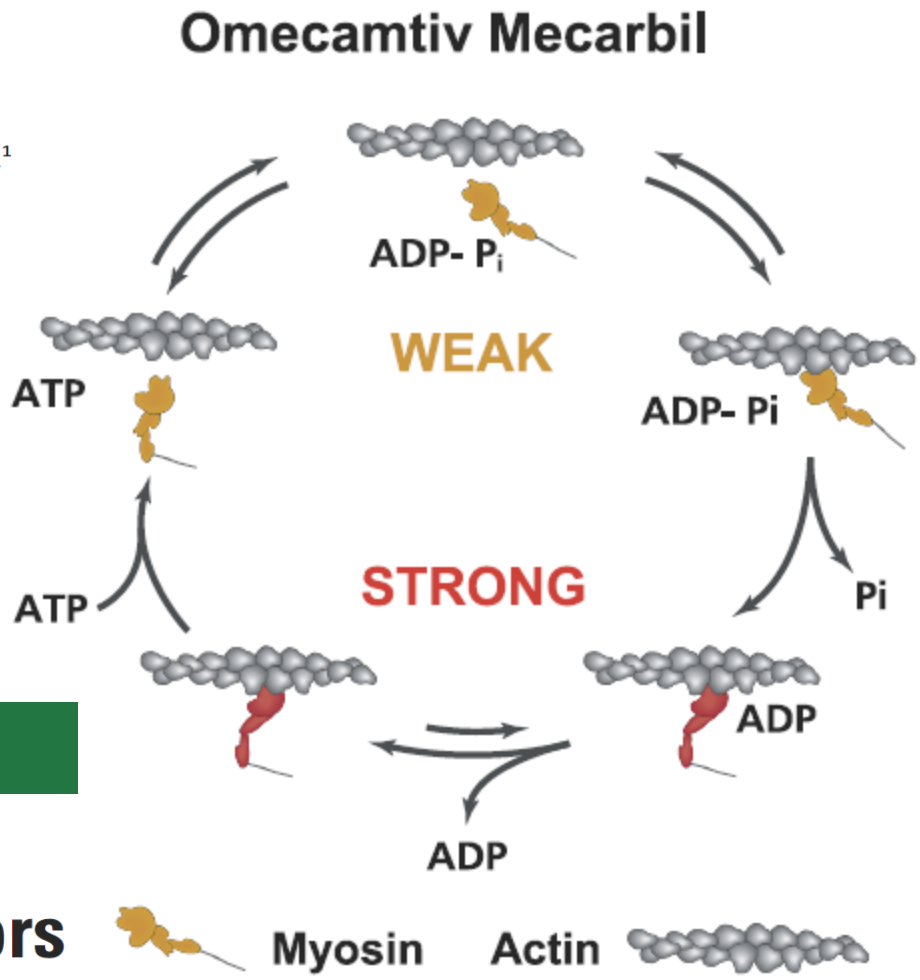


Cardiac myosin activator : omecamptiv Mecarbil

Cardiac Myosin Activation: A Potential Therapeutic Approach for Systolic Heart Failure

Fady I. Malik,[1*] James J. Hartman,[1] Kathleen A. Elias,[1] Bradley P. Morgan,[1] Hector Rodriguez,[1] Katjuša Brejc,[1] Robert L. Anderson,[1] Sandra H. Sueoka,[1] Kenneth H. Lee,[1] Jeffrey T. Finer,[1] Roman Sakowicz,[1] Ramesh Baliga,[1] David R. Cox,[1] Marc Garard,[1] Guillermo Godinez,[1] Raja Kawas,[1] Erica Kraynack,[1] David Lenzi,[1] Pu Ping Lu,[1] Alexander Muci,[1] Congrong Niu,[1] Xiangping Qian,[1] Daniel W. Pierce,[1] Maria Pokrovskii,[1] Ion Suehiro,[1] Sheila Sylvester,[1] Todd Tochimoto,[1] Corey Valdez,[1] Wenyue Wang,[1] Tatsuo Katori,[2] David A. Kass,[2] You-Tang Shen,[3,5] Stephen F. Vatner,[3,4] David J. Morgans[1]

