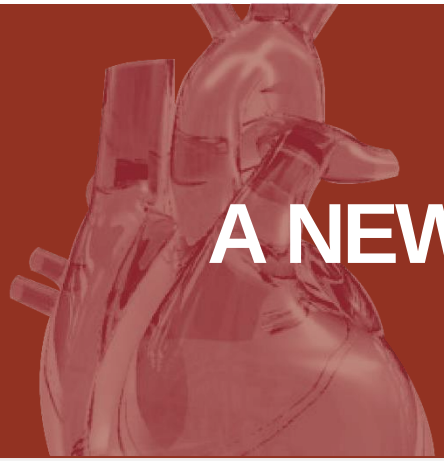

A NEW HOPE FOR HEART FAILURE

NOVARTIS
PHARMACEUTICALS

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Declaration of Interest

- Consultant and Speaker Engagement:
  - Boehringer Ingelheim
  - Pfizer
  - Bayer
  - Medtronic
  - Biotronik
  - Novartis
  - Abbot
  - Bbraun

Disclaimer

- The information provided in this presentation is intended for scientific education purpose
- LCZ696 (ARNI) has not been available yet in Indonesia

HF is a common clinical condition

Approximately 1–2% of the adult population in developed countries has HF, with the prevalence rising to ≥10% among persons 70 years of age or older[1]

Over 650,000 new cases of HF are diagnosed annually in the USA[2] and more than 25,000 new cases are reported every year in the UK[3]

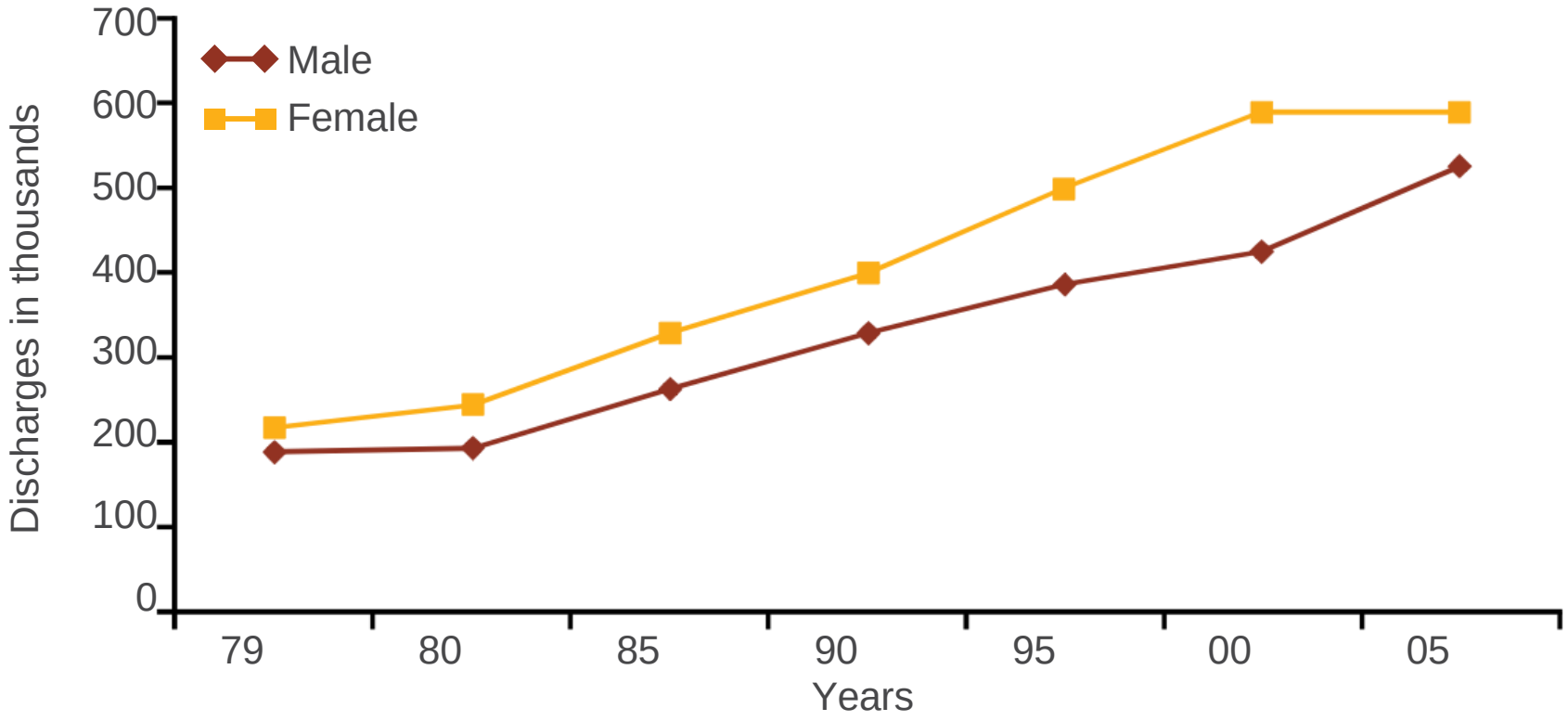
The mortality rate for patients with chronic HF is as high as 50% at 5 years post-diagnosis[4–5]

HF=heart failure

1. McMurray et al. Eur Heart J 2012;33:1787–847; 2. Yancy et al. JACC 2013;62:e147–239
3. Townsend et al. 2012 Coronary heart disease statistics 2012 edition.
Available at: https://www.bhf.org.uk/publications/statistics/coronary-heart-disease-statistics-2012
4.Roger et al. JAMA 2004;292:344–50; 5. Levy et al. NEJM 2002;347:1397–402

HF is increasing in prevalence

Hospital discharges for HF by gender (USA: 1979–2006)*



*Hospital discharges include people discharged alive, dead and of unknown status
HF=heart failure

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

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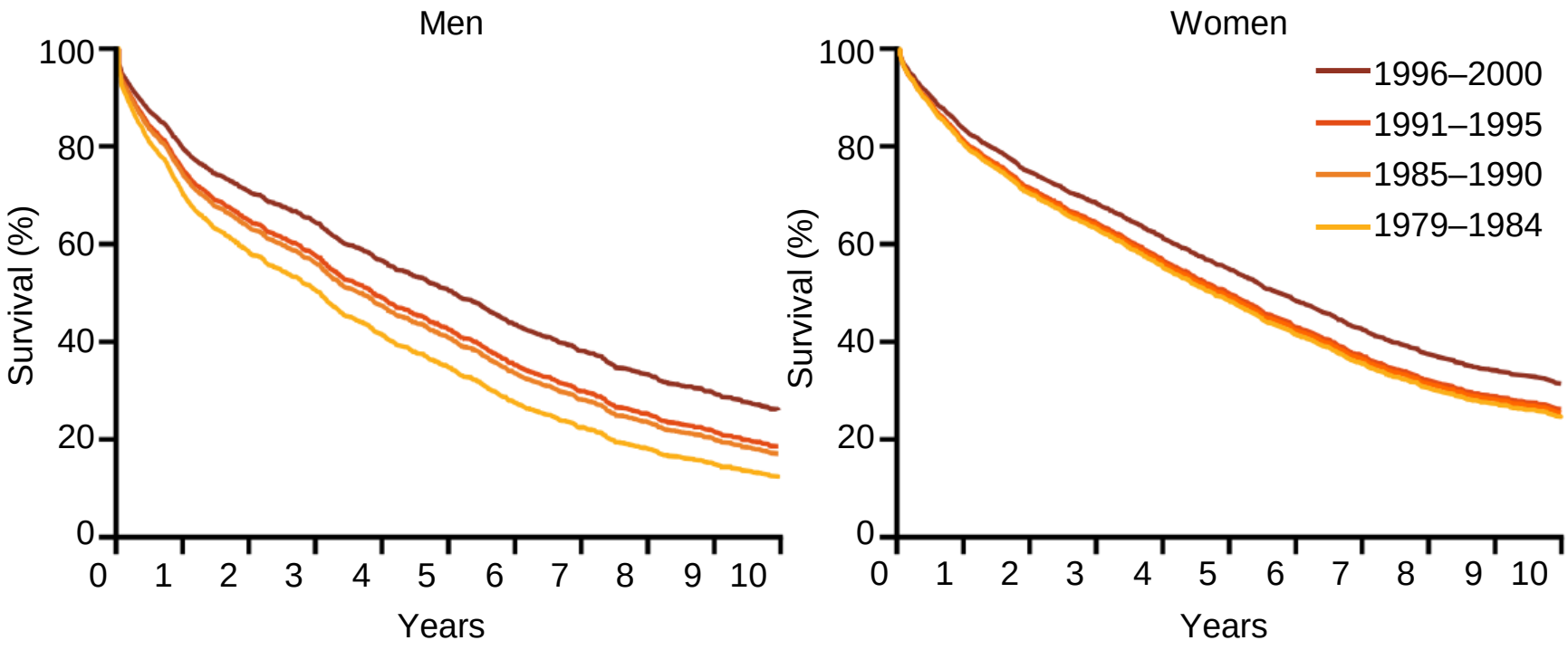
Survival rates have improved over time

Epidemiology

Temporal trends in 5-year mortality after the diagnosis of HF by gender show improvements in survival …



... nevertheless, there remains a high rate of residual 5-year mortality

Population-based cohort study analysing data from the Rochester Epidemiology Project, Minnesota, USA. 4,537 patients with a diagnosis of HF between 1979 and 2000 were included. Framingham criteria and clinical criteria were used to validate the diagnosis.

Roger et al. JAMA 2004;292:344–50

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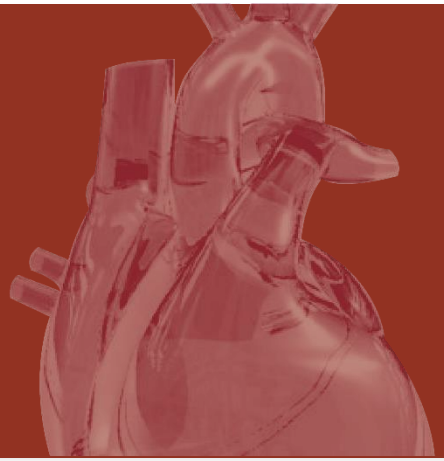
Heart Failure Clinic 2017

Heart Failure Clinic 2022



EVOLUTION OF THE HEART FAILURE TREATMENT LANDSCAPE

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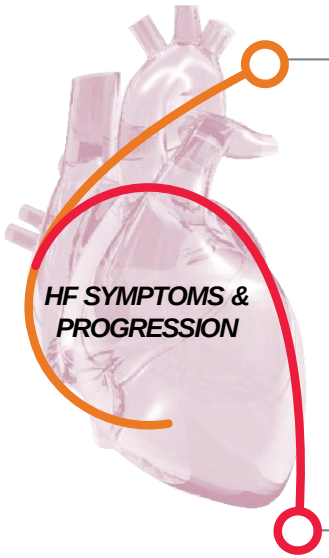
Decline in systolic function leads to activation of major neurohormonal systems



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↑

Ang: angiotensin; AT_1R: angiotensin II type 1 receptor; HF: heart failure; NPs: natriuretic peptides; NPRs: natriuretic peptide receptors; RAAS: renin-angiotensin-aldosterone system

Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42; Kemp & Conte. Cardiovascular Pathology 2012;365–371; Schrier & Abraham. N Engl J Med 1999;341:577–85

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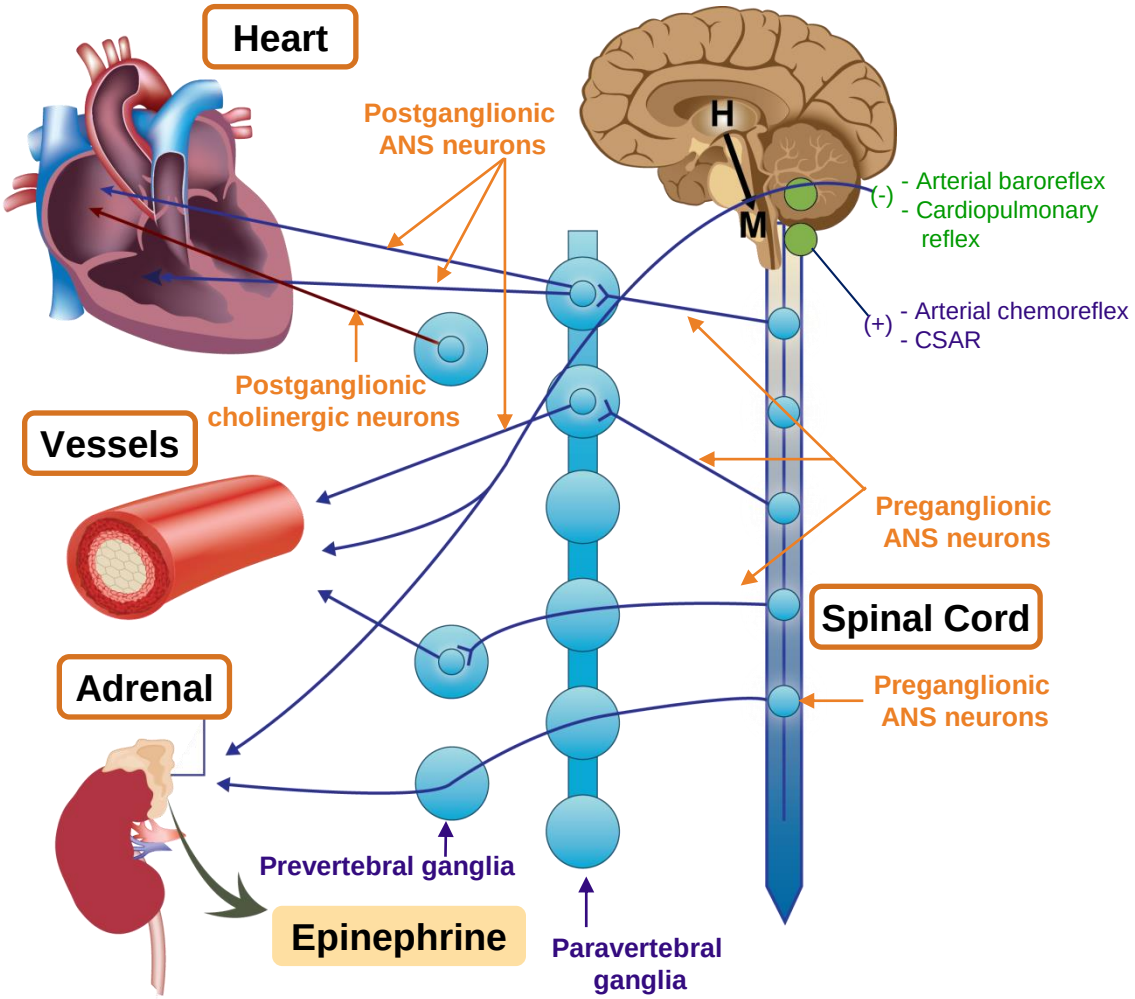
Sympathetic (or adrenal) Nervous System

Pathophysiology

- The SNS exerts a wide variety of cardiovascular effects:
  - Heart rate acceleration
  - Increased cardiac contractility
  - Peripheral vasoconstriction



ANS: autonomic nervous system; CSAR: cardiac sympathetic afferent reflex; SNS: sympathetic nervous system

Lymperopoulos et al. Circ Res 2013;113:739–53

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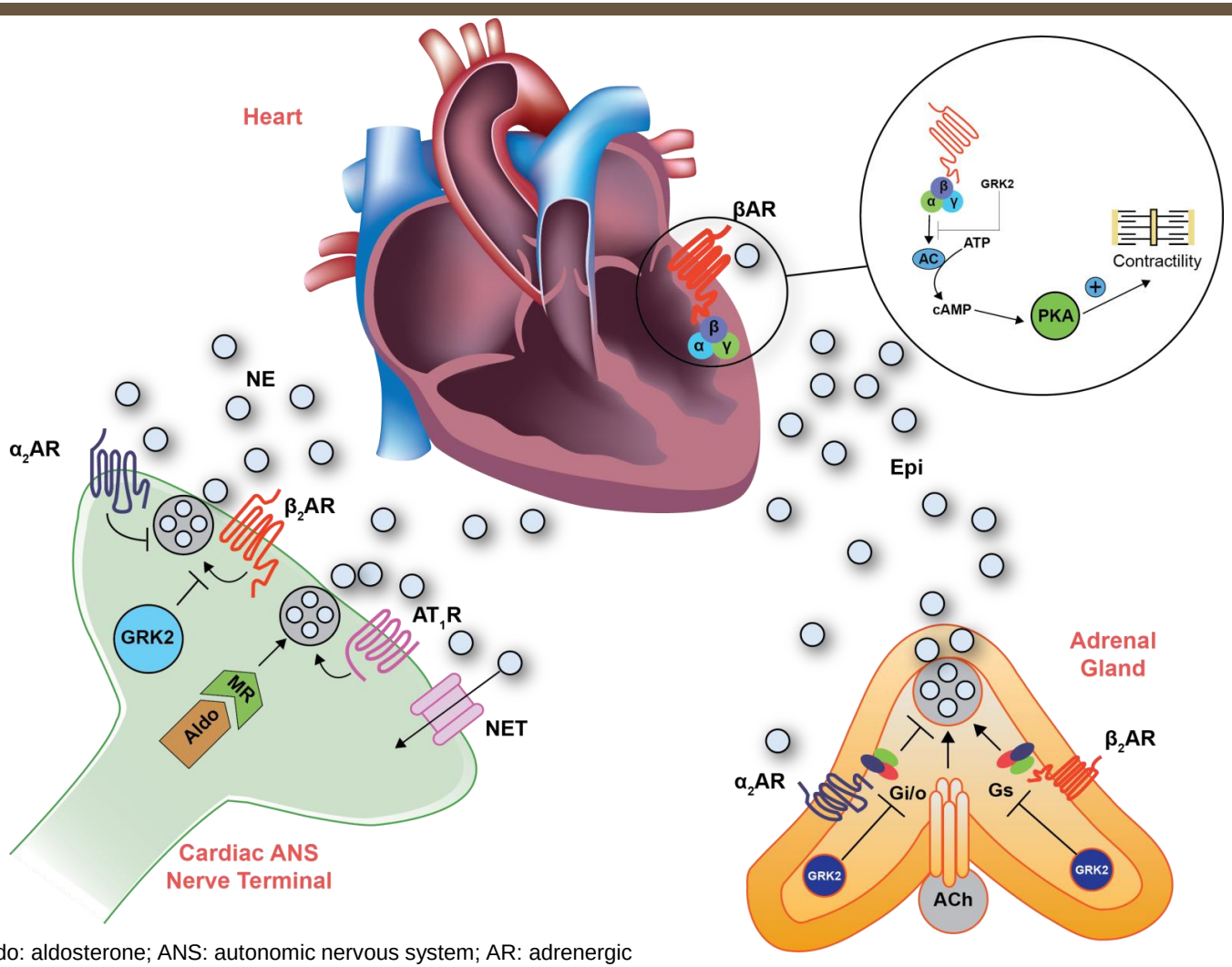
Sympathetic (or adrenal) Nervous System

Pathophysiology

- The SNS exerts its effects mainly via:
  - Release of norepinephrine by cardiac nerve terminals
  - Release of epinephrine by adrenal glands



AC; adenylate cyclase; Ach: acetylcholine; Aldo: aldosterone; ANS: autonomic nervous system; AR: adrenergic receptor; AT_1R; angiotensin II receptor, type 1; ATP; adenosine triphosphate; cAMP; Cyclic adenosine monophosphate; Epi: epinephrine; Gi/o: inhibitory/other G protein; Gs: stimulatory G protein; GRK2; G protein–coupled receptor kinase 2; MR: mineralocorticoid receptor; NE: norepinephrine; NET: norepinephrine transporter; PKA; protein kinase A; SNS: sympathetic nervous system

