HJÄRTSVIKT GOTTSKÄ

170919

Ulf AHREMARK

Medicinkliniken Halmstad

REMISS TILL KARDIOLOG

Bör innehålla:

- Relevant anamnes
- EKG
- Kliniska fynd,

  ödem, rassel viktökning, hjärtauskultation, mm.
- NTproBNP + annan relevant lab.
- Blodtryck
- Aktuell medicinering

Gärna Rtg Pulm

UTREDNING PÅ KARDIOLOGMOTTAGNING

EKOKARDIOGRAFI
TRANSTHORAKALT ELLER TRANSESOPHAGALT
ARBETSPROV
HOLTER

VIDARE UTREDNING MED T.EX.
KORONARANGIOGRAFI
MYOKARDSCINTIGRAFI
MR-HJÄRTA
ULTRALJUD LUNGA
MYOKARDBIOPSI
ELEKTROFYSIOLOGI

Ekokardiografi

Vid förhöjt BNP/NT-proBNP

RiksSvikt
nationellt hjärtsviktsregister

Ekokardiografi

- Diagnostiserar de flesta tillstånd
- Obligatorisk undersökning vid diagnos av hjärtsvikt, (eller annan metod för att värdera punpfuktion)
- Kan vara en flaskhals i utredningen

EF Ejektionsfraktion

Termen används för att ange
hur stor andel av blodinnehållet
i hjärtats vänstra kammare
som pumpas ut under kammarens
sammandragningsfas (systole).

EF Ejektionsfraktion
Mått på systolisk pumpfunktion

>50%	Normal LVEF
40-49%	Lätt nedsatt LV-funktion
30-39%	Måttligt nedsatt
<30%	Uttalat nedsatt EF

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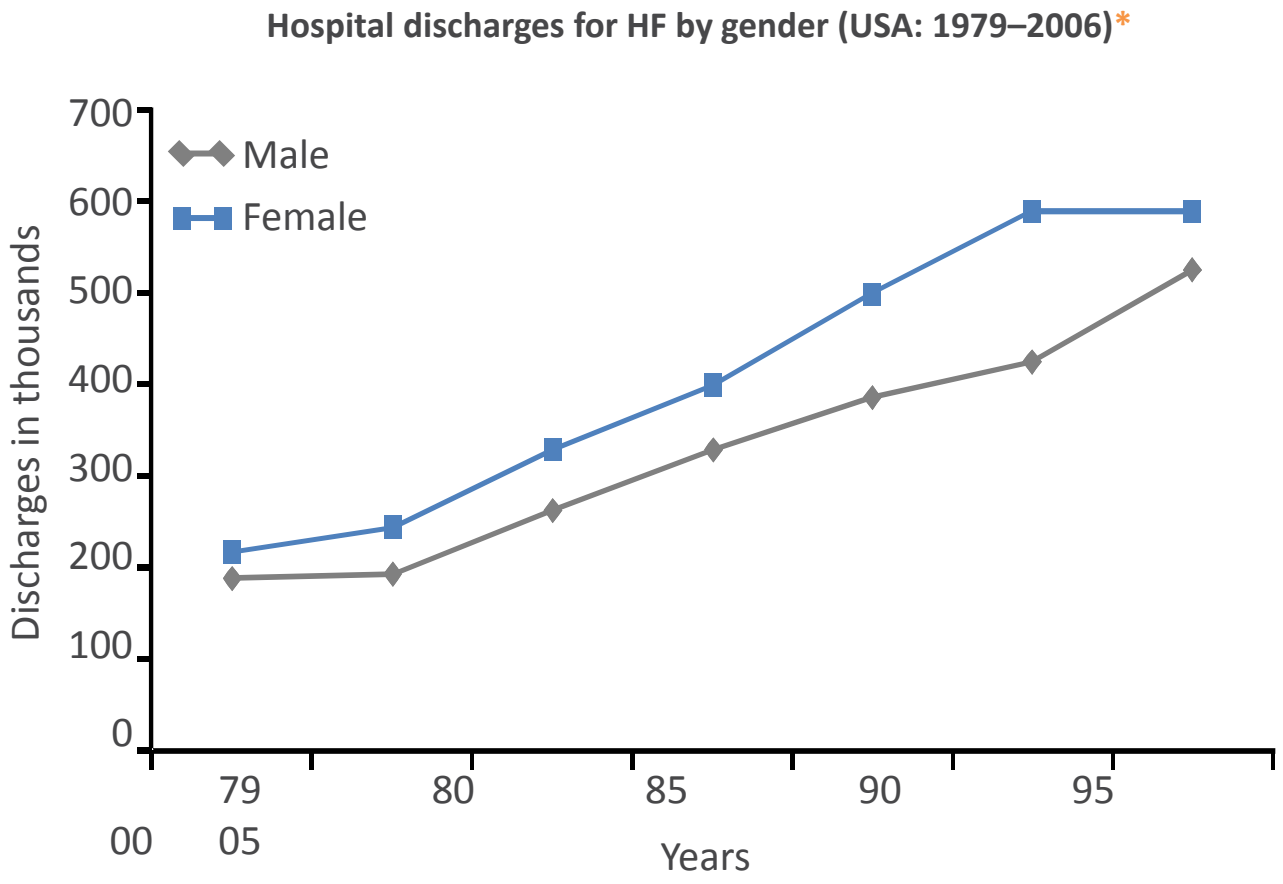
HF is increasing in prevalence



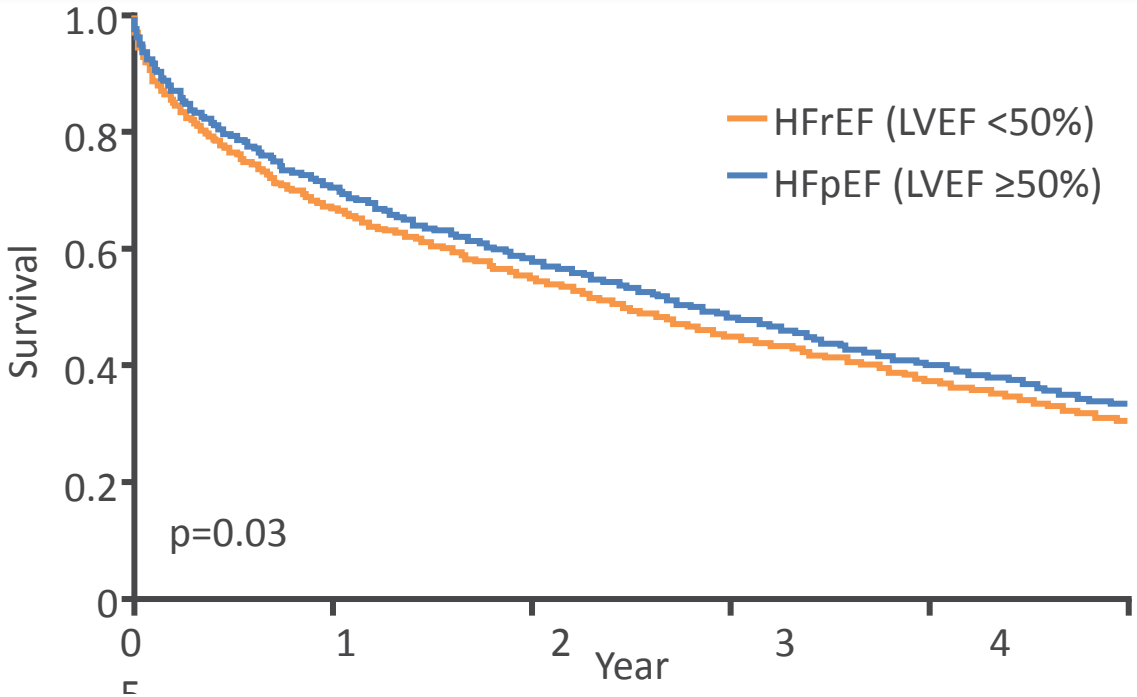
*Hospital discharges include people discharged alive, dead and of unknown status

HF: heart failure; USA: United States of America

Lloyd-Jones et al. Circulation 2010;121:e46–e215

HFpEF and HFrEF are associated with similarly high levels of mortality

- Survival rate among patients with a discharge diagnosis of HF in the USA was slightly higher among patients with HFpEF than those with HFrEF between 1987–2001[1]
  - respective mortality rates were 29% and 32% at 1 year and 65% and 68% at 5 years



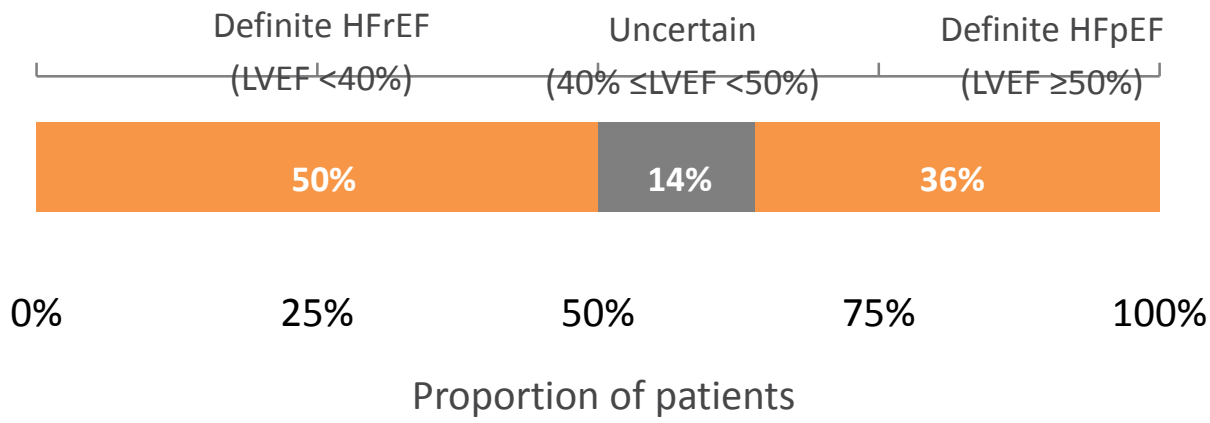
- HFpEF is associated with significant morbidity and mortality, despite having a slightly higher survival rate compared with HFrEF[2,3]

HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; USA: United States of America

1. Owan et al. N Engl J Med 2006;355:251–9; 2. Bidiche et al. Swiss Med Wkly 2010;140:66–72;

3. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). Eur Heart J 2012;33:1750–7

Definition of HFrEF and HFpEF



HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction

Steinberg et al. Circulation 2012;126:65–75

HJÄRTSVIKT

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BEHANDLINGSPRINCIPER 2017

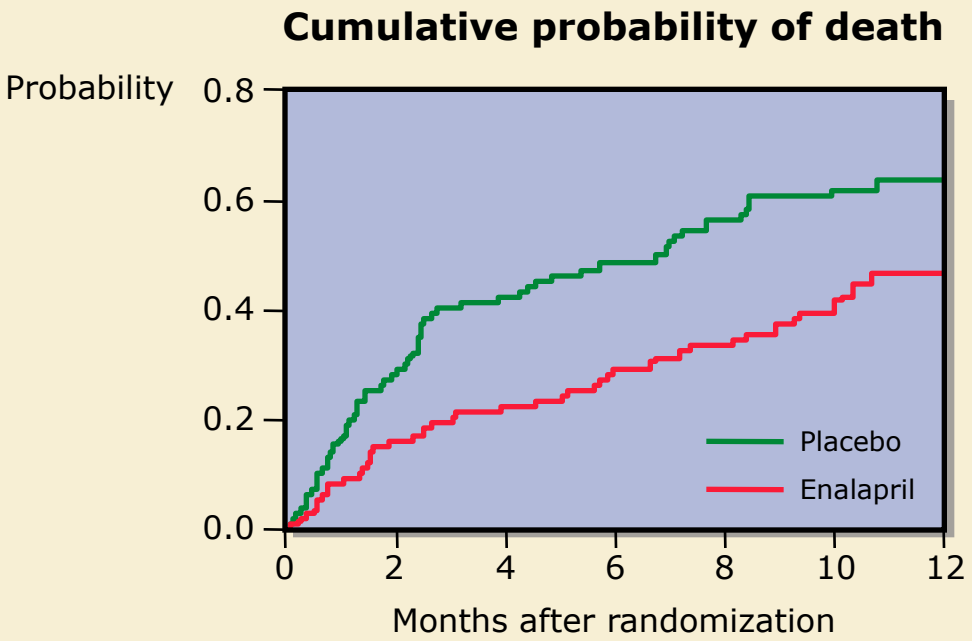
- DIURETIKA
- -loop -tiazider
- ACE-HÄMMARE
- ARB
- BETABLOCKERARE
- ALDOSTERONANTAGONISTER
- NEPRILYSININHIBITOR
- IVABRADIN
- I.V. JÄRN
- CRT ICD CRT-D

GENERELL HANDLÄGGNING

- BEHANDLA ALLT REVERSIBELT - ischemi - PCI eller CABG - korrigera klaffsjukdom

- ICKE FARMAKOLOGISK BEHANDLING
  - fysisk aktivitet
  - rökstopp
  - viktreduktion
  - sänkt saltintag
  - sänkt vätskeintag

CONSENSUS: Cooperative North Scandinavian Enalapril Survival Study
- RESULTS continued -



Placebo:	126	78	59	47	34	24	17
Enalapril:	127	98	82	73	59	42	26

CONSENSUS Trial Study Group. *N Engl J Med* 1987;**316**:1429–35.

STUDIER 25 ÅR SENARE

ETT MINDRE URVAL

ACTIV-HF
ATTACH
CHARM
CIBIS II
CONSENSUS II
DIAL
DIMT
EMIAT
EPHESUS
GESICA
IMPRESS
MADIT-II
MIRACLE-ICD
OPTIME-CHF
PEP-CHF
PRIME-2
RADIANCE
REMATCH
RESOLVD
SAVE
SOLVD-Treatment
TRACE
V-HEFT-1
VAL-HeFT
WARCEF
TOPCAT

AIRE
BEST
CHF-STAT
COMET
COPERNICUS
DIAMOND
EARTH
EMT
FACE
HEART
INSYNC
MDC
MOXCON
OPTIMAAL
PICO
PROFILE
RALES
RENEWAL
REVASC
SCD-HEFT
SMILE
US-CARVEDILOL
V-HEFT-II
VeSG
SHIFT
FAR-HF

ANZ-Carvedilol
CARIBE
CHRISTMAS
COMPANION
CAPRICORN
DIG
ELITE
ENABLE
FEST
HY-C
LIDO
MERIT-HF
MUSTIC
OVERTURE
PRAISE -1
PROMISE
REACH-I
RECOVER
RITZ-2
SENIORS
TORIC
VALIANT
VHEFT-III
VEST
CIBIS-ELD
PARADIGM-HF

ATLAS
CARMEN
CIBIS 1
CONSENSUS I
DEFINITE
DINAMIT
ELITE II
ENCOR
FIRST
IMPACT-HF
MACH-1
MIRACLE
NETWORK
PATH-CHF
PRAISE-II
PROVED
REFLECT
RENAISSANCE
RITZ-4
SOLVD-Prevention
SWORD
VEST
VMAC
WATCH
EMPHASIS
CONFIRM-HF

FARMAKOLOGISK BEHANDLING

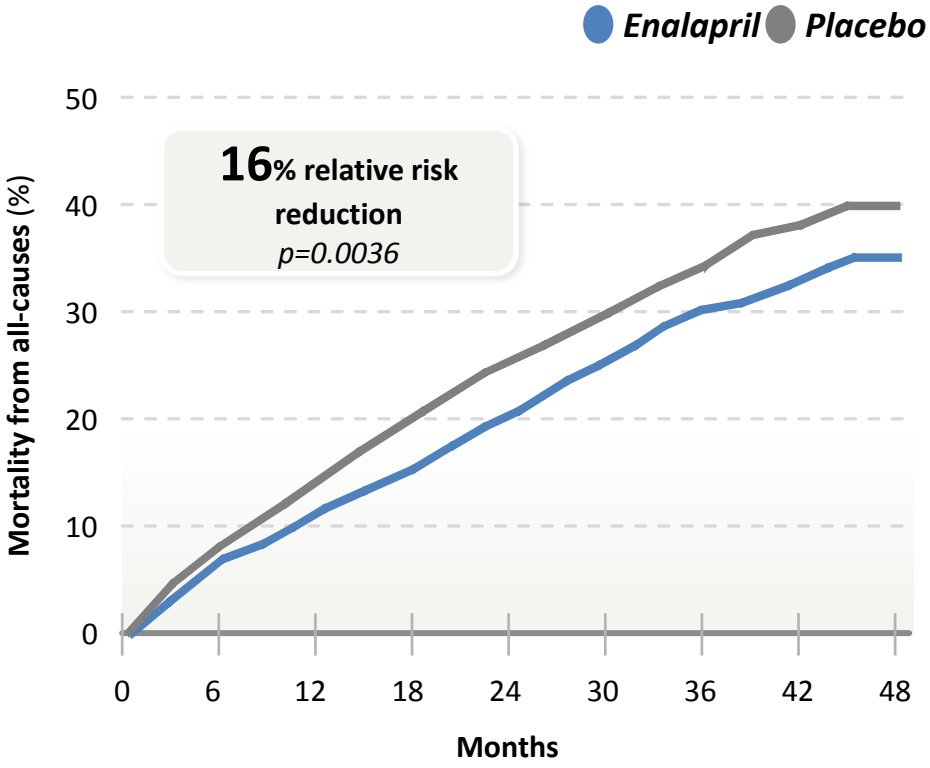
- NYHA 1 : ACE-hämmare
  Betablockerare

NYHA 2 : ACE-hämmare
Betablockerare
Loopdiuretika vb
ARB vid ACE-intolerans. Digoxin endast vid fli/fla
Aldosteronantagonister : spironolakton, eplerenon
Neprilysininhibitor
Ivabradin
I.v. Järn

NYHA 3/4: Diuretika
ACE-hämmare
Betablockerare (Carvedilol i kl 4)
Spironolakton, eplerenon
Neprilysininhibitor
Ivabradin
I.v. Järn

SOLVD-Treatment: enalapril (ACEI) significantly reduced the risk of mortality in patients with HFrEF

SOLVD-Treatment	
Intervention	Enalapril 2.5–20 mg* QD vs placebo*
Number of patients	2,569
Average age (years)	61
Female (%)	19.7
LVEF	≤35% (NYHA I–IV)
Primary outcome	All-cause mortality
Mean follow-up (months)	41.4



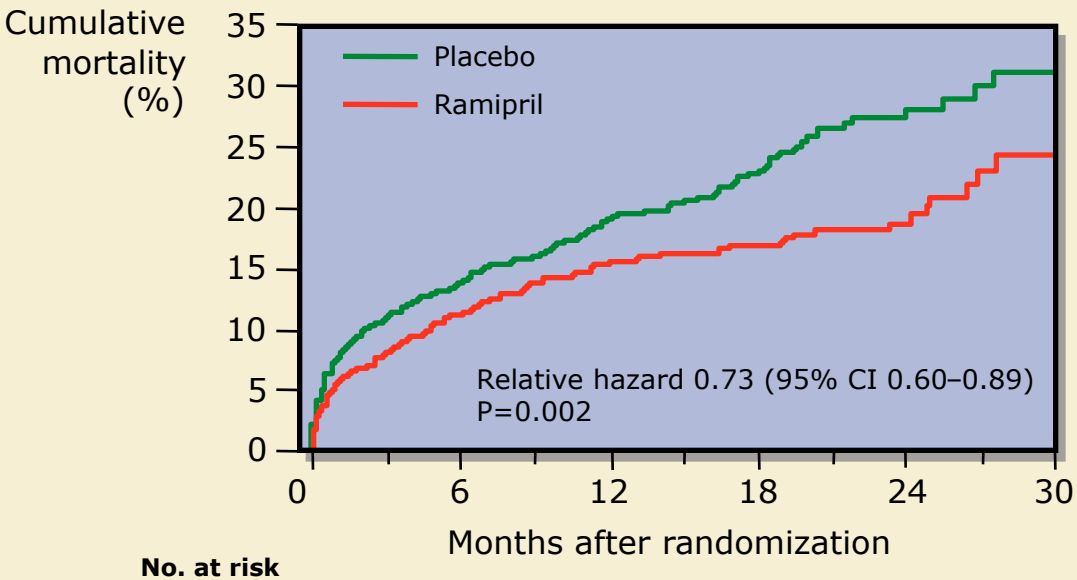
** On top of standard therapy for HF.*

ACEI: angiotensin-converting-enzyme inhibitor; HF: heart failure; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; QD: once daily; SOLVD: Studies of Left Ventricular Dysfunction

SOLVD Investigators. N Engl J Med 1991;325:293–302

AIRE: Acute Infarction Ramipril Efficacy study
- RESULTS continued-

All-cause mortality



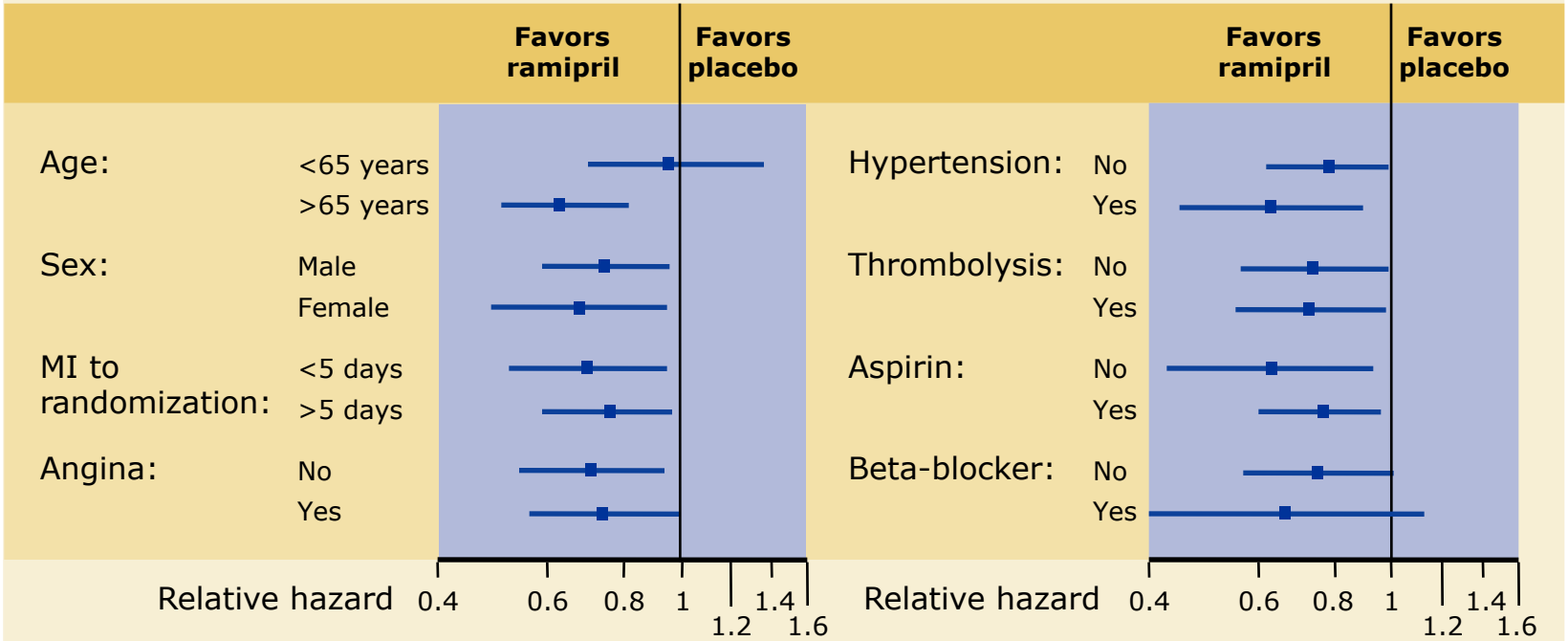
No. at risk

Ramipril	1004	889	592	290	123	45
Placebo	982	845	575	287	98	44

AIRE Study Investigators. *Lancet* 1993;**342**:821–8.

AIRE: Acute Infarction Ramipril Efficacy study
- RESULTS continued-

Effect of ramipril on subgroups



AIRE Study Investigators. *Lancet* 1993;**342**:821–8.

Är alla ACEi lika bra ?