Online Science March 2011



PERSPECTIVES

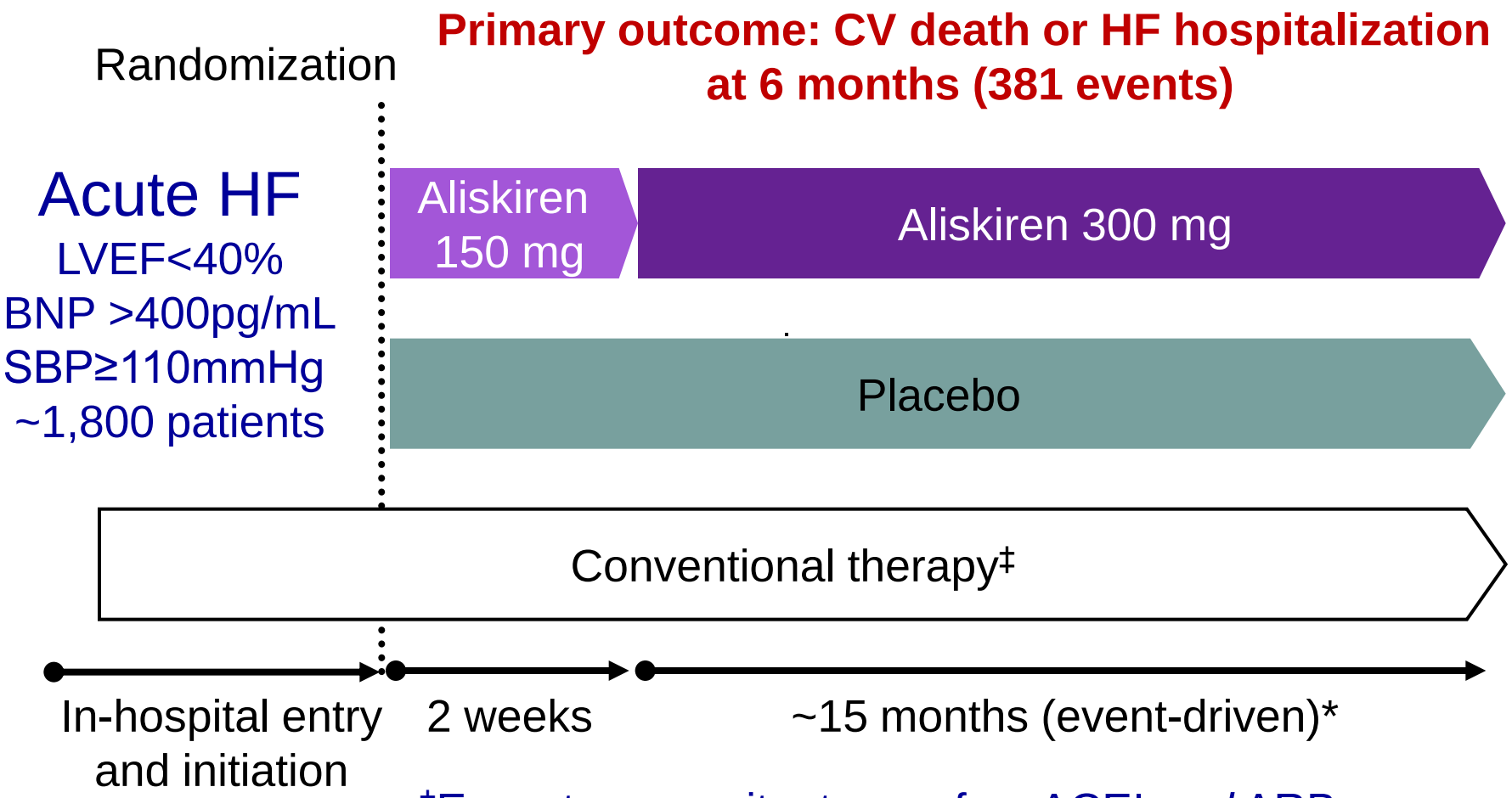
MEDICINE

Chemically Tuned Myosin Motors

Leslie A. Leinwand[1] and Richard L. Moss[2]