Lymperopoulos et al. Circ Res 2013;113:739–53

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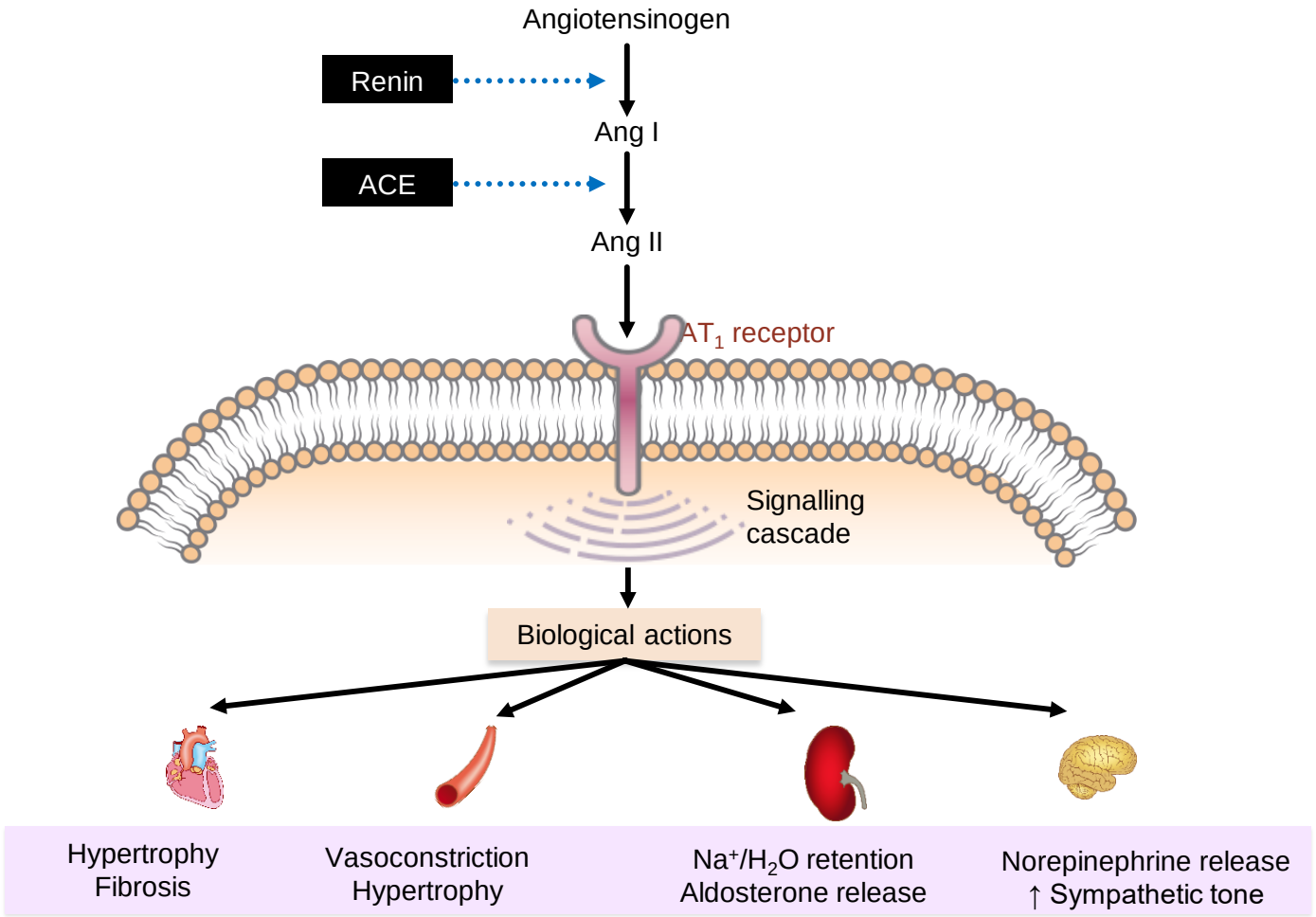
Renin Angiotensin Aldosterone System

Initially compensatory and subsequently pathological



ACE: angiotensin converting enzyme; Ang: angiotensin; A T_1:angiotensin II type 1; RAAS: renin-angiotensin-aldosterone system

Francis et al. Ann Intern Med 1984;101:370–7; Von Lueder et al. Circ Heart Fail 2013;6:594–605

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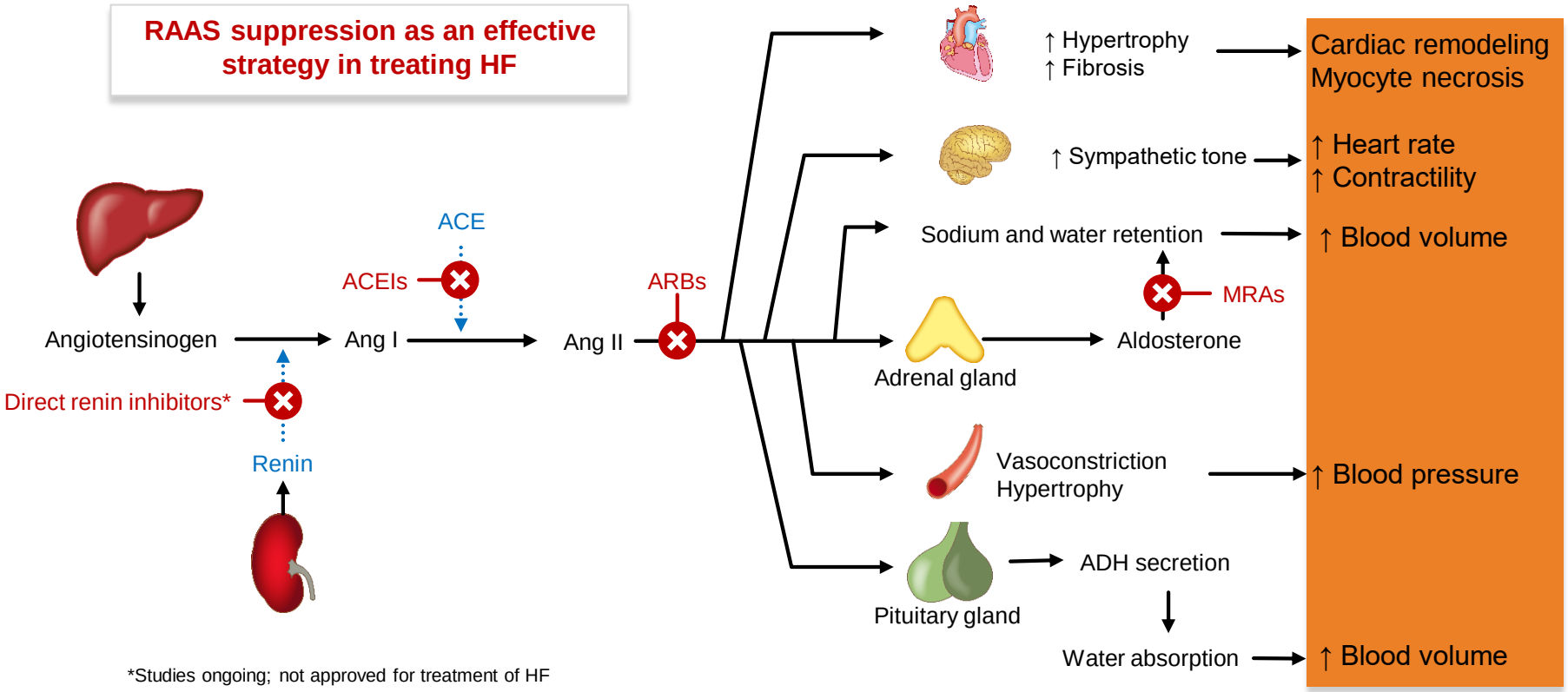
Renin Angiotensin Aldosterone System

Pathophysiology - sustained RAAS activation in HF

Cardiac dysfunction leads to RAAS activation…

…sustained activation puts further strain on the weakened heart, creating a vicious cycle

RAAS suppression as an effective strategy in treating HF



*Studies ongoing; not approved for treatment of HF

ACE: angiotensin-converting enzyme; ACEI: angiotensin-converting-enzyme inhibitor; ADH: antidiuretic hormone; ARB: angiotensin receptor blocker; Ang: angiotensin; HF: heart failure; MRA: mineralocorticoid receptor antagonist; RAAS: renin-angiotensin-aldosterone system

Zaman et al. Nat Rev Drug Discov 2002;1:621–36; Schrier & Abraham. N Engl J Med 1999;341:577–85; Brewster et al. Am J Med Sci 2003;326:15–24; Schmeider. Am J Hypertens 2005;18:720–30; McMurray et al. Eur Heart J 2012;33:1787–847

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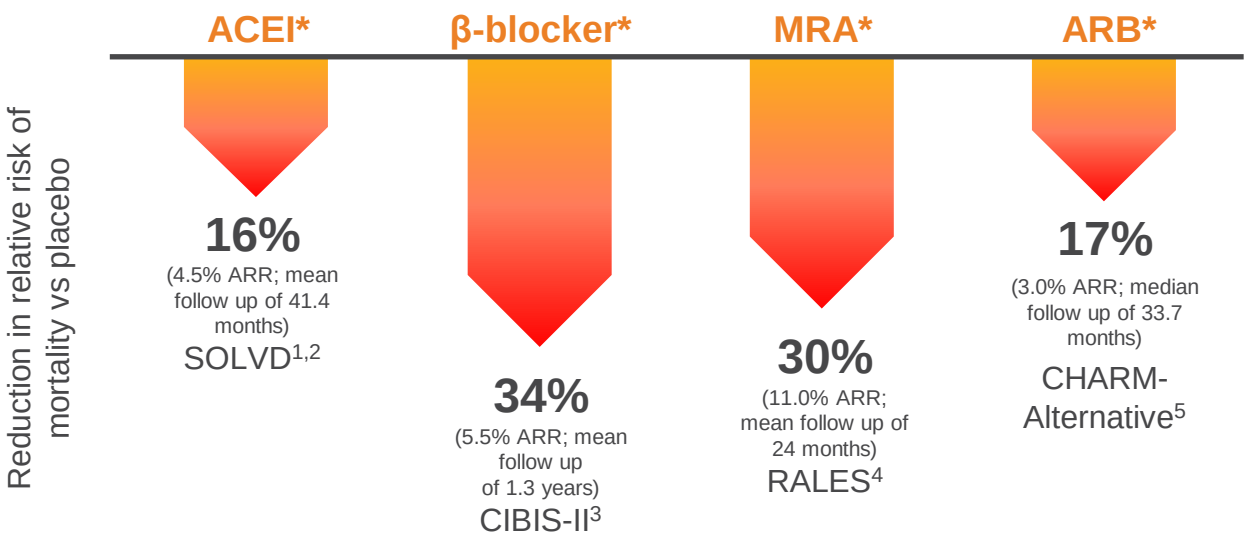
Mortality in HFrEF remains high despite the introduction of new therapies that improve survival

- Survival rates in chronic HF have improved with the introduction of new therapies[1]



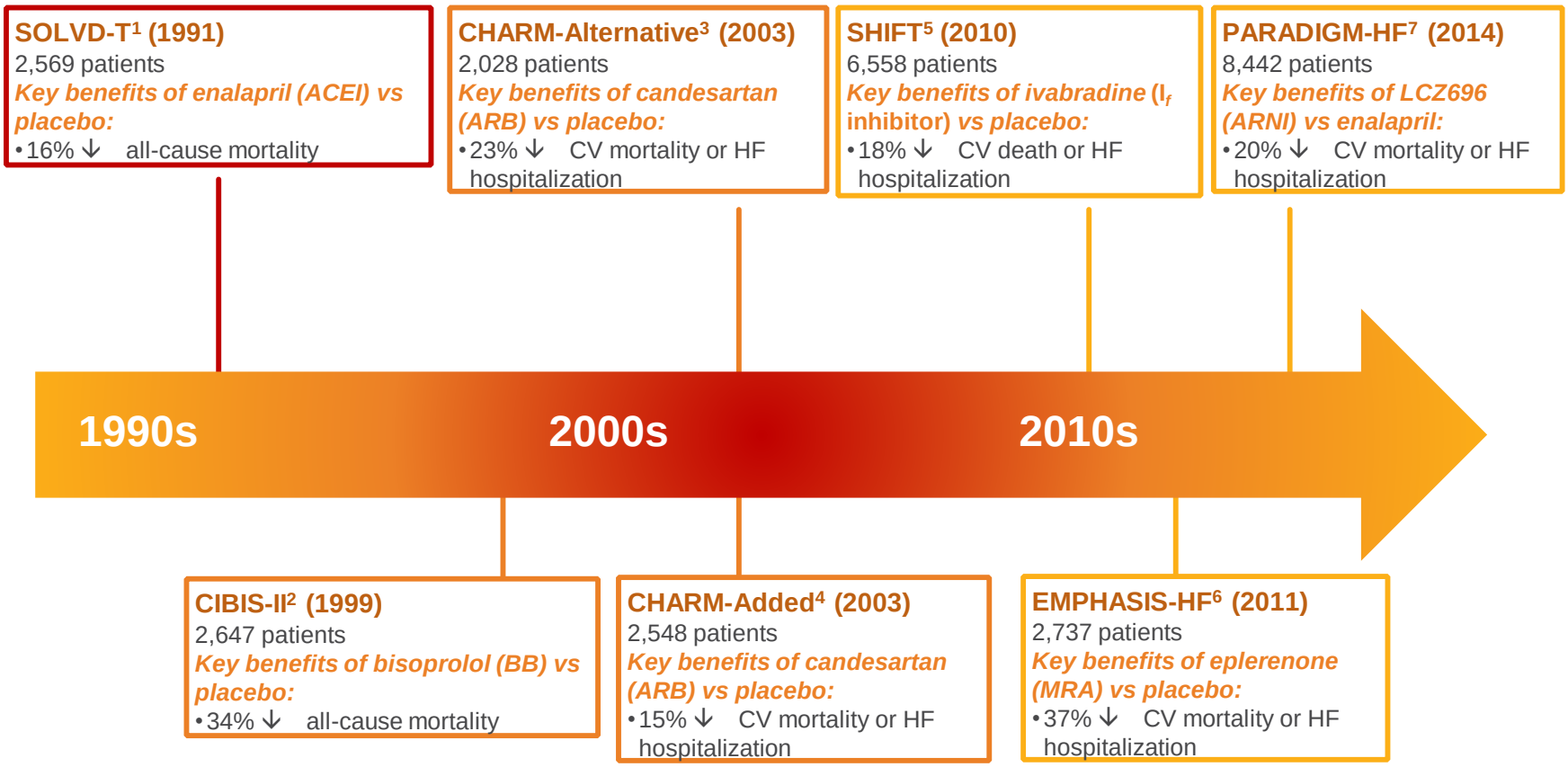
- However, significant mortality remains – ~50% of patients die within 5 years of diagnosis[6–8]

*On top of standard therapy at the time of study (except in CHARM-Alternative where background ACEI therapy was excluded). Patient populations varied between trials and as such relative risk reductions cannot be directly compared. SOLVD (Studies of Left Ventricular Dysfunction), CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) and RALES (Randomized Aldactone Evaluation Study) enrolled chronic HF patients with LVEF≤35%. CHARM-Alternative (Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity) enrolled chronic HF patients with LVEF≤40%

ACEI=angiotensin-converting-enzyme inhibitor; ARB=angiotensin receptor blocker; HF=heart failure; ARR=absolute risk reduction; HFrEF=heart failure with reduced ejection fraction; LVEF=left ventricular ejection fraction; MRA=mineralocorticoid receptor antagonist

1. McMurray et al. Eur Heart J 2012;33:1787–847; 2. SOLVD Investigators. N Engl J Med 1991;325:293–302; 3. CIBIS-II Investigators. Lancet 1999;353:9–13; 4. Pitt et al. N Engl J Med 1999;341:709-17; 5. Granger et al. Lancet 2003;362:772–66. 6. Go et al. Circulation 2014;129:e28-e292; 7. Yancy et al. Circulation 2013;128:e240–327; 8. Levy et al. N Engl J Med 2002;347:1397–402

Landmark trials in patients with HFrEF

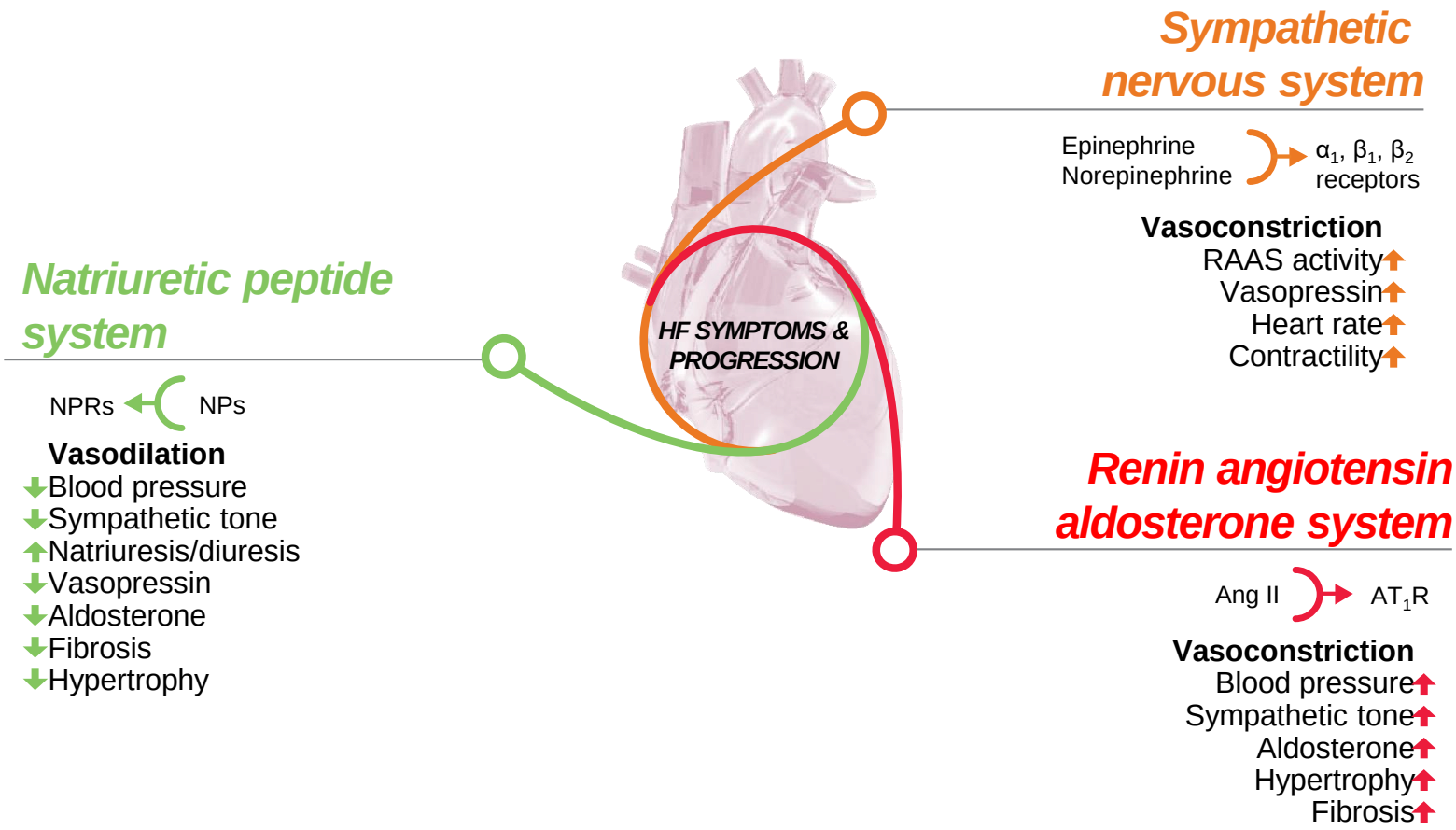


LCZ696 (ARNI) has not been available yet in Indonesia

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;362:767–771; 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

Decline in systolic function leads to activation of major neurohormonal systems



Ang: angiotensin; AT_1R: angiotensin II type 1 receptor; HF: heart failure; NPs: natriuretic peptides; NPRs: natriuretic peptide receptors; RAAS: renin-angiotensin-aldosterone system

Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42; Kemp & Conte. Cardiovascular Pathology 2012;365–371; Schrier & Abraham. N Engl J Med 1999;341:577–85

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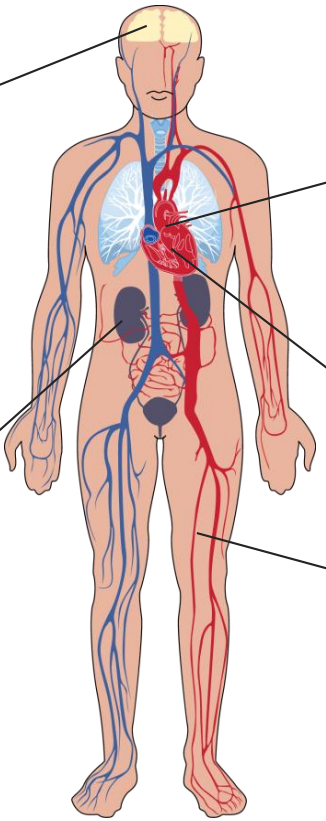
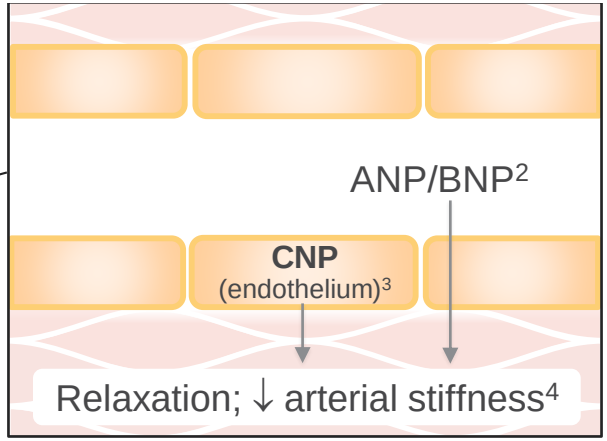
Natriuretic peptides have beneficial actions in HF

Release of ANP and BNP from heart and CNP in vasculature[1,2]

↓ Sympathetic outflow[2]
↓ Vasopressin[2]
↓ Salt appetite and water intake[2]





↓ Hypertrophy[2,5–7]
↓ Fibroblast proliferation[4,8,9]

Na^+/H_2O loss[2]
↓ Aldosterone[2]
↓ Renin[2]

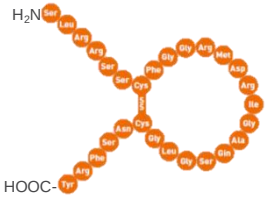
Vasodilation[2,3,4]
↓ Systemic vascular resistance[4]
↓ Pulmonary artery pressure[4]
↓ Pulmonary capillary wedge pressure[4]
↓ Right atrial pressure[4]

ANP=atrial natriuretic peptide; BNP=B-type natriuretic peptide; CNP=C-type natriuretic peptide; HF=heart failure; H_20=water; NA=sodium