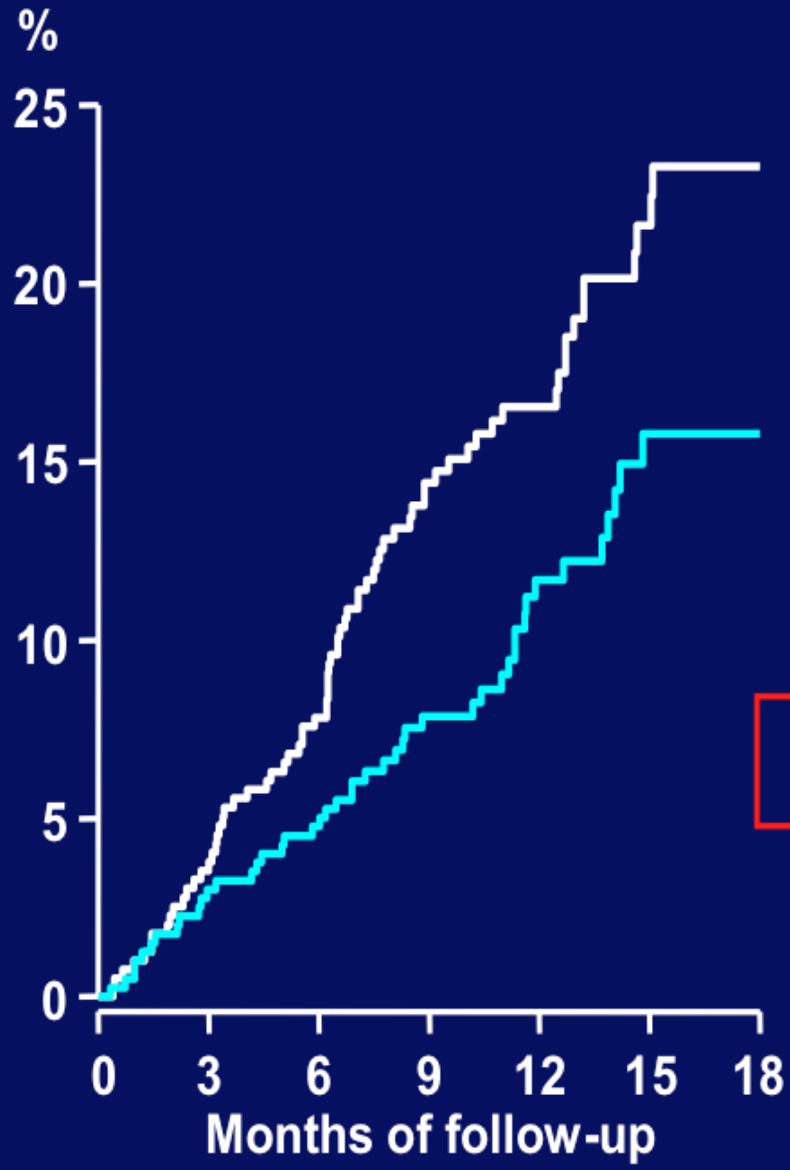
- Sannolikt rör det sig om en klasseffekt.
- I Sverige finns följande preparat med dokumenterad effekt på hjärtsvikt.
  ENALAPRIL
  KAPTOPRIL
  RAMIPRIL
  LISINOPRIL
  CILAZAPRIL
  KINAPRIL

3. BETARECEPTOR-BLOCKERARE

- Minskar sympatikus och katecholaminer (stresshormoner)
- Positiva effekter på hemodynamik, kliniska symtom, arbetsförmåga och VK-funktion.
- Minskar plötslig död (arrytmi), hjärtsviktsdöd och sjukhusvård
- Seloken Zoc®, Emconcor® (bisoprolol), Kredex®(karvedilol,även vasodilaterande och skall användas vid njurinsuff hos sviktpat)

MERIT-HF post-hoc subgroup analysis - severe heart failure

Total mortality

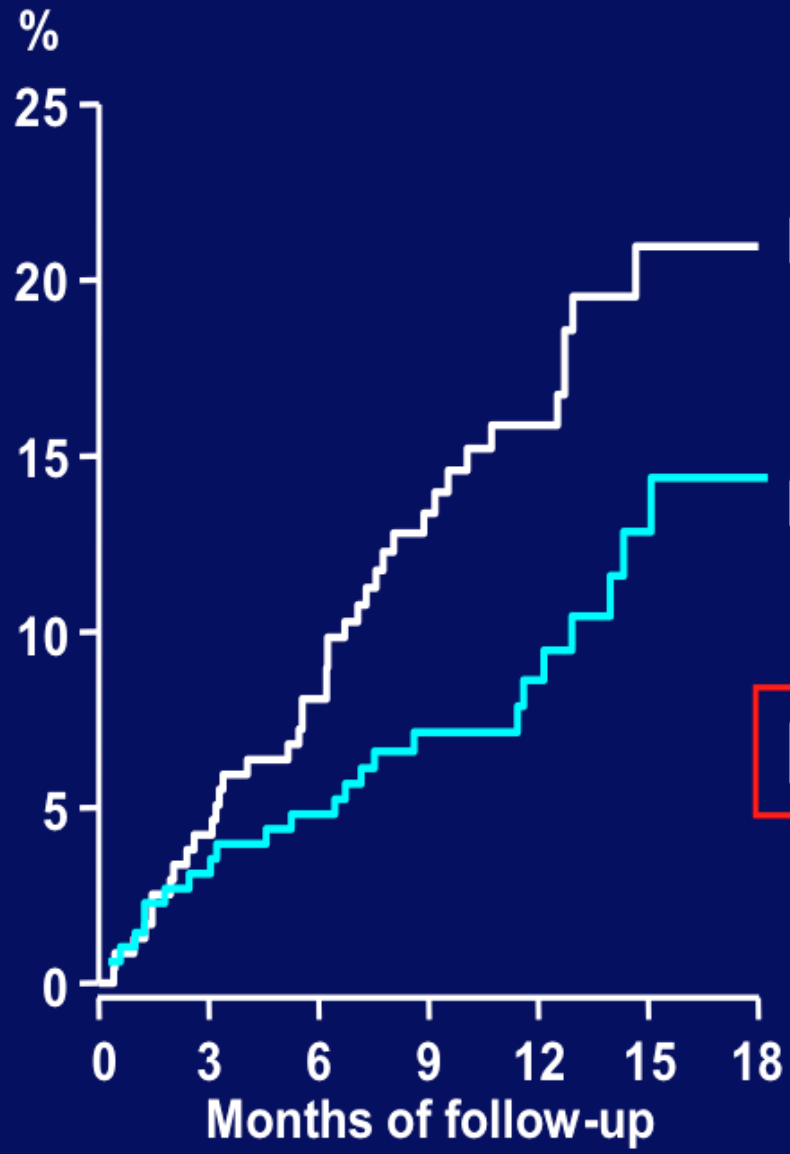


Risk reduction = 39%

Goldstein S et al, J Am Coll Cardiol 2001;38:932-8

MERIT-HF post-hoc subgroup analysis - severe heart failure

Sudden death

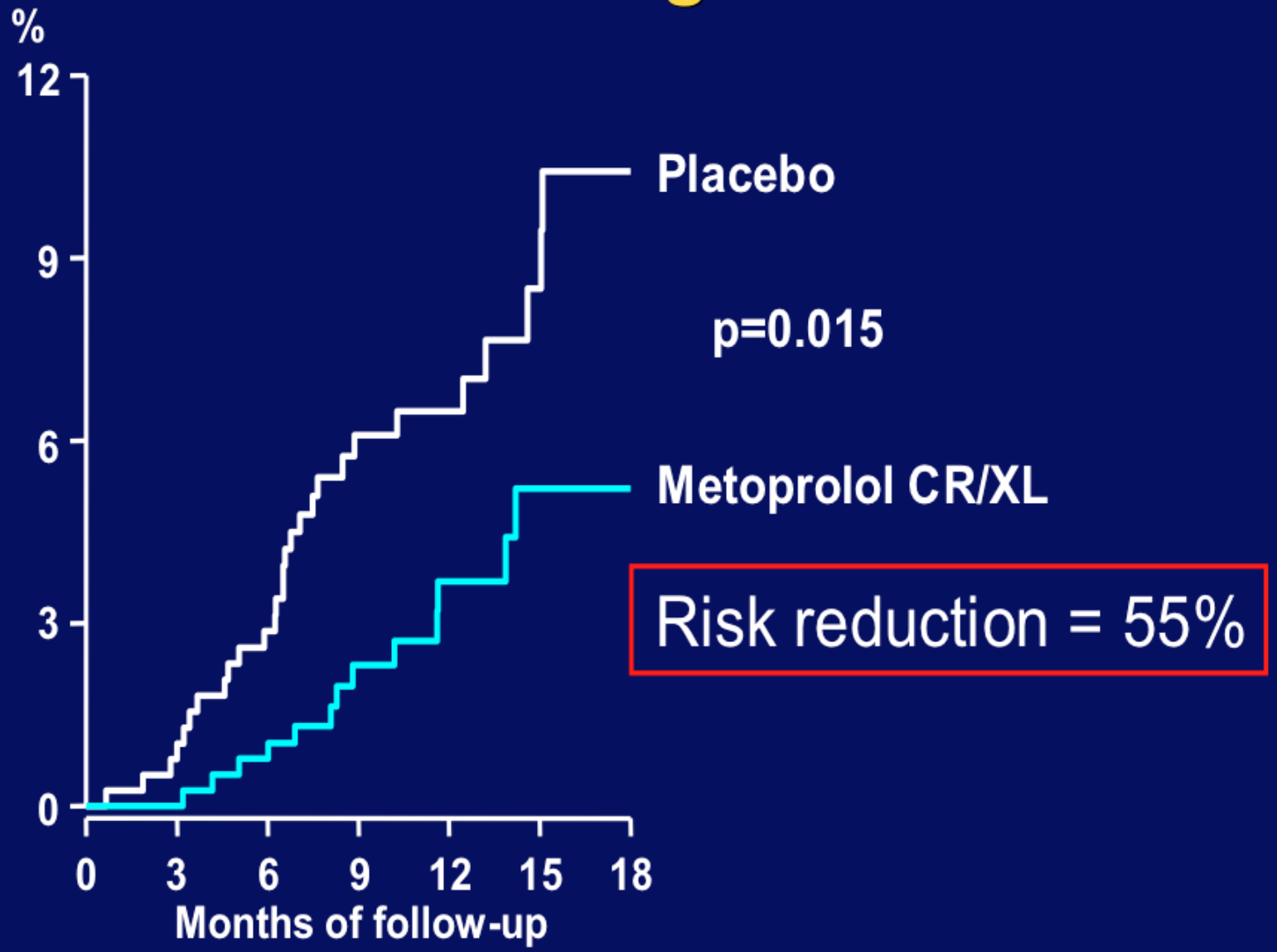


Risk reduction = 45%

Goldstein S et al, J Am Coll Cardiol 2001;38:932-8

MERIT-HF post-hoc subgroup analysis - severe heart failure

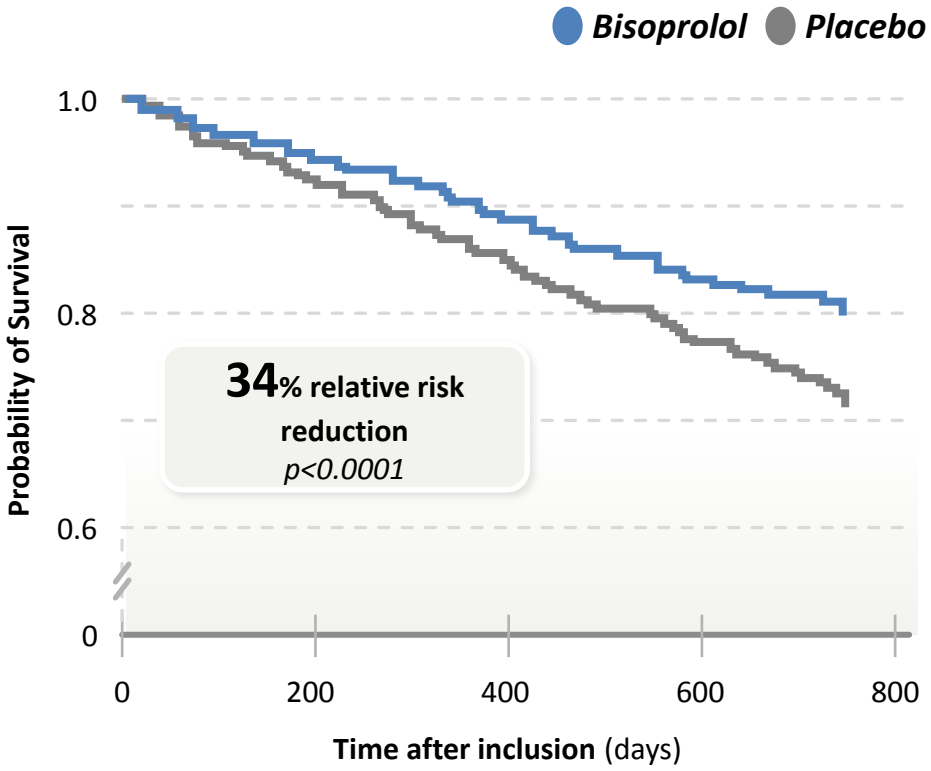
Death from worsening heart failure



Goldstein S et al, J Am Coll Cardiol 2001;38:932-8

CIBIS-II: bisoprolol (BB) significantly reduced all-cause mortality in patients with HFrEF

CIBIS-II	
Intervention	Bisoprolol 1.25–10 mg* QD vs placebo*
Number of patients	2,647
Average age (years)	61
Female (%)	20
LVEF	≤35% (NYHA III–IV)
Primary outcome	All-cause mortality
Mean follow-up (years)	1.3



* On top of standard therapy with diuretics and ACEIs

ACEI: angiotensin-converting-enzyme inhibitor; BB: beta blocker; CIBIS: Cardiac Insufficiency Bisoprolol Study II; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; QD: once daily

CIBIS-II Investigators. Lancet 1999;353:9–13

COPERNIKUS: Karvedilol vs placebo vid CHF

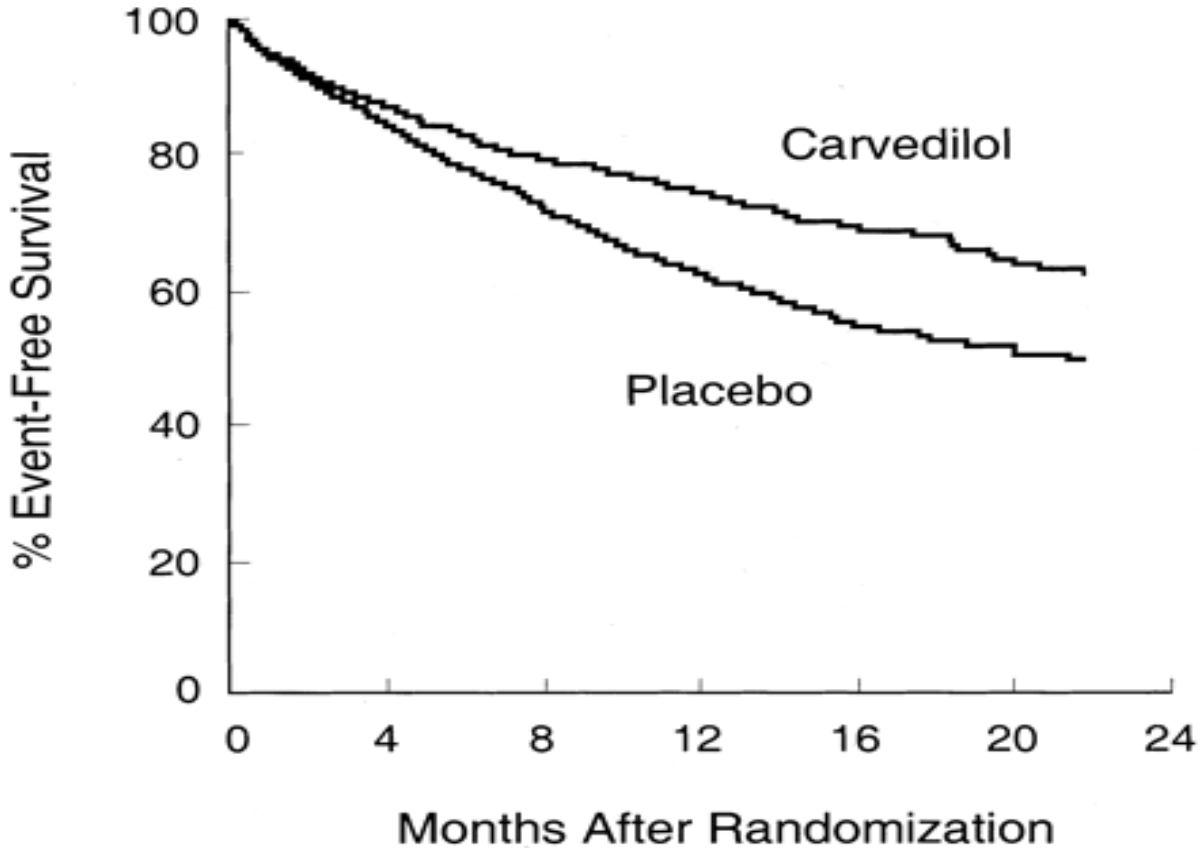
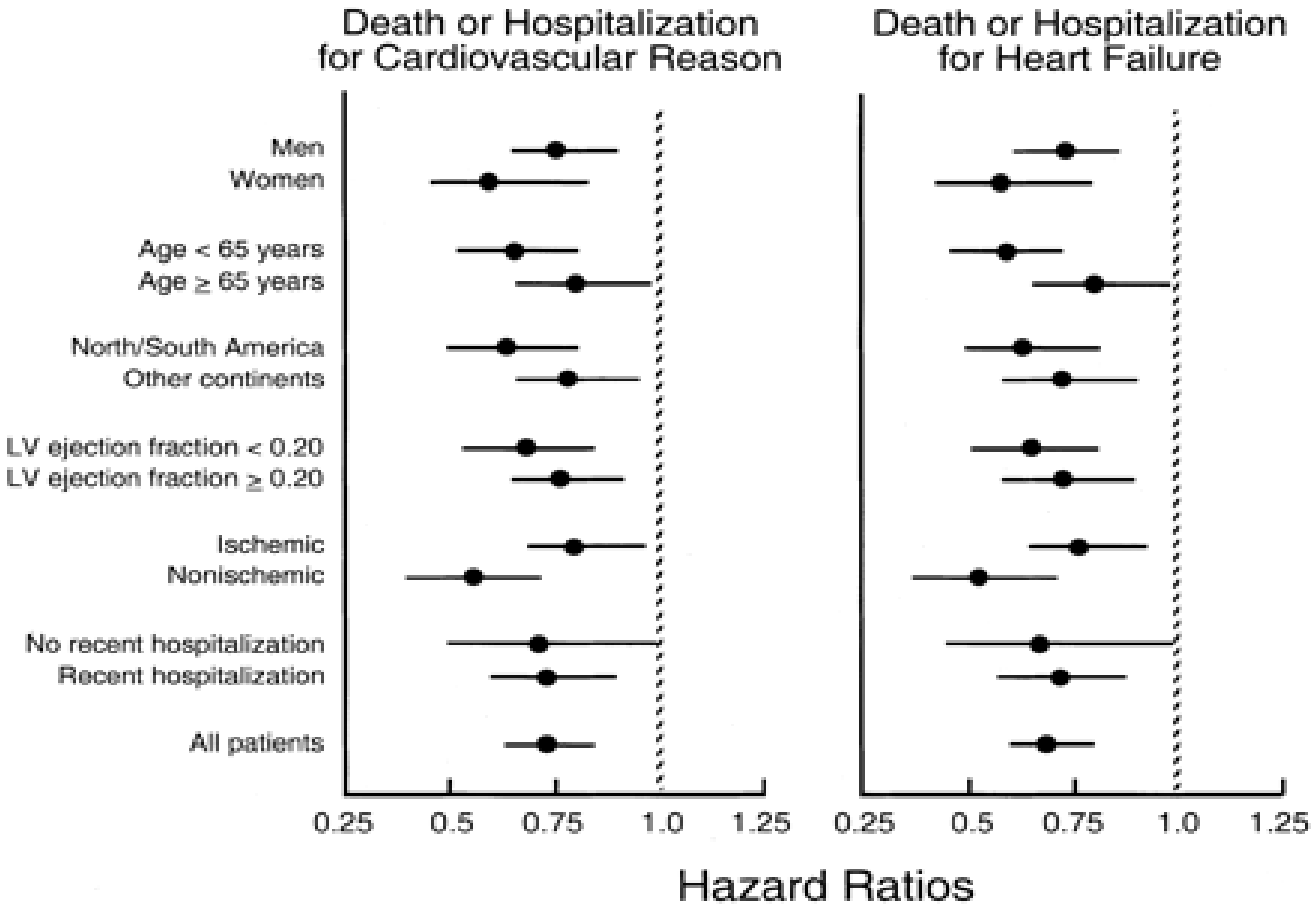


Figure 2. Kaplan-Meier analysis of time to death or hospitalization for heart failure in all patients randomized to placebo or carvedilol.
The 31% lower risk in the carvedilol group was highly significant (*P*=0.000004).

COPERNIKUS: KARVEDILOL VS PLACEBO VID CHF



ACE-hämmarfrågor

- Hög dos vs låg dos
- ACE i vs BB
- ACE i och njursvikt

ACEi låg vs hög dos

- Det mesta av effekten verkar dyka upp redan vid låg dos
- Lägre antal sjukhusinläggningar vid hög dos
- Något mer biverkningar på hög dos
- Ingen säker mortalitetskillnad
- Höj till högsta (väl)tolererade dos

ACEi eller β-blockerare
Vilken tar vi först ?

- CIBIS 3 – studien anger att det inte spelar någon roll ….. **Men förslagsvis**
- ACEi kvarstår som förstaval
- Sätt in β-bl. ovanpå låg dos ACEi
- Titrera upp β-bl.-dosen
- Titrera sedan upp ACEi dosen stegvis

ACEI OCH NJURSVIKT

När törs vi försöka ?

- Vid måttlig njursvikt – fösiktig in och upptitrering (Krea <250µmol/l ; GFR 30-60 ml/h/1,73m²)
- Tillse adekvat vätskebalans
- Låga doser
- Undvik NSAID
- Monitorera njurfunktion och kaliumvärde

- Vid svårare njursvikt undvik ACEi

ARB vs ACEi

- ARB är inte bättre än ACEi
- 2 ARB har visat sig vara lika bra som ACEi vid CHF - candesartan och valsartan
- ACEi är fortsatt förstahandsval
- ARB har färre och mildare biverkningar och utgör ett självklart alternativ vid ACE-intolerans

ARB som tillägg till ACEi -behandling vid hjärtsvikt

- 2 studier visar visar liten tilläggseffekt vid kombinationsbehandling. Även negativa studier finns.
- Kombinationen ACEi, ARB och aldosteron-antagonister rekommenderas inte. Studier saknas.

Att sätta in β-blockerare

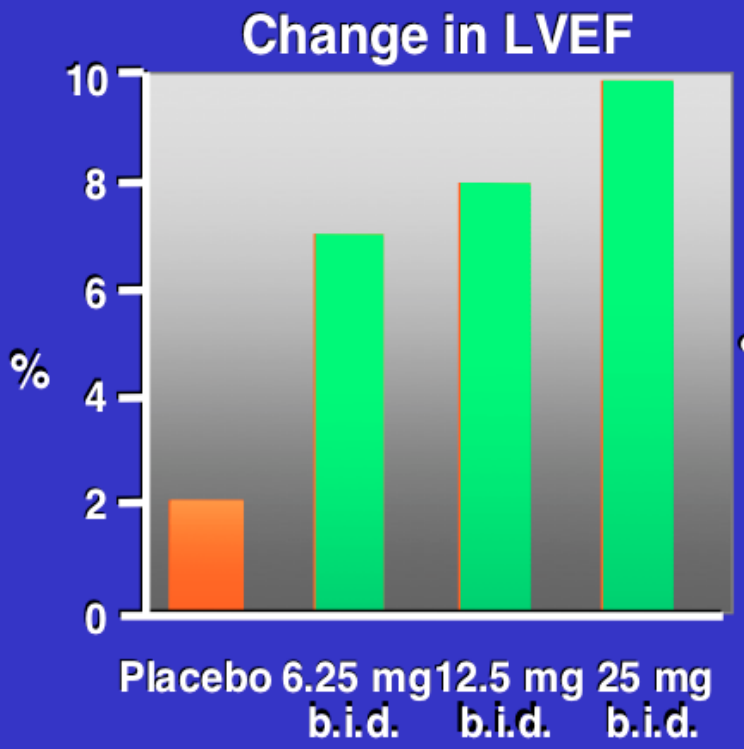
- Starta när patienten är: Adekvat hydrerad - ej övervätskad
- Insatt på en stabil diuretikados
- Insatt på åtminstonde lågdos ACEi

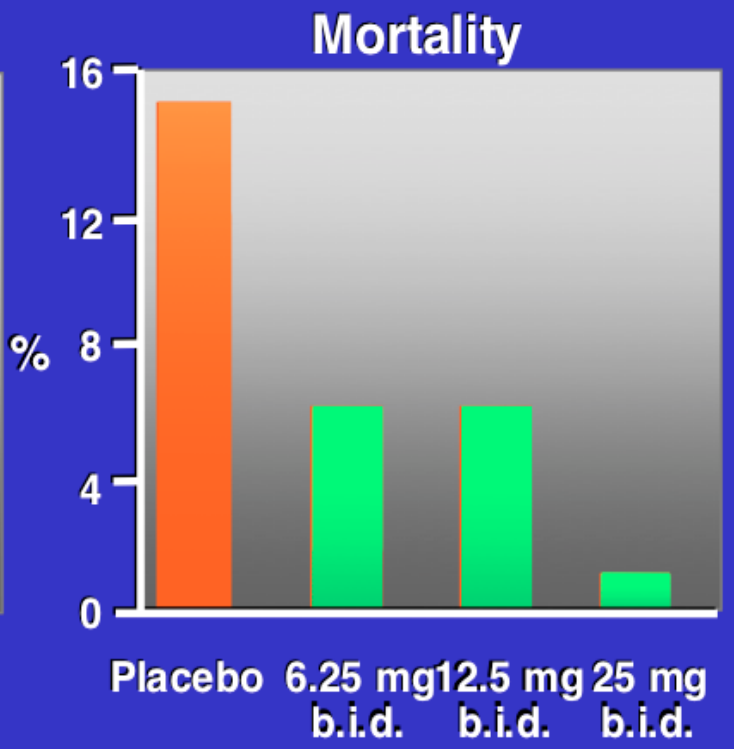
- Lågt och sakta: Starta med en låg dos
- Öka dosen gradvis (var 2a-4e vecka)

- NYHA – klass: Klass I – IV

- Informera patienten: Ev. subjektiv försämring innan förbättring
- Daglig vikt – rapportera viktökning ≥ 2kg
- Justera diuretikatillförsel efter vikt
- Tar ca 2-3 månader innan klinisk förbättring
- Succesiv utsättning om nödvändigt

Carvedilol Dose - EF and Mortality





EF dose response p<0.001

Mortality dose response p<0.01

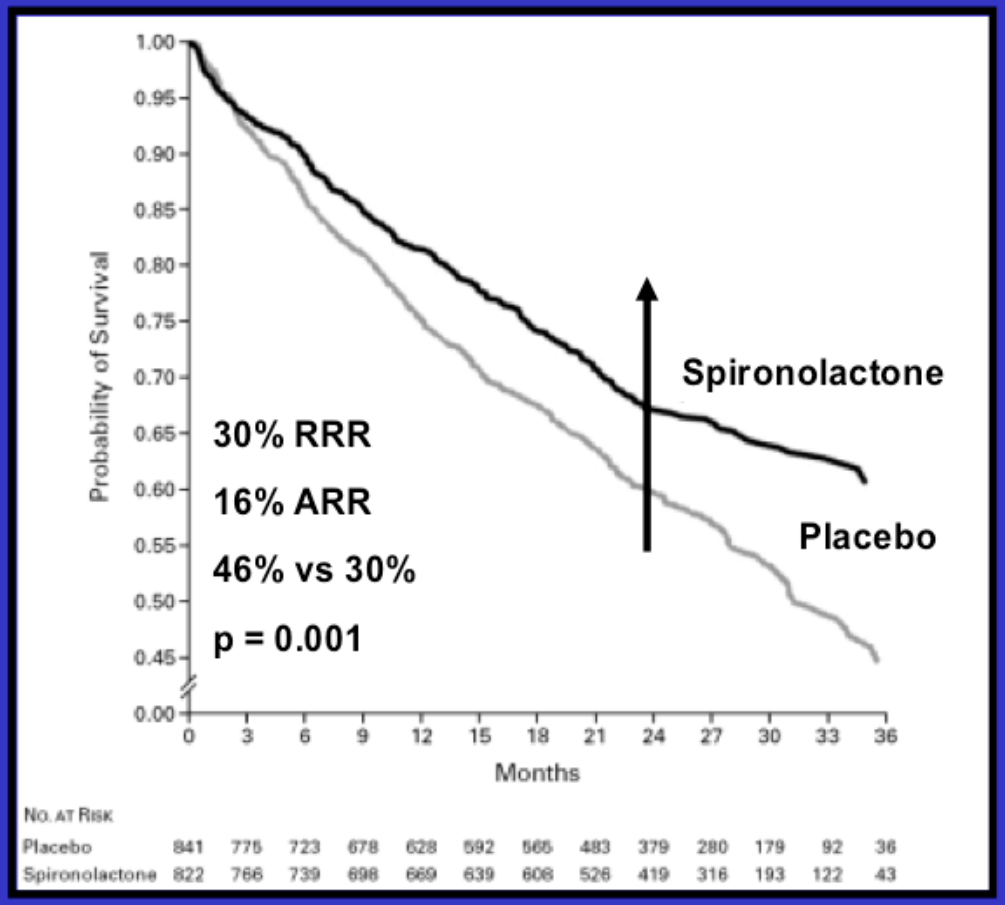
Lombardi WL et al. Clinical Cardiology 2001;24:757

Vilken β-blockerare och vilken dos ?