ASTRONAUT design overview

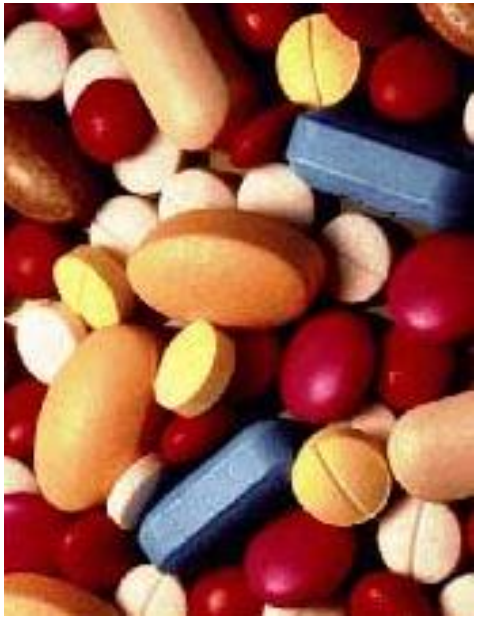
AliSkiren TRial ON Acute heart failure oUTcomes

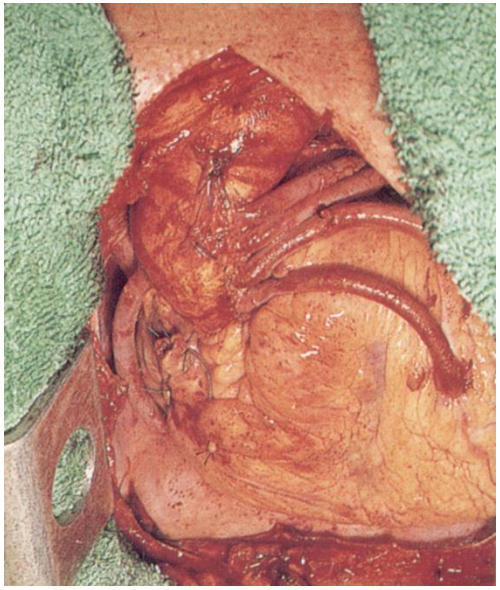


‡Except concomitant use of an ACEI *and* ARB

*Follow-up at Week 2, Month 1, 2 and 3, with on-going assessments every 3 months thereafter