1. Mangiafico et al. Eur Heart J 2013;34:886–93; 2. Levin et al. N Engl J Med 1998;339;321–8; 3. Lumsden et al. Curr Pharm Des 2010;16:4080–8; 4. Langenickel & Dole. Drug Discovery Today: Ther Strateg 2012;9:e131–9; 5. Gardner et al. Hypertension 2007;49:419–26; 6. Tokudome et al. Circulation 2008;117;2329–39; 7. Horio et al. Hypertension 2000;35:19–24; 8. D'Souza et al. Pharmacol Ther 2004;101:113–29; 9. Cao & Gardner. Hypertension 1995;25:227–34

The heart acts as an endocrine organ releasing NPs in response to mechanical stretch countering some effects of the RAAS

Atrial natriuretic peptide (ANP)



- Expressed in the **atria**
- Measurable in plasma

Effects:

- Vasorelaxation
- ↑ Diuresis/natriuresis
- ↓ Proliferation
- ↓ Hypertrophy
- ↓ Aldosterone
- ↓ Sympathetic tone
- ↓ Cardiac preload
- ↑ Venous capacitance

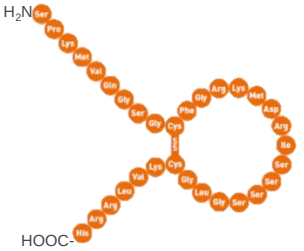
C-type natriuretic peptide (CNP)

- Expressed in **vascular endothelial cells** and **central nervous system**
- Not detectable in plasma – primarily synthesized in vasculature, acting locally in tissues

Effects:

- Vasorelaxation
- More potent dilation of veins than ANP and BNP
- ↓ Proliferation
- Bone growth regulation

B-type natriuretic peptide (BNP)



- Expressed in **atrial** and **ventricular** tissue
- Measurable in plasma

Effects:

- Vasorelaxation
- ↑ Diuresis/natriuresis
- ↓ Aldosterone
- ↓ Sympathetic tone

NP: natriuretic peptide; RAAS: renin angiotensin aldosterone system

Levin et al. N Engl J Med 1998;339;321–8; Gardner et al. Hypertension 2007;49:419–26; Pandey. J Am Soc Hypertens 2008;2:210–6; Von Lueder et al. Pharmacol Ther 2014;144:41-49; Potter. FEBS J 2011;278:1808–17; Lumsden et al. Curr Pharm Des 2010;16:4080–8; Mangiafico et al. Eur Heart J 2013;34:886–93

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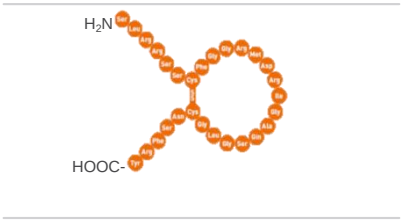
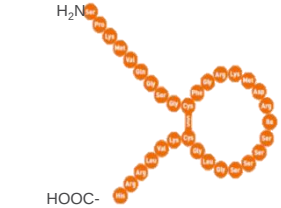
Neprilysin hydrolyzes ANP, BNP and CNP, but not NT-proBNP

Atrial natriuretic peptide (ANP)[1]



$t_{½}$ in circulation[3] = ~2 mins

B-type natriuretic peptide (BNP)[1]



$t_{½}$ in circulation[3] = ~20 mins

C-type natriuretic peptide (CNP)[1]

$t_{½}$ in circulation[3] = ~3 mins

N-terminal-proBNP (NT-proBNP)[2]

$t_{½}$ in circulation[4] = ~120 mins

- Neprilysin hydrolyzes ANP, BNP and CNP[1,3]
- Neprilysin inhibition predominantly enhances the effects of ANP, BNP and CNP,[1] leading to:
  - Vasorelaxation[5]
  - ↑ Diuresis/natriuresis[5]
  - ↓ Proliferation[6]
  - ↓ Hypertrophy[5]
  - ↓ Aldosterone[5]
  - ↓ Sympathetic tone[5]
  - ↓ Cardiac preload[5]
  - ↑ Venous capacitance[5]

- Neprilysin does not hydrolyze NT-proBNP[5]
- NT-proBNP remains a useful biomarker of therapeutic effect and prognosis during neprilysin inhibition[5]

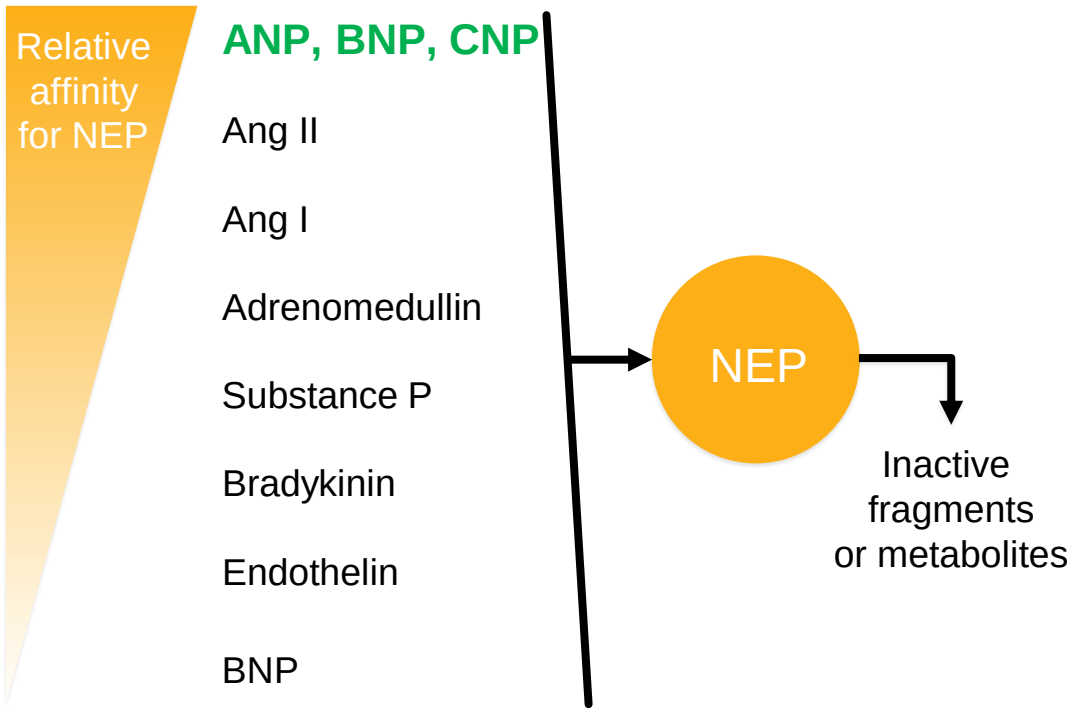
ANP=atrial natriuretic peptide;
BNP=B-type natriuretic peptide;
CNP=C-type natriuretic peptide; NT-proBNP=N-terminal pro-B-type natriuretic peptide; $t_{1/2}$=half-life

1. Von Lueder et al. Circ Heart Fail 2013;6:594–605; 2. McKie & Burnett. Mayo Clin Proc 2005;80:1029–36; 3. Potter. FEBS J 2011;278:1808–17; 4. Kim & Januzzi. Circulation 2011;123:2015–19; 5. Langenickel & Dole. Drug Discovery Today: Ther Strateg 2012;9:e131–9; 6. Levin et al. N Engl J Med 1998;339;321–8

Metabolism of vasoactive peptides by Neprilysin

NEP has many substrates metabolized with differing levels of affinity

Metabolism of natriuretic and other vasoactive peptides by NEP[1–9]*



Implications for NEP inhibition

- NEP substrates can have opposing biological actions[10]
- Overall effect is dependent upon the **net effect** on NEP metabolism of individual substrates[10]
- Benefits in enhancing NP system may be offset by increased Ang II[11]
- Needs to be complemented by simultaneous RAAS suppression[2,11,12]

**Not an exhaustive list of all neprilysin substrates; the most relevant substrates for cardiovascular physiology are listed*

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

1. Erdos & Skidgel. FASEB J 1989;3:145–51; 2. Levin et al. N Engl J Med 1998;339;321–8; 3. Stephenson et al. Biochem J 1987;243:183–7; 4. Lang et al. Clin Sci 1992;82:619–23; 5. Kenny et al. Biochem J 1993;291:83–8; 6. Skidgel et al. Peptides 1984;5:769–76; 7. Abassi et al. Metabolism 1992;41:683–5; 8. Murphy et al. Br J Pharmacol 1994;113:137–42; 9. Jiang et al. Hypertens Res 2004;27:109–17; 10. Langenickel & Dole. Drug Discovery Today: Ther Strateg 2012;9:e131–9; 11. Richards et al. J Hypertens 1993;11:407–16; 12. Ferro et al. Circulation 1998;97:2323–30

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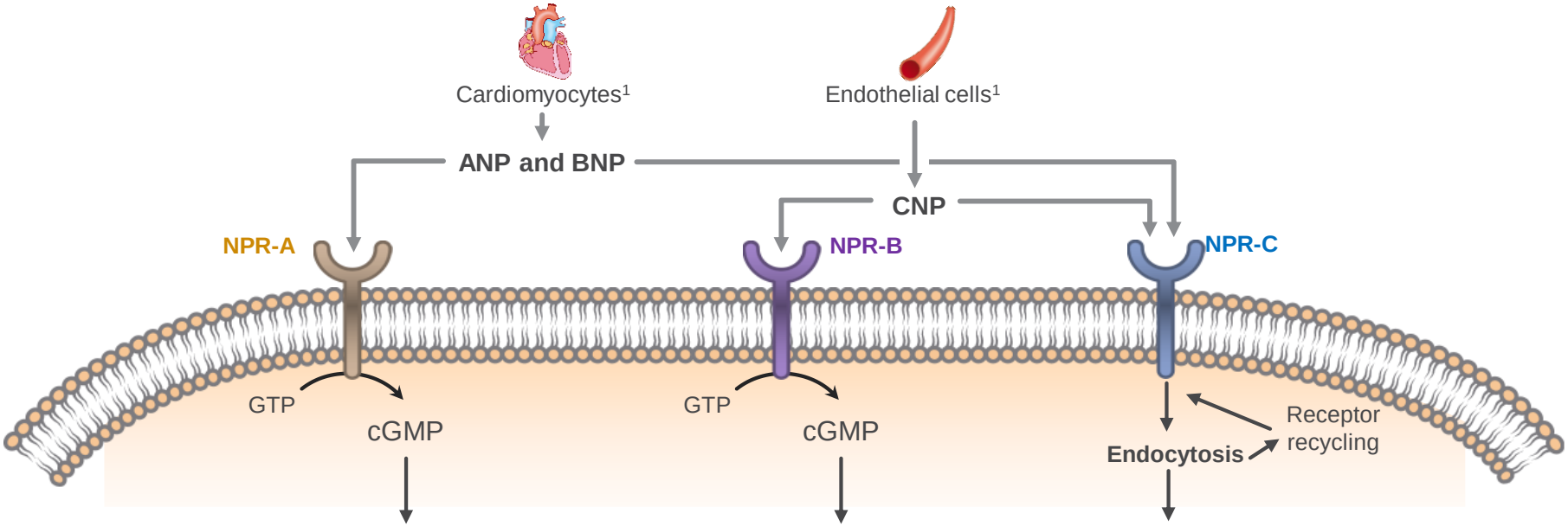
Natriuretic peptides mediate a wide range of physiological effects via their receptors



- Vasodilation[1,2]
- Antihypertrophy[1,2]
- Antiproliferation[2]
- Vascular regeneration[1]
- Myocardial relaxation[1]
- Diuresis, natriuresis[1,2]
- Antiapoptosis[1]
- Anti-aldosterone[1]
- Renin secretion inhibition[1,3]
- Reduced sympathetic tone[4]
- Lipolysis[1]

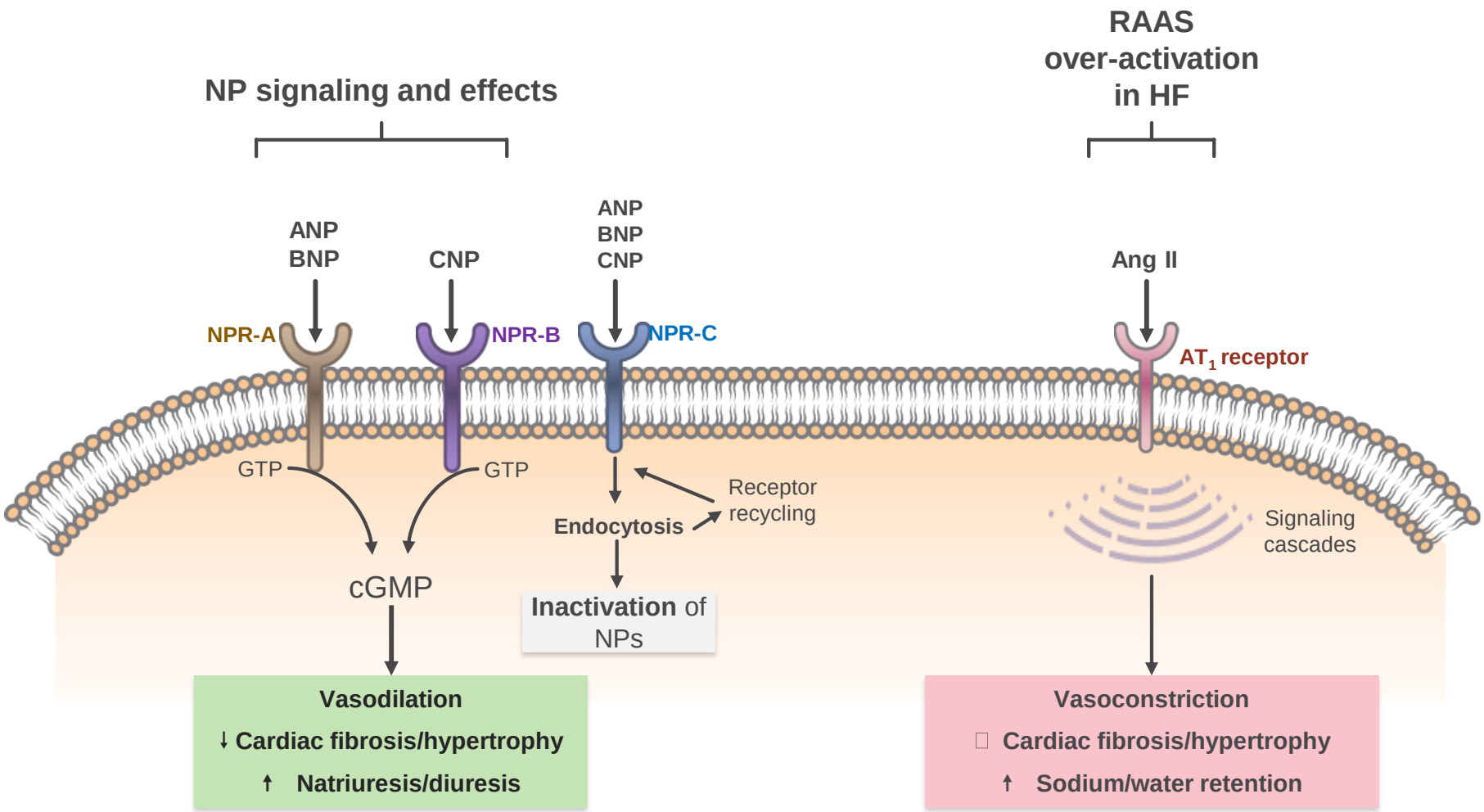
- Vasodilation[1,2]
- Antihypertrophy[1,2]
- Antiproliferation[2]
- Vascular regeneration[1]
- Venodilation[1]
- Antifibrosis[1]

Inactivation of NPs[1,2,5]

ANP=atrial natriuretic peptide; BNP=B-type natriuretic peptide; cGMP=cyclic guanosine monophosphate; CNP=C-type natriuretic peptide; GTP=guanosine triphosphate; NP=natriuretic peptide; NPR=natriuretic peptide receptor

1. Mangiafico et al. Eur Heart J 2013;34:886–93; 2. Gardner et al. Hypertension 2007;49:419–26; 3. Pandey. J Am Soc Hypertens 2008;2:210–26; 4. Levin et al. N Engl J Med 1998;339;321–8
5. Von Lueder et al. Pharmacol Ther 2014;144:41–9

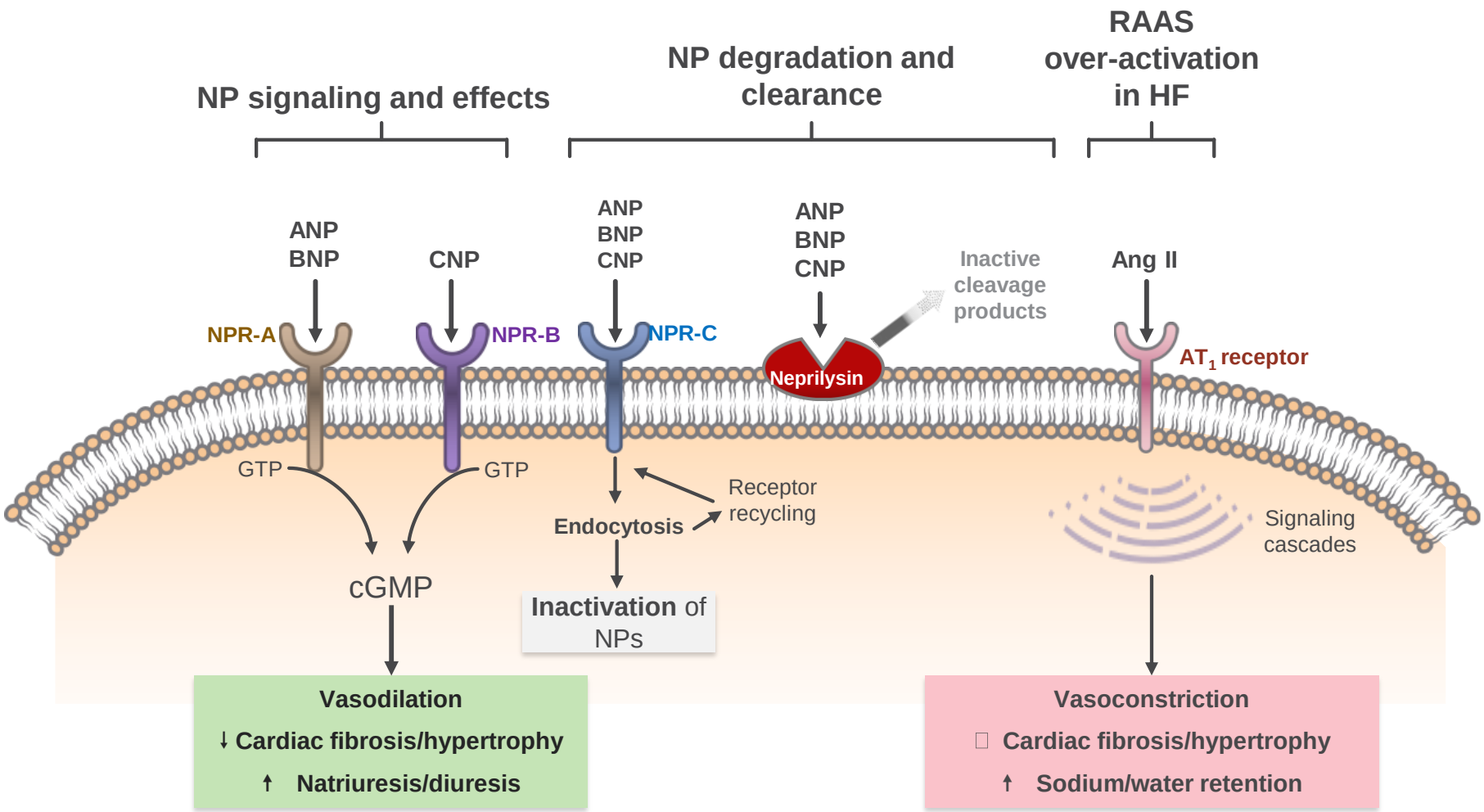
The cardiovascular and renal effects of the natriuretic peptide system oppose those of the RAAS



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 and Griendling. Am J Physiol Cell Physiol 2007;292:C82–97