- Det finns anledning att sikta på måldoser även hos äldre patienter– dvs fösök uppnå högsta tolererade eller evidensbaserade dos

- Metoprolol (Seloken Zoc) 200 mg x1
- Bisoprolol (Emconcor CHF) 10 mgx1
- Karvedilol (Kredex) 25mgx2

RALES Study – NYHA class III

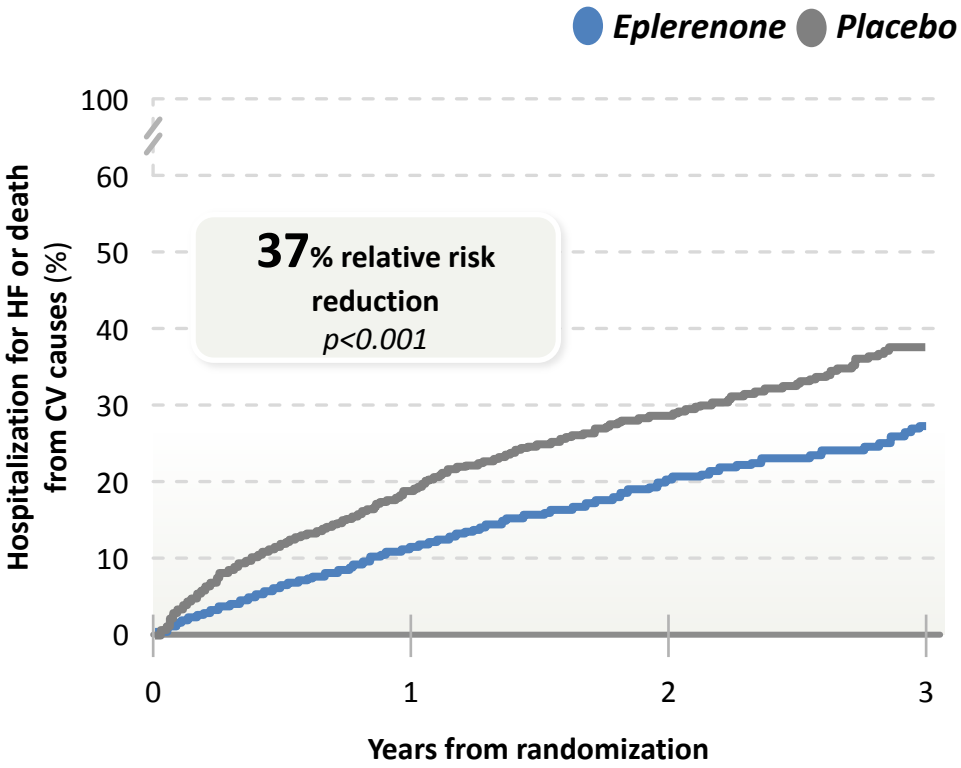


- 30 % reduction in rate of hospitalisations
- (90% to 63%; p = 0.001)

•Pitt et al. N Engl J Med 1999:341:709-17

EMPHASIS-HF: eplerenone (MRA) significantly reduced the risk of CV mortality and hospitalization in patients with HFrEF

EMPHASIS-HF	
Intervention	Eplerenone 50 mg* QD vs placebo*
Number of patients	2,737
Average age (years)	68.7
Female (%)	22.3
LVEF	≤35% (NYHA II)
Primary outcome	Composite of CV mortality or HF hospitalization
Median follow-up (months)	21

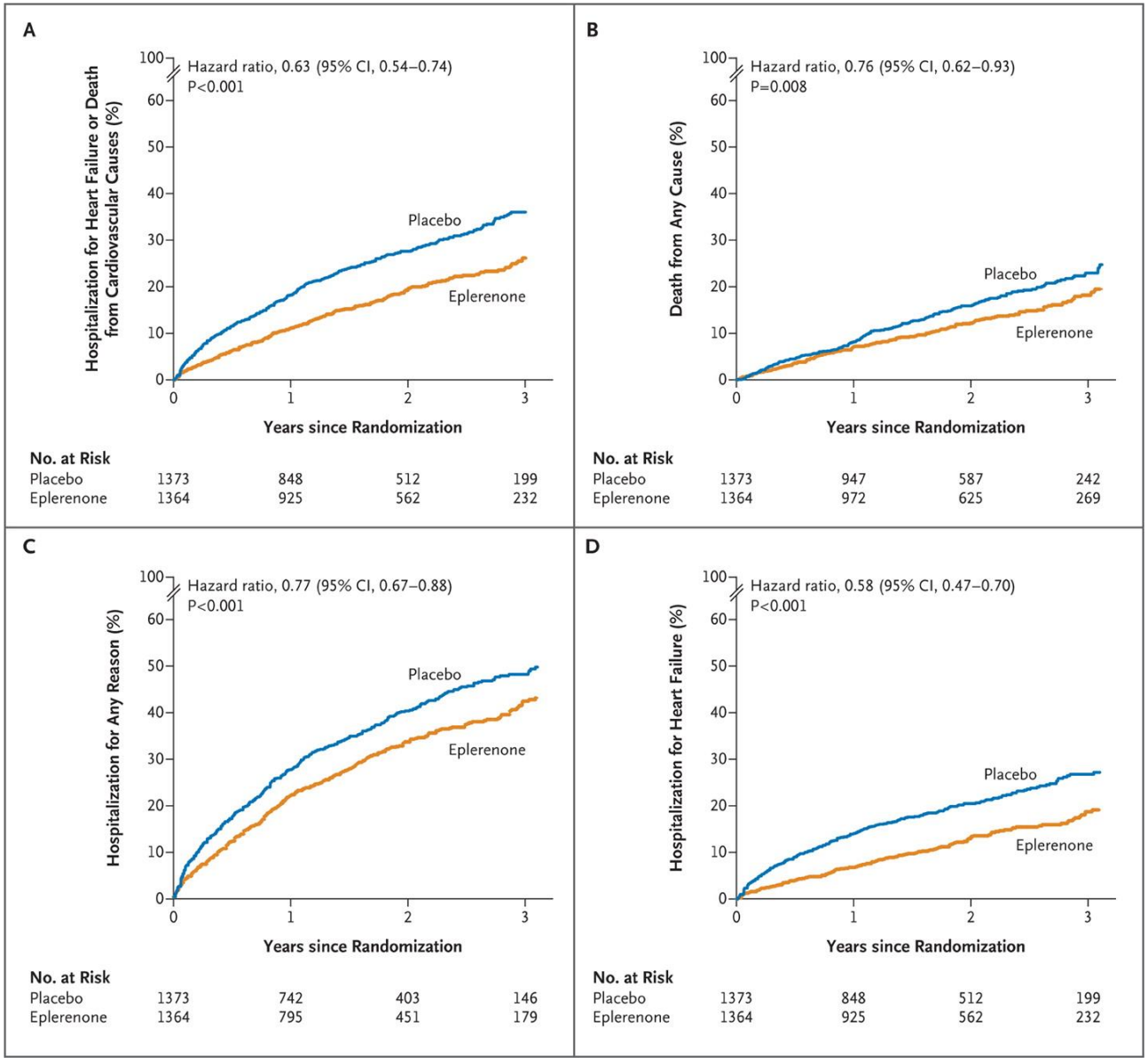


* On top of standard therapy for HF

EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure; CV: cardiovascular; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; QD: once daily.

Zannad et al. N Engl J Med 2011;364:11–21

EMPHASIS - HF


A
Hospitalization for Heart Failure or Death from Cardiovascular Causes (%)
Hazard ratio, 0.63 (95% CI, 0.54–0.74)
P<0.001
Placebo
Eplerenone
Years since Randomization
No. at Risk
Placebo 1373 848 512 199
Eplerenone 1364 925 562 232
B
Death from Any Cause (%)
Hazard ratio, 0.76 (95% CI, 0.62–0.93)
P=0.008
Placebo
Eplerenone
Years since Randomization
No. at Risk
Placebo 1373 947 587 242
Eplerenone 1364 972 625 269
C
Hospitalization for Any Reason (%)
Hazard ratio, 0.77 (95% CI, 0.67–0.88)
P<0.001
Placebo
Eplerenone
Years since Randomization
No. at Risk
Placebo 1373 742 403 146
Eplerenone 1364 795 451 179
D
Hospitalization for Heart Failure (%)
Hazard ratio, 0.58 (95% CI, 0.47–0.70)
P<0.001
Placebo
Eplerenone
Years since Randomization
No. at Risk
Placebo 1373 848 512 199
Eplerenone 1364 925 562 232

ALDOSTERONANTAGONISTER

- Spironolakton och Eplerenon är enkla läkemedel att förskriva
  - 25mg x1 utan titrering

- FÖRSIKTIGHET
- >5 % risk för hyperkalemi. Noggrann monitorering fordras.
- 10 % risk för gynekomasti (<1% med eplerenon)

Rekomendationer för aldosteronantagonism vid hjärtsvikt

- NYHA kass II-IV. Ännu ej vid mildare hjärtsvikt
- K+ <5,0 mmol/L och kreatinin <250µmol/L
- Spironolakton 25mgx1 ingen upptitrering
- Kontrollera K+ 1gång /1-2 v. i en dryg månad sedan var 3:e månad.
-
- Avbryt om K+ >6.0 eller kreatinin stiger signifikant
- Om smärtsam gynekomasti byt till eplerenon 25mgx1. Hyperkalemirisken kvarstår
- Sannolikt antiproliferativa effekter. Minskad kollageninlagring.

The NEW ENGLAND JOURNAL of MEDICINE

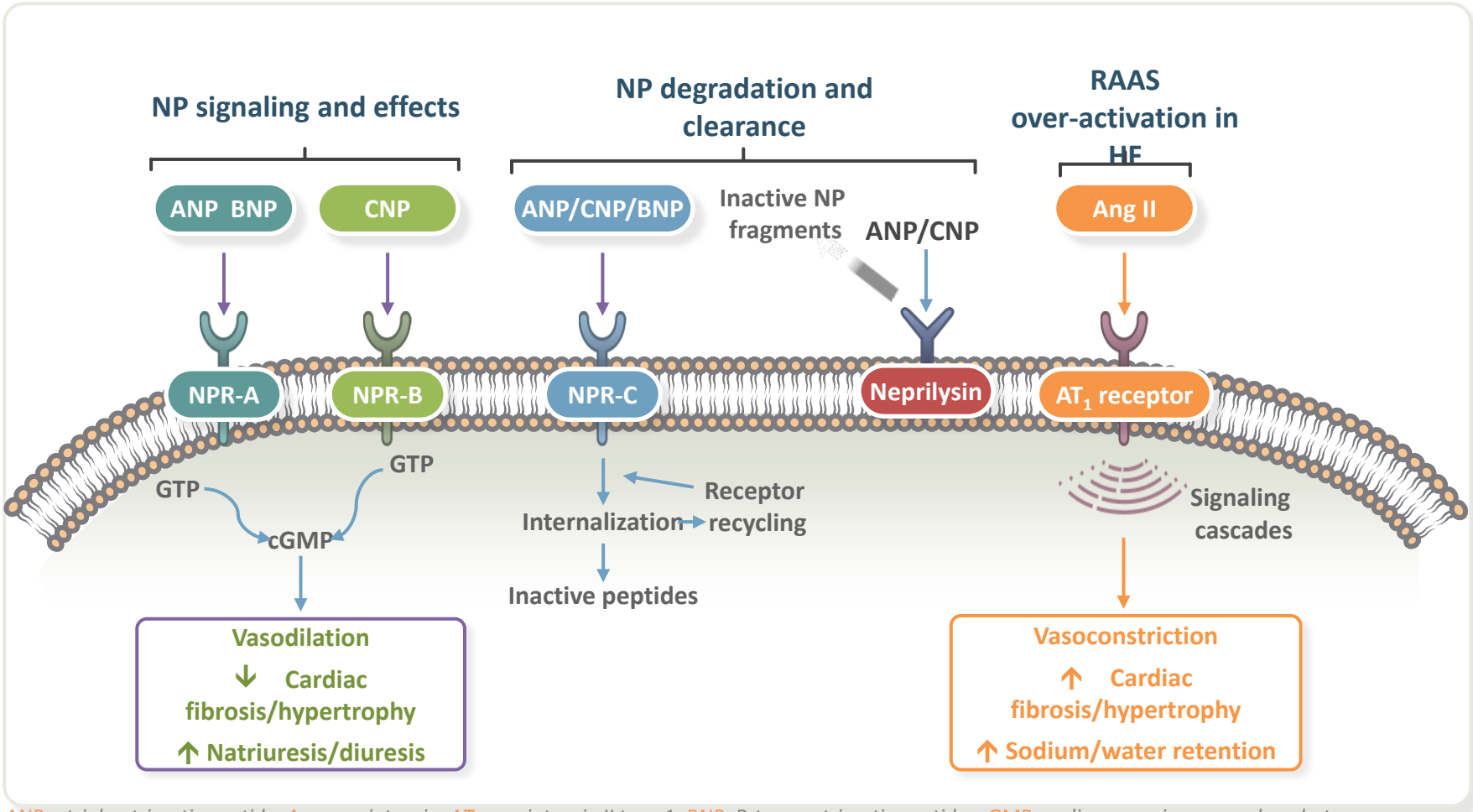
ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D. for the PARADIGM-HF Investigators and Committees

N Engl J Med 2014; 371:993-1004 | September 11, 2014 | DOI: 10.1056/NEJMoa1409077

Natriuretic peptides are cleared by NPR-C and neprilysin



ANP: atrial natriuretic peptide; Ang: angiotensin; AT_1: angiotensin II type 1; BNP: B-type natriuretic peptide; cGMP: cyclic guanosine monophosphate; CNP: C-type natriuretic peptide; GTP: guanosine triphosphate; HF: heart failure; NP: natriuretic peptide; NPR: natriuretic peptide receptor; RAAS: renin-angiotensin-aldosterone system

Levin et al. N Engl J Med 1998;339;321–8; Gardner et al. Hypertension 2007;49:419–26; Molkentin. J Clin Invest 2003;111:1275–77; Nishikimi et al. Cardiovasc Res 2006;69:318–28; Guo et al. Cell Res 2001;11:165–80; Von Lueder et al. Circ Heart Fail 2013;6:594–605; Yin et al. Int J Biochem Cell 2003;35:780–3; Mehta & Griendling. Am J Physiol Cell Physiol 2007;292:C82–97

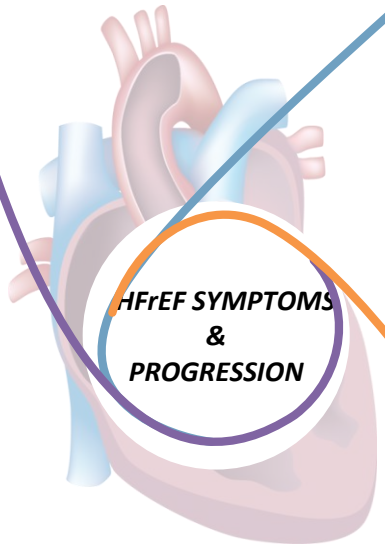
Overactivation of the RAAS and SNS is detrimental in HFrEF and underpins the basis of therapy

Natriuretic peptide system[1]

NPRs ← NPs

Vasodilation

- ↓ Blood pressure
- ↓ Sympathetic tone
- ↑ Natriuresis/diuresis
- ↓ Vasopressin
- ↓ Aldosterone
- ↓ Fibrosis
- ↓ Hypertrophy



Sympathetic nervous system

Epinephrine
Norepinephrine → α_1, β_1, β_2 receptors

Vasoconstriction

- RAAS activity ↑
- Vasopressin ↑
- Heart rate ↑
- Contractility ↑

Renin-angiotensin-aldosterone-system

Ang II → AT_1R

Vasoconstriction

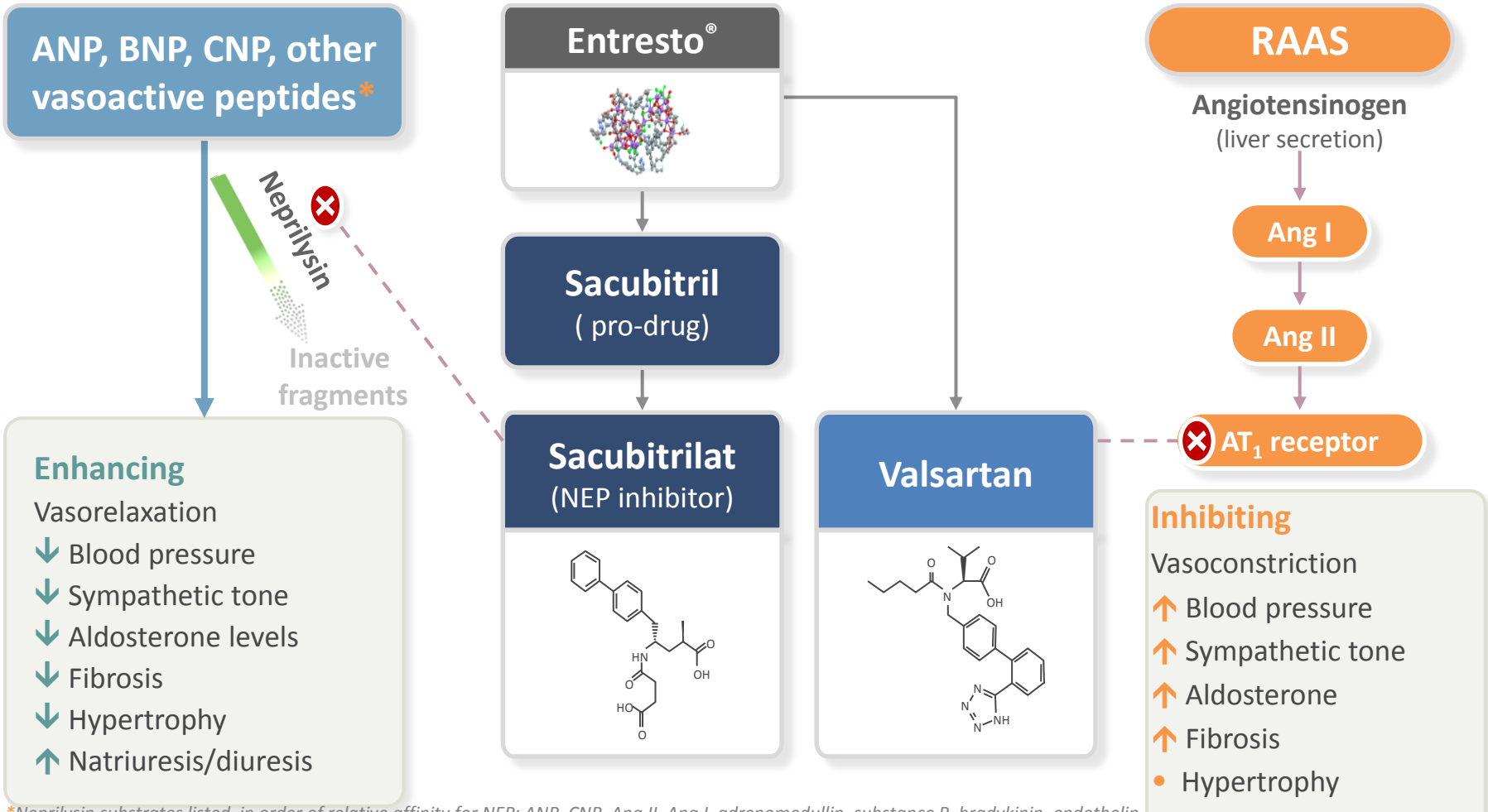
- Blood pressure ↑
- Sympathetic tone ↑
- Aldosterone ↑
- Hypertrophy ↑
- Fibrosis ↑

- The crucial importance of the RAAS is supported by the beneficial effects of ACEIs, ARBs and MRAs[1]
- Benefits of β-blockers indicate that the SNS also plays a key role[1]

ACEI: angiotensin-converting-enzyme inhibitor; Ang: angiotensin; ARB: angiotensin receptor blocker; AT_1R: angiotensin II type 1 receptor; MRA: mineralocorticoid receptor antagonist; NPs: natriuretic peptides; NPRs: natriuretic peptide receptors; RAAS: renin-angiotensin-aldosterone system; SNS: sympathetic nervous system

1. McMurray et al. Eur Heart J 2012;33:1787–847; Figure References: Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42; Kemp & Conte. Cardiovascular Pathology 2012;365–71;
Schrier & Abraham. N Engl J Med 2009;341:577–85

LCZ696 simultaneously inhibits neprilysin (via Sacubitrilat) and blocks AT_1 receptors (via valsartan)

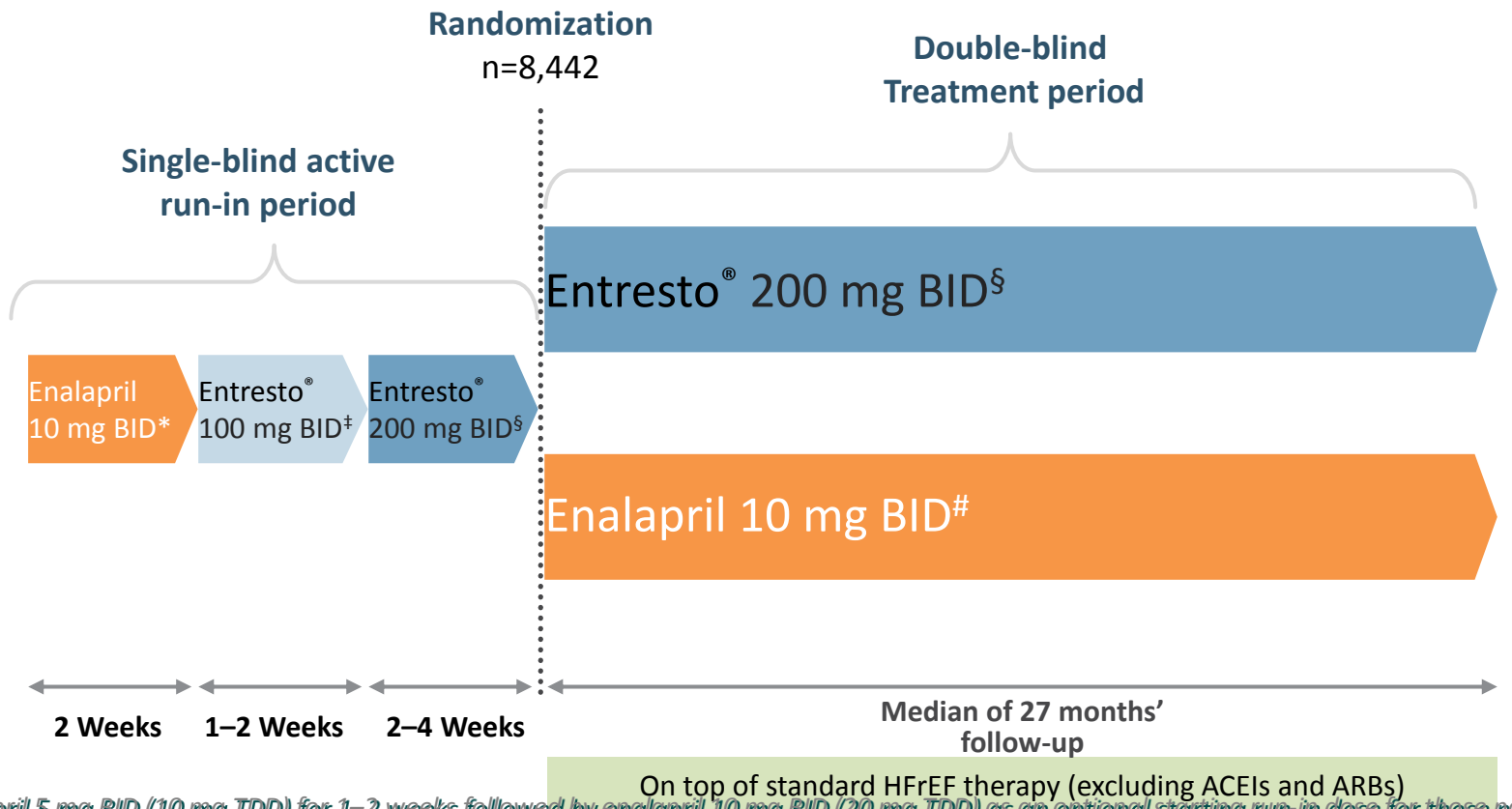


*Neprilysin substrates listed in order of relative affinity for NEP: ANP, CNP, Ang II, Ang I, adrenomedullin, substance P, bradykinin, endothelin-1, BNP

Ang: angiotensin; *ANP:* atrial natriuretic peptide; *AT_1:* angiotensin II type 1; *BNP:* B-type natriuretic peptide; *CNP:* C-type natriuretic peptide; *NEP:* neprilysin; *RAAS:* renin-angiotensin-aldosterone system

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: 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

ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BID: twice daily; HFrEF: heart failure with reduced ejection fraction; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; TDD: total daily dose

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;371:993–1004

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*

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BNP: B-type natriuretic peptide; FC: functional class; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

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

PARADIGM-HF: key exclusion criteria

- History of angioedema
- eGFR <30 mL/min/1.73 m^2 at screening, end of enalapril run-in or randomization, or a >35% decrease in eGFR between screening and end of enalapril run-in or between screening and randomization
- Serum potassium >5.2 mmol/L at screening OR >5.4 mmol/L at the end of the enalapril run-in or end of the Entresto® run-in
- Requirement for treatment with both ACEI and ARBs
- Symptomatic hypotension, SBP <100 mmHg at screening, OR SBP <95 mmHg at end of enalapril
  run-in or at randomization
- Current acute decompensated HF
- History of severe pulmonary disease
- Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid, or other major CV surgery, PCI, or carotid angioplasty within the 3 months prior to screening

ACEI: angiotensin-converting-enzyme inhibitor; ARNI: angiotensin receptor neprilysin inhibitor; ARB: angiotensin receptor blocker; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HF: heart failure; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; PCI: percutaneous coronary intervention; SBP: systolic blood pressure

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

PARADIGM-HF: primary objective

- To evaluate the effect of Entresto® 200 mg BID compared with enalapril 10 mg BID, in addition to conventional HFrEF treatment, in delaying **time to first occurrence** of either **CV death** or **HF hospitalization**[1]