Surgery

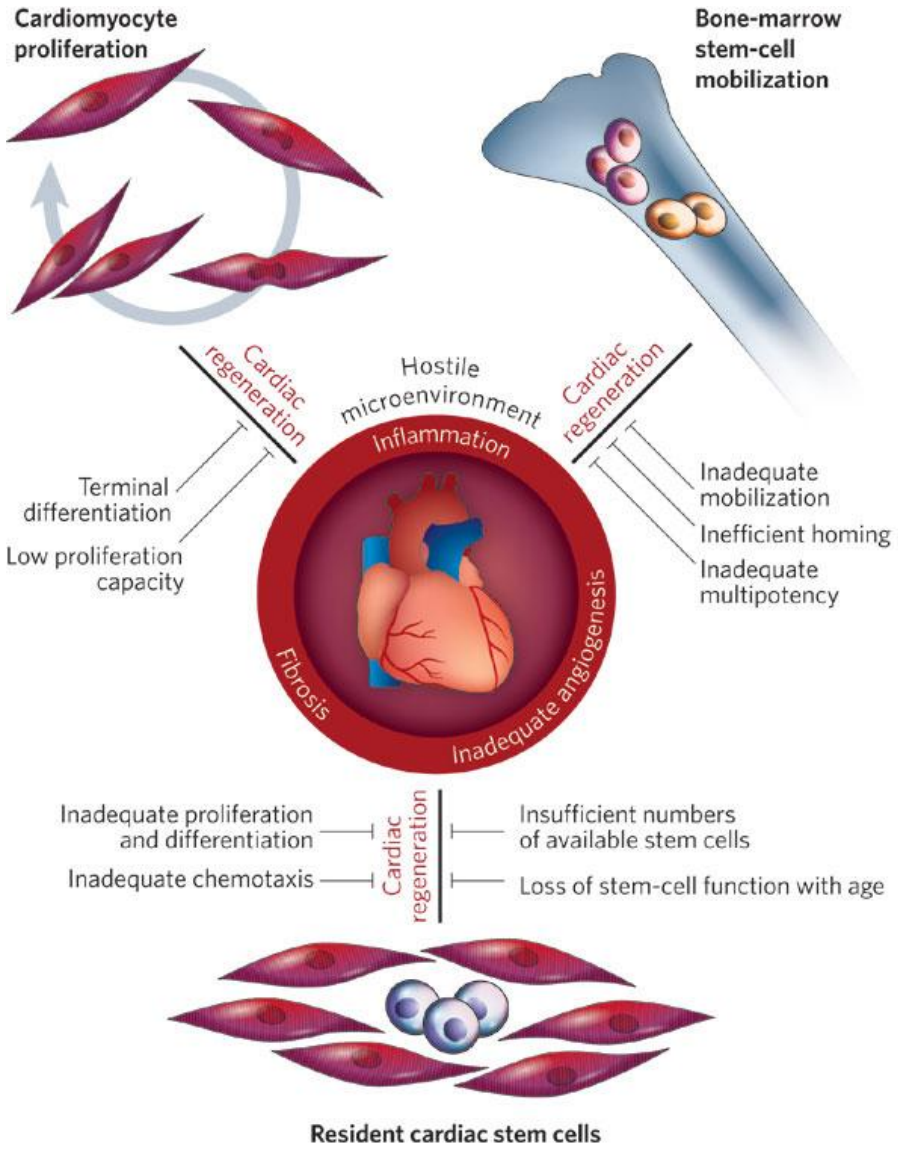




Surgical Treatment for Ischemic Heart Failure (STICH)

STICH: coronary revascularization results

“Regenerative medicine”: stem cell therapy



Not discussed because of time

- **Other positive treatment trials: e.g. DIG (digoxin); HF-ACTION (exercise); GISSI-HF (PUFA); A-HeFT (H-ISDN); ASCEND-HF (nesiritide in acute HF)**
- **Important neutral treatment trials: e.g. CORONA, GISSI-HF (both rosuvastatin); I-PRESERVE (irbesartan in HF-PEF); AF-CHF (rate vs. rhythm control); PROTECT (rolofylline - renal function); STICH (LV remodeling surgery).**
- **Important negative treatment trials: e.g. ANDROMEDA (dronedarone)**
- **Monitoring trials: – BNP/NT-pro BNP; remote monitoring; implanted monitors (CHAMPION)**

Summary: heart failure clinical trial milestones

- **1987** ACE inhibitors, severe HF (CONSENSUS)
- **1991** ACE inhibitor mild/mod HF (SOLVD)
- **1999** Aldosterone antagonist severe HF (RALES)
- **1999-2001** Beta blockers mild-severe HF (CIBIS-2, MERIT-HF, COPERNICUS)
- **2001-2003** ARBs mild/mod HF (Val-HeFT, CHARM)
- **2004/5** CRT severe HF (COMPANION, CARE-HF)
- **2005** ICD (SCD-HeFT)
- **2009** HeartMate II (LVAD)
- **2009** HF-ACTION (exercise)
- **2010** I_f current inhib. (SHIFT)
- **2010** CRT mild/mod HF (MADIT-CRT, RAFT)
- **2010** Aldo. Antag. mild/ mod HF (EMPHASIS-HF)

EUROPEAN SOCIETY OF CARDIOLOGY®

2011

Treatment algorithm for patients with symptomatic heart failure (NYHA functional class II – IV) and a reduced left ventricular ejection fraction (LVEF ≤35%)