Natriuretic peptides are cleared by NPR-C and neprilysin



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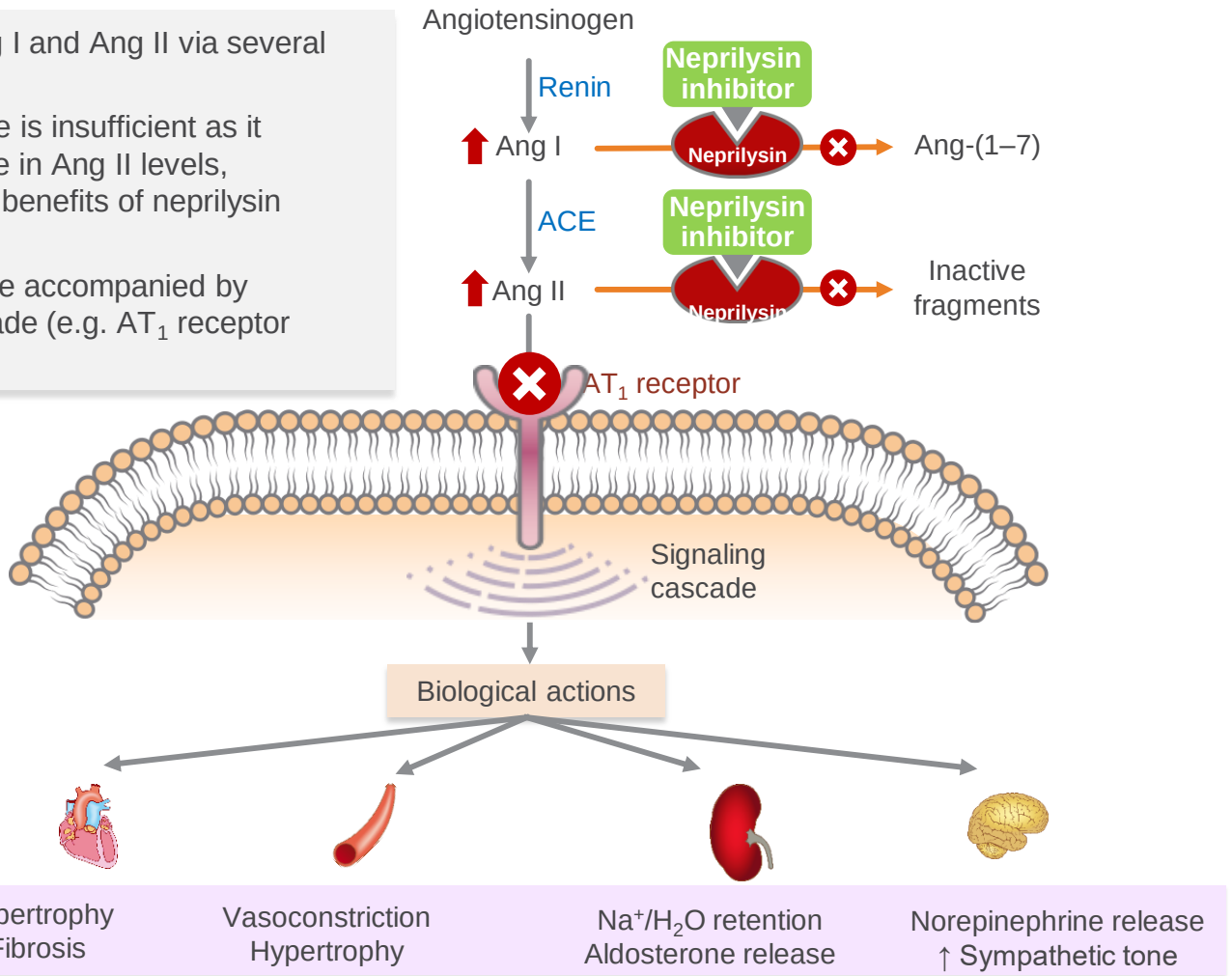
Yin et al. Int J Biochem Cell 2003;35:780–3; Mehta and Griendling. Am J Physiol Cell Physiol 2007;292:C82–97; Mangiafico et al. Eur Heart J 2013;34:886–93; Potter. FEBS J 2011;278:1808–17

Neprilysin inhibition must be accompanied by simultaneous RAAS blockade

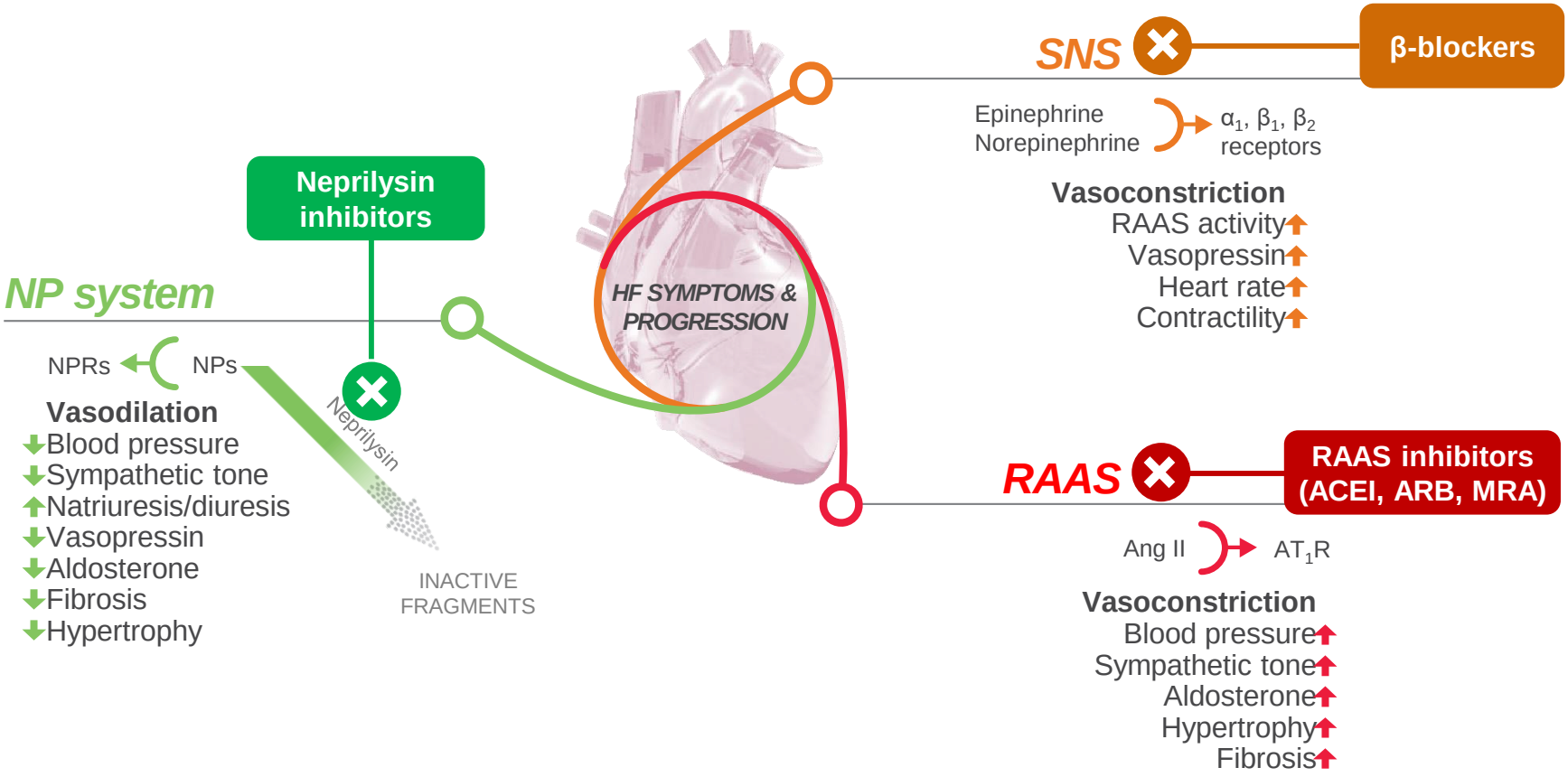
- Neprilysin metabolizes Ang I and Ang II via several pathways[1,2]
- Inhibition of neprilysin alone is insufficient as it associated with an increase in Ang II levels, counteracting the potential benefits of neprilysin inhibition[2]
- Neprilysin inhibition must be accompanied by simultaneous RAAS blockade (e.g. AT_1 receptor blockade)[2]



ACE=angiotensin-converting enzyme; AT_1=angiotensin II type 1; Ang=angiotensin; H_20=water; Na=sodium; RAAS=renin-angiotensin- aldosterone system

1. Von Lueder et al. Circ Heart Fail 2013;6:594–605
2. Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9

Evolution of pharmacologic approaches in HF:
Neprilysin inhibition as a new therapeutic strategy[1]



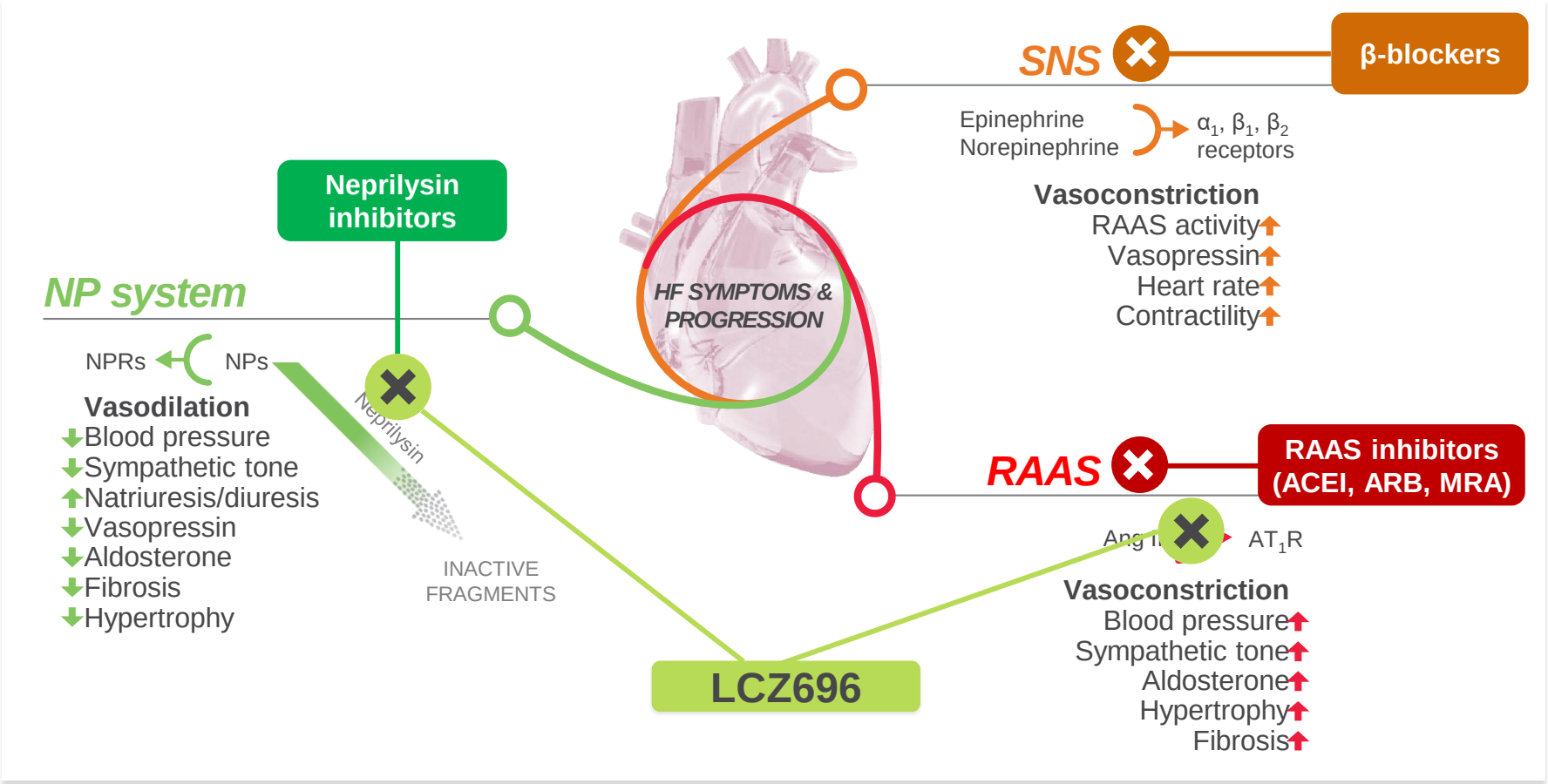
- Neprilysin inhibitors: natriuretic and other vasoactive peptides enhancement

ACEI=angiotensin-converting enzyme inhibitor; Ang=angiotensin; ARB=angiotensin receptor blocker; AT_1R = angiotensin II type 1 receptor; HF=heart failure; MRA=mineralocorticoid receptor antagonist; NP=natriuretic peptide; NPRs=natriuretic peptide receptors; RAAS=renin-angiotensin-aldosterone system; SNS=sympathetic nervous system

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

Evolution of pharmacologic approaches in HF:

LCZ696 as a new alternative to an ACEI or ARBs in patients with HFrEF[1]

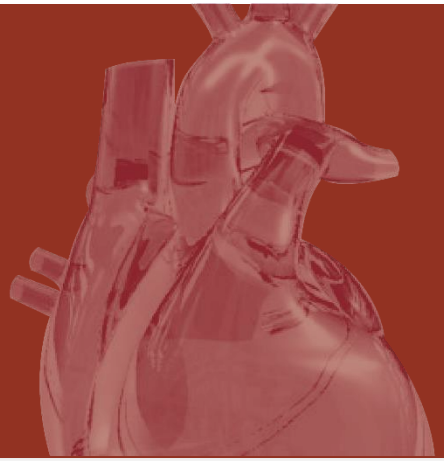


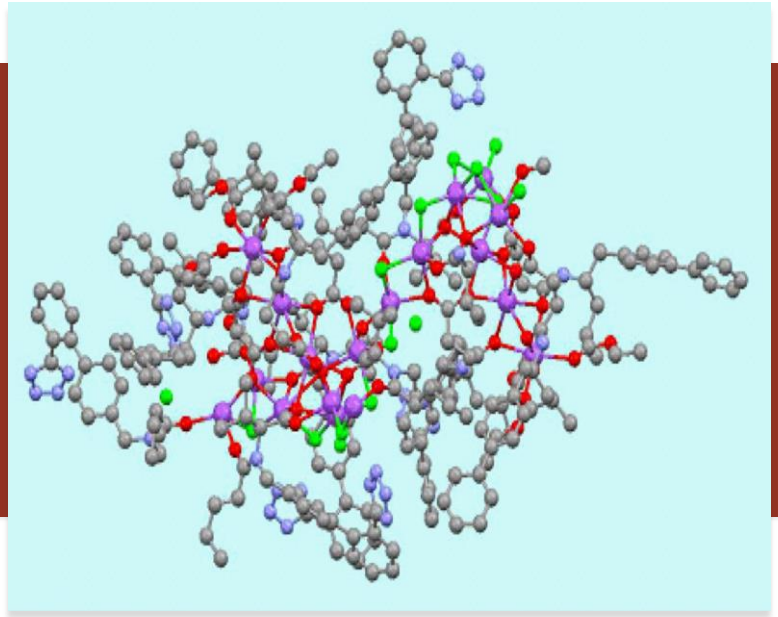
- LCZ696: enhancement of natriuretic and other vasoactive peptides, with simultaneous RAAS suppression

LCZ696 (ARNI) has not been available yet in Indonesia

ACEI=angiotensin-converting enzyme inhibitor; Ang=angiotensin; ARB=angiotensin receptor blocker; AT_1R=angiotensin II type 1 receptor; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; MRA=mineralocorticoid receptor antagonist; NP=natriuretic peptide; NPRs=natriuretic peptide receptors; RAAS=renin-angiotensin-aldosterone system; SNS=sympathetic nervous system

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





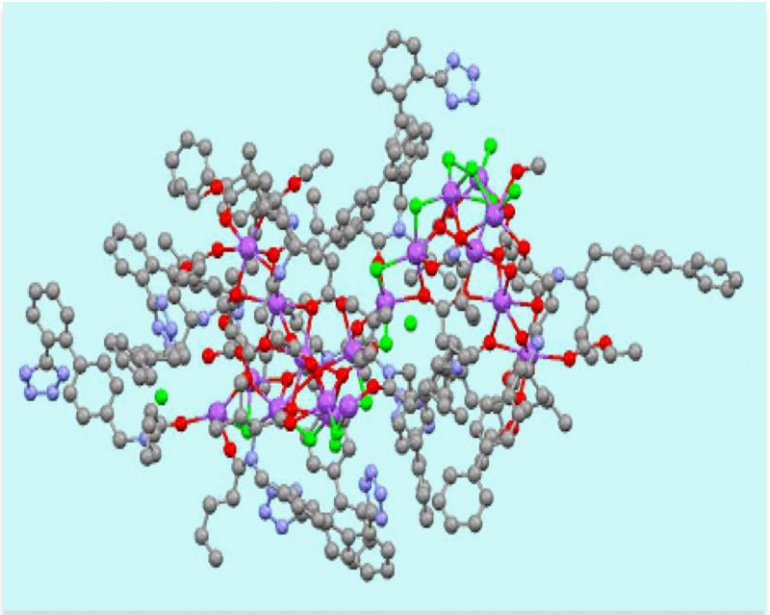
A New Hope

NOVARTIS PHARMACEUTICALS

LCZ696 is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI)

- LCZ696 is a novel drug which delivers simultaneous neprilysin inhibition and AT_1 receptor blockade[1–3]
- LCZ696 is a salt complex that comprises the two active components:[2,3]
  - sacubitril (AHU377) – a pro-drug; further metabolized to the neprilysin inhibitor LBQ657, and
  - valsartan – an AT_1 receptor blocker

  in a 1:1 molar ratio



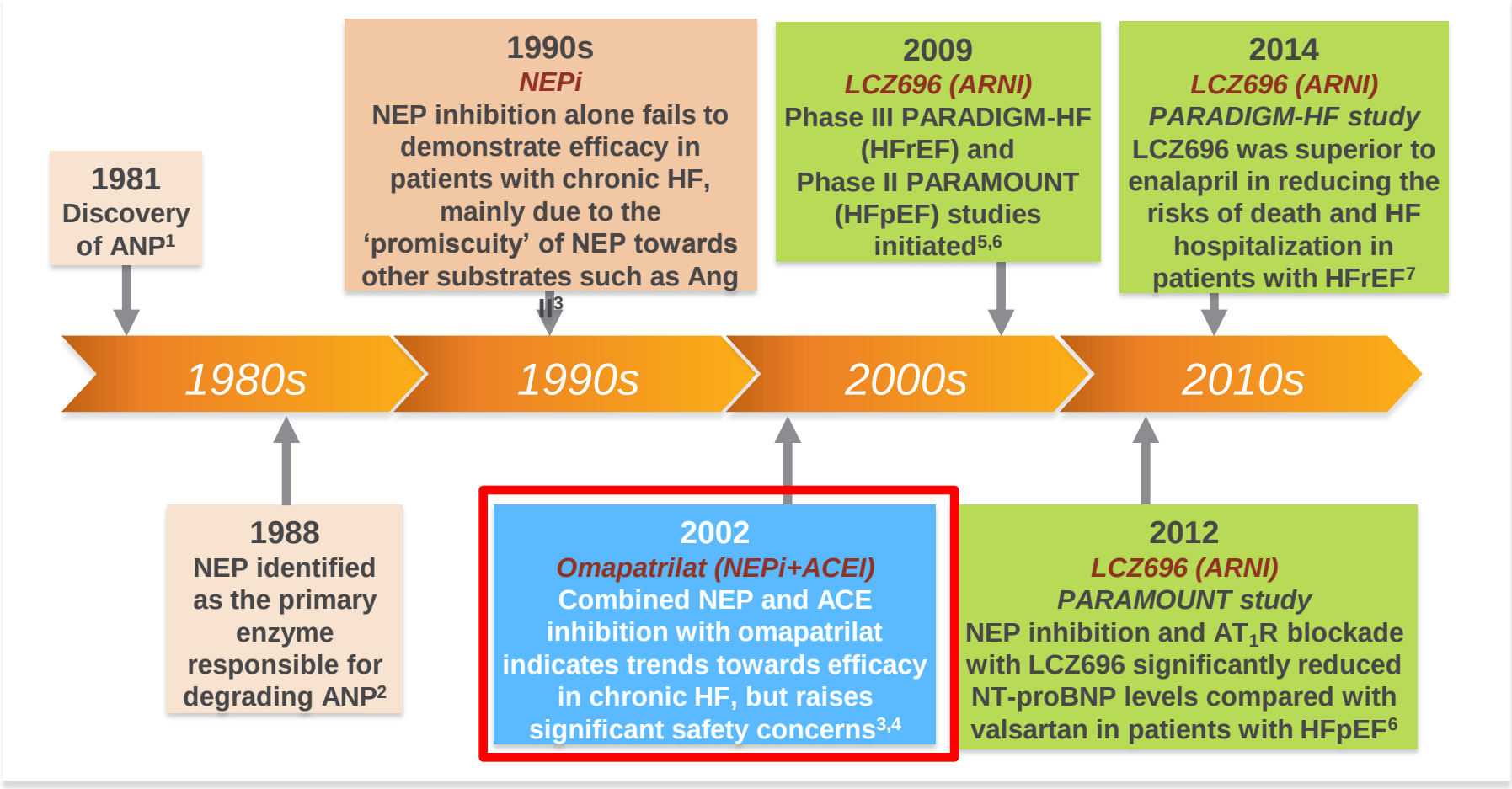
3D LCZ696 structure[2]