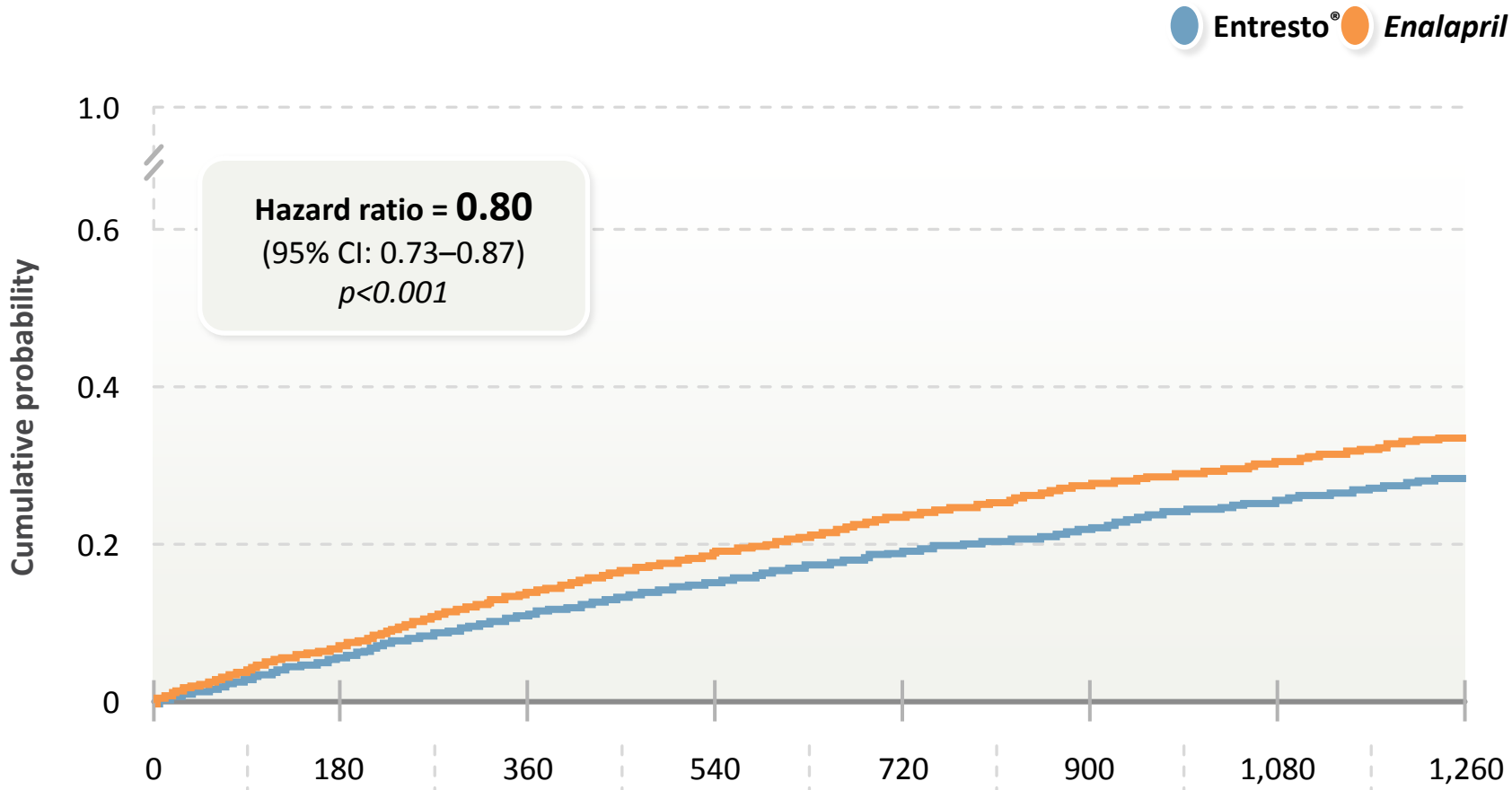
Rationale for endpoint selection

- Primary outcome of CV death or HF hospitalization was chosen as the one that best reflects the major mortality and morbidity burden of HFrEF[1,2]
  - ~80% of deaths in recent trials in patients with HFrEF are CV related[3–5]
  - HF is associated with a high risk of hospitalization,[6] representing the leading cause of hospitalization in patients aged ≥65 years[6–9]
- The most commonly used primary endpoint in recent HF trials: CHARM-Added, SHIFT and EMPHASIS-HF[1]

ACE: angiotensin-converting enzyme; ACEI: angiotensin-converting-enzyme inhibitor; ARNI: angiotensin receptor neprilysin inhibitor; BID: twice daily; CHARM-Added: Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity in patients with HFrEF who were on ACE inhibitors; CV: cardiovascular; EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; SHIFT: Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial

1. McMurray et al. Eur J Heart Fail 2013;15:1062–73; 2. Dunlay et al. Circ Cardiovasc Qual Outcomes 2011;4:68–75; 3. McMurray et al. Lancet 2003;362:767–77; 4. Swedberg et al. Lancet 2010;376:875–88; 5. Zannad et al. N Engl J Med 2011;364:11–2; 6. Cowie et al. Oxford Health policy Forum 2014; 7. Hunt et al. J Am Coll Cardiol 2009;53:e1–90; 8. Yancy et al. Circulation 2013;128:e240–327; 9. Rodriguez-Artalejo et al. Rev Esp Cardiol 2004;57:163–70

Primary endpoint: death from CV causes or first hospitalization for HF



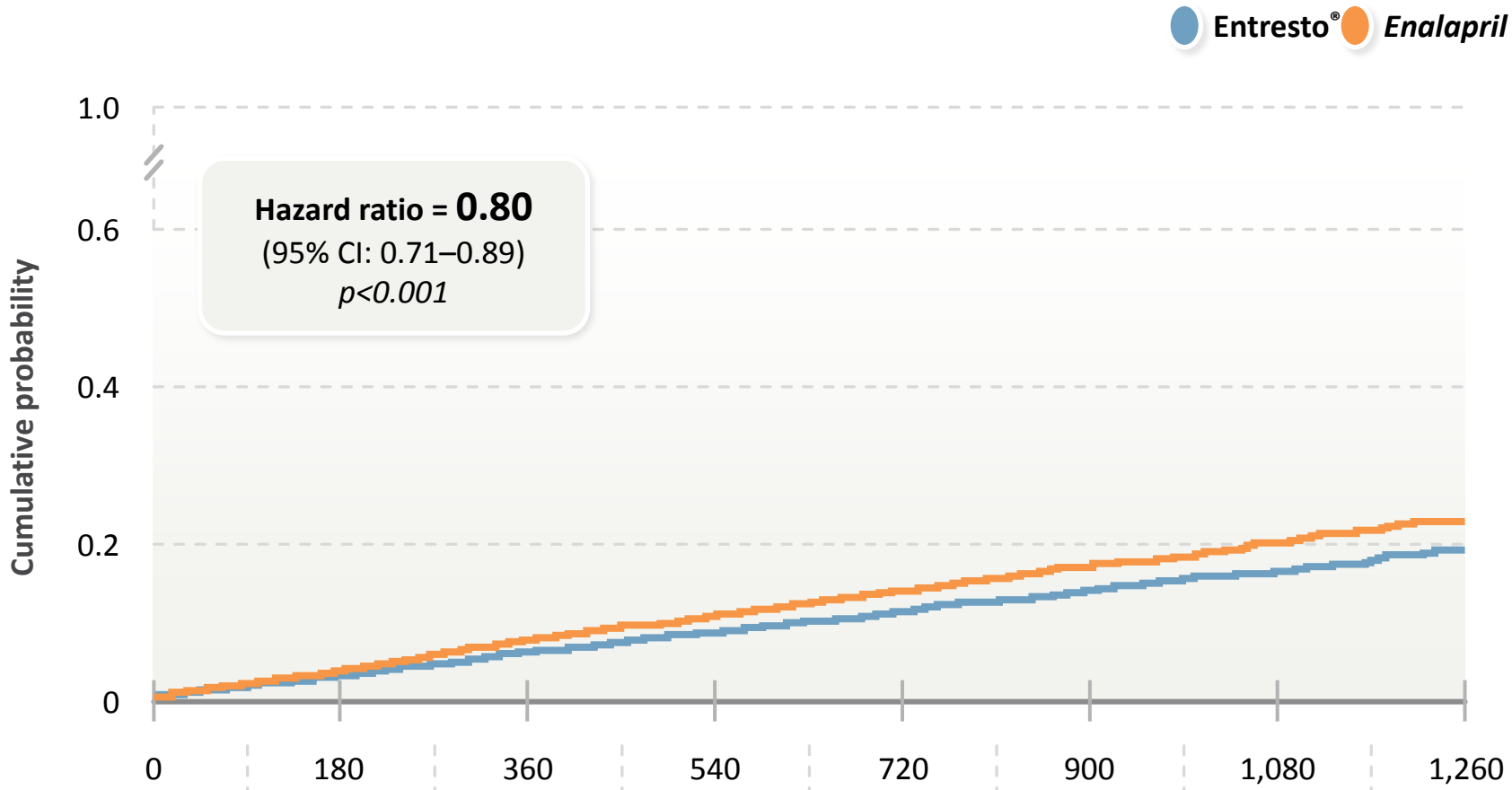
No. at risk

Entresto®	4,187	3,922	3,663	3,018	2,257	1,544	896	249
Enalapril	4,212	3,883	3,579	2,922	2,123	1,488	853	236

CI: confidence interval; CV: cardiovascular; HF: heart failure

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

Components of primary endpoint: death from CV causes



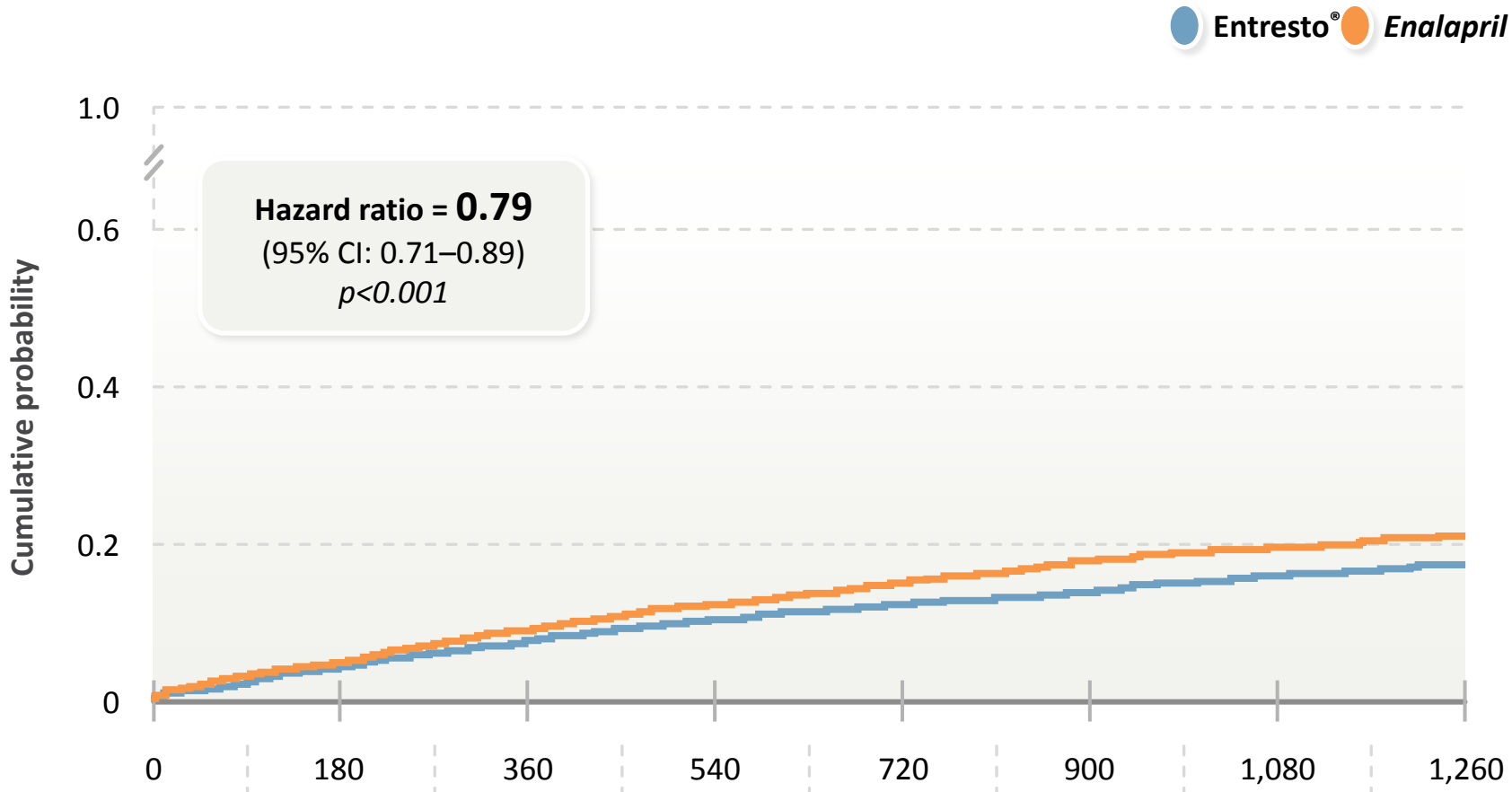
No. at risk

Entresto®	4,187	4,056	3,891	3,282	2,478	1,716	1,005	280
Enalapril	4,212	4,051	3,860	3,231	2,410	1,726	994	279

CI: confidence interval; CV: cardiovascular; HF: heart failure

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

Components of primary endpoint: first hospitalization for HF



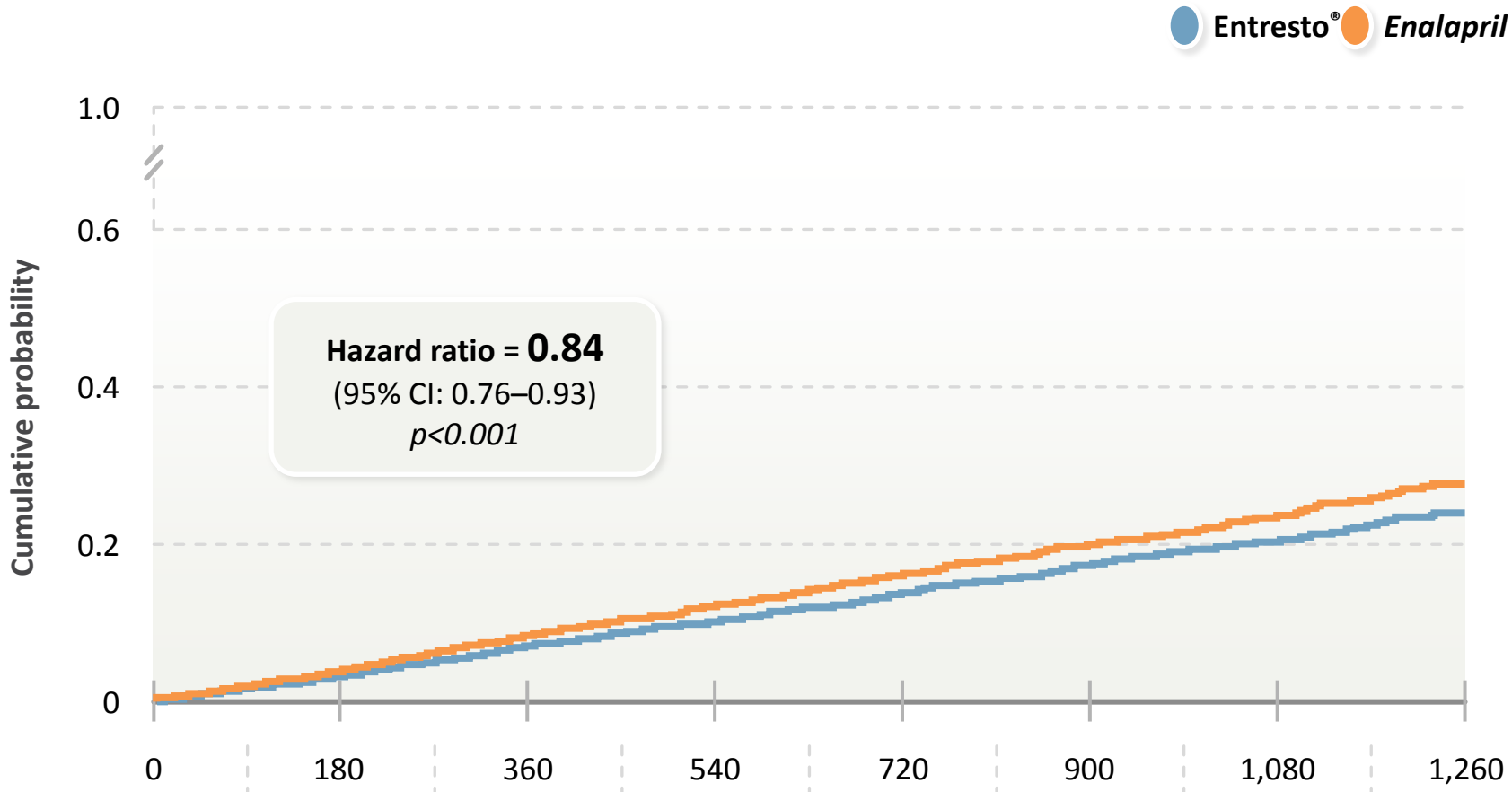
No. at risk

Entresto®	4,187	3,922	3,663	3,018	2,257	1,544	896	249
Enalapril	4,212	3,883	3,579	2,922	2,123	1,488	853	236

CI: confidence interval; CV: cardiovascular; HF: heart failure

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

Death from any cause



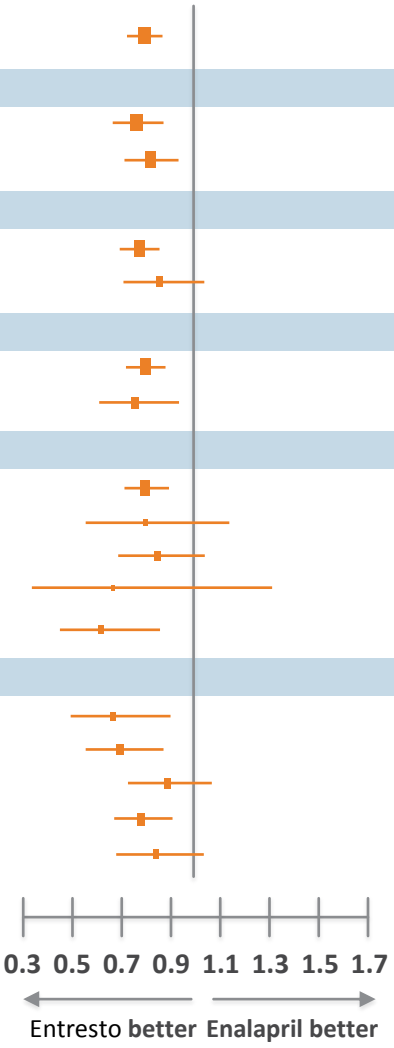
No. at risk								
Entresto®	4,187	4,056	3,891	3,282	2,478	1,716	1,005	280
Enalapril	4,212	4,051	3,860	3,231	2,410	1,726	994	279

CI: confidence interval

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

Pre-specified subgroup analysis for the primary endpoint (CV death or HF hospitalization) – 1 of 3

Subgroup, n patients	Entresto®	Enalapril	p value for interaction
All patients	4,187	4,212	
Age			0.47
<65 years	2,111	2,168	
≥65 years	2,076	2,044	
Age			0.32
<75 years	3,403	3,433	
≥75 years	784	779	
Sex			0.63
Male	3,308	3,259	
Female	879	953	
Race			0.58
White	2,763	2,781	
Black	213	215	
Asian	759	750	
Native American	84	88	
Other	368	378	
Region			0.37
North America	310	292	
Latin America	713	720	
Western Europe and other	1,026	1,025	
Central Europe	1,393	1,433	
Asia-Pacific	745	742	



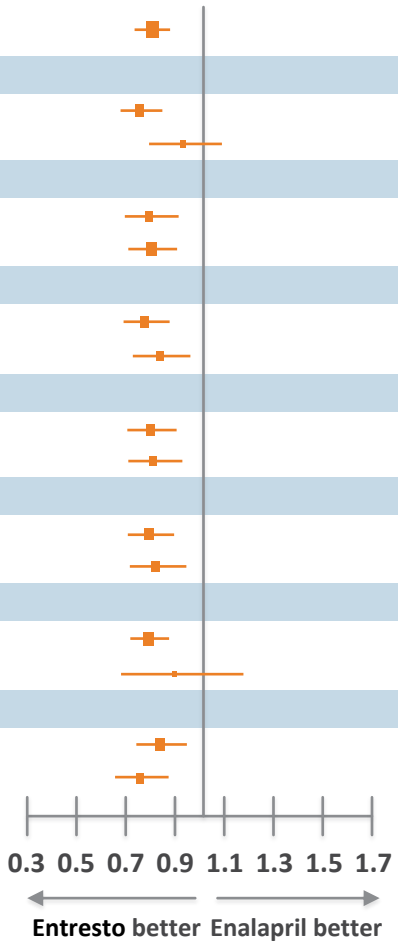
*The size of the square corresponds to the number of patients within each subgroup

CI: confidence interval; CV: cardiovascular; HF: heart failure

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

Pre-specified subgroup analysis for the primary endpoint (CV death or HF hospitalization) – 2 of 3

Subgroup, n patients	Entresto®	Enalapril	Hazard ratio* (95% CI)	p value for interaction
All patients	4,187	4,212		
NYHA class				0.03‡
I or II	3,178	3,130		
III or IV	1,002	1,076		
Estimated GFR				0.91
<60 mL/min/1.73 m2	1,541	1,520		
≥60 mL/min/1.73 m2	2,646	2,692		
Diabetes				0.40
No	2,736	2,756		
Yes	1,451	1,456		
Systolic blood pressure				0.87
≤Median	2,298	2,299		
>Median	1,889	1,913		
Ejection fraction				0.71
≤Median	2,239	2,275		
>Median	1,948	1,936		
Ejection fraction				0.36
≤35%	3,715	3,722		
>35%	472	489		
Atrial fibrillation				0.25
No	2,670	2,638		
Yes	1,517	1,574		



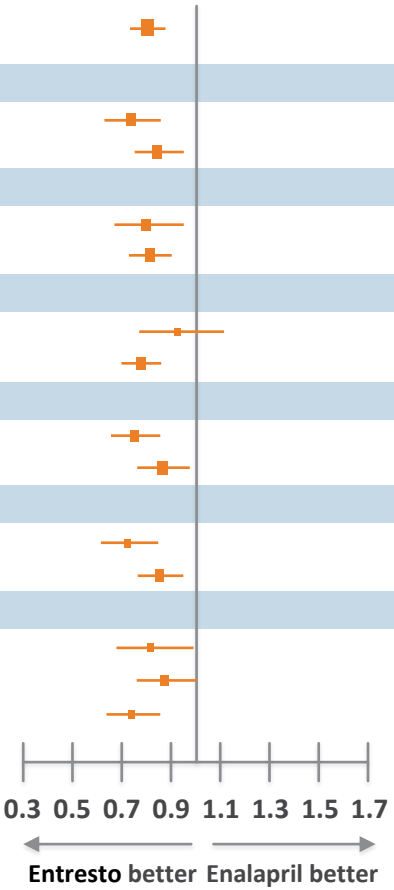
**The size of the square corresponds to the number of patients within each subgroup; ‡A nominally significant interaction between NYHA class at randomization and the effect of treatment on the primary endpoint (p=0.03, unadjusted for multiple comparisons) was not seen for the interaction of NYHA class and treatment effect on CV mortality (p=0.76).*

CI: confidence interval; CV: cardiovascular; GFR: glomerular filtration rate; HF: heart failure; NYHA: New York Heart Association

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

Pre-specified subgroup analysis for the primary endpoint (CV death or HF hospitalization) – 3 of 3

Subgroup, n patients	Entresto®	Enalapril	Hazard ratio* (95% CI)	p value for interaction
All patients	4,187	4,212		
NT-proBNP				0.16
≤Median	2,079	2,116		
>Median	2,103	2,087		
Hypertension				0.87
No	1,218	1,241		
Yes	2,969	2,971		
Prior use of ACEI				0.09
No	921	946		
Yes	3,266	3,266		
Prior use of aldosterone antagonist				0.10
No	1,916	1,812		
Yes	2,271	2,400		0.10
Prior hospitalization for HF				
No	1,580	1,545		
Yes	2,607	2,667		0.27
Time since diagnosis of HF				
≤1 year	1,275	1,248		
>1 to 5 years	1,621	1,611		
>5 years	1,291	1,353		



*The size of the square corresponds to the number of patients within each subgroup

ACEI: angiotensin-converting-enzyme inhibitor; CI: confidence interval; CV: cardiovascular; HF: heart failure; NT-proBNP: N-terminal pro-B-type natriuretic peptide

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

Summary of results – efficacy

Primary outcome

- 20% reduction in CV death or HF hospitalization with Entresto® compared with enalapril
  - 20% reduction in CV mortality
  - 21% reduction in HF hospitalization

Secondary outcomes

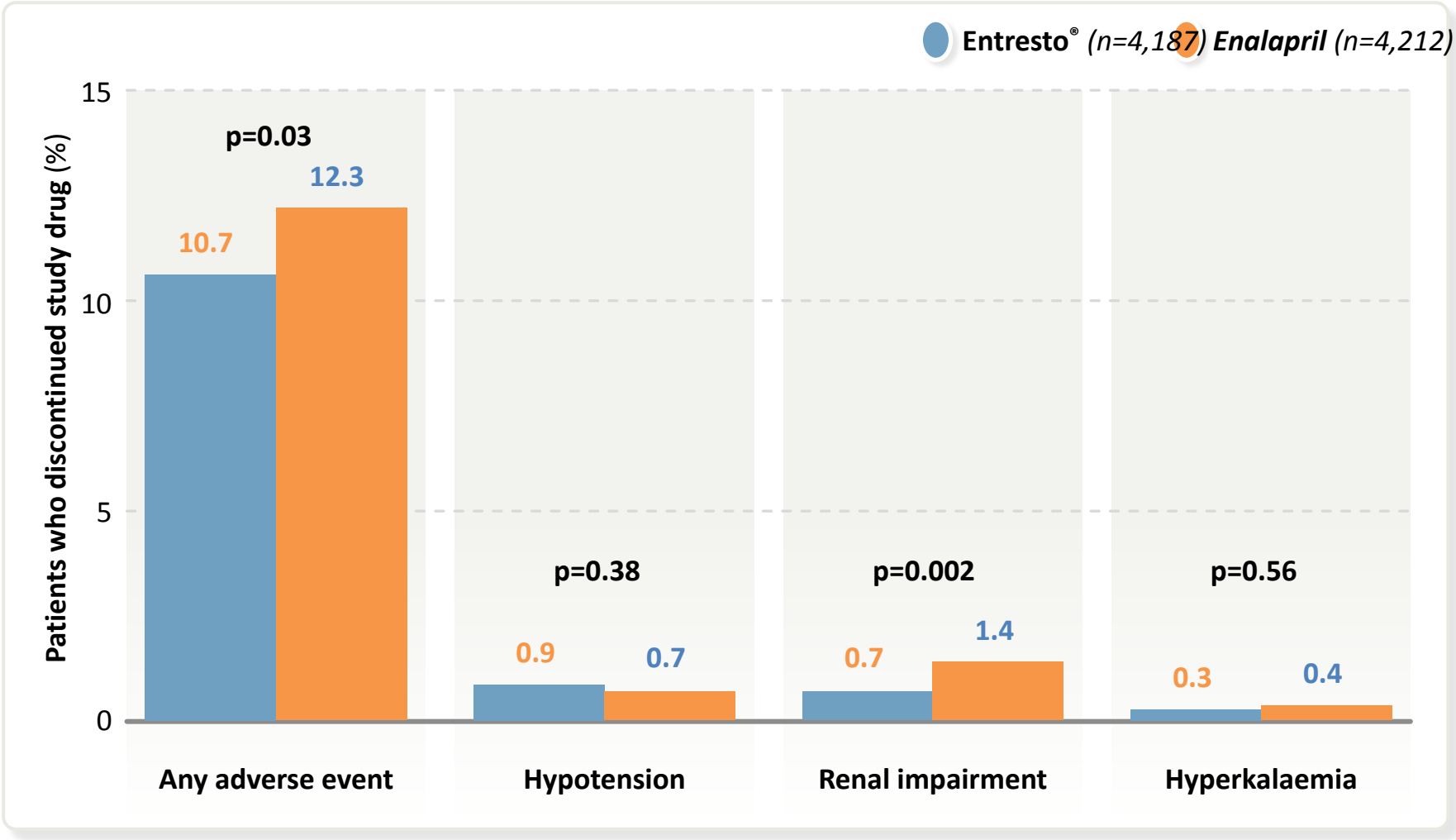
- 16% reduction in all-cause mortality with Entresto® vs enalapril
- No significant difference in incidence of new onset atrial fibrillation between treatment groups
- No significant difference in protocol-defined decline in renal function between treatment groups

CV: cardiovascular; GFR: glomerular filtration rate; HF: heart failure; KCCQ: Kansas City Cardiomyopathy Questionnaire

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

Adverse events leading to permanent study drug discontinuation

- Fewer patients in the Entresto group than in the enalapril group discontinued study drug due to an adverse event (10.7 vs 12.3%; p=0.03)



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

Cardiac resynchronization therapy-CRT
eller
Biventrikulär pacemaker

INDIKATIONER:

* På toppen av OPTIMAL LÄKEMEDELSBEH
* NYHA-klass II-IV
* EF < 35%
* QRS > 130 ms
  Bäst resultat vid SINUSRYTM
* Symptomatisk hjärtsvikt + PM-indikation +
  EF < 35% + risk för hög grad av HK-pacing.