LCZ696 (ARNI) has not been available yet in Indonesia

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

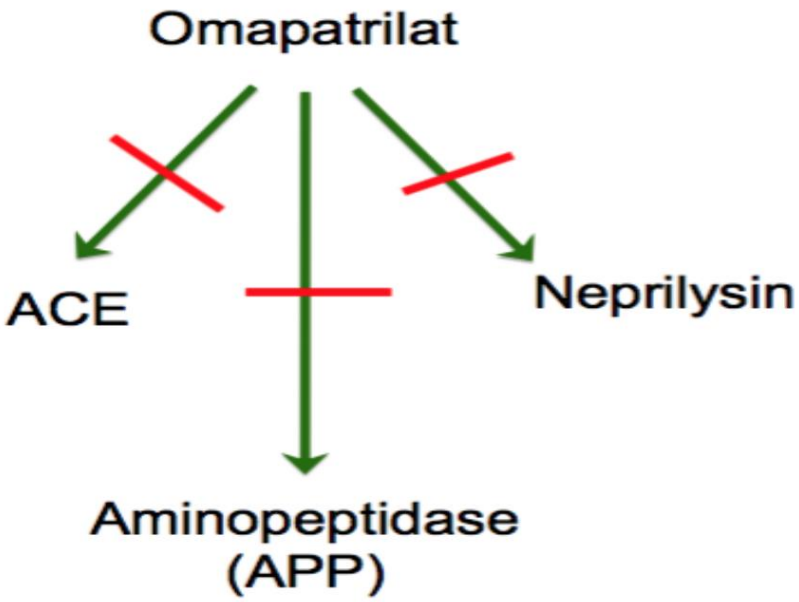
Vasopeptidase inhibitors timeline



LCZ696 (ARNI) has not been available yet in Indonesia

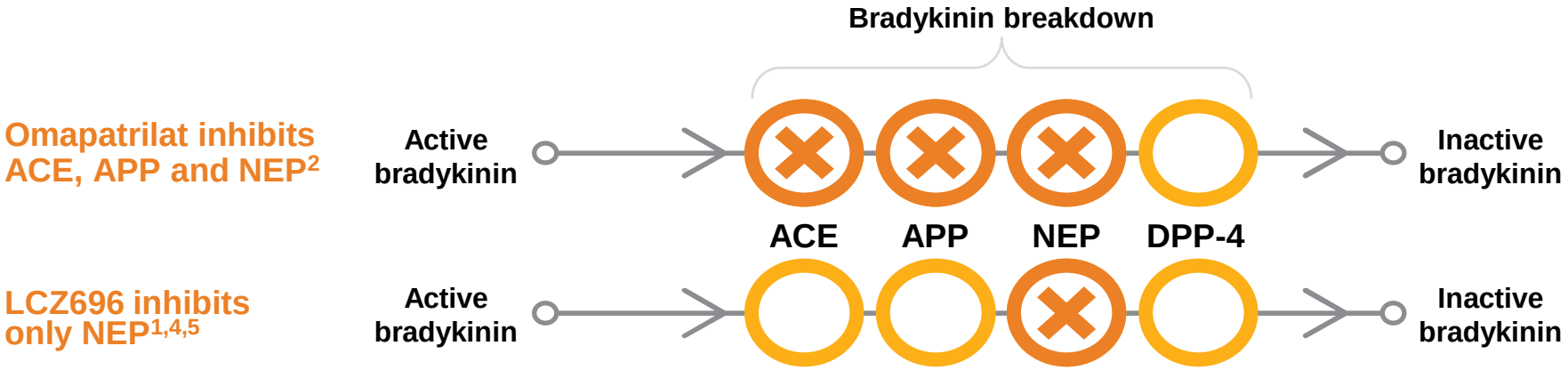
1. de Bold et al. Life Sci 1981;28:89–94;
2. Sonnenberg et al. Peptides 1988;9:173–80;
3. Von Lueder et al. Pharmacol Ther 2014;144:41–9; 4. Packer et al. Circulation 2002;106:920–6; 5. McMurray et al. Eur J Heart Fail 2013;15:1062–73;
6. Solomon et al. Lancet 2012;380:1387–95;
7. McMurray et al. N Engl J Med 2014;371:993–1004

Omapatrilat and dual ACE-NEP inhibition



Bradykinin breakdown in Omapatrilat and LCZ696

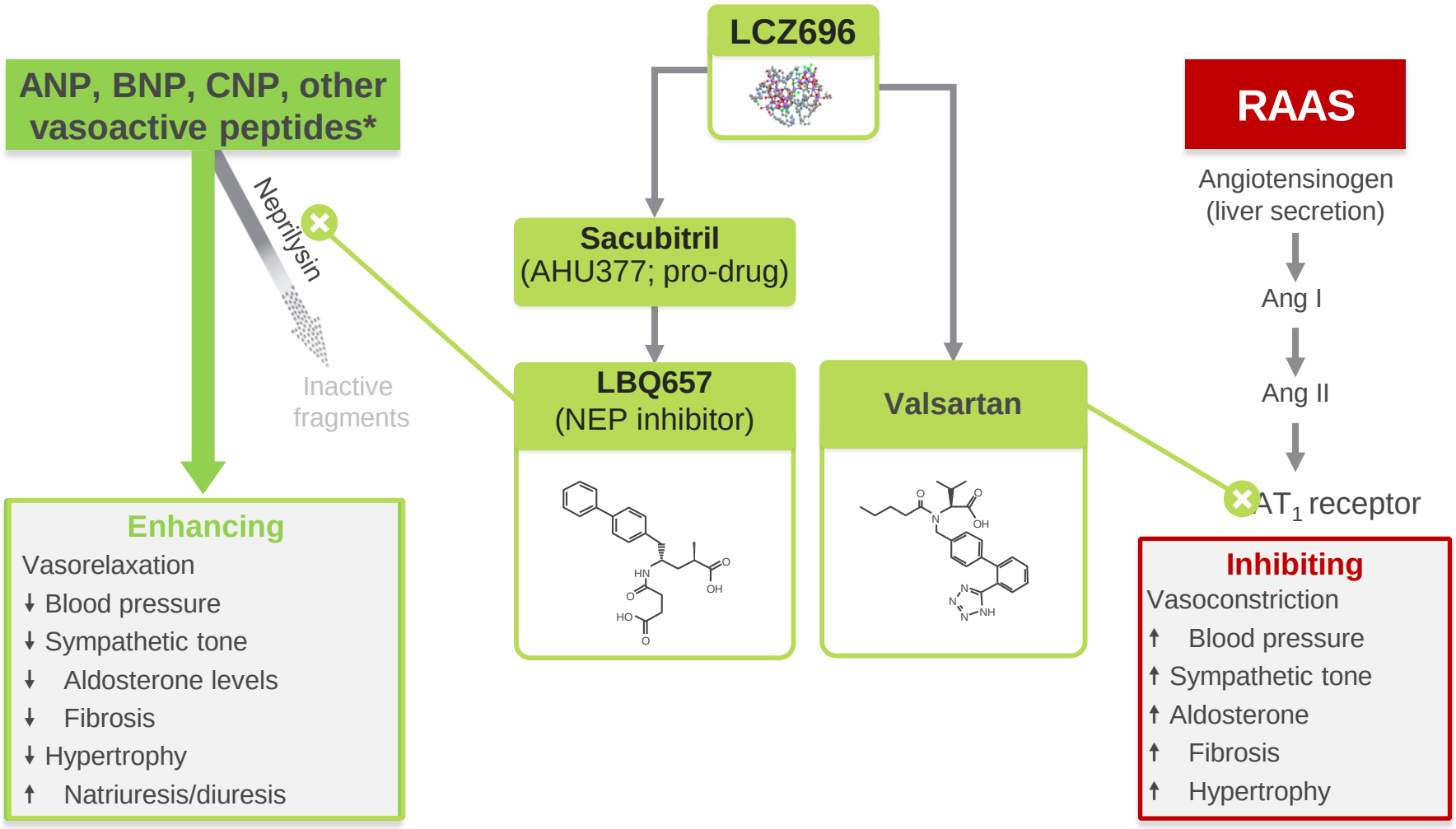
- Bradykinin is a substrate of neprilysin and other vasopeptidases (ACE, APP, DPP-4) – its elevation has been associated with cough and angioedema[2,3]
- Omapatrilat inhibits three enzymes (ACE, APP, NEP) involved in the breakdown of bradykinin, which is likely to be responsible for the development of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



LCZ696 (ARNI) has not been available yet in Indonesia

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

LCZ696 simultaneously inhibits neprilysin (via LBQ657) and blocks AT_1 receptors (via valsartan)

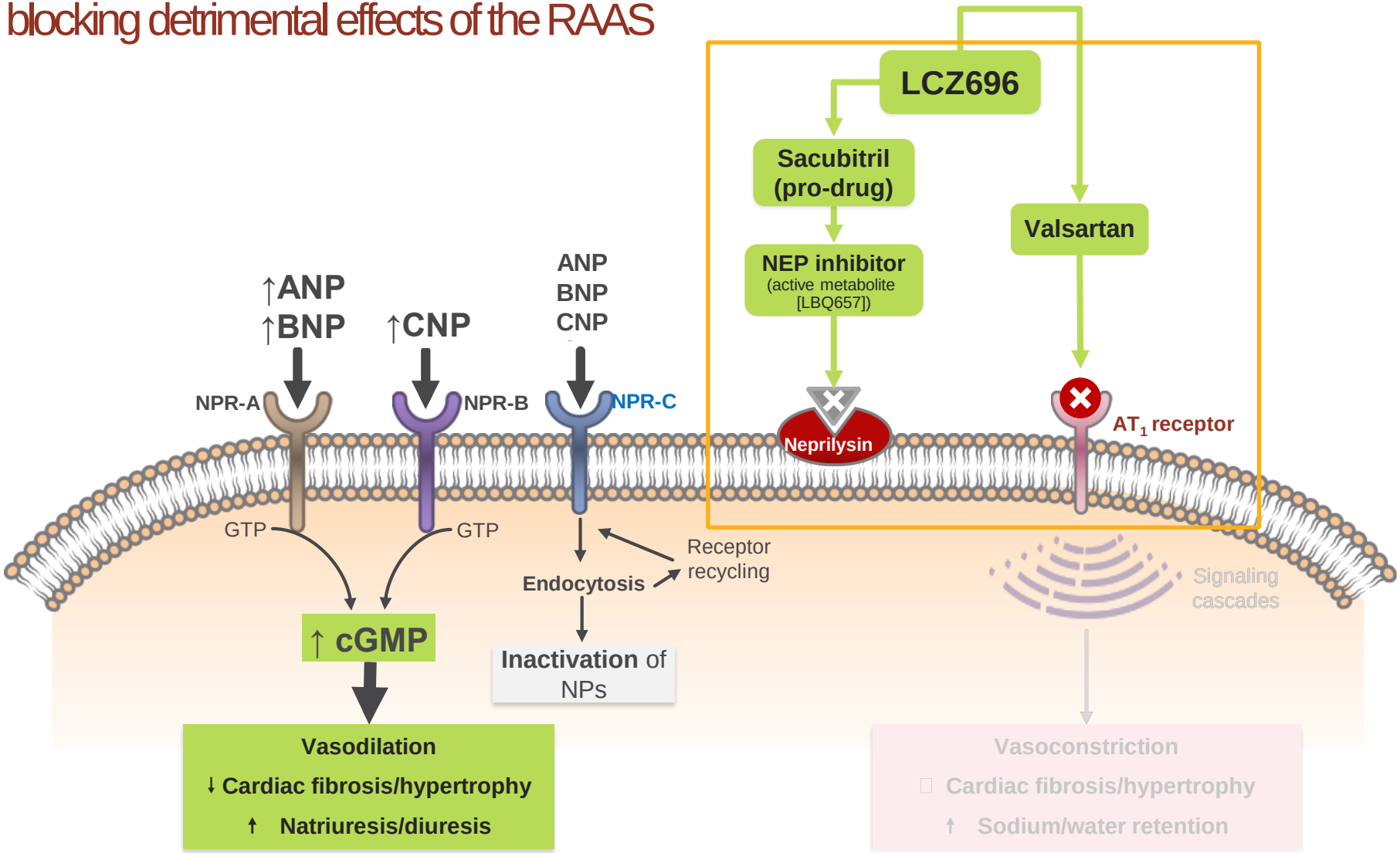


LCZ696 (ARNI) has not been available yet in Indonesia

*Neprilysin substrates listed in order of relative affinity for neprilysin: 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

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



LCZ696 (ARNI) has not been available yet in Indonesia

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; NEP=neprilysin; 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 and Griendling. Am J Physiol Cell Physiol 2007;292:C82–97; Langenickel & Dole. Drug Discovery Today: Ther Strateg 2012;9:e131–9

Angiotensin receptor neprilysin inhibitors (ARNIs), such as LCZ696, overcome the challenges associated with previous approaches to neprilysin inhibition

- ARNIs overcome increased RAAS activation seen with neprilysin inhibition (NEPi) monotherapy and are not expected to be associated with the excessive increase in bradykinin seen with ACEI+NEPi[1,2]

			Omapatrilat	LCZ696
	NEPi	ACEI	NEPi + ACEI[a]	ARNI[b]
Effects on peptide levels[1,3–6]				
Angiotensin II	↑	↓	↓	↑
Renin	↓	↑	↔ ↑	↑
Aldosterone	↓	↔	↓	↓
NPs or cGMP	↑	↓/↔	↑	↑
Endothelin-1	↑	↔	↑	↓
Big-Endothelin-1			↑	
Bradykinin	↑	↑	↑↑	↑
Physiological effects[1]				
Blood pressure	↔	↓	↓	↓
Sodium excretion	↑	↑	↑	↑↑
CV hypertrophy	↔ ↓	↓	↓↓	↓↓
CV fibrosis	↓	↓	↓↓	↓↓

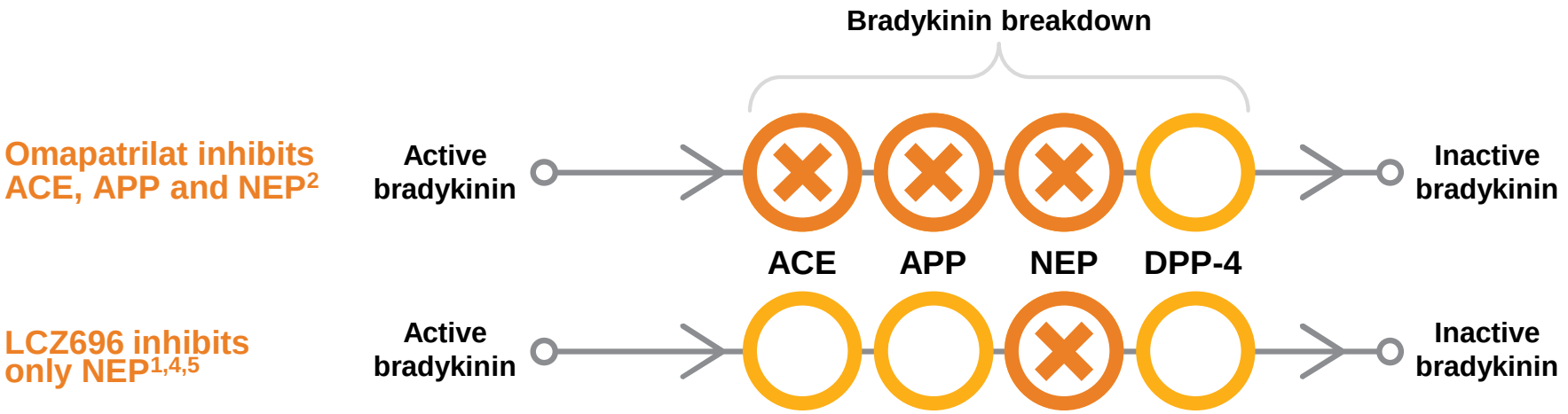
[a]Only data for omapatrilat considered; [b]Only data for LCZ696 considered

ACEI=angiotensin-converting enzyme inhibitor; ARNI=angiotensin receptor neprilysin inhibitor; cGMP=cyclic guanosine monophosphate; CV=cardiovascular; NEPi=neprilysin inhibitor; NP=natriuretic peptide; RAAS=renin-angiotensin-aldosterone system

1. Von Lueder et al. Pharmacol Ther 2014;144:41–9;
2. McMurray et al. Eur J Heart Fail 2014;16:817–25;
3. Gu et al. J Clin Pharmacol 2010;50:401–14;
4. Andersen et al. J Renin Angiotensin Aldosterone Syst 2009;10;157–67; 5. Rosenberg et al. Cardiovasc Drugs Ther 2008;22:305–11;
6. Crozier et al. Clin Exp Pharmacol Physiol 1989;16:417–24

LCZ696 actively inhibits neprilysin and the AT_1 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]



- In PARADIGM-HF, a higher proportion of patients in the LCZ696 group than in the enalapril group had non-serious angioedema, but LCZ696 was not associated with an increase in serious angioedema[6]
- There was a lower incidence of cough in the LCZ696 group compared with enalapril[6]

LCZ696 (ARNI) has not been available yet in Indonesia

The information presented in this slide is from publically available data and not head-to–head clinical trials.
ACE=angiotensin-converting enzyme; APP=aminopeptidase P; AT_1= angiotensin II type 1; DPP-4=dipeptidyl peptidase; NEP=neprilysin; NYHA=New York Heart Association; 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. 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

PARADIGM-HF Study

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

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

LCZ696 (ARNI) has not been available yet in Indonesia

NOVARTIS PHARMACEUTICALS

PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

PARADIGM-HF:

- Is the first study to test the effect of LCZ696 on morbidity and mortality in patients with HFrEF
  - primarily evaluates whether simultaneous angiotensin receptor neprilysin inhibition with **LCZ696** compared with **enalapril**, in addition to conventional HF treatment…

    …delays **time to first occurrence of either CV death or HF hospitalization**…

    …in patients with stable NYHA FC II–IV HF and *reduced* ejection fraction (**LVEF ≤40%***)
- Determined the place of the ARNI LCZ696 as an alternative to an ACEI (enalapril) in patients with chronic systolic HFrEF
- May change the approach to neurohormonal modulation in HFrEF

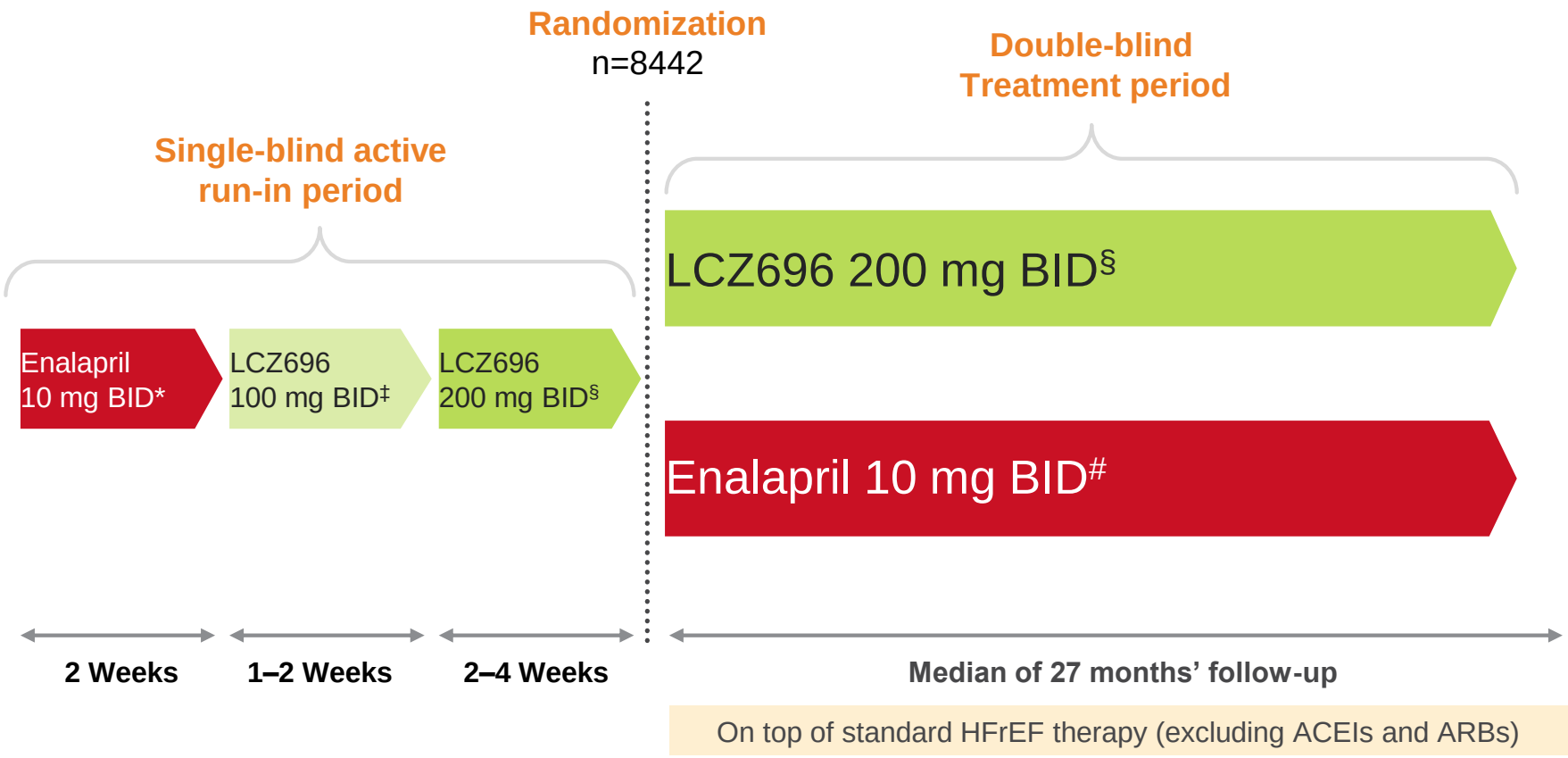
LCZ696 (ARNI) has not been available yet in Indonesia

*The ejection fraction entry criteria was lowered to ≤35% in a protocol amendment.
ACEI=angiotensin-converting enzyme inhibitor; ARNI=angiotensin receptor neprilysin inhibitor; CV=cardiovascular; FC=functional class; HF=heart failure; HFrEF=heart failure with reduced ejection fraction; LVEF=left ventricular ejection fraction; NYHA= New York Heart Association

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

NOVARTIS PHARMACEUTICALS

PARADIGM-HF: study design



LCZ696 (ARNI) has not been available yet in Indonesia

*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; 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

Enalapril 10 mg BID was chosen as the appropriate comparator dose

- Enalapril 10 mg BID is the regulatory 'gold-standard' ACEI based upon SOLVD-T and CONSENSUS trial data[1–3]
  - SOLVD-T (patients with mild-to-moderately symptomatic HF) and CONSENSUS (patients with severely symptomatic HF) showed a survival benefit with enalapril 10 mg BID[1,2]
  - the mean daily enalapril dose achieved in PARADIGM-HF (18.9 mg) was higher than or similar to doses used in SOLVD-T (16.6 mg) and CONSENSUS (18.4 mg), respectively[1,2,4]

Key HF trials with enalapril*

Trial	N	Target dose (mg)	Mean daily dose (mg)
CONSENSUS	127	20 BID	**18.4**
SOLVD-T	1,285	10 BID	**16.6**
SOLVD-P	2,111	10 BID	16.7
V-HeFT II	403	10 BID	15.0
OVERTURE	2,884	10 BID	17.7
CARMEN	190	10 BID	16.8
PARADIGM-HF	4,212	10 BID	**18.9**

LCZ696 (ARNI) has not been available yet in Indonesia

*Adapted from McMurray et al. Eur J Heart Fail 2013;15:1062–73
ACEI=angiotensin-converting enzyme inhibitor; BID=twice daily; CARMEN=Carvedilol and ACE-Inhibitor Remodelling Mild Heart Failure EvaluatioN; CONSENSUS=Cooperative North Scandinavian Enalapril Survival Study; HF=heart failure; Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events; PARADIGM-HF=Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; SOLVD=Studies of Left Ventricular Dysfunction

1. CONSENSUS Study Group. N Engl J Med 1987;316:1429–35
2. SOLVD Investigators. N Engl J Med 1991;325:293–3022
3. McMurray et al. Eur J Heart Fail 2013;15:1062–73
4. McMurray et al. N Engl J Med 2014;371:993–1004

PARADIGM-HF: LCZ696 dose selection rationale

AT_1 receptor blockade

- LCZ696 200 mg BID delivers similar exposures to valsartan as Diovan® 160 mg BID, the dose recommended for treatment of HF and MI (based on Val-HeFT and VALIANT)[1–3]

NEP inhibition

- Biomarker analysis indicates that LCZ696 200 mg provides ~90% of its maximal NEP inhibition[1,4]
- Both LCZ696 400 and 200 mg QD (but not 100 mg LCZ696) provided meaningful pharmacodynamic effect (BP lowering) attributable to NEP inhibtion[5]
- BID dosing is considered essential to obtain 24-hour NEP inhibition[1,6]
- BID dosing mitigates risk of post-dose hypotension (two smaller doses, compared to one larger once-daily dose, as used in the OVERTURE study with omapatrilat)[1,6]

LCZ696 (ARNI) has not been available yet in Indonesia

AT_1=angiotensin II type 1; BID=twice daily; BP=blood pressure; HF=heart failure; MI=myocardial infarction; NEP=neprilysin; OVERTURE=Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events; PARADIGM-HF=Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; QD=once daily; Val-HeFT=valsartan heart failure trial; VALIANT=valsartin in acute myocardial infarction

1. McMurray et al. Eur J Heart Fail 2013;15:1062–732;
2. Cohn et al. N Engl J Med 2001;345:1667–75;
3. Pfeffer et al. N Engl J Med 2003;349:1893–1906;
4. Gu et al. J Clin Pharmacol 2010;50:401–14
5. Ruilope et al. Lancet 2010;375:1255–66;
6. Packer et al. Circulation 2002;106:920–6

NOVARTIS PHARMACEUTICALS

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)

LCZ696 (ARNI) has not been available yet in Indonesia

*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; 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 LCZ696 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

LCZ696 (ARNI) has not been available yet in Indonesia

ACEI=angiotensin-converting enzyme 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 LCZ696 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]

LCZ696 (ARNI) has not been available yet in Indonesia

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 I_f 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

NOVARTIS PHARMACEUTICALS

PARADIGM-HF: secondary objectives

- To assess whether LCZ696 was superior to enalapril in:
  - improving quality of life (assessed by KCCQ score)
  - delaying time to all-cause mortality
  - delaying time to new-onset atrial fibrillation
  - delaying time to decline of renal function as defined by:
    - 50% decline in eGFR from baseline, or
    - >30 mL/min/1.73 m^2 decline in eGFR relative to baseline and to a value of <60 mL/min/1.73 m^2 (indicating the development of moderate renal dysfunction), or
    - development of end-stage renal disease

LCZ696 (ARNI) has not been available yet in Indonesia

eGFR=estimated glomerular filtration rate; KCCQ=Kansas City Cardiomyopathy Questionnaire; 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

NOVARTIS PHARMACEUTICALS

PARADIGM-HF: safety endpoints

- Monitoring for:
  - serious adverse events
  - hyperkalemia
  - symptomatic hypotension
  - increased serum creatinine
  - angioedema
  - other adverse events

- DMC performed a safety assessment after the first 100, 300 and 600 patients completed the single-blind run-in period
- Number of patients exposed to LCZ696 was limited to 600 until DMC completed a 4-week of double-blind therapy safety evaluation for the initial 200 randomized patients

LCZ696 (ARNI) has not been available yet in Indonesia

DMC=data monitoring committee;
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

Patient population and baseline characteristics

LCZ696 (ARNI) has not been available yet in Indonesia

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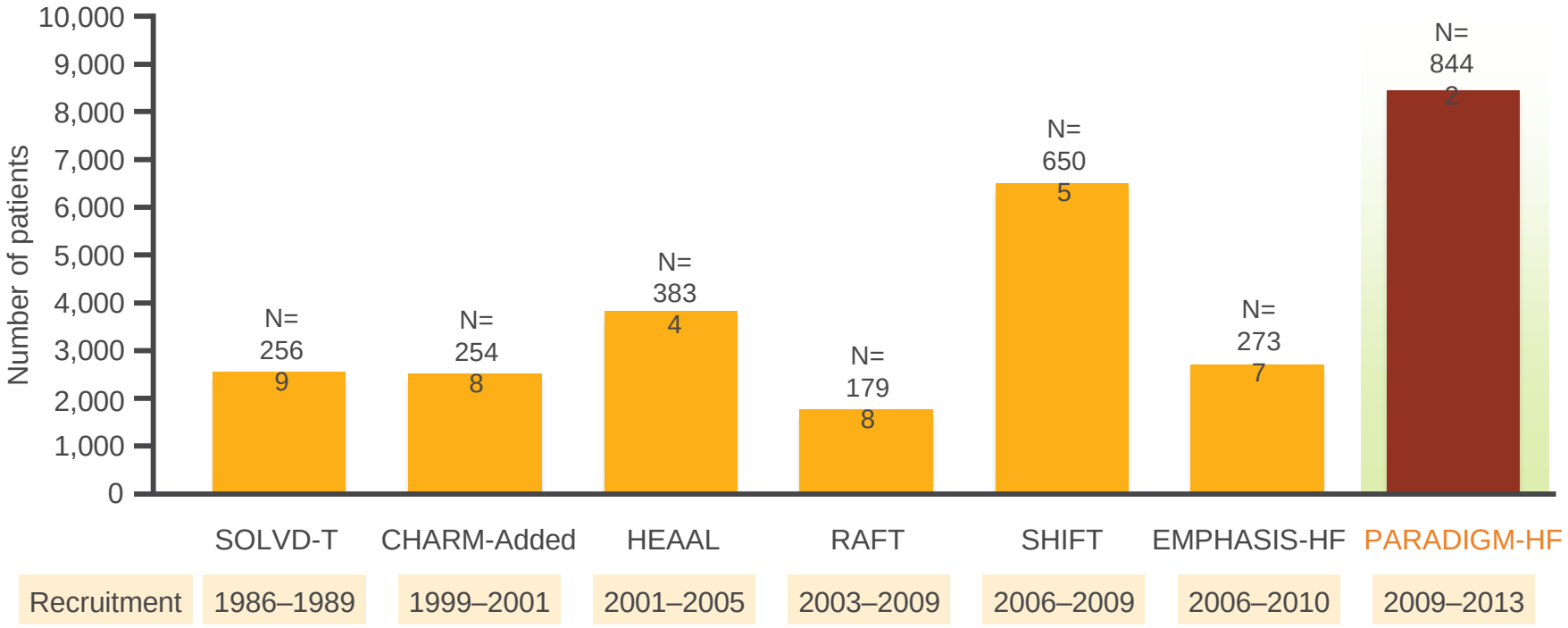
PARADIGM-HF: the largest mortality-morbidity trial in patients with HFrEF



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CHARM-Added=Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity-Added trial; EMPHASIS-HF=Eplerenone in Mild Patients Hospitalization And Survival study in Heart Failure; HEAAL=Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan; 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; RAFT=Resynchronization/Defibrillation for Ambulatory Heart Failure Trial; SHIFT=Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial; SOLVD-T=Studies of Left Ventricular Dysfunction Treatment trial

McMurray et al. Eur J Heart Fail 2014;16:817–25

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

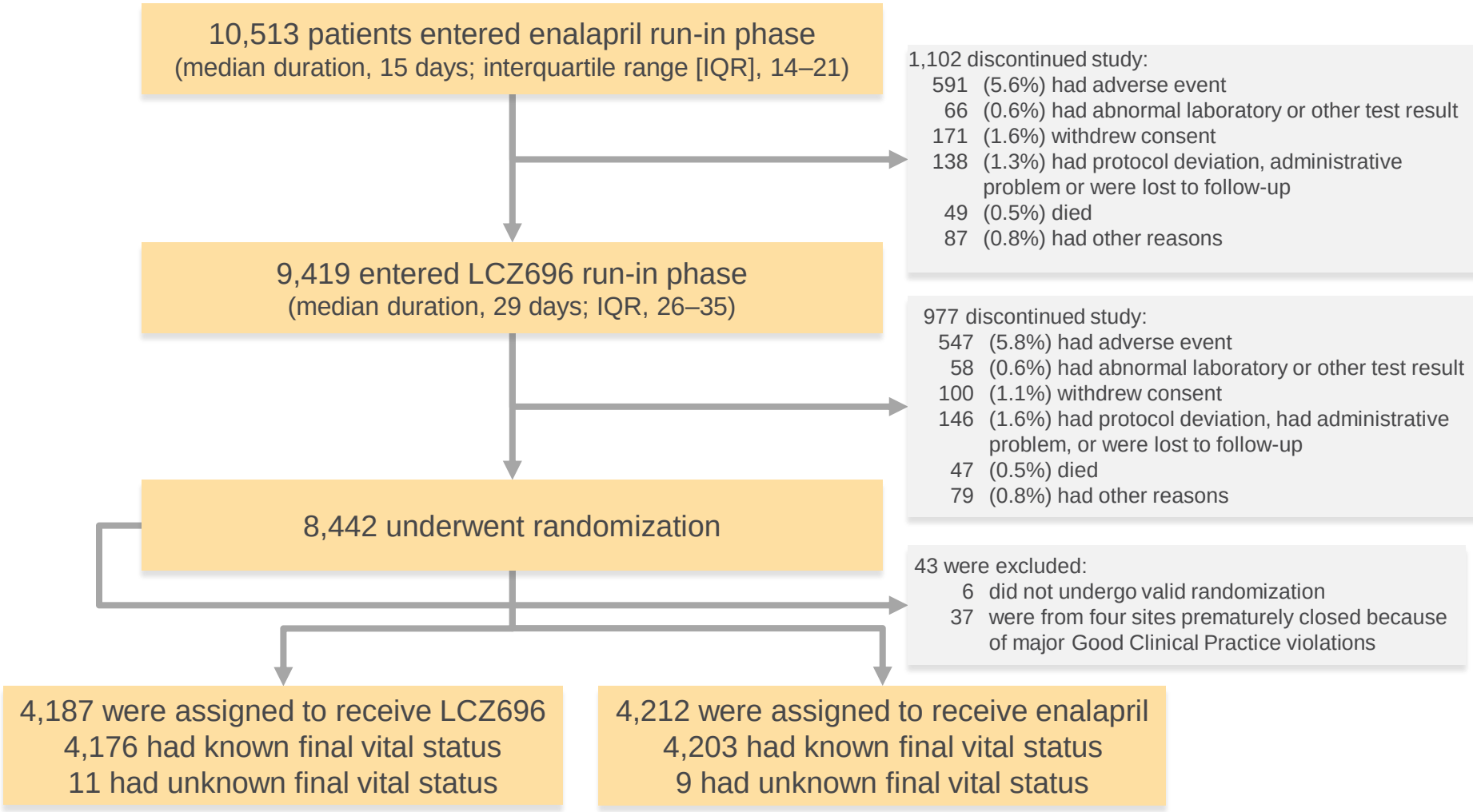
- 8,442 patients were randomized at 985 sites in 47 countries

LCZ696 (ARNI) has not been available yet in Indonesia

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: patient disposition



LCZ696 (ARNI) has not been available yet in Indonesia

IQR=interquartile range; PARADIGM-HF=Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

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

PARADIGM-HF: summary of baseline characteristics

Characteristic*	LCZ696 (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	*2,998 (71.6)*	*2,921 (69.3)*
III	*969 (23.1)*	*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)*

LCZ696 (ARNI) has not been available yet in Indonesia

*Mean ± standard deviation, unless stated. 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 J Med 2014;371:993–1004

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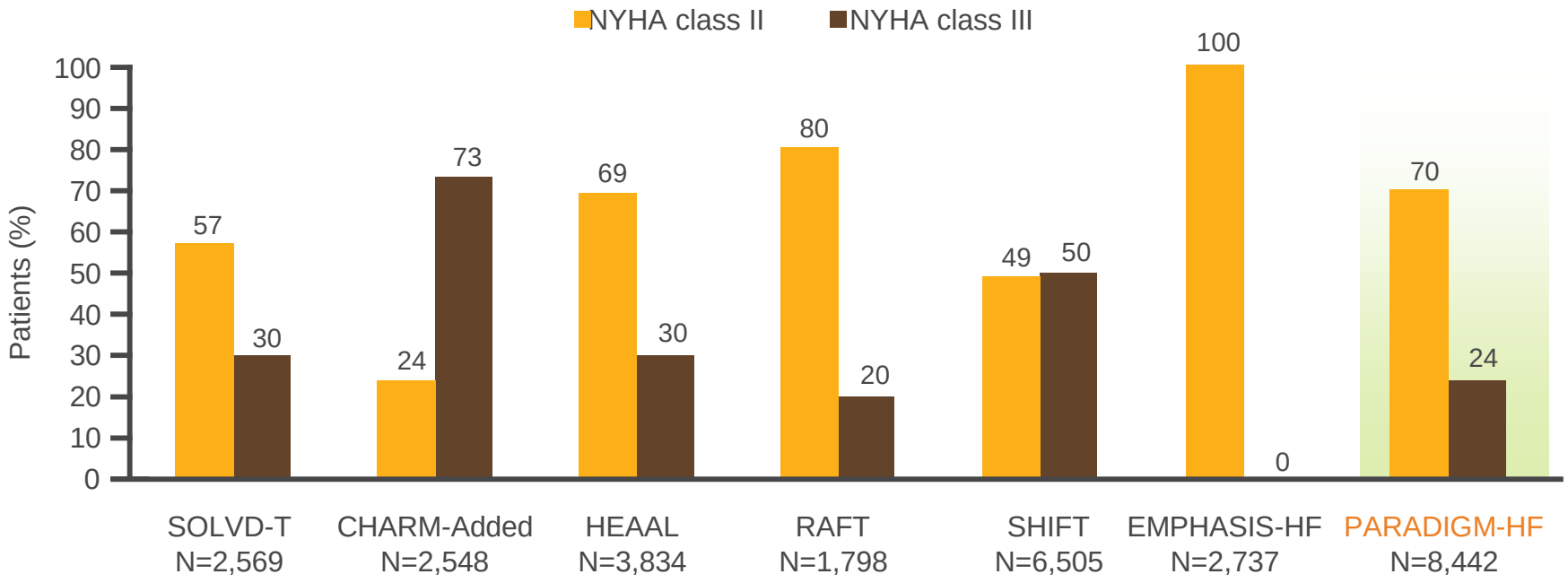
PARADIGM-HF: consistent with most other trials in HFrEF, the majority of patients were in NYHA class II at baseline

- 70% of patients were NYHA class II – greater than in SOLVD-T (57%), possibly due to greater use of disease-modifying drugs/devices prior to enrolment in PARADIGM-HF



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McMurray et al. Eur J Heart Fail 2014;16:817–25

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PARADIGM-HF
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Results

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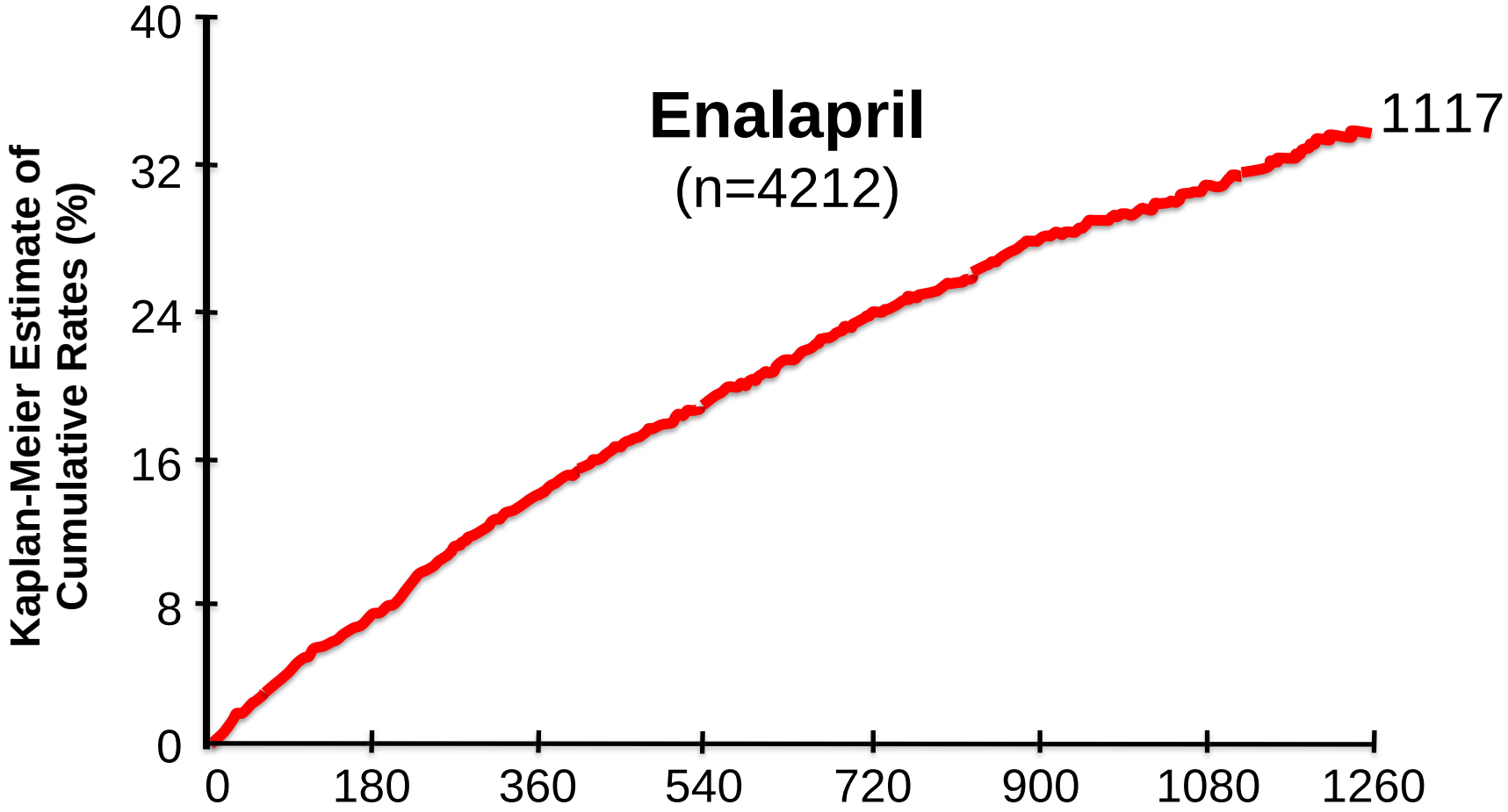
PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