Implantable cardioverter defibillator-ICD

INDIKATIONER

- Överlevt hjärtstillestånd (ej första 48 tim vid hjärtinfarkt)
- Allvarlig kammartakykardi
- Ejektionsfraktion < 35 % , 3 mån efter hjärtinfarkt
- Pat med hjärtsvikt i funktionsgrupp 2-3 och ejektionsfraktion < 35% trots optimal sviktbehandling
- Vissa hjärtmuskelsjukdomar med hög risk för plötslig död.

Försök sänka pulsen. Det är den enskilda parameter som korrelerar bäst till överlevnad.
Om vi inte når målet med betablockerare SR<70
Kan vi pröva en sinusknutehämmare

SINUSKNUTEHÄMNING MED IVABRADIN

SHIFTSTUDIEN

Inclusion criteria

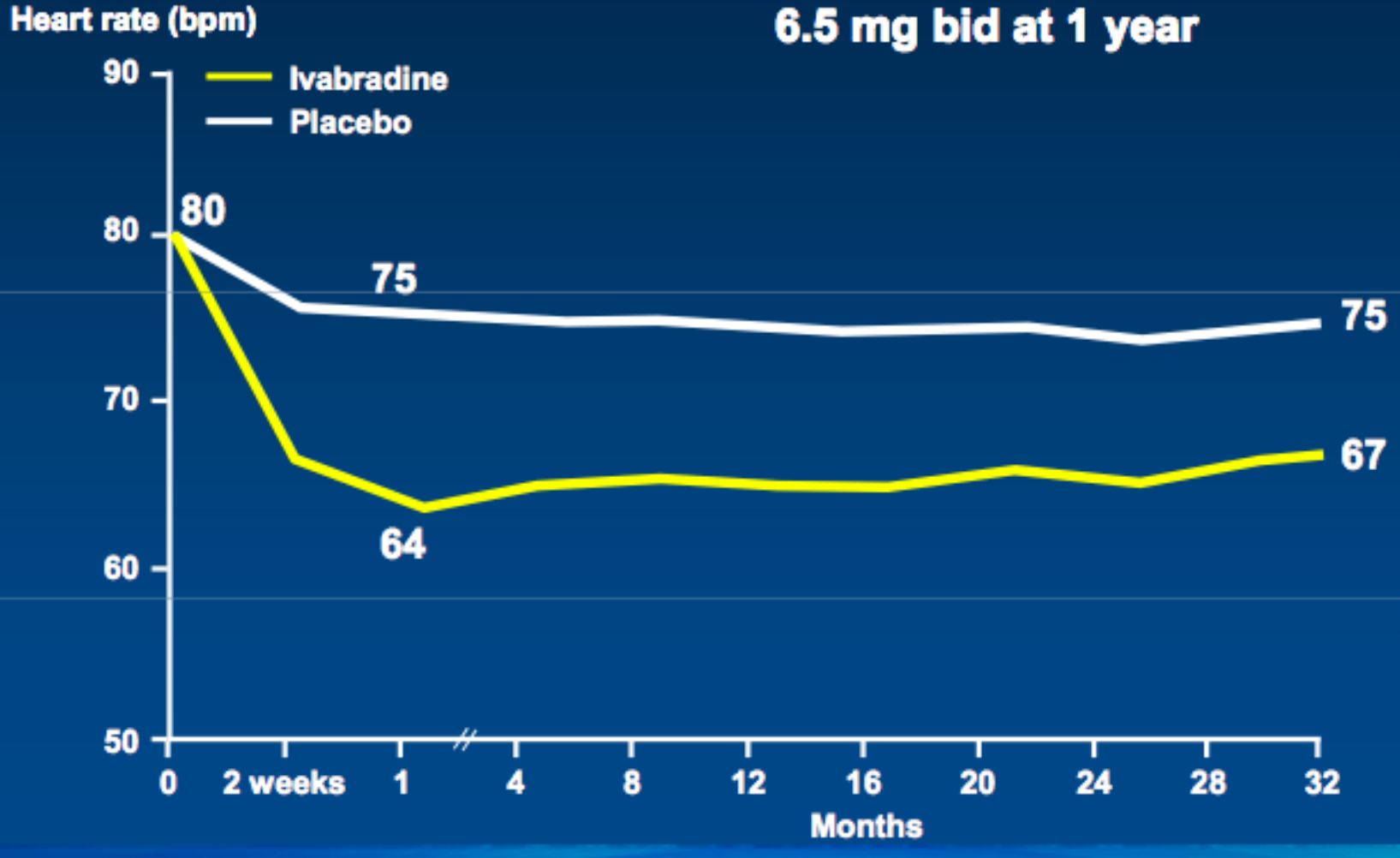
- ≥18 years
- Class II to IV NYHA heart failure
- Ischaemic/non-ischaemic aetiology
- LV systolic dysfunction (EF ≤35%)
- Heart rate ≥70 bpm
- Sinus rhythm
- Documented hospital admission for worsening heart failure ≤12 months

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

www.shift-study.com

Mean heart rate reduction

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

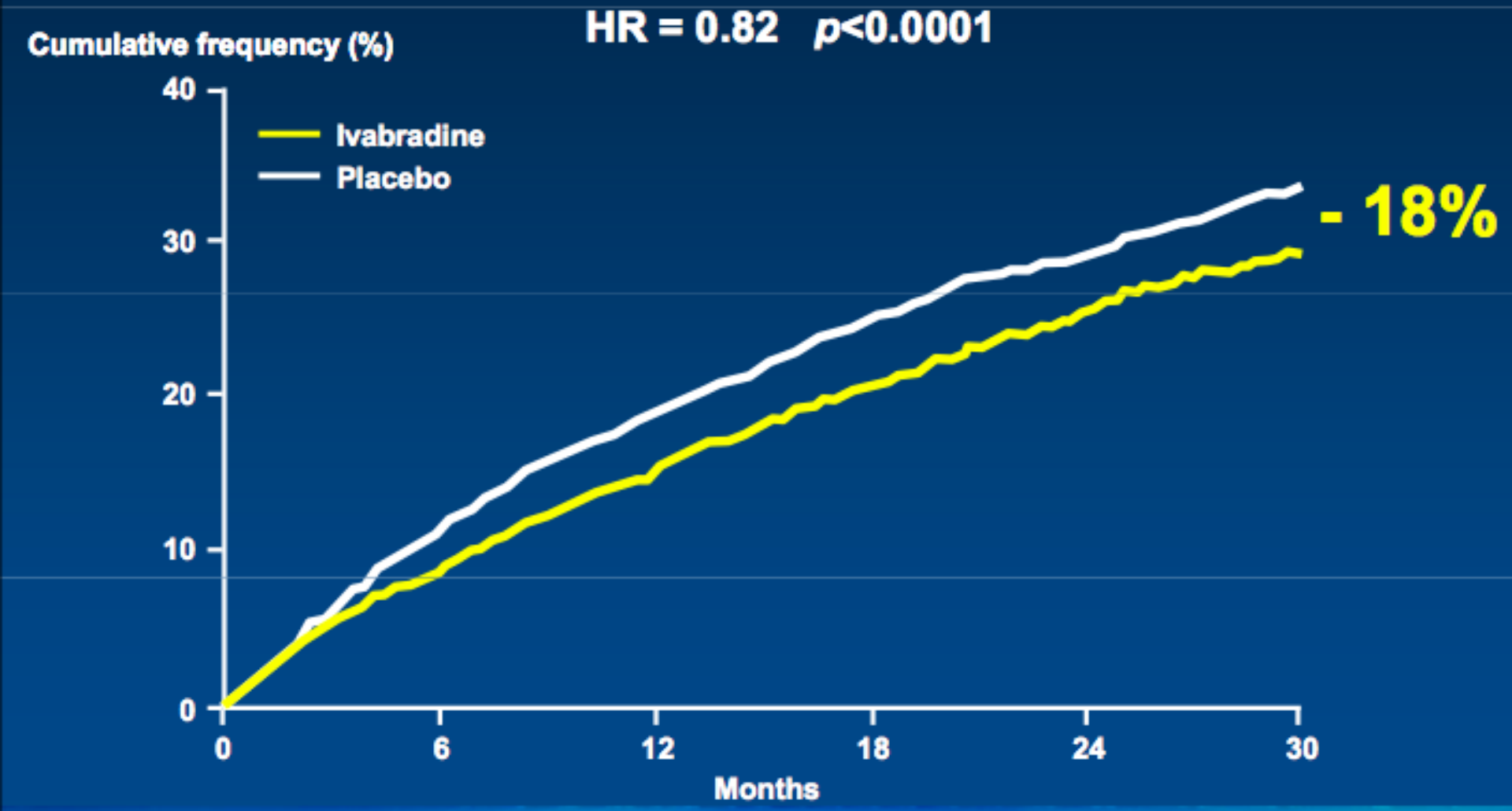


Swedberg K, et al. *Lancet.* 2010;DOI:10.1016/S0140-6736(10)61198-1.

Primary composite endpoint

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

HR = 0.82 $p<0.0001$



Swedberg K, et al. *Lancet.* 2010;DOI:10.1016/S0140-6736(10)61198-1.

Intravenöst Järn-Confirm -HF

Ferrocarboxymaltos (Ferinject)

Förbättrad: Gångsträcka (6 min walktest)

Förbättrad QoL

Förbättrad NYHA-klass

Vid HB < 150, Ferritin < 100

eller Ferritin 100-299 vid transferrinmättnad < 20 %

Medel och mediandos 1500 mg över ett års tid.

Både patienter med och utan anemi förbättras.

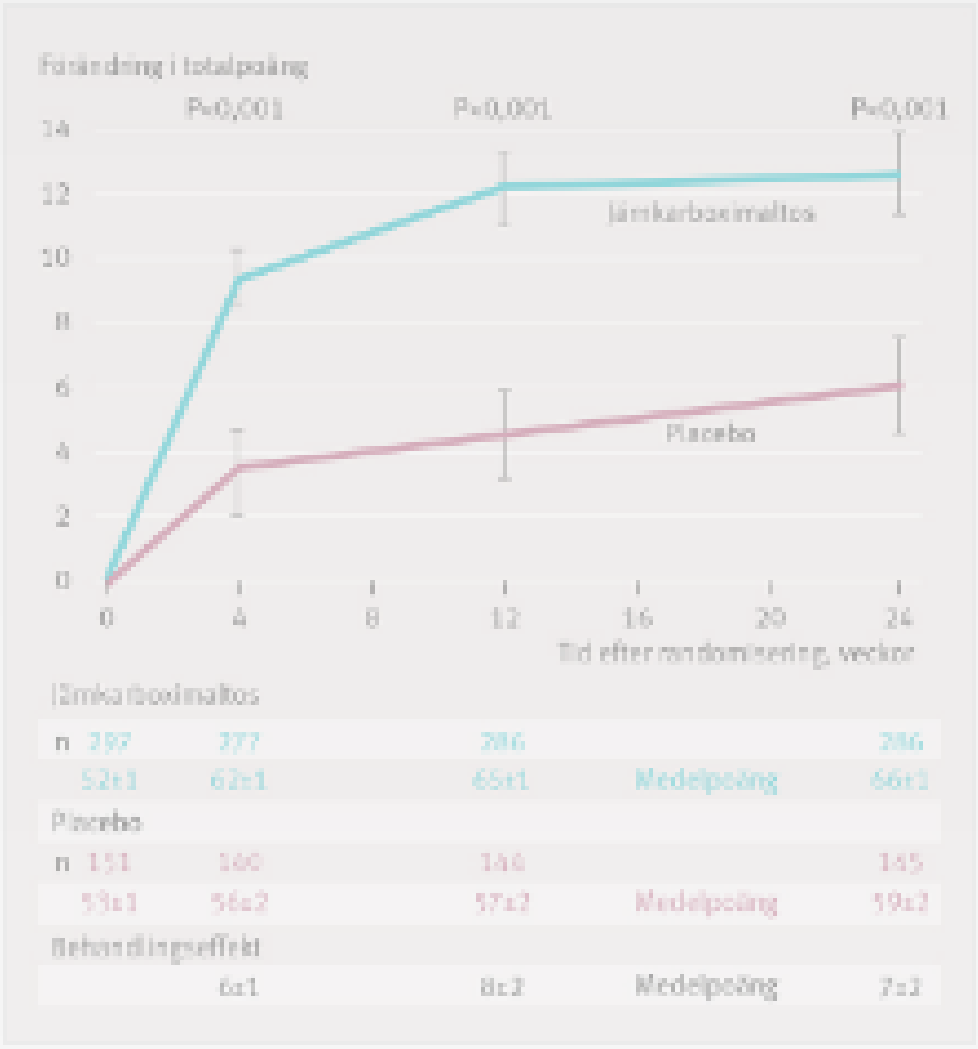
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

Stefan D. Anker, M.D., Ph.D., Josep Comin Colet, M.D., Gerasimos Filippatos, M.D., Ronnie Willenheimer, M.D., Kenneth Dickstein, M.D., Ph.D., Helmut Drexler, M.D., Thomas F. Lüscher, M.D., Boris Bart, M.D., Waldemar Banasiak, M.D., Ph.D., Joanna Niegowska, M.D., Bridget-Anne Kirwan, Ph.D., Claudio Mori, M.D., Barbara von Eisenhart Rothe, M.D., Stuart J. Pocock, Ph.D., Philip A. Poole-Wilson, M.D., and Piotr Ponikowski, M.D., Ph.D. for the FAIR-HF Trial Investigators

N Engl J Med 2009; 361:2436-2448 | December 17, 2009 | DOI: 10.1056/NEJMoa0908355



Figur 1. Förändring av hälsorelaterad livskvalitet enligt Kansas City cardiomyopathy questionnaire (KCCQ), presenterad som totalpoäng mellan 0 och 100, med högre värden vid bättre livskvalitet. Från [11].

Figur 2. Tid till inläggning på sjukhus på grund av försämrad hjärtsvikt i CONFIRM-HF-studien, beräknad med Kaplan–Meier-metoden. Från [12].

Intravenöst Järn-Confirm -HF

Ferrocarboxymaltos (Ferinject)

Förbättrad: Gångsträcka (6 min walktest)

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Förbättrad NYHA-klass

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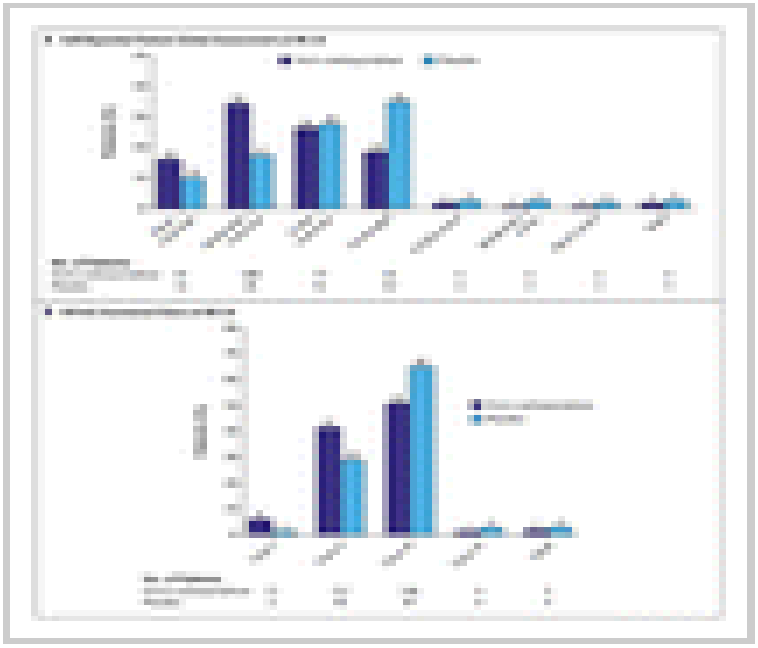
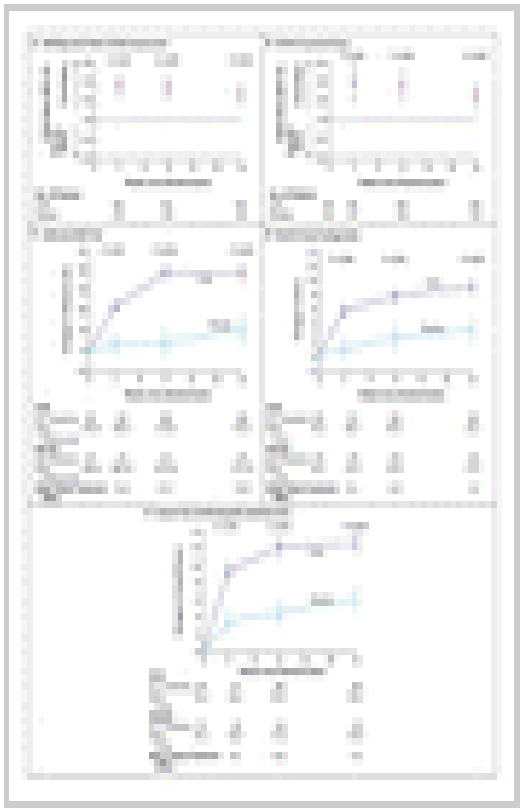


Self-Reported Patient Global Assessment and New York Heart Association (NYHA) Functional Class at Week 24, According to Assigned Study Treatment.



Main Secondary Outcomes during the Study, According to Assigned Study Treatment.


TACK FÖR ATT
NI LYSSNADE

Sacubitril/valsartan - Entresto®

Overview of Heart Failure, Entresto® and PARADIGM-HF Trial

This presentation or parts thereof is intended for non-promotional educational purposes by healthcare professionals. The scientific information is based on publicly available data as of March 8th 2016. As a result, there may be discrepancies from any subsequent publications.

SE1604468999

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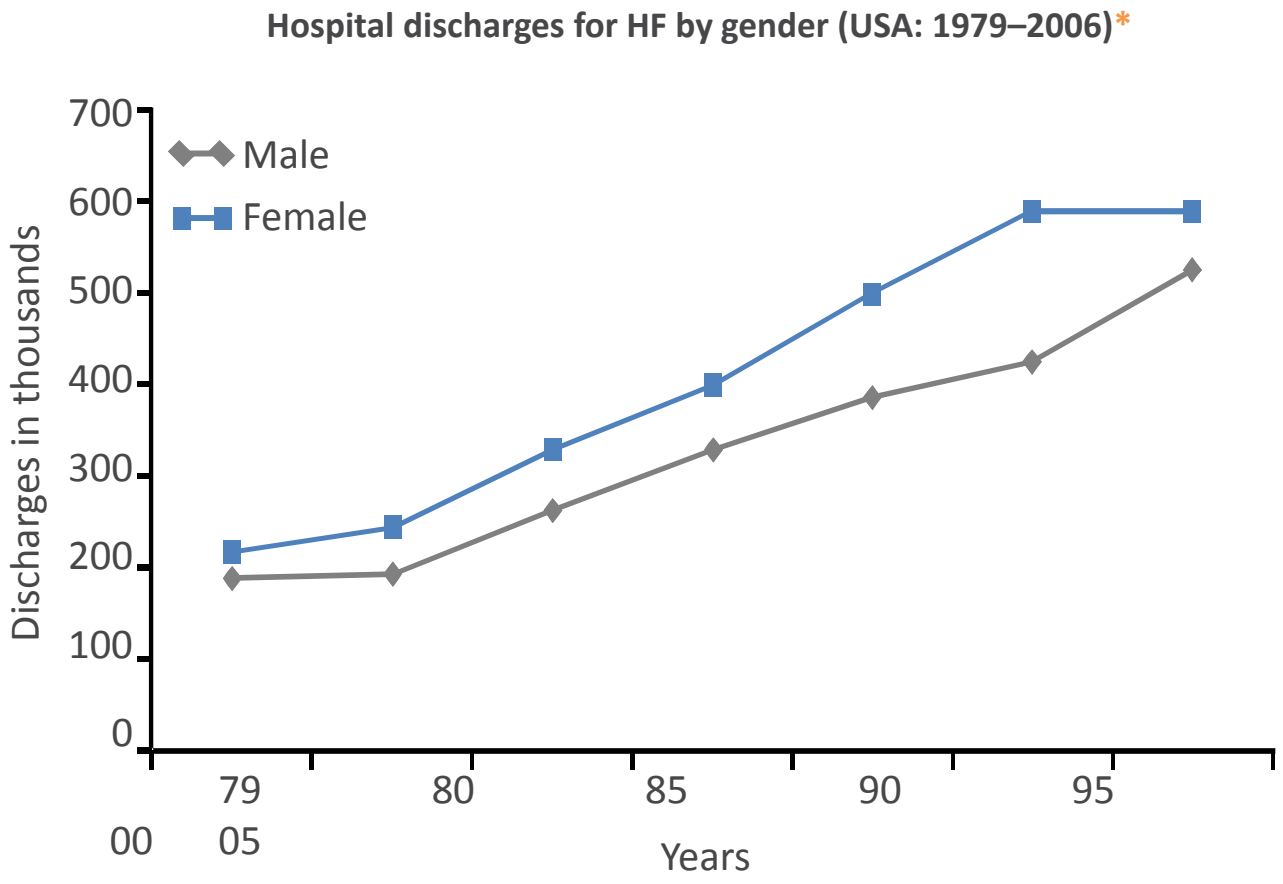
Overview of heart failure	05
Landmark trials in patients with HFrEF	09
Entresto®	14
PARADIGM-HF	20

HFrEF: heart failure with reduced ejection fraction

HF is increasing in prevalence

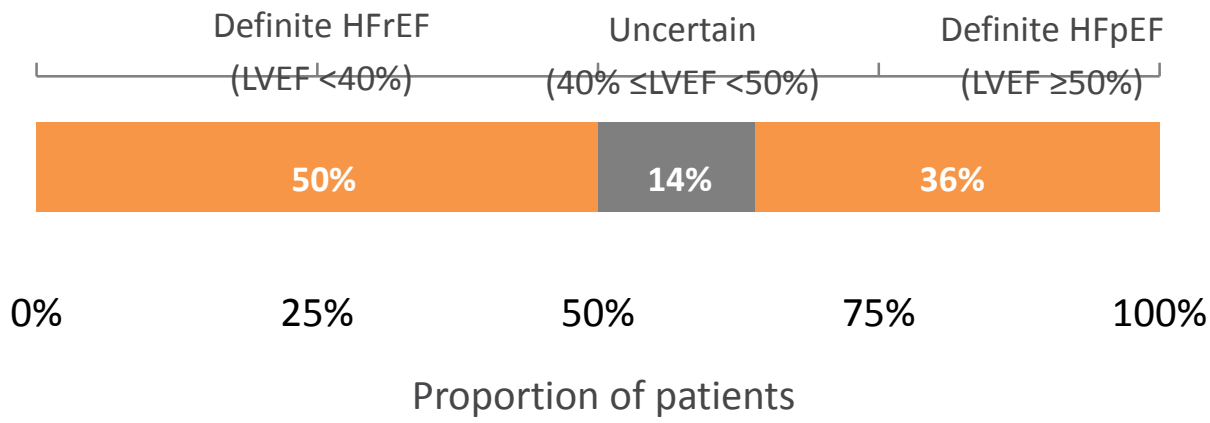


*Hospital discharges include people discharged alive, dead and of unknown status

HF: heart failure; USA: United States of America

Lloyd-Jones et al. Circulation 2010;121:e46–e215

Definition of HFrEF and HFpEF

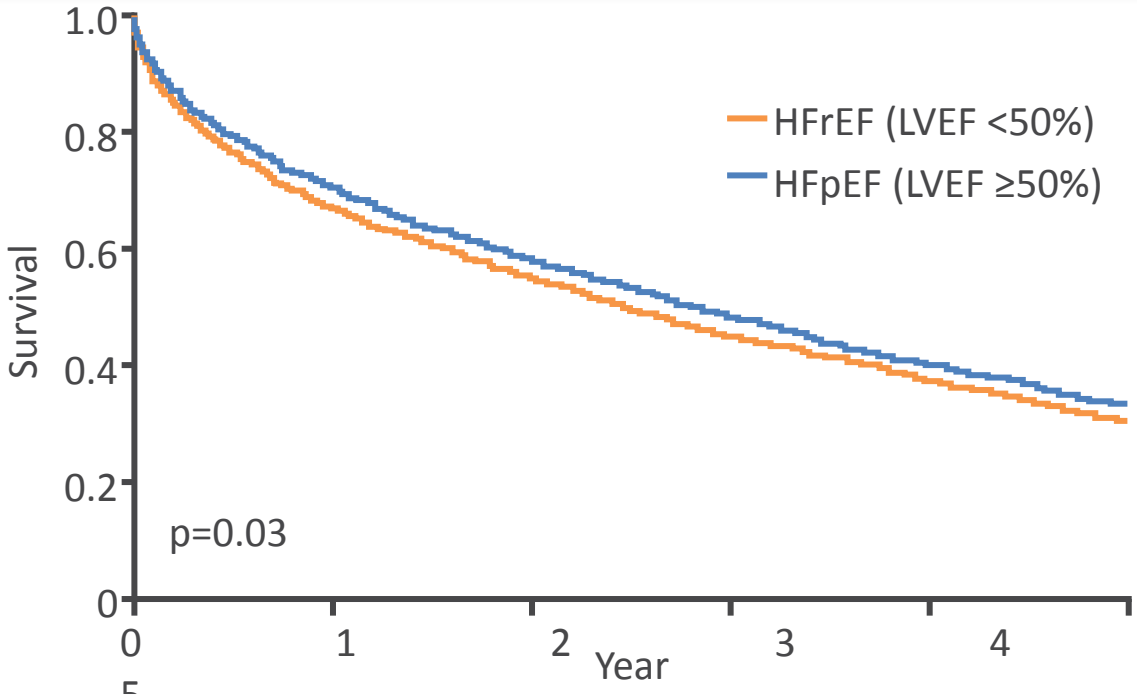


HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction

Steinberg et al. Circulation 2012;126:65–75

HFpEF and HFrEF are associated with similarly high levels of mortality

- Survival rate among patients with a discharge diagnosis of HF in the USA was slightly higher among patients with HFpEF than those with HFrEF between 1987–2001[1]
  - respective mortality rates were 29% and 32% at 1 year and 65% and 68% at 5 years