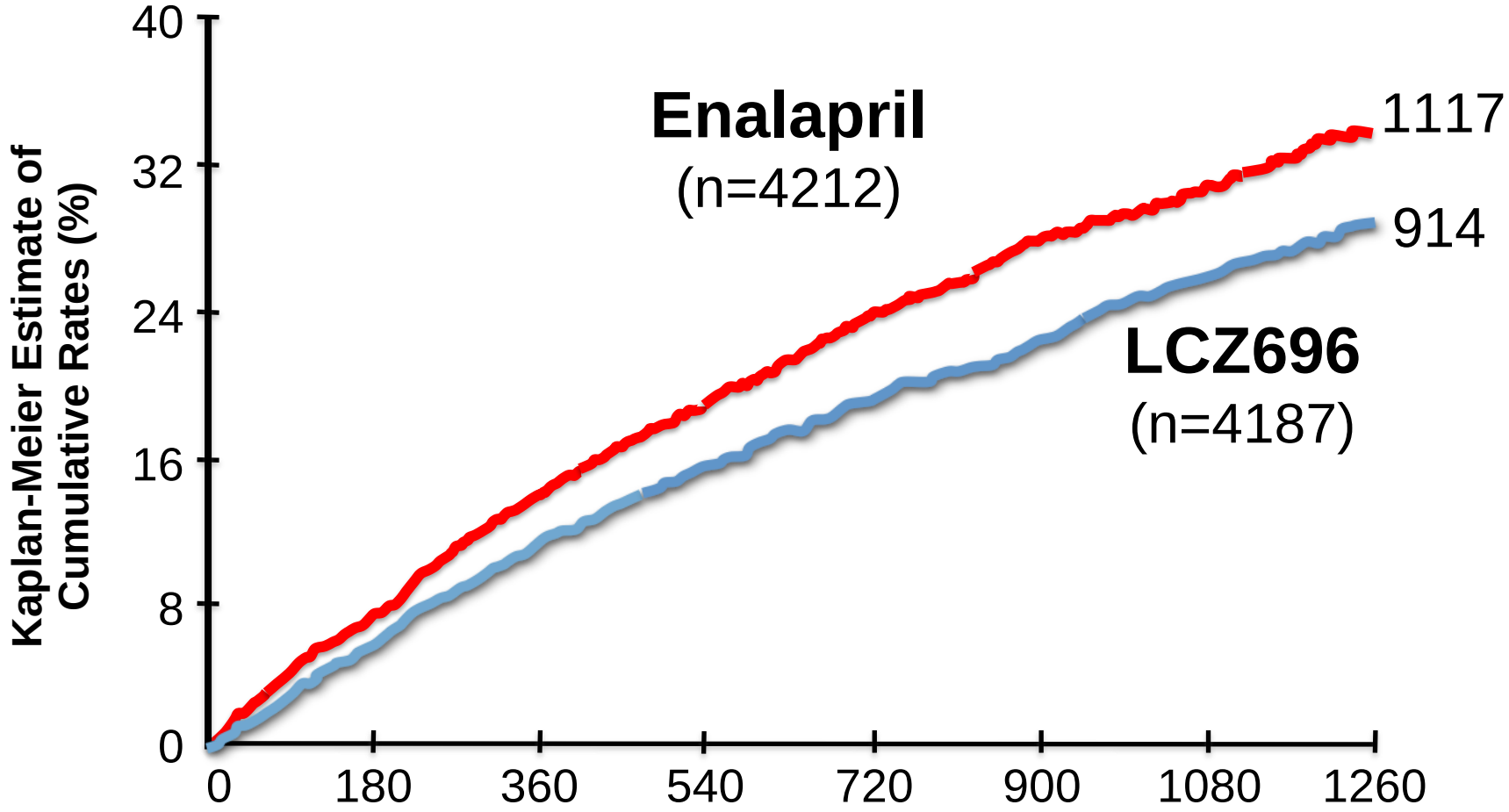


Patients at Risk

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

LCZ696 (ARNI) has not been available yet in Indonesia

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



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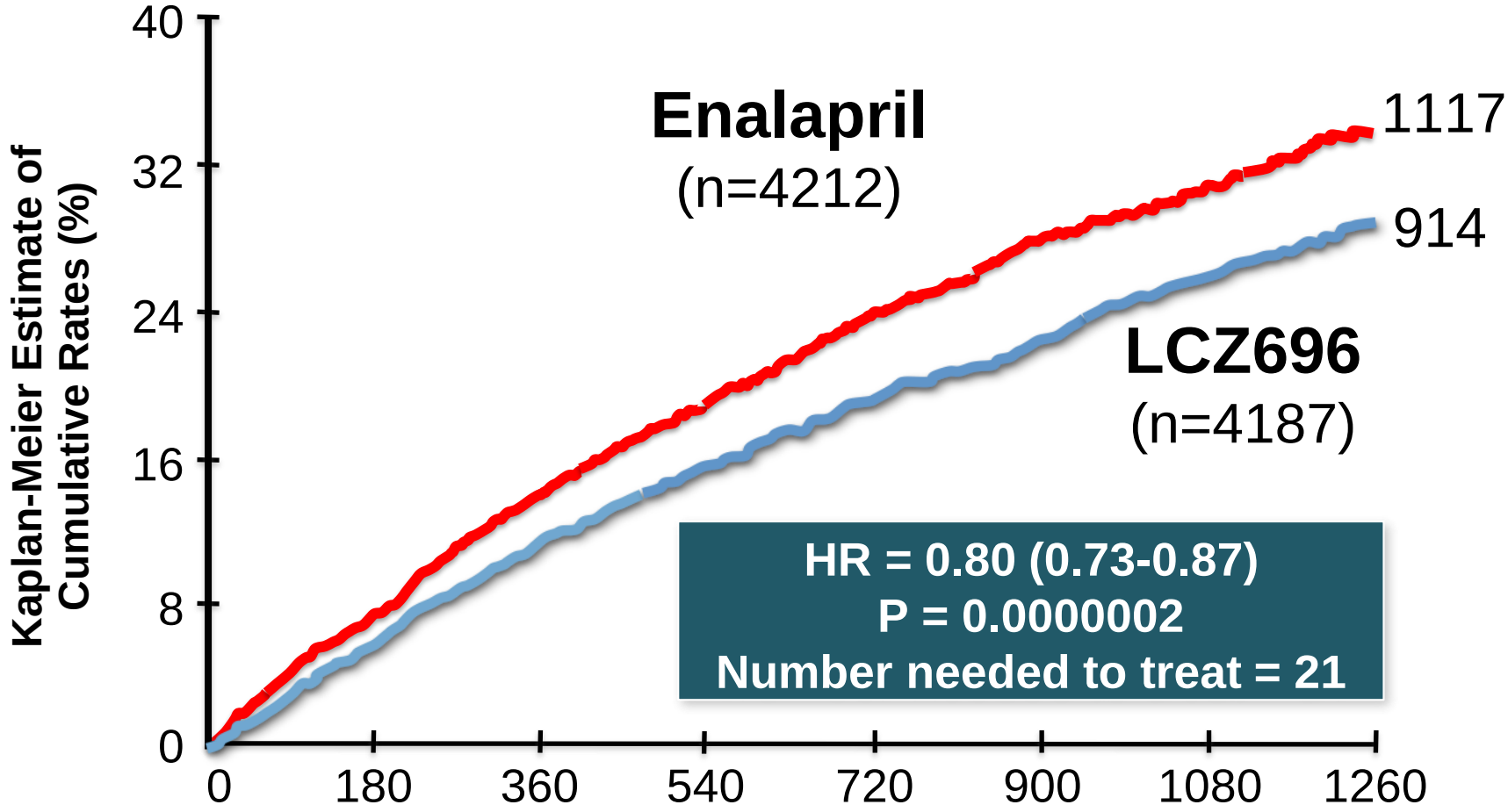

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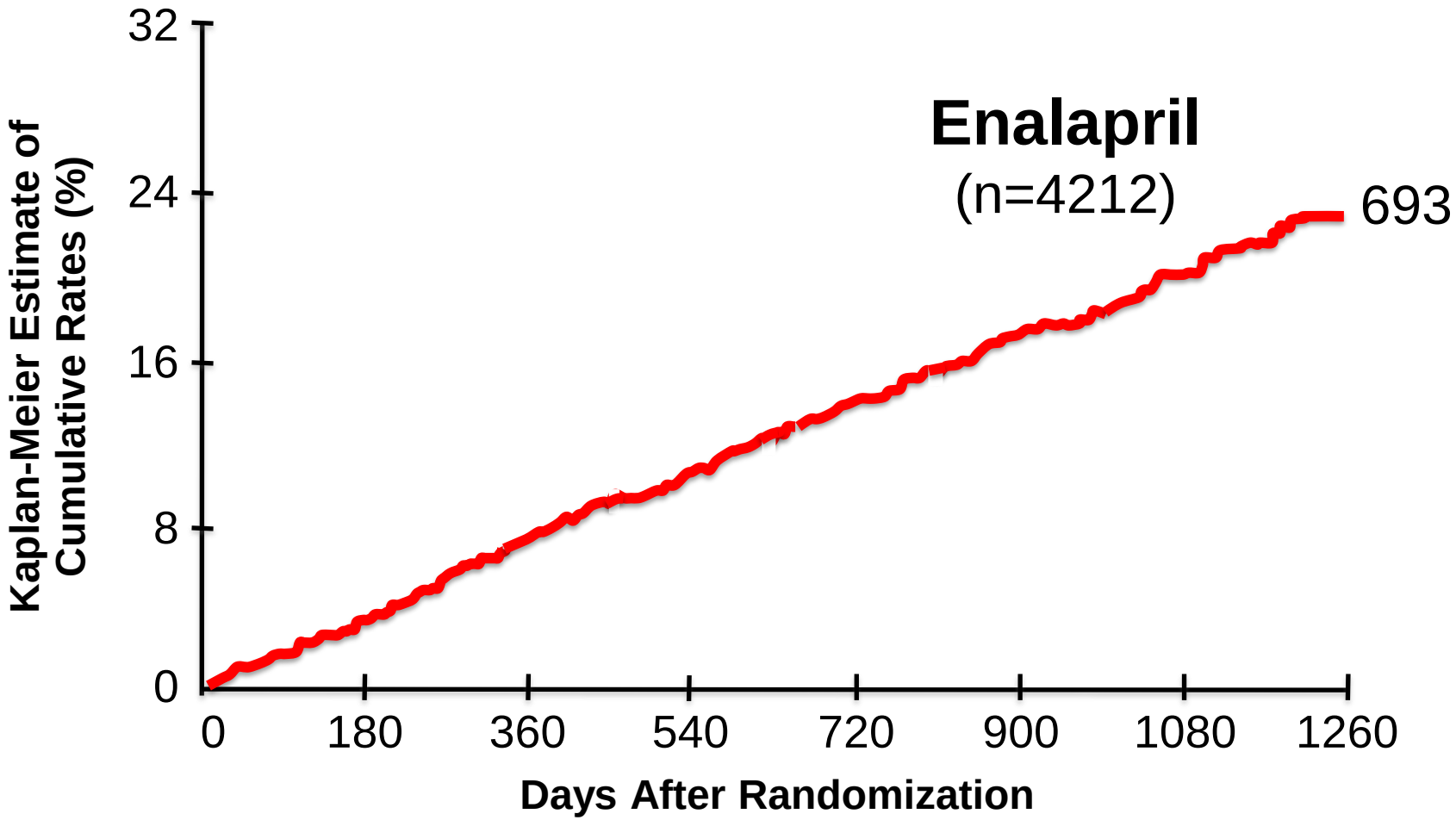
PARADIGM-HF: Cardiovascular Death



Patients at Risk

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

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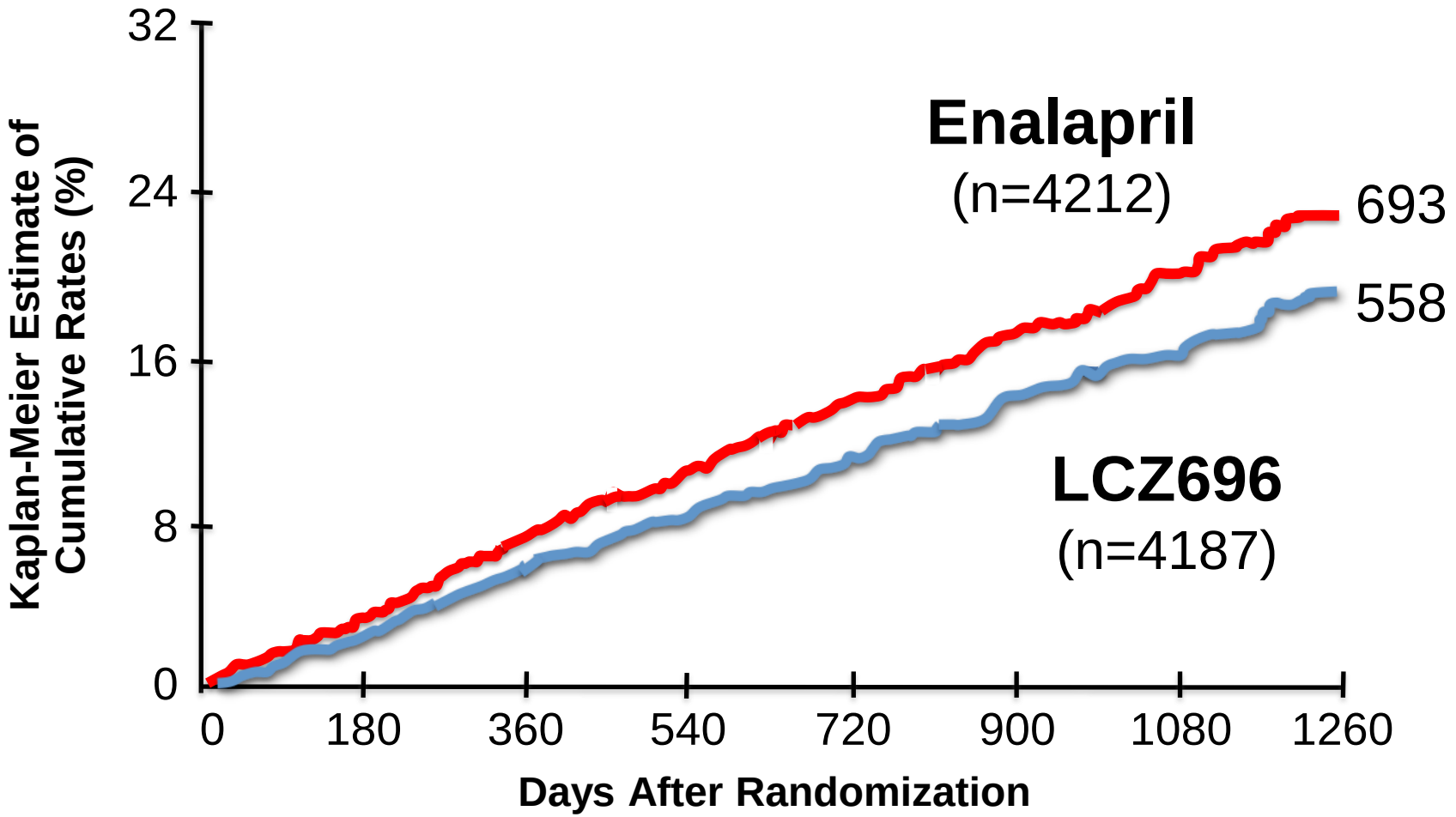
PARADIGM-HF: Cardiovascular Death



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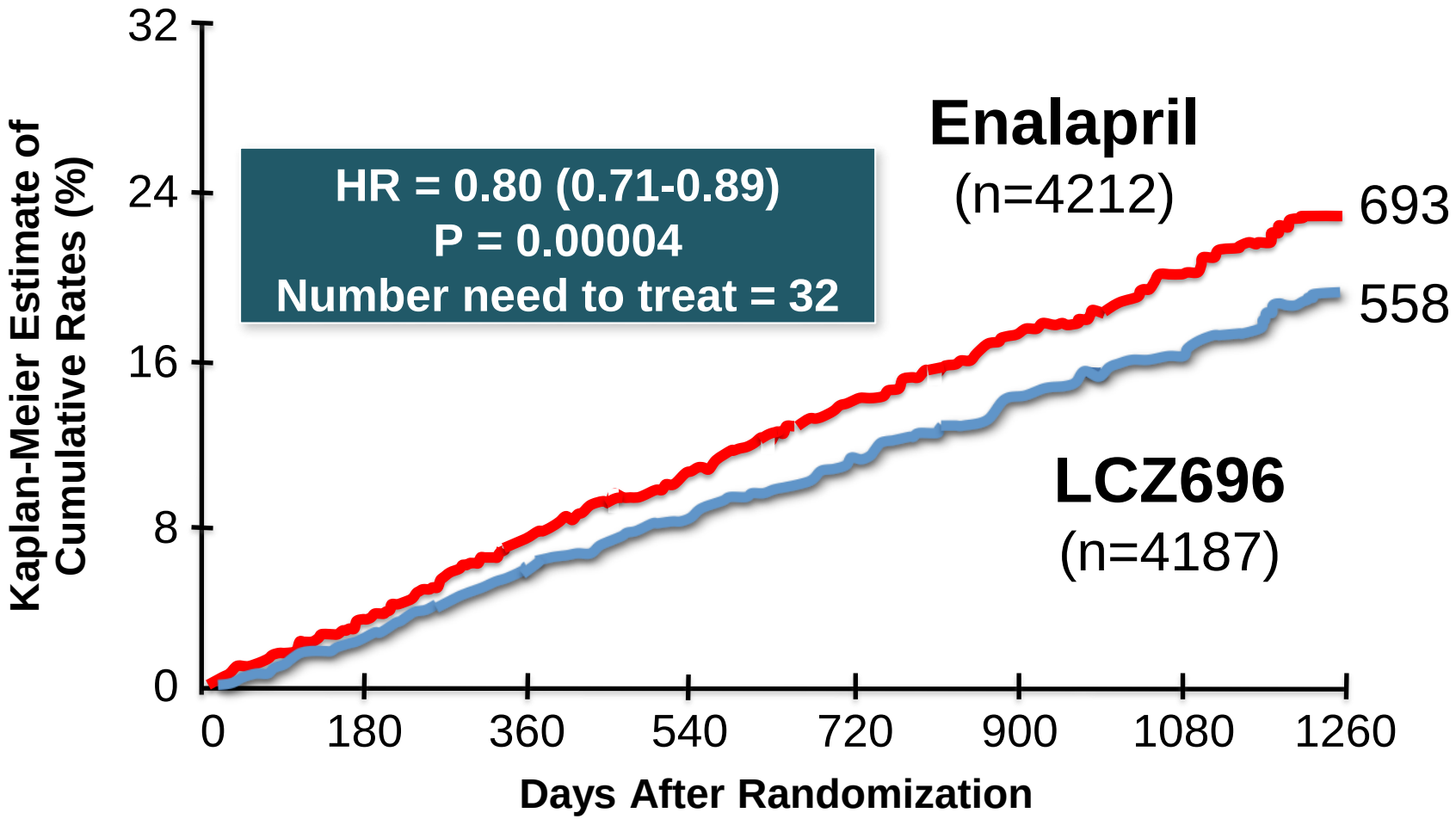
PARADIGM-HF: Cardiovascular Death



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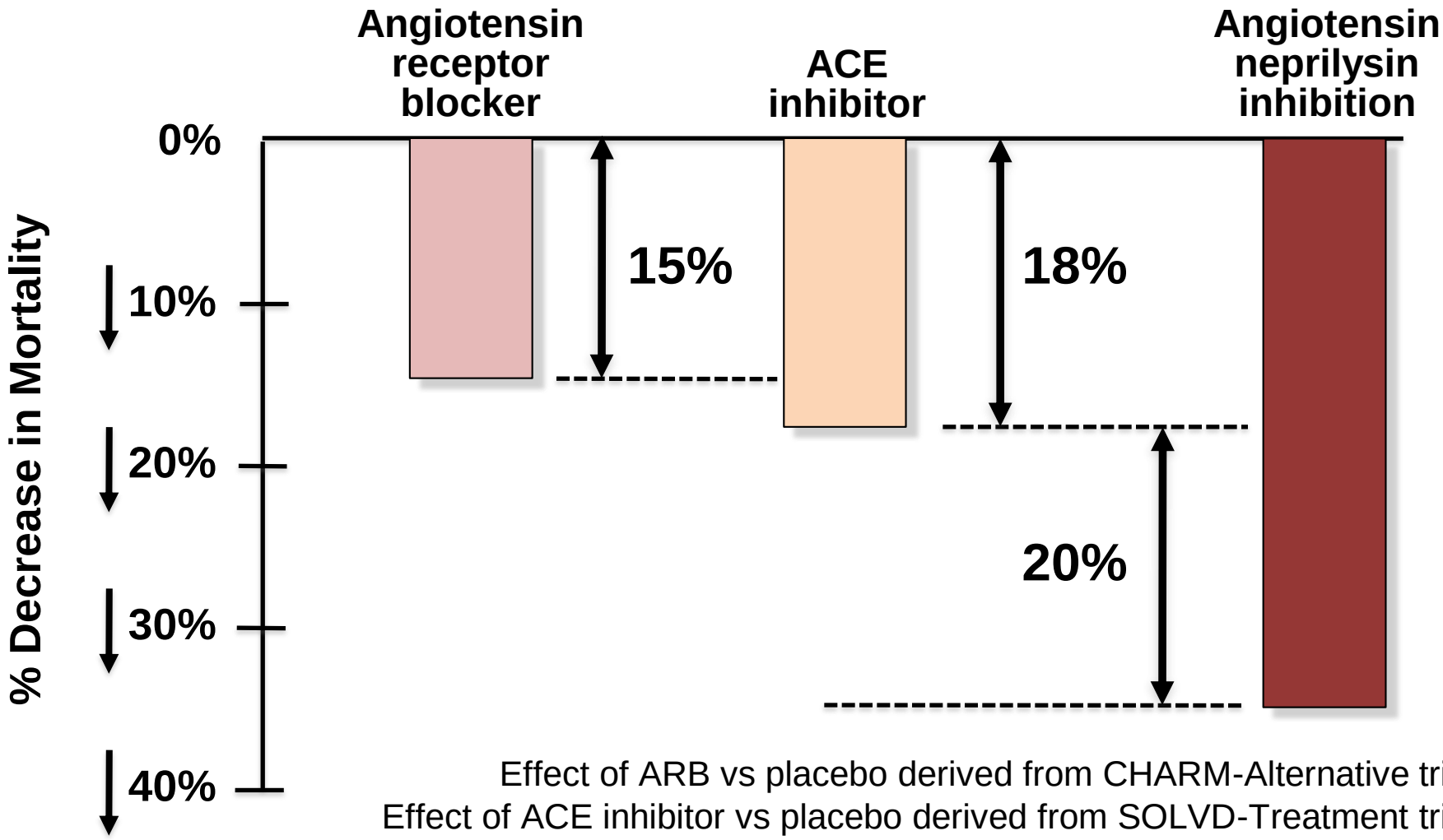
Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System