- HFpEF is associated with significant morbidity and mortality, despite having a slightly higher survival rate compared with HFrEF[2,3]

HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; USA: United States of America

1. Owan et al. N Engl J Med 2006;355:251–9; 2. Bidiche et al. Swiss Med Wkly 2010;140:66–72;

3. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). Eur Heart J 2012;33:1750–7

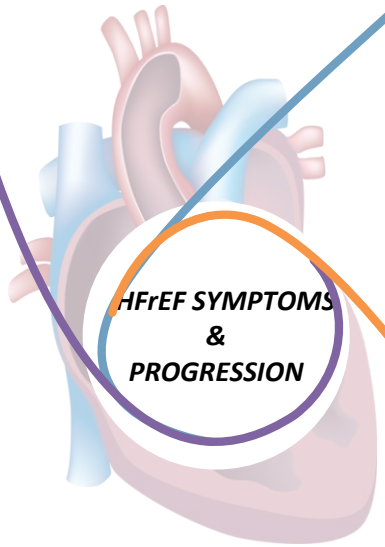
Overactivation of the RAAS and SNS is detrimental in HFrEF and underpins the basis of therapy

Natriuretic peptide system[1]

NPRs ← NPs

Vasodilation

- ↓ Blood pressure
- ↓ Sympathetic tone
- ↑ Natriuresis/diuresis
- ↓ Vasopressin
- ↓ Aldosterone
- ↓ Fibrosis
- ↓ Hypertrophy



Sympathetic nervous system

Epinephrine
Norepinephrine → α_1, β_1, β_2 receptors

Vasoconstriction

- RAAS activity ↑
- Vasopressin ↑
- Heart rate ↑
- Contractility ↑

Renin-angiotensin-aldosterone-system

Ang II → AT_1R

Vasoconstriction

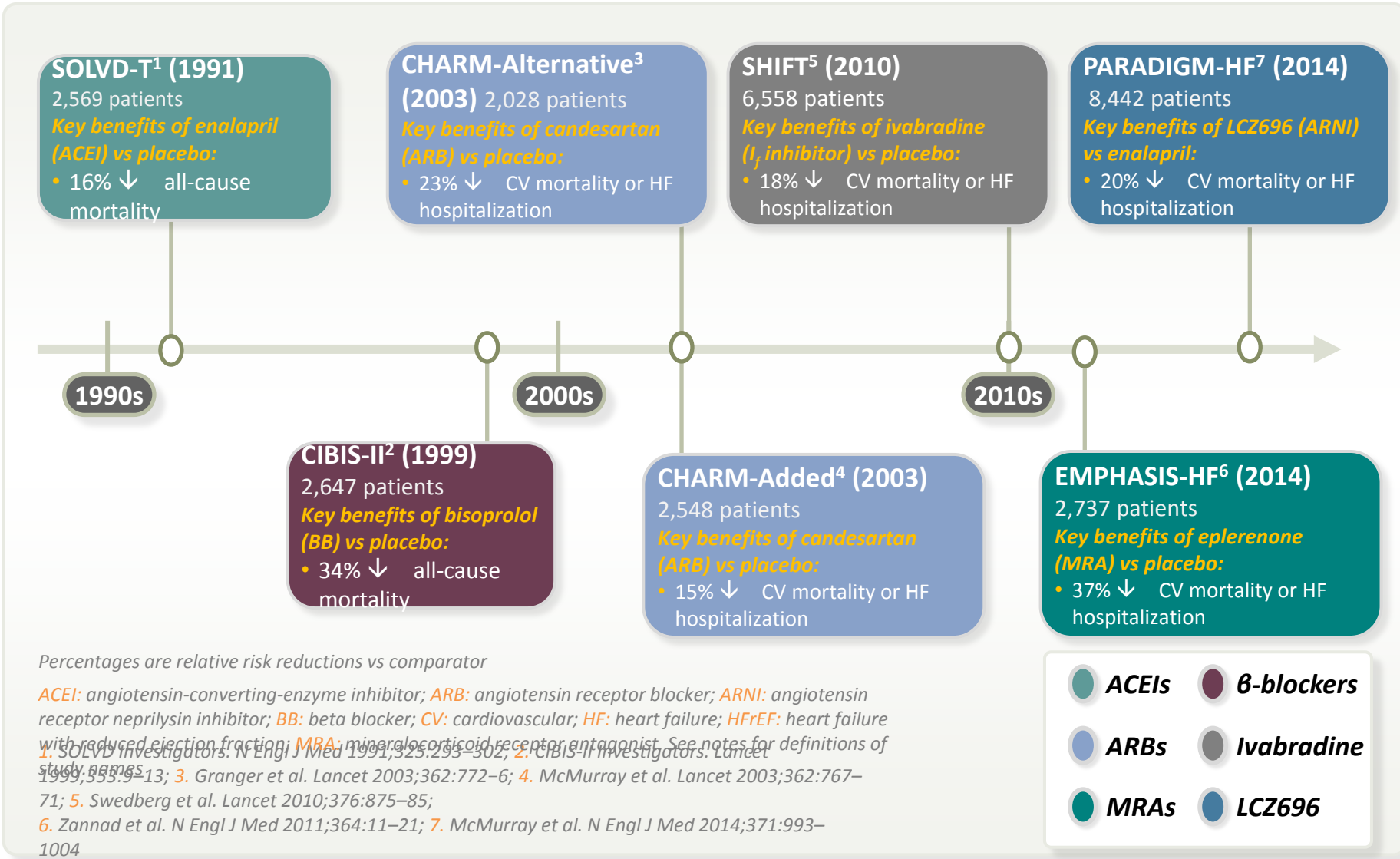
- Blood pressure ↑
- Sympathetic tone ↑
- Aldosterone ↑
- Hypertrophy ↑
- Fibrosis ↑

- The crucial importance of the RAAS is supported by the beneficial effects of ACEIs, ARBs and MRAs[1]
- Benefits of β-blockers indicate that the SNS also plays a key role[1]

ACEI: angiotensin-converting-enzyme inhibitor; Ang: angiotensin; ARB: angiotensin receptor blocker; AT_1R: angiotensin II type 1 receptor; MRA: mineralocorticoid receptor antagonist; NPs: natriuretic peptides; NPRs: natriuretic peptide receptors; RAAS: renin-angiotensin-aldosterone system; SNS: sympathetic nervous system

1. McMurray et al. Eur Heart J 2012;33:1787–847; Figure References: Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42; Kemp & Conte. Cardiovascular Pathology 2012;365–71;
Schrier & Abraham. N Engl J Med 2009;341:577–85

Landmark trials in patients with HFrEF



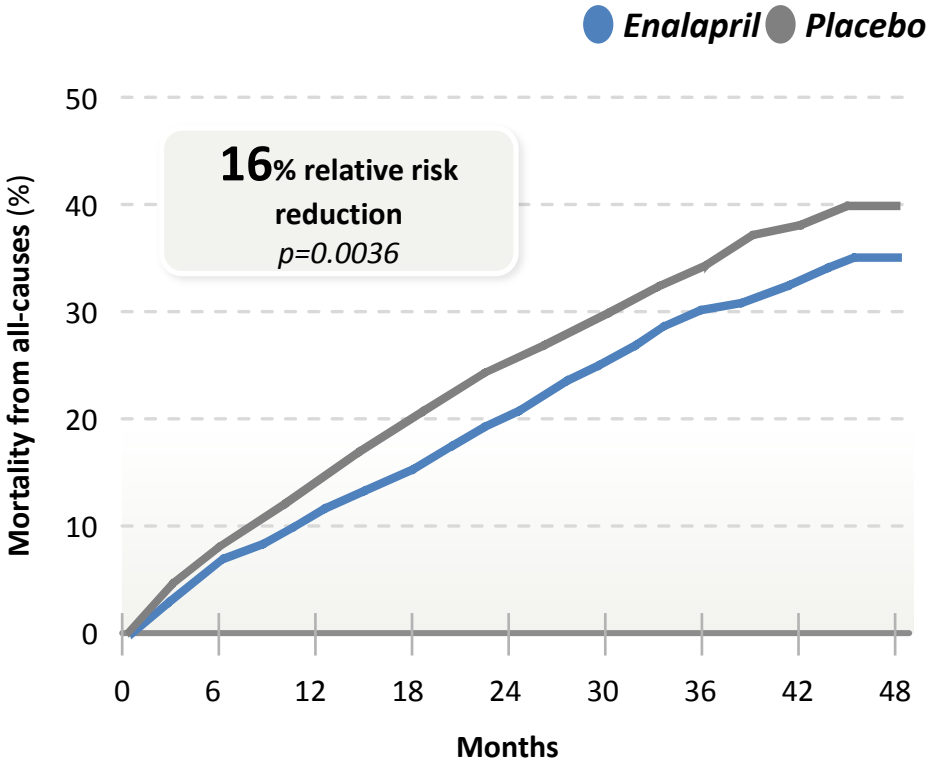
Percentages are relative risk reductions vs comparator

ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BB: beta blocker; CV: cardiovascular; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; MRA: mineralocorticoid receptor antagonist. See notes for definitions of study names

1. SOLVD Investigators. N Engl J Med 1991;325:293–302; 2. CIBIS-II Investigators. Lancet 1999;353:9–13; 3. Granger et al. Lancet 2003;362:772–6; 4. McMurray et al. Lancet 2003;362:767–71; 5. Swedberg et al. Lancet 2010;376:875–85; 6. Zannad et al. N Engl J Med 2011;364:11–21; 7. McMurray et al. N Engl J Med 2014;371:993–1004

SOLVD-Treatment: enalapril (ACEI) significantly reduced the risk of mortality in patients with HFrEF

SOLVD-Treatment	
Intervention	Enalapril 2.5–20 mg* QD vs placebo*
Number of patients	2,569
Average age (years)	61
Female (%)	19.7
LVEF	≤35% (NYHA I–IV)
Primary outcome	All-cause mortality
Mean follow-up (months)	41.4



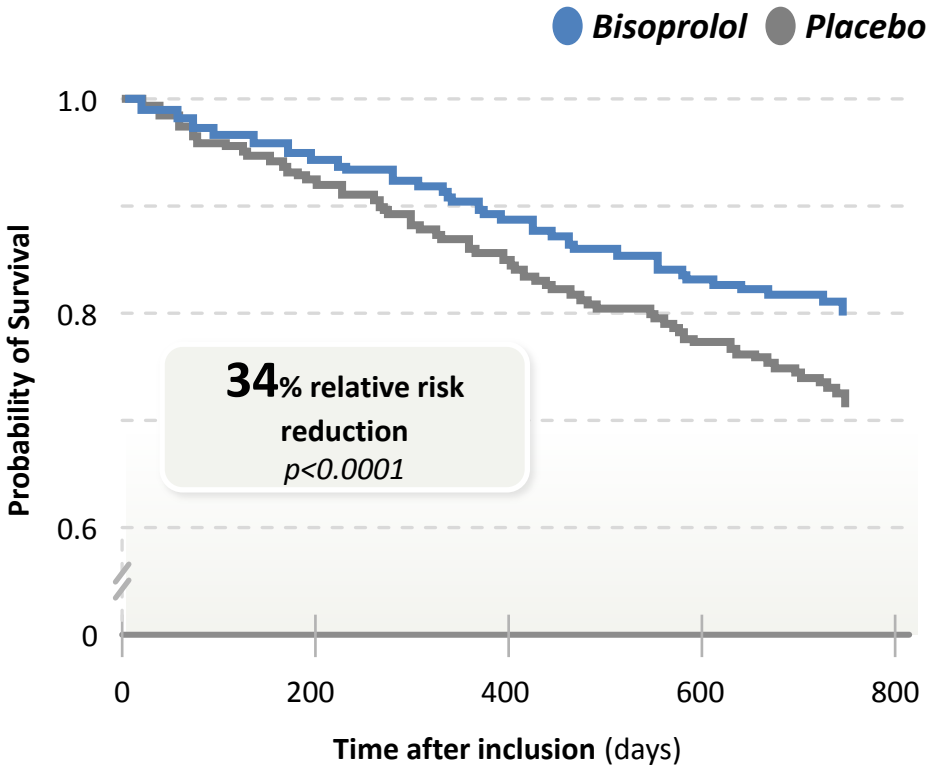
** On top of standard therapy for HF.*

ACEI: angiotensin-converting-enzyme inhibitor; HF: heart failure; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; QD: once daily; SOLVD: Studies of Left Ventricular Dysfunction

SOLVD Investigators. N Engl J Med 1991;325:293–302

CIBIS-II: bisoprolol (BB) significantly reduced all-cause mortality in patients with HFrEF

CIBIS-II	
Intervention	Bisoprolol 1.25–10 mg* QD vs placebo*
Number of patients	2,647
Average age (years)	61
Female (%)	20
LVEF	≤35% (NYHA III–IV)
Primary outcome	All-cause mortality
Mean follow-up (years)	1.3



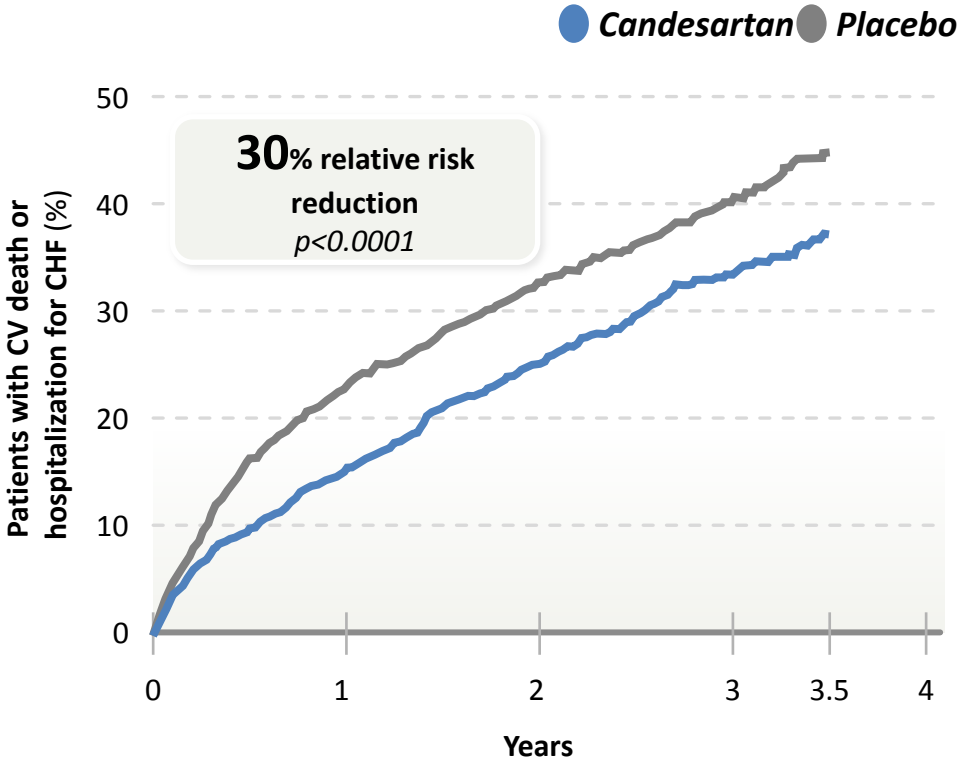
* On top of standard therapy with diuretics and ACEIs

ACEI: angiotensin-converting-enzyme inhibitor; BB: beta blocker; CIBIS: Cardiac Insufficiency Bisoprolol Study II; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; QD: once daily

CIBIS-II Investigators. Lancet 1999;353:9–13

CHARM-Alternative: candesartan (ARB) significantly reduced CV mortality and morbidity in patients with HFrEF

CHARM-Alternative	
Intervention	Candesartan 32 mg QD vs placebo
Number of patients	2,028
Average age (years)	66.6
Female (%)	31.9
LVEF	≤40% (NYHA II–IV)
Primary outcome	Composite of CV mortality or CHF hospitalization
Median follow-up (months)	33.7

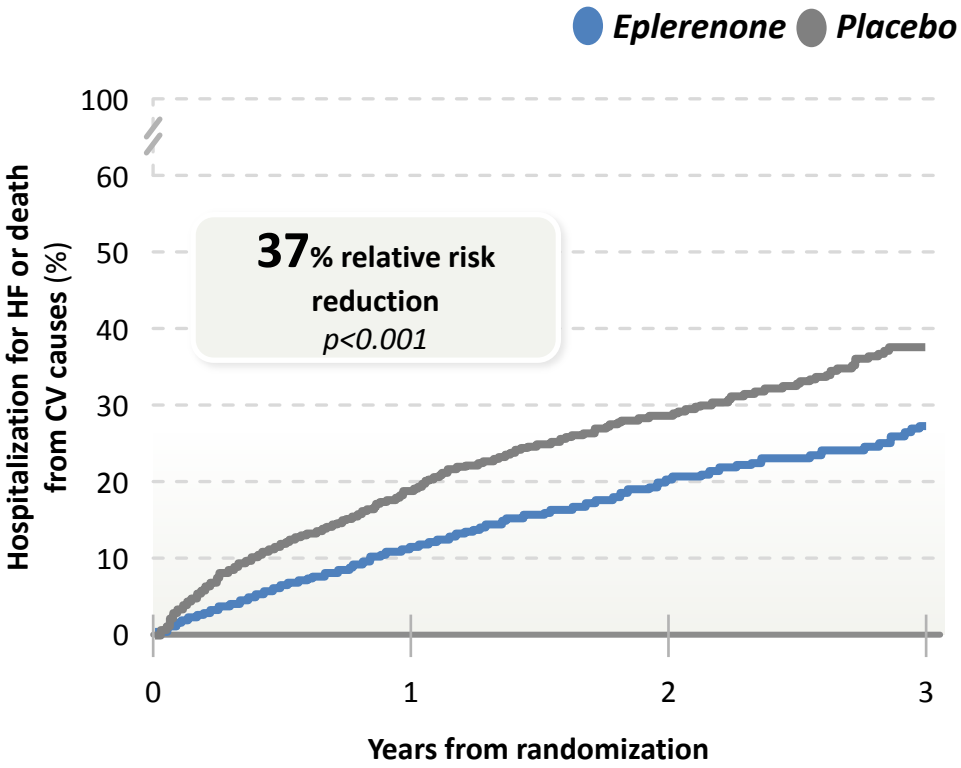


ARB: angiotensin receptor blocker; CHARM: Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity; CHF: chronic heart failure; CV: cardiovascular; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; QD: once daily

Granger et al. Lancet 2003;362:772–6

EMPHASIS-HF: eplerenone (MRA) significantly reduced the risk of CV mortality and hospitalization in patients with HFrEF

EMPHASIS-HF	
Intervention	Eplerenone 50 mg* QD vs placebo*
Number of patients	2,737
Average age (years)	68.7
Female (%)	22.3
LVEF	≤35% (NYHA II)
Primary outcome	Composite of CV mortality or HF hospitalization
Median follow-up (months)	21



* On top of standard therapy for HF

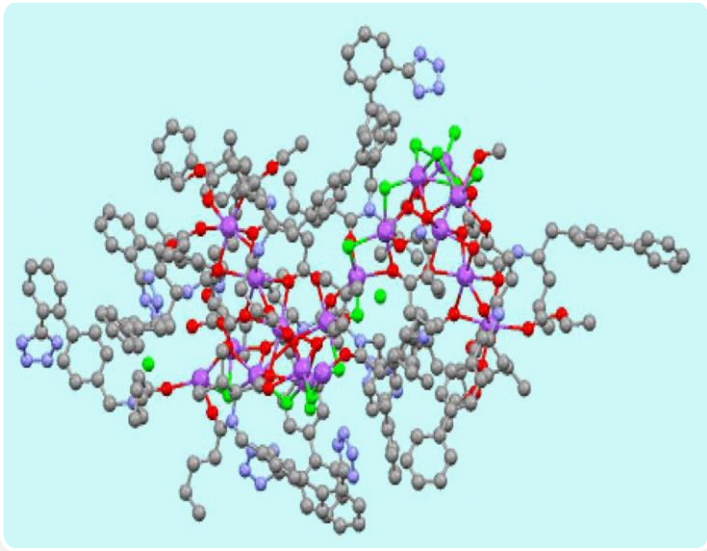
EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure; CV: cardiovascular; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; QD: once daily.

Zannad et al. N Engl J Med 2011;364:11–21

LCZ696 is a novel drug which delivers simultaneous neprilysin inhibition and AT_1 receptor blockade[1–3]

- Entresto® is a salt complex that comprises the two active components in a 1:1 molar ratio:[2,3]
  - Sacubitril – a pro-drug; further metabolized to the neprilysin inhibitor Sacubitrilat, and
  - valsartan – an AT_1 receptor blocker

    in a 1:1 molar ratio

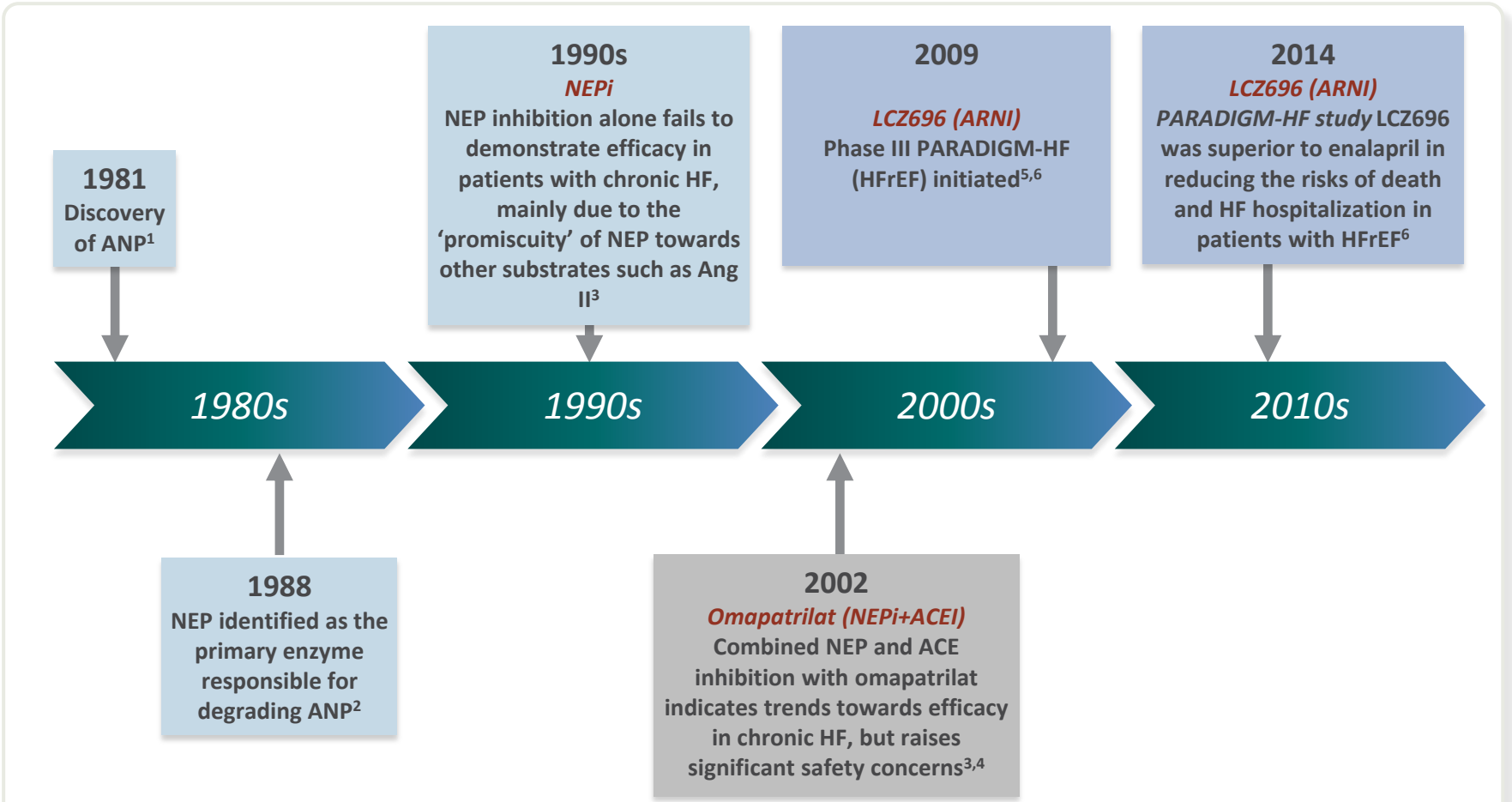


3D Entresto structure[2]

ARNI: angiotensin receptor neprilysin inhibitor; AT_1: angiotensin II type 1

1. Bloch & Basile. J Clin Hypertens 2010;12:809–12; 2. Gu et al. J Clin Pharmacol 2010;50:401–14; 3. Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9

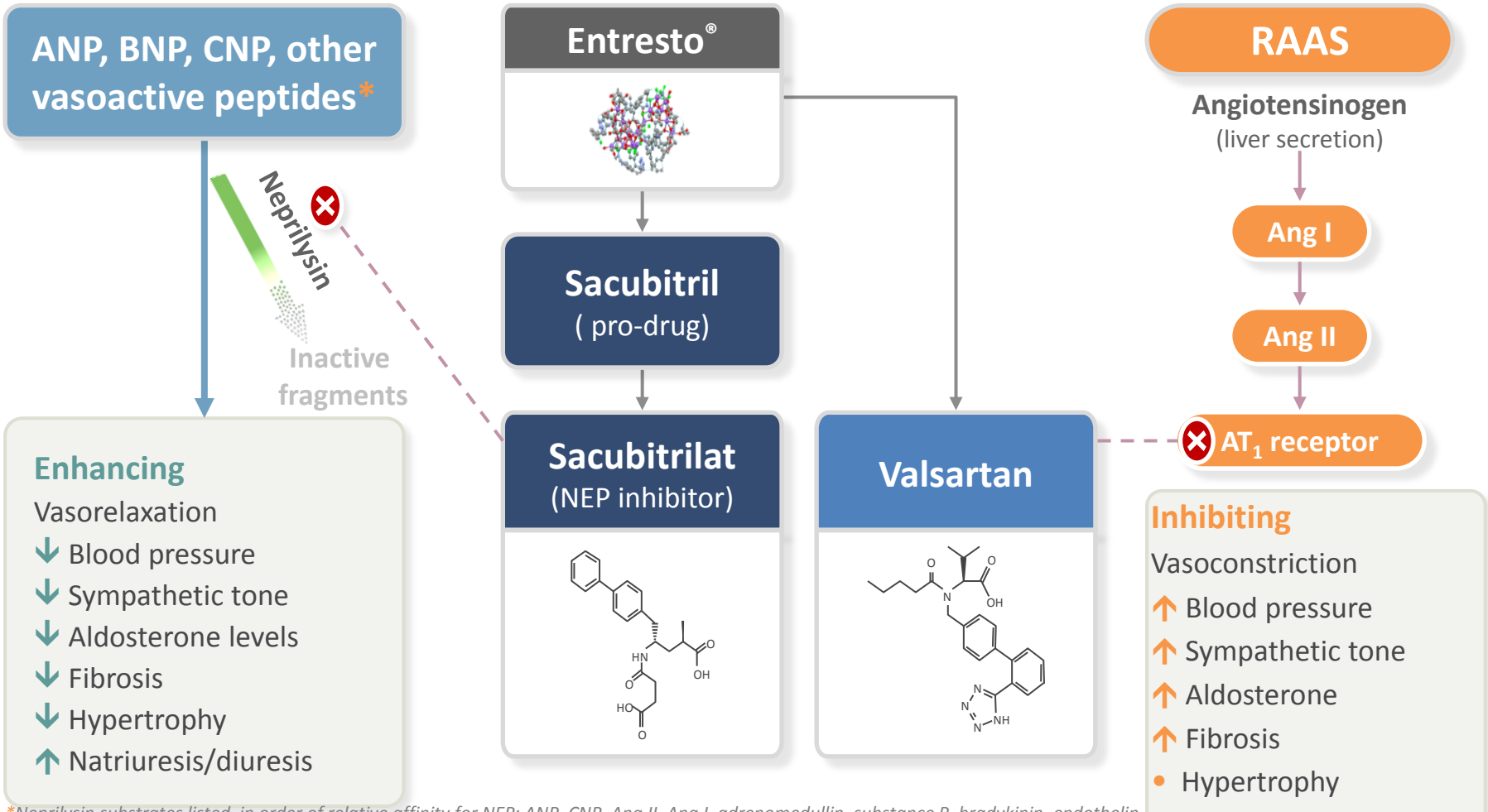
LCZ696 is the first agent to demonstrate a significant clinical benefit with NP system enhancement in chronic HF with reduced ejection fraction



ACE: angiotensin-converting enzyme; ACEI: angiotensin-converting-enzyme inhibitor; Ang: angiotensin; ANP: atrial natriuretic peptide; ARNI: angiotensin receptor neprilysin inhibitor; AT_1R: angiotensin II type 1 receptor; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; NEP: neprilysin; NEPi: neprilysin inhibition; NP: natriuretic peptide; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

1. de Bold et al. Life Sci 1981;28:89–94; 2. Sonnenberg et al. Peptides 1988;9:173–80; 3. Von Lueder et al. Pharmacol Ther 2014;144:41–9; 4. Packer et al. Circulation 2002;106:920–6; 5. McMurray et al. Eur J Heart Fail 2013;15:1062–73; 6. McMurray et al. N Engl J Med 2014;371:993–1004

LCZ696 simultaneously inhibits neprilysin (via Sacubitrilat) and blocks AT_1 receptors (via valsartan)

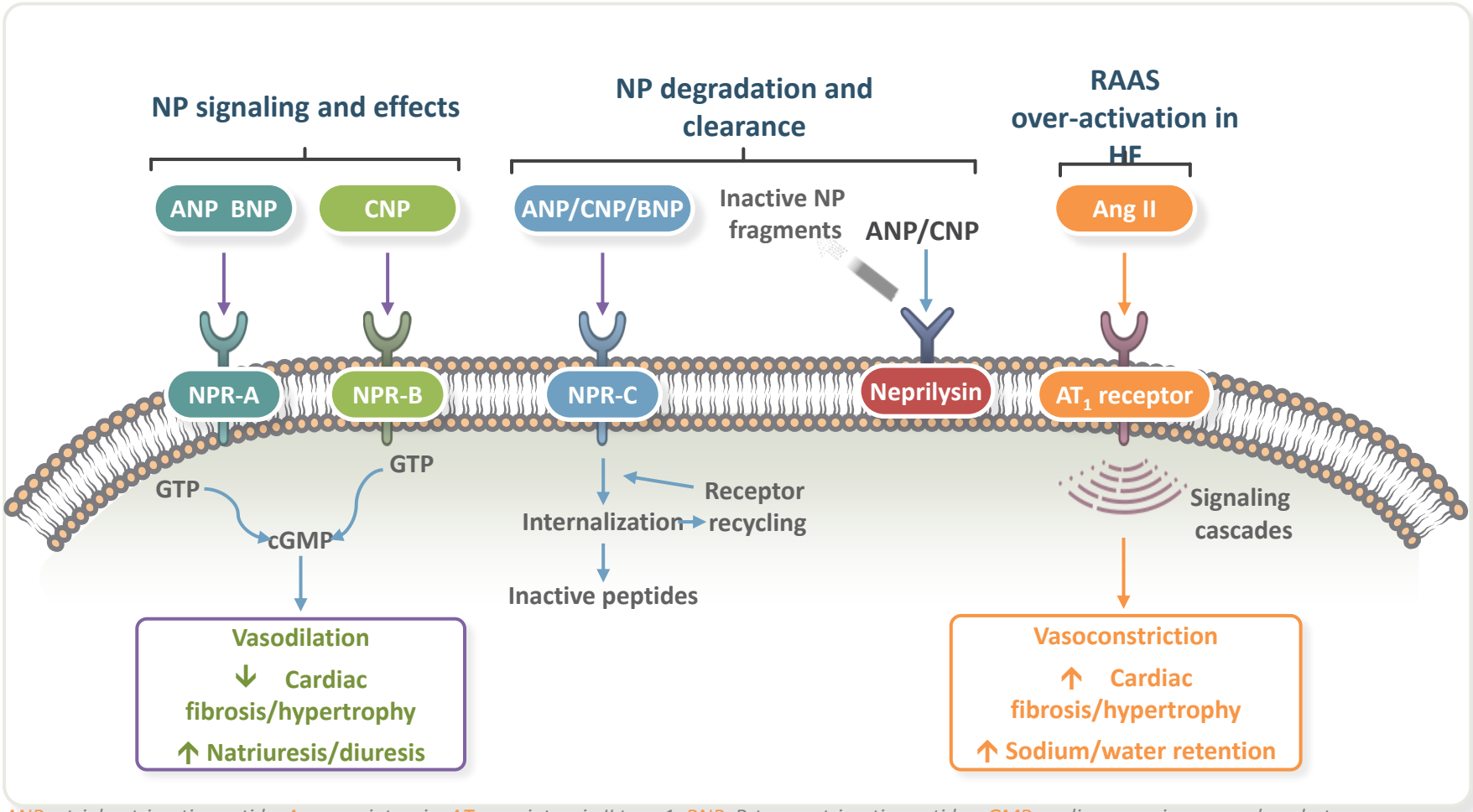


*Neprilysin substrates listed in order of relative affinity for NEP: ANP, CNP, Ang II, Ang I, adrenomedullin, substance P, bradykinin, endothelin-1, BNP

Ang: angiotensin; *ANP:* atrial natriuretic peptide; *AT_1:* angiotensin II type 1; *BNP:* B-type natriuretic peptide; *CNP:* C-type natriuretic peptide; *NEP:* neprilysin; *RAAS:* renin-angiotensin-aldosterone system

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

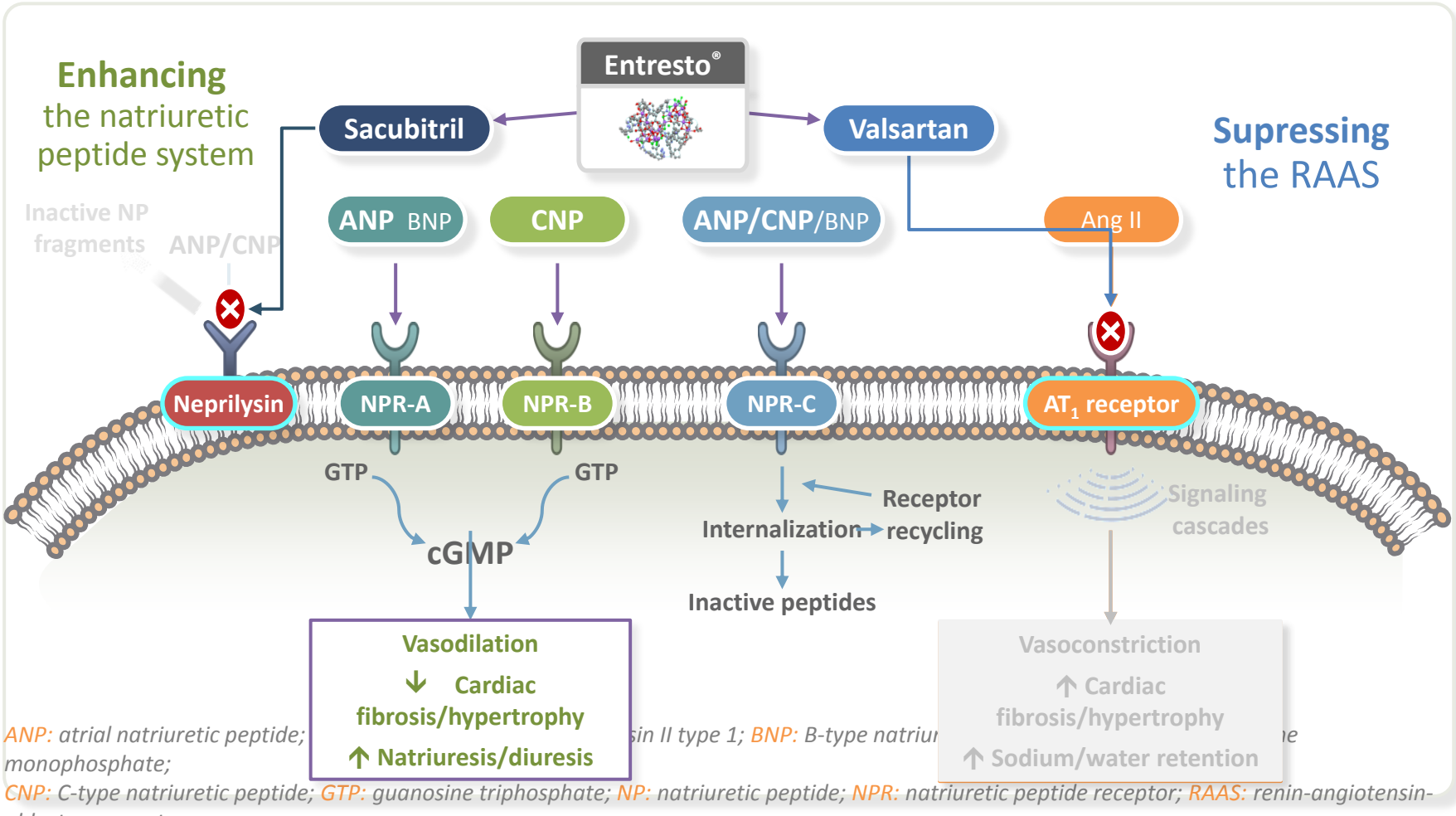
Natriuretic peptides are cleared by NPR-C and neprilysin



ANP: atrial natriuretic peptide; Ang: angiotensin; AT_1: angiotensin II type 1; BNP: B-type natriuretic peptide; cGMP: cyclic guanosine monophosphate; CNP: C-type natriuretic peptide; GTP: guanosine triphosphate; HF: heart failure; NP: natriuretic peptide; NPR: natriuretic peptide receptor; RAAS: renin-angiotensin-aldosterone system

Levin et al. N Engl J Med 1998;339;321–8; Gardner et al. Hypertension 2007;49:419–26; Molkentin. J Clin Invest 2003;111:1275–77; Nishikimi et al. Cardiovasc Res 2006;69:318–28; Guo et al. Cell Res 2001;11:165–80; Von Lueder et al. Circ Heart Fail 2013;6:594–605; Yin et al. Int J Biochem Cell 2003;35:780–3; Mehta & Griendling. Am J Physiol Cell Physiol 2007;292:C82–97

LCZ696 simultaneously enhances the beneficial effects of the NP system while blocking detrimental effects of the RAAS

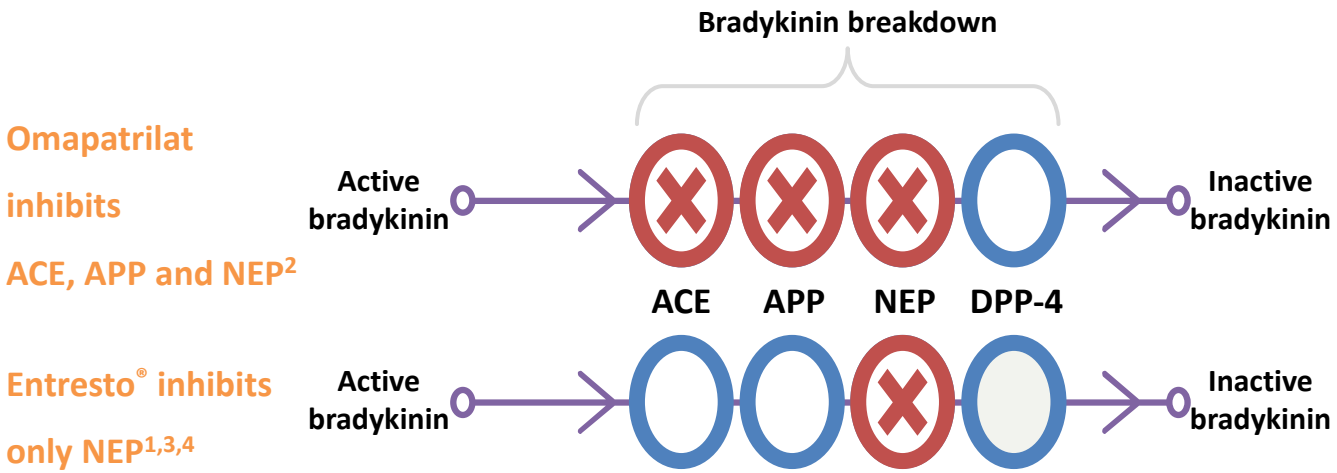


ANP: atrial natriuretic peptide; sin II type 1; BNP: B-type natriu e monophosphate;
CNP: C-type natriuretic peptide; GTP: guanosine triphosphate; NP: natriuretic peptide; NPR: natriuretic peptide receptor; RAAS: renin-angiotensin-aldosterone system

Levin et al. N Engl J Med 1998;339:321–8; Gardner et al. Hypertension 2007;49:419–26; Molkentin. J Clin Invest 2003;111:1275–77; Nishikimi et al. Cardiovasc Res 2006;69:318–28; Guo et al. Cell Res 2001;11:165–80; Von Lueder et al. Circ Heart Fail 2013;6:594–605; Yin et al. Int J Biochem Cell 2003;35:780–3; Mehta & Griendling. Am J Physiol Cell Physiol 2007;292:C82–97; Langenickel & Dole. Drug Discovery Today: Ther Strateg 2012;9:e131–9

LCZ696 actively inhibits neprilysin and the AT1 receptor, thus enabling alternative degradation pathways for bradykinin[1]

- Bradykinin is a substrate of neprilysin and other vasopeptidases (ACE, APP, DPP-4) – its elevation has been associated with cough and angioedema[2,3]
- Omapatrilat inhibits three enzymes (ACE, APP, NEP) involved in the breakdown of bradykinin, which is likely to be responsible for the development of angioedema[2]



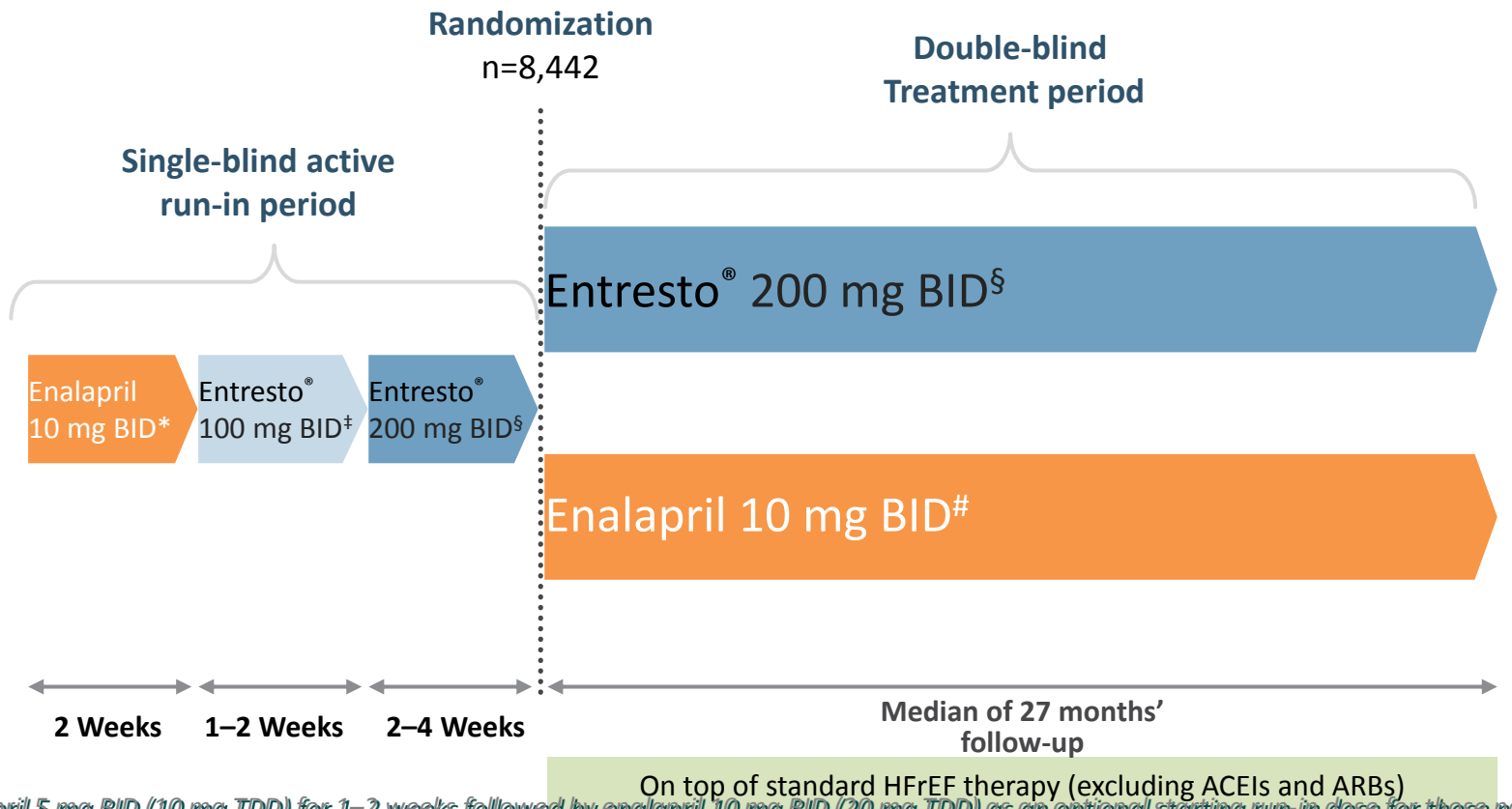
ACE: angiotensin-converting enzyme; APP: aminopeptidase P; AT_1: angiotensin II type 1; DPP-4: dipeptidyl peptidase-4; NEP: neprilysin

The information presented in this slide is from publicly available data and not head-to–head clinical trials

1. McMurray et al. Eur J Heart Fail. 2014;16:817–25; 2. Fryer et al. Br J Pharmacol 2008;153:947–55; 3. Semple. J Hypertens Suppl 1995;13:S17–21; 4. Gu et al. J Clin Pharmacol 2010;50:401–14; 5. McMurray et al. Eur J Heart Fail. 2013;15:1062–73; 6. McMurray, et al. N Engl J Med 2014;371:993–1004

Study Design

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

ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BID: twice daily; HFrEF: heart failure with reduced ejection fraction; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; TDD: total daily dose

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;371:993–1004

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*

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BNP: B-type natriuretic peptide; FC: functional class; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

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

PARADIGM-HF: key exclusion criteria

- History of angioedema
- eGFR <30 mL/min/1.73 m^2 at screening, end of enalapril run-in or randomization, or a >35% decrease in eGFR between screening and end of enalapril run-in or between screening and randomization
- Serum potassium >5.2 mmol/L at screening OR >5.4 mmol/L at the end of the enalapril run-in or end of the Entresto® run-in
- Requirement for treatment with both ACEI and ARBs
- Symptomatic hypotension, SBP <100 mmHg at screening, OR SBP <95 mmHg at end of enalapril
  run-in or at randomization
- Current acute decompensated HF
- History of severe pulmonary disease
- Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid, or other major CV surgery, PCI, or carotid angioplasty within the 3 months prior to screening

ACEI: angiotensin-converting-enzyme inhibitor; ARNI: angiotensin receptor neprilysin inhibitor; ARB: angiotensin receptor blocker; CV: cardiovascular; eGFR: estimated glomerular filtration rate; HF: heart failure; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; PCI: percutaneous coronary intervention; SBP: systolic blood pressure

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

PARADIGM-HF: primary objective

- To evaluate the effect of Entresto® 200 mg BID compared with enalapril 10 mg BID, in addition to conventional HFrEF treatment, in delaying **time to first occurrence** of either **CV death** or **HF hospitalization**[1]

Rationale for endpoint selection

- Primary outcome of CV death or HF hospitalization was chosen as the one that best reflects the major mortality and morbidity burden of HFrEF[1,2]
  - ~80% of deaths in recent trials in patients with HFrEF are CV related[3–5]
  - HF is associated with a high risk of hospitalization,[6] representing the leading cause of hospitalization in patients aged ≥65 years[6–9]
- The most commonly used primary endpoint in recent HF trials: CHARM-Added, SHIFT and EMPHASIS-HF[1]

ACE: angiotensin-converting enzyme; ACEI: angiotensin-converting-enzyme inhibitor; ARNI: angiotensin receptor neprilysin inhibitor; BID: twice daily; CHARM-Added: Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity in patients with HFrEF who were on ACE inhibitors; CV: cardiovascular; EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; SHIFT: Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial

1. McMurray et al. Eur J Heart Fail 2013;15:1062–73; 2. Dunlay et al. Circ Cardiovasc Qual Outcomes 2011;4:68–75; 3. McMurray et al. Lancet 2003;362:767–77; 4. Swedberg et al. Lancet 2010;376:875–88; 5. Zannad et al. N Engl J Med 2011;364:11–2; 6. Cowie et al. Oxford Health policy Forum 2014; 7. Hunt et al. J Am Coll Cardiol 2009;53:e1–90; 8. Yancy et al. Circulation 2013;128:e240–327; 9. Rodriguez-Artalejo et al. Rev Esp Cardiol 2004;57:163–70

PARADIGM-HF: the most geographically diverse trial in patients with HFrEF

- 8,442 patients were randomized at 985 sites in 47 countries[1,2]

ACEI: angiotensin-converting-enzyme inhibitor; ARNI: angiotensin receptor neprilysin inhibitor; HFrEF: heart failure with reduced ejection fraction; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

1. McMurray et al. Eur J Heart Fail 2014;16:817–25; 2. McMurray et al. Eur J Heart Fail 2013;15:1062–73

PARADIGM-HF: summary of baseline characteristics

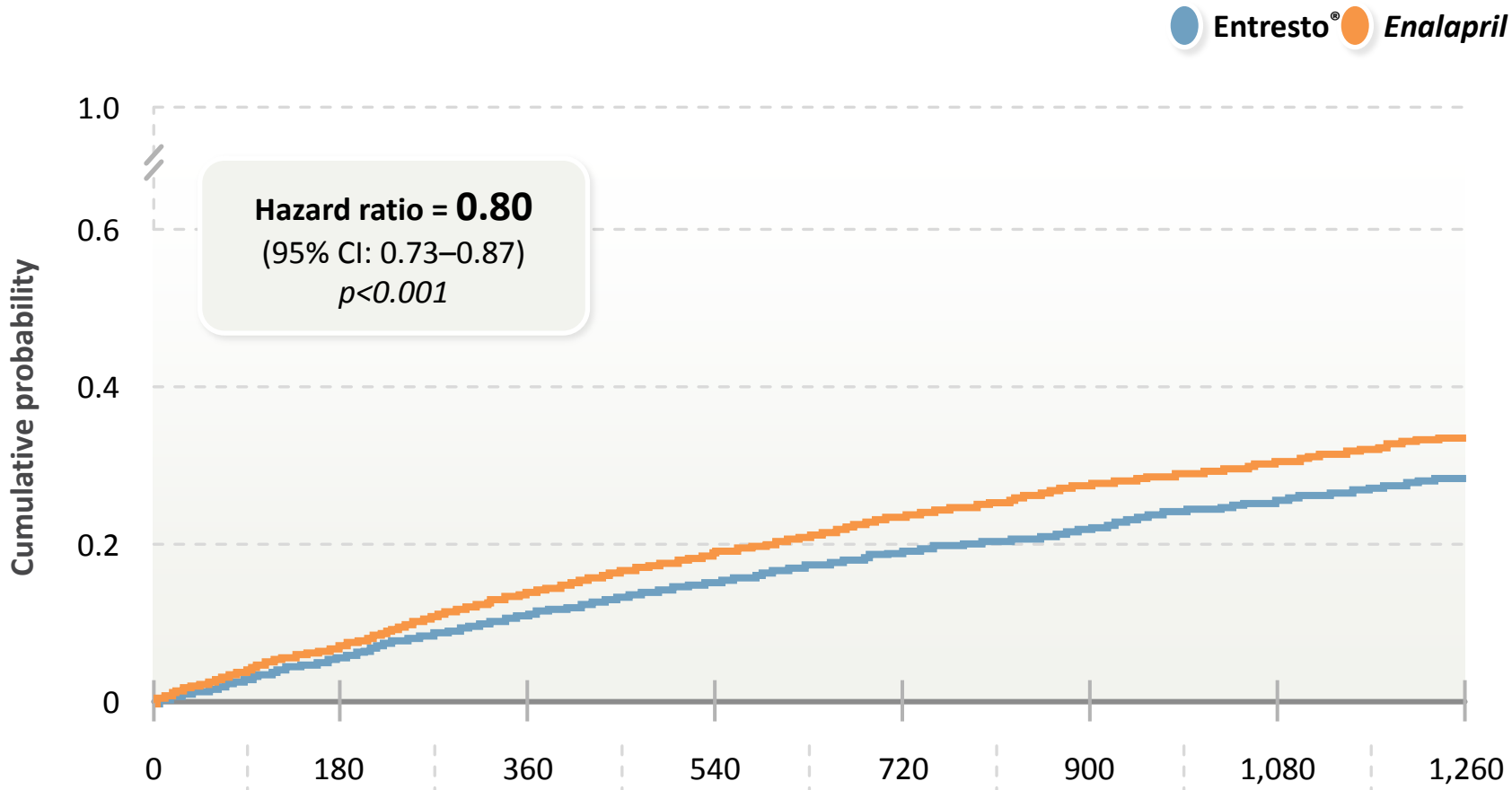
Characteristic*	Entresto® (n=4,187)	Enalapril (n=4,212)
Age, years	63.8 ± 11.5	63.8 ± 11.3
Women, n (%)	879 (21.0)	953 (22.6)
Ischemic cardiomyopathy, n (%)	2,506 (59.9)	2,530 (60.1)
LV ejection fraction, %	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class, n (%) II III	2,998 (71.6) 969 (23.1)	2,921 (69.3) 1,049 (24.9)
SBP, mmHg	122 ± 15	121 ± 15
Heart rate, beats/min	72 ± 12	73 ± 12
NT-proBNP, pg/mL (IQR)	1,631 (885–3,154)	1,594 (886–3,305)
BNP, pg/mL (IQR)	255 (155–474)	251 (153–465)
History of diabetes, n (%)	1,451 (34.7)	1,456 (34.6)
Treatments at randomization, n (%)		
Diuretics	3,363 (80.3)	3,375 (80.1)
Digitalis	1,223 (29.2)	1,316 (31.2)
β-blockers	3,899 (93.1)	3,912 (92.9)
Mineralocorticoid antagonists	2,271 (54.2)	2,400 (57.0)
ICD	623 (14.9)	620 (14.7)
CRT	292 (7.0)	282 (6.7)