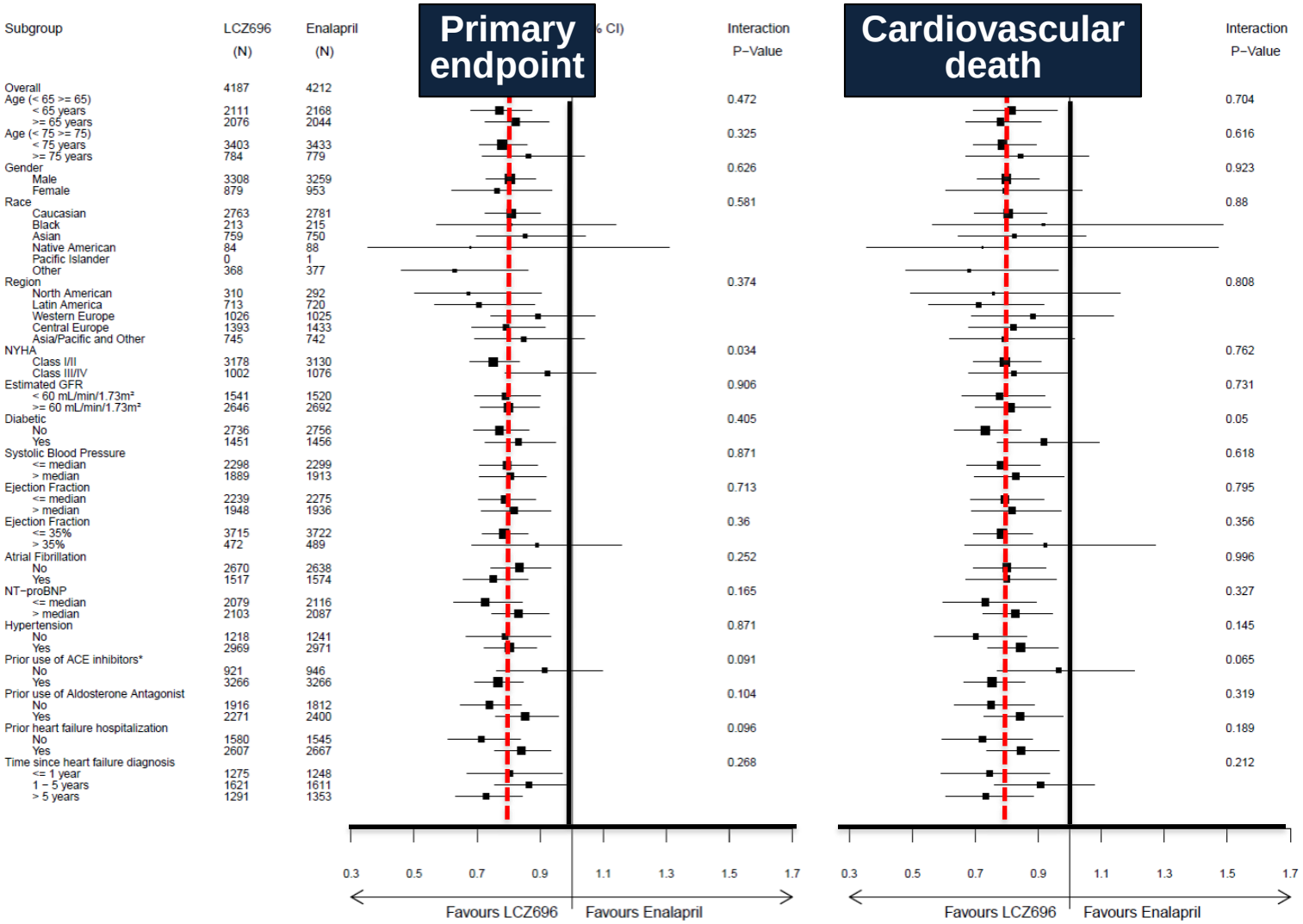


Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial

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

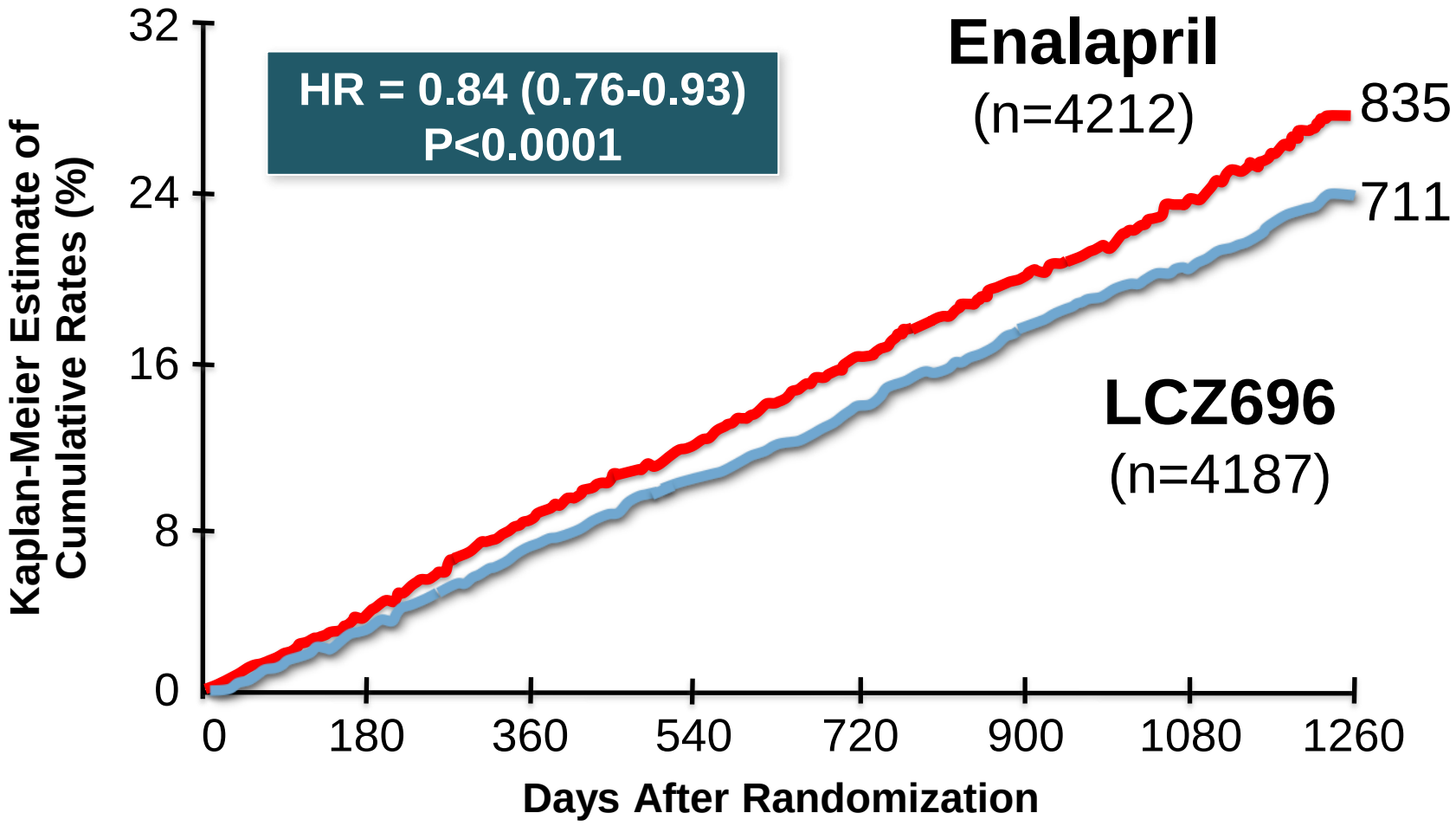
	LCZ696 (n=4187)	Enalapril (n=4212)	Hazard Ratio (95% CI)	P Value
Primary endpoint	914 (21.8%)	1117 (26.5%)	0.80 (0.73-0.87)	0.0000002
Cardiovascular death	558 (13.3%)	693 (16.5%)	0.80 (0.71-0.89)	0.00004
Hospitalization for heart failure	537 (12.8%)	658 (15.6%)	0.79 (0.71- 0.89)	0.00004

LCZ696 vs Enalapril on Primary Endpoint and on Cardiovascular Death, by Subgroups



LCZ696 (ARNI) has not been available yet in Indonesia

PARADIGM-HF: All-Cause Mortality



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Enalapril	4212	4051	3860	3231	2410	1726	994	279

LCZ696 (ARNI) has not been available yet in Indonesia

PARADIGM-HF: Effect of LCZ696 vs Enalapril on Secondary Endpoints

	LCZ696 (n=4187)	Enalapril (n=4212)	Treatment effect	P Value
KCCQ clinical summary score at 8 months	– 2.99 ± 0.36	– 4.63 ± 0.36	1.64 (0.63, 2.65)	0.001
New onset atrial fibrillation	84/2670 (3.2%)	83/2638 (3.2%)	Hazard ratio 0.97 (0.72,1.31)	0.84
Protocol-defined decline in renal function	94/4187 (2.3%)	108/4212 (2.6%)	Hazard ratio 0.86 (0.65, 1.13)	0.28

LCZ696 (ARNI) has not been available yet in Indonesia

PARADIGM-HF: Adverse Events

	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Prospectively identified adverse events			
Symptomatic hypotension	588	388	< 0.001
Discontinuation for adverse event			
Discontinuation for hypotension	36	29	NS

LCZ696 (ARNI) has not been available yet in Indonesia

PARADIGM-HF: Adverse Events

	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Prospectively identified adverse events			
Serum potassium > 6.0 mmol/l	181	236	0.007
Serum creatinine ≥ 2.5 mg/dl	139	188	0.007
Cough	474	601	< 0.001
Discontinuation for adverse event	**449**	**516**	**0.02**
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001

LCZ696 (ARNI) has not been available yet in Indonesia

PARADIGM-HF: Adverse Events

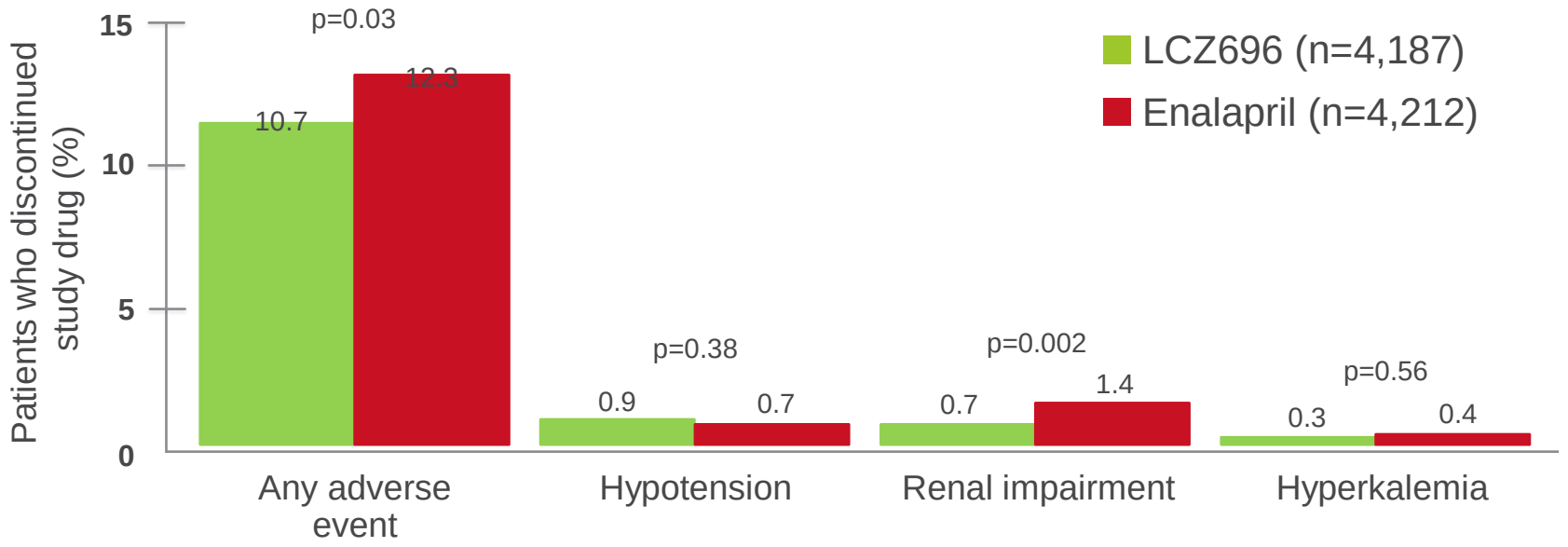
	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Prospectively identified adverse events			
Symptomatic hypotension	588	388	< 0.001
Serum potassium > 6.0 mmol/l	181	236	0.007
Serum creatinine ≥ 2.5 mg/dl	139	188	0.007
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001
Angioedema (adjudicated)			
Medications, no hospitalization	16	9	NS
Hospitalized; no airway compromise	3	1	NS
Airway compromise	0	0	----

Fewer patients in the LCZ696 group than in the enalapril group stopped their study medication because of an AE (10.7 vs 12.3%, p=0.03)

LCZ696 (ARNI) has not been available yet in Indonesia

Adverse events leading to permanent study drug discontinuation

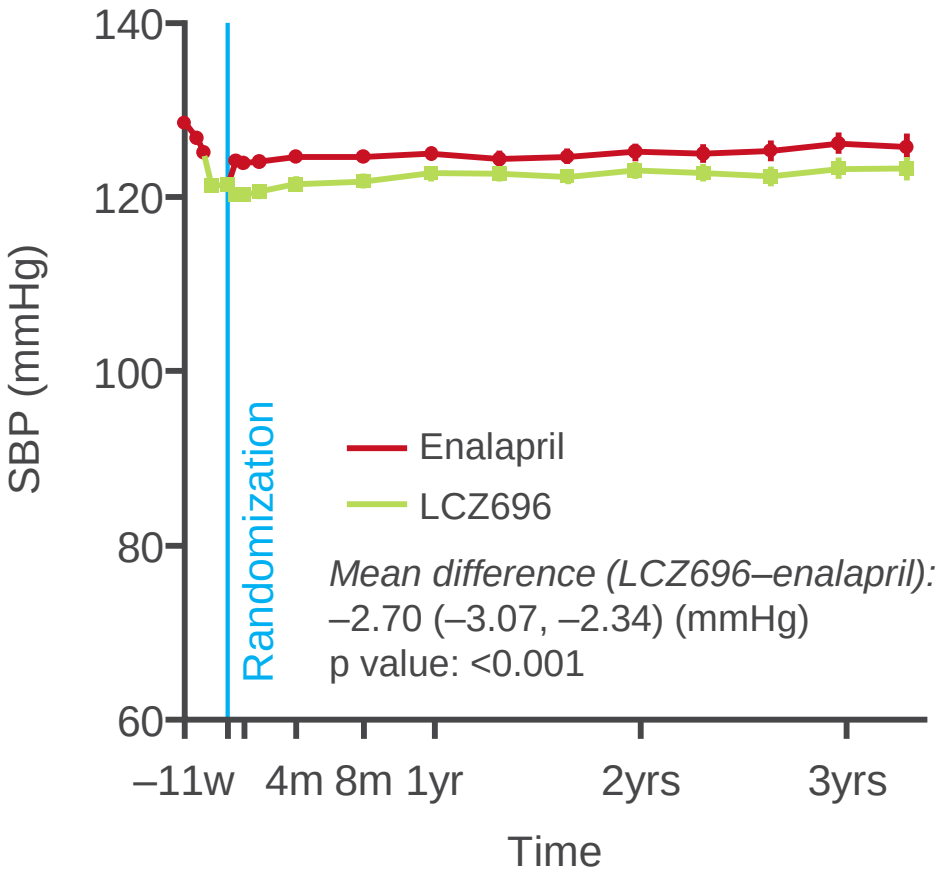
- Fewer patients in the LCZ696 group than in the enalapril group discontinued study drug due to an adverse event (10.7 vs 12.3%; p=0.03)



LCZ696 (ARNI) has not been available yet in Indonesia

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

Systolic blood pressure during run-in and after randomization



- Compared with the randomization level, the mean SBP at 8 months was 3.2 ± 0.4 mmHg lower in the LCZ696 group than in the enalapril group ($p<0.001$)
- When modeled as a time-dependent covariate, the difference in BP was not a determinant of the incremental benefits of LCZ696

LCZ696 (ARNI) has not been available yet in Indonesia

BP=blood pressure; SBP=systolic blood pressure

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

Summary of results – efficacy

- **Primary outcome**
  - 20% reduction in CV death or HF hospitalization with LCZ696 compared with enalapril
    - 20% reduction in CV mortality
    - 21% reduction in HF hospitalization
- **Secondary outcomes**
  - 16% reduction in all-cause mortality with LCZ696 vs enalapril
  - LCZ696 superior to enalapril in reducing symptoms and physical limitations of HF (indicated by KCCQ score)
  - 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

LCZ696 (ARNI) has not been available yet in Indonesia

CV=cardiovascular; HF=heart failure;
KCCQ=Kansas City Cardiomyopathy Questionnaire

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

Most common adverse events* (safety population)

Event, n (%)	LCZ696 (n=4,203)	Enalapril (n=4,229)
Number of patients with at least one AE	*3,419 (81.35)*	*3,503 (82.83)*
Hypotension	*740 (17.61)*	*506 (11.97)*
Cardiac failure	*730 (17.37)*	*832 (19.67)*
Hyperkalemia	*488 (11.61)*	*592 (14.00)*
Renal impairment	*426 (10.14)*	*487 (11.52)*
Cough	*369 (8.78)*	*533 (12.60)*
Dizziness	*266 (6.33)*	*206 (4.87)*
Atrial fibrillation	*251 (5.97)*	*236 (5.58)*
Pneumonia	*227 (5.40)*	*237 (5.60)*
Edema peripheral	*215 (5.12)*	*213 (5.04)*
Dyspnea	*213 (5.07)*	*306 (7.24)*
Nasopharyngitis	*204 (4.85)*	*175 (4.14)*
Upper respiratory tract infection	*203 (4.83)*	*201 (4.75)*
Urinary tract infection	*199 (4.73)*	*195 (4.61)*
Diarrhea	*194 (4.62)*	*189 (4.47)*
Bronchitis	*183 (4.35)*	*224 (5.30)*
Angina pectoris	*172 (4.09)*	*170 (4.02)*
Anemia	*168 (4.00)*	*201 (4.75)*
Back pain	*164 (3.90)*	*138 (3.26)*
Influenza	*159 (3.78)*	*132 (3.12)*
Hypokalemia	*139 (3.31)*	*107 (2.53)*
Cardiac failure chronic	*135 (3.21)*	*155 (3.67)*
Cardiac failure congestive	*133 (3.16)*	*167 (3.95)*

LCZ696 (ARNI) has not been available yet in Indonesia

*≥2% of patients in any group
AE=adverse event

McMurray et al. N Engl J Med 2014;371:993–1004 (Supplementary appendix)

Summary of results – safety

- The superiority of LCZ696 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 LCZ696 group developed renal impairment, hyperkalemia or cough than in the enalapril group
- The LCZ696 group had a higher proportion of patients with non-serious angioedema, but LCZ696 was not associated with an increase in serious angioedema

LCZ696 (ARNI) has not been available yet in Indonesia

Summary

- The PARADIGM-HF study met the primary endpoint:
  - LCZ696 treatment reduced the risk of death from cardiovascular causes or hospitalization for heart failure by 20% compared to ACE inhibition with enalapril in patients with HFrEF[1]
  - LCZ696 was more effective than the ACE inhibitor enalapril in reducing cardiovascular and all-cause mortality[1]
- Greater decreases in NT-proBNP and troponin T levels in patients treated with LCZ696 are consistent with the beneficial clinical effects of LCZ696 observed in the PARADIGM-HF study[2]
- Elevations of BNP and cGMP observed during treatment with LCZ696 reflect neprilysin inhibition[2]

LCZ696 (ARNI) has not been available yet in Indonesia

ACE=angiotensin-converting enzyme; BNP=B-type natriuretic peptide; cGMP=cyclic guanosine monophosphate; HFrEF=heart failure with reduced ejection fraction; 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. McMurray et al. N Engl J Med 2014;371:993–1004
2. Packer et al. Circulation 2015;131:54–61

Implications of clinical progression analysis results

- In PARADIGM-HF, LCZ696, compared with enalapril, was both more effective in reducing all-cause and cardiovascular mortality and in preventing the clinical progression of heart failure in surviving patients with HFrEF
- Patients who were treated with LCZ696 were less likely to:
  - develop worsening of heart failure
  - require hospitalization, intensification of heart failure therapy or heart failure device implantation or cardiac transplantation
  - report deteriorating quality of life

LCZ696 (ARNI) has not been available yet in Indonesia

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

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

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