** Mean ± standard deviation, unless stated*

ACEI: angiotensin-converting-enzyme inhibitor; ARNI: angiotensin receptor neprilysin inhibitor; BNP: B-type natriuretic peptide; CRT: cardiac resynchronization therapy; ICD: implantable cardioverter defibrillator; IQR: interquartile range; LV: left ventricular; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; SBP: systolic blood pressure

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

Primary endpoint: death from CV causes or first hospitalization for HF



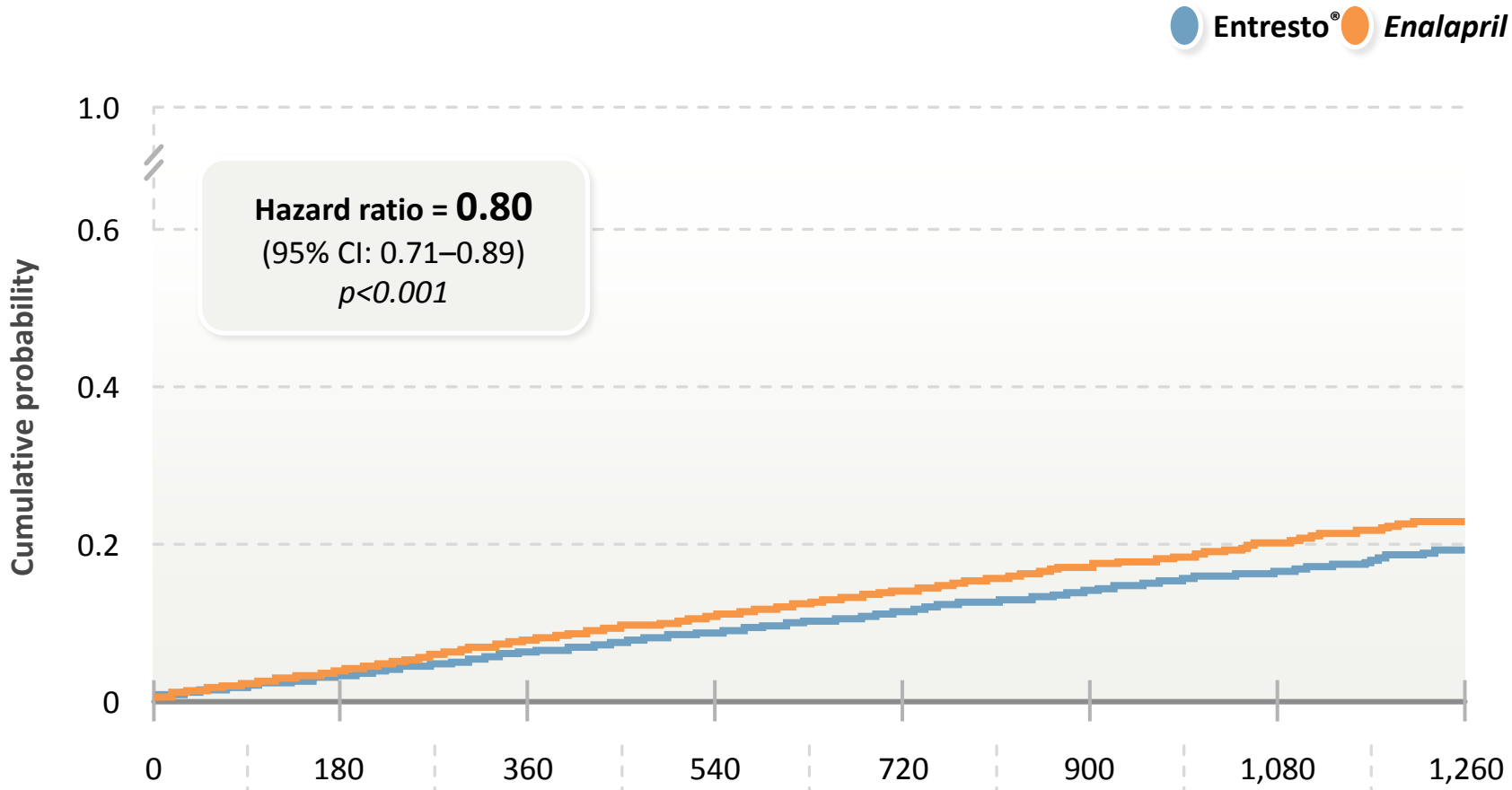
No. at risk

Entresto®	4,187	3,922	3,663	3,018	2,257	1,544	896	249
Enalapril	4,212	3,883	3,579	2,922	2,123	1,488	853	236

CI: confidence interval; CV: cardiovascular; HF: heart failure

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

Components of primary endpoint: death from CV causes



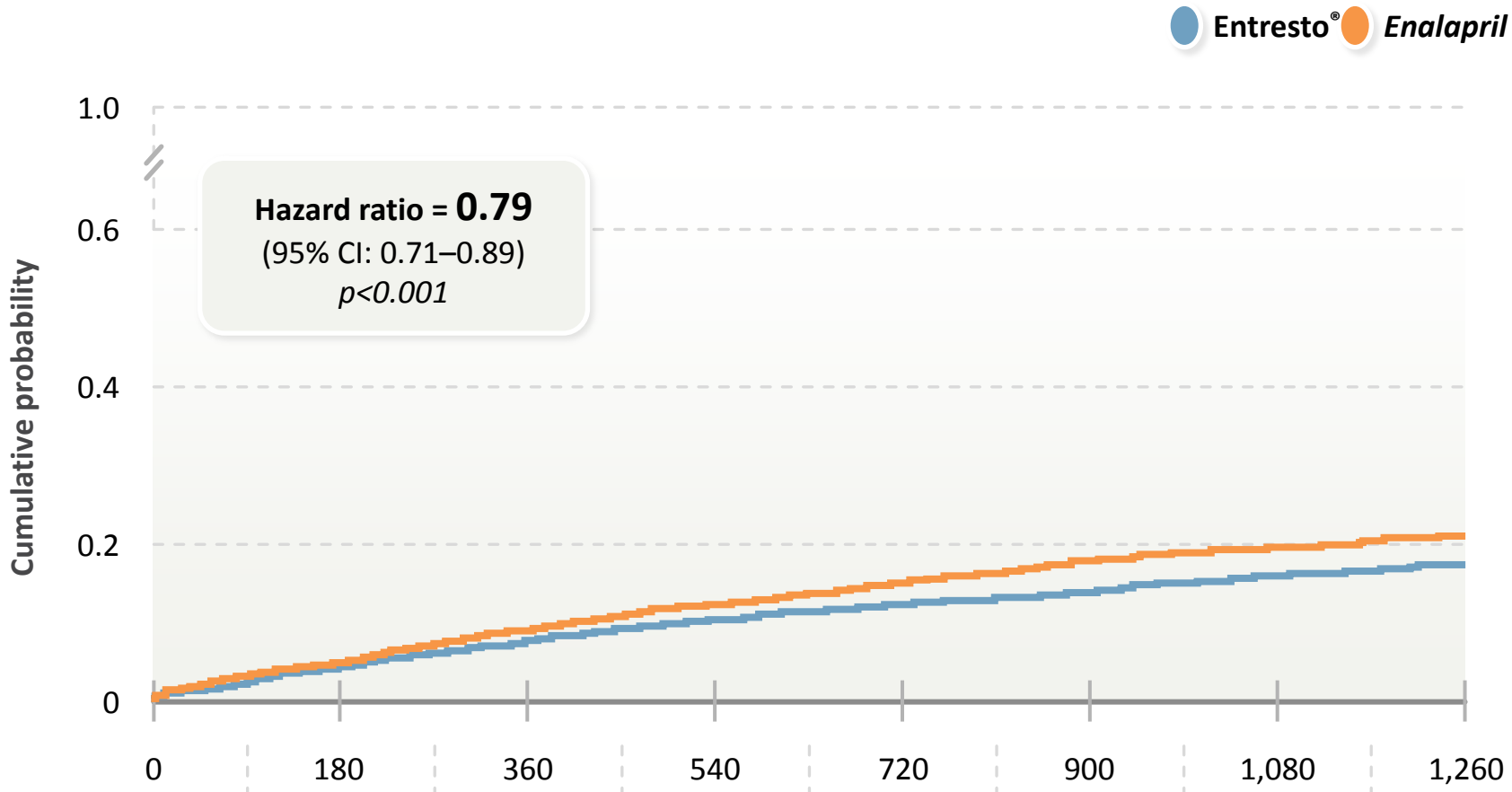
No. at risk

Entresto®	4,187	4,056	3,891	3,282	2,478	1,716	1,005	280
Enalapril	4,212	4,051	3,860	3,231	2,410	1,726	994	279

CI: confidence interval; CV: cardiovascular; HF: heart failure

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

Components of primary endpoint: first hospitalization for HF



No. at risk

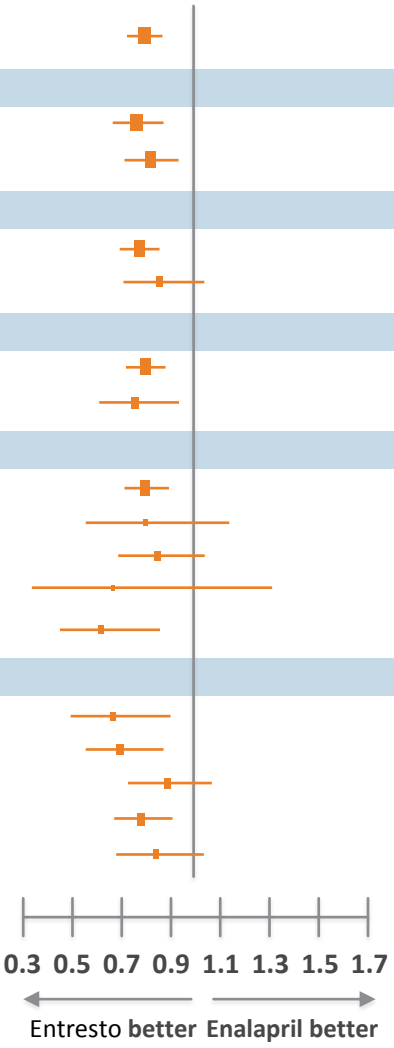
Entresto®	4,187	3,922	3,663	3,018	2,257	1,544	896	249
Enalapril	4,212	3,883	3,579	2,922	2,123	1,488	853	236

CI: confidence interval; CV: cardiovascular; HF: heart failure

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

Pre-specified subgroup analysis for the primary endpoint (CV death or HF hospitalization) – 1 of 3

Subgroup, n patients	Entresto®	Enalapril	p value for interaction
All patients	4,187	4,212	
Age			0.47
<65 years	2,111	2,168	
≥65 years	2,076	2,044	
Age			0.32
<75 years	3,403	3,433	
≥75 years	784	779	
Sex			0.63
Male	3,308	3,259	
Female	879	953	
Race			0.58
White	2,763	2,781	
Black	213	215	
Asian	759	750	
Native American	84	88	
Other	368	378	
Region			0.37
North America	310	292	
Latin America	713	720	
Western Europe and other	1,026	1,025	
Central Europe	1,393	1,433	
Asia-Pacific	745	742	



*The size of the square corresponds to the number of patients within each subgroup

CI: confidence interval; CV: cardiovascular; HF: heart failure

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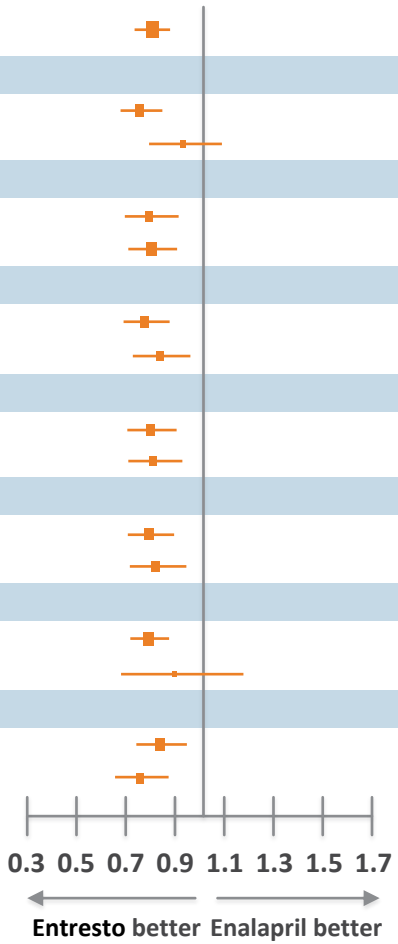
Pre-specified subgroup analysis for the primary endpoint (CV death or HF hospitalization) – 2 of 3

Subgroup, n patients	Entresto®	Enalapril	Hazard ratio* (95% CI)	p value for interaction
All patients	4,187	4,212		
NYHA class				0.03‡
I or II	3,178	3,130		
III or IV	1,002	1,076		
Estimated GFR				0.91
<60 mL/min/1.73 m2	1,541	1,520		
≥60 mL/min/1.73 m2	2,646	2,692		
Diabetes				0.40
No	2,736	2,756		
Yes	1,451	1,456		
Systolic blood pressure				0.87
≤Median	2,298	2,299		
>Median	1,889	1,913		
Ejection fraction				0.71
≤Median	2,239	2,275		
>Median	1,948	1,936		
Ejection fraction				0.36
≤35%	3,715	3,722		
>35%	472	489		
Atrial fibrillation				0.25
No	2,670	2,638		
Yes	1,517	1,574		



**The size of the square corresponds to the number of patients within each subgroup; ‡A nominally significant interaction between NYHA class at randomization and the effect of treatment on the primary endpoint (p=0.03, unadjusted for multiple comparisons) was not seen for the interaction of NYHA class and treatment effect on CV mortality (p=0.76).*

CI: confidence interval; CV: cardiovascular; GFR: glomerular filtration rate; HF: heart failure; NYHA: New York Heart Association

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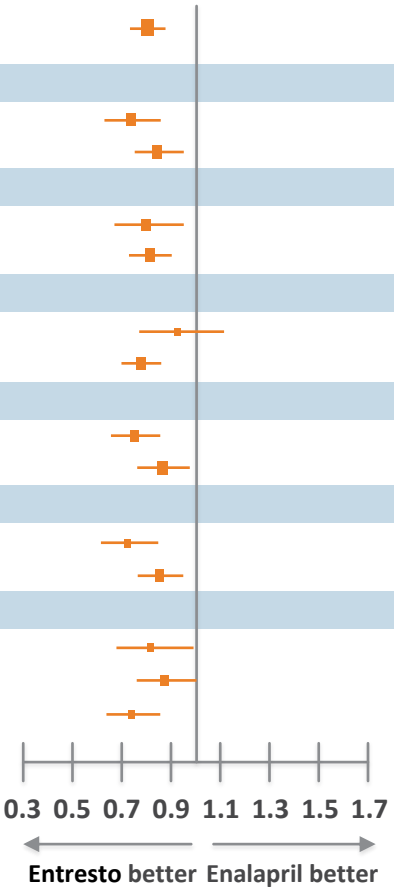
Pre-specified subgroup analysis for the primary endpoint (CV death or HF hospitalization) – 3 of 3

Subgroup, n patients	Entresto®	Enalapril	Hazard ratio* (95% CI)	p value for interaction
All patients	4,187	4,212		
NT-proBNP				0.16
≤Median	2,079	2,116		
>Median	2,103	2,087		
Hypertension				0.87
No	1,218	1,241		
Yes	2,969	2,971		
Prior use of ACEI				0.09
No	921	946		
Yes	3,266	3,266		
Prior use of aldosterone antagonist				0.10
No	1,916	1,812		
Yes	2,271	2,400		0.10
Prior hospitalization for HF				
No	1,580	1,545		
Yes	2,607	2,667		0.27
Time since diagnosis of HF				
≤1 year	1,275	1,248		
>1 to 5 years	1,621	1,611		
>5 years	1,291	1,353		



*The size of the square corresponds to the number of patients within each subgroup

ACEI: angiotensin-converting-enzyme inhibitor; CI: confidence interval; CV: cardiovascular; HF: heart failure; NT-proBNP: N-terminal pro-B-type natriuretic peptide

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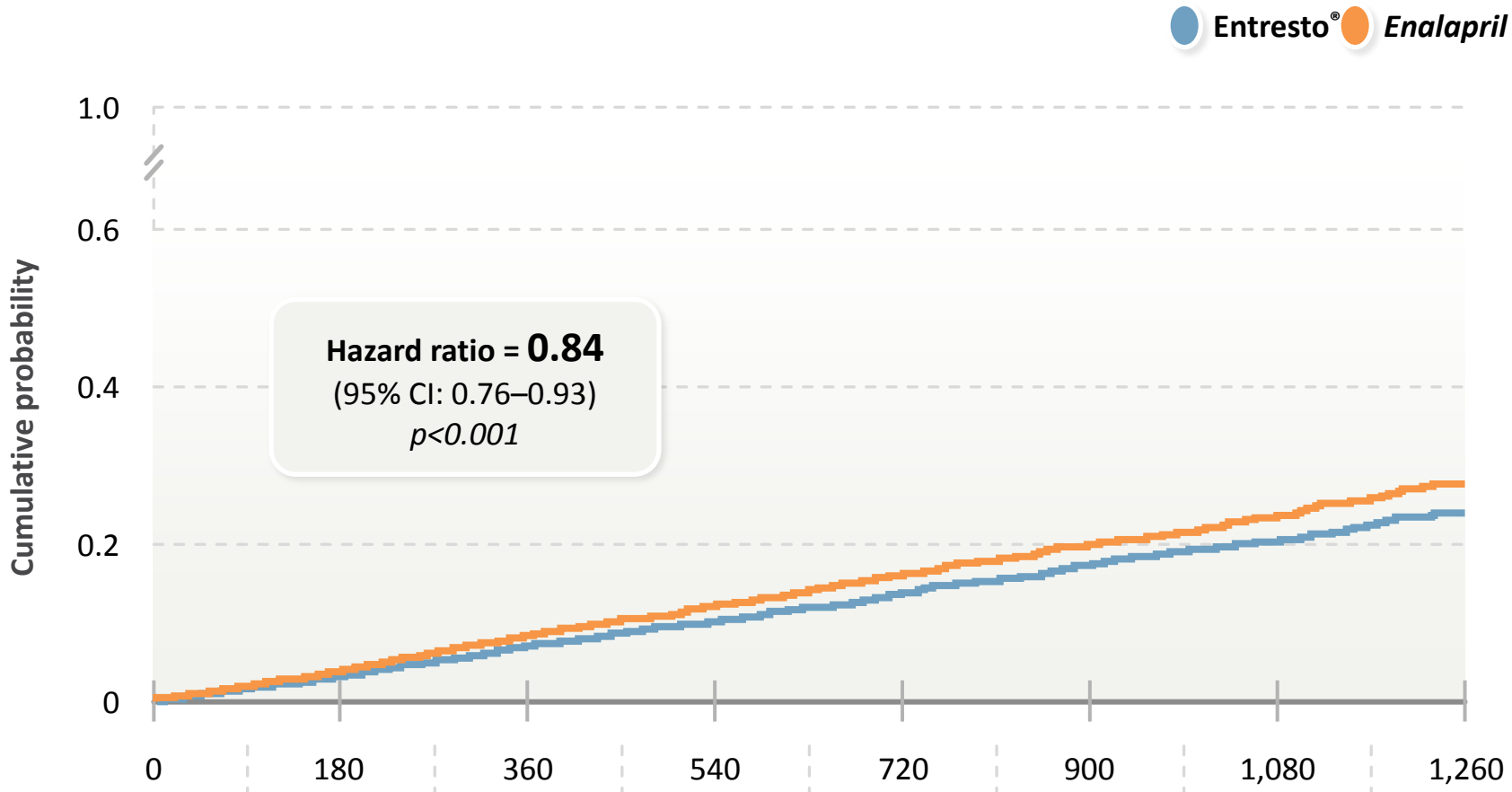
Death from any cause



No. at risk								
Entresto®	4,187	4,056	3,891	3,282	2,478	1,716	1,005	280
Enalapril	4,212	4,051	3,860	3,231	2,410	1,726	994	279

CI: confidence interval

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Summary of results – efficacy

Primary outcome

- 20% reduction in CV death or HF hospitalization with Entresto® compared with enalapril
  - 20% reduction in CV mortality
  - 21% reduction in HF hospitalization

Secondary outcomes

- 16% reduction in all-cause mortality with Entresto® vs enalapril
- No significant difference in incidence of new onset atrial fibrillation between treatment groups
- No significant difference in protocol-defined decline in renal function between treatment groups

CV: cardiovascular; GFR: glomerular filtration rate; HF: heart failure; KCCQ: Kansas City Cardiomyopathy Questionnaire

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Prospectively defined safety events

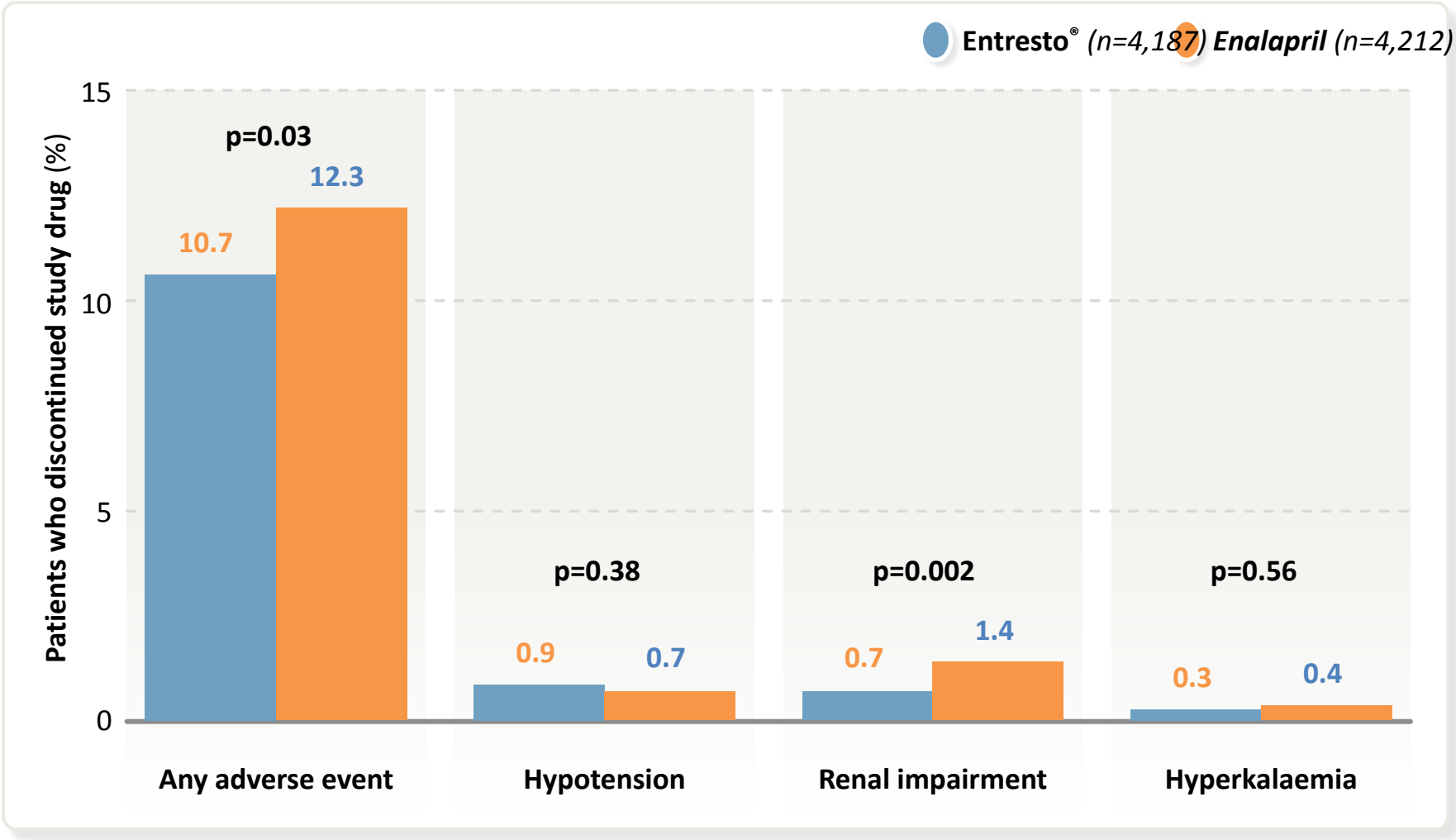
Event, n (%)	Entresto® (n=4,187)	Enalapril (n=4,212)	p-value
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with SBP <90 mmHg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dL	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dL	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 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 Entresto group than in the enalapril group stopped their study medication because of an AE (10.7 vs 12.3%, p=0.03)

AE: adverse events; SBP: systolic blood pressure; McMurray et al. N Engl J Med 2014;371:993–1004

Adverse events leading to permanent study drug discontinuation

- Fewer patients in the Entresto group than in the enalapril group discontinued study drug due to an adverse event (10.7 vs 12.3%; p=0.03)



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Summary of results – safety

- The superiority of Entresto® over enalapril was not accompanied by important safety concerns
- Fewer patients stopped their study medication because of an adverse event in the LCZ696 group than in the enalapril group
- There was no increase in the rate of discontinuation due to possible hypotension-related adverse effects, despite a higher rate of symptomatic hypotension in the LCZ696 group
- Fewer patients in the Entresto® group developed renal impairment, hyperkalemia or cough than in the enalapril group
- The Entresto® group had a higher proportion of patients with non-serious angioedema, but Entresto® was not associated with an increase in serious angioedema

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