

Heart Failure Management: From in-hospital to community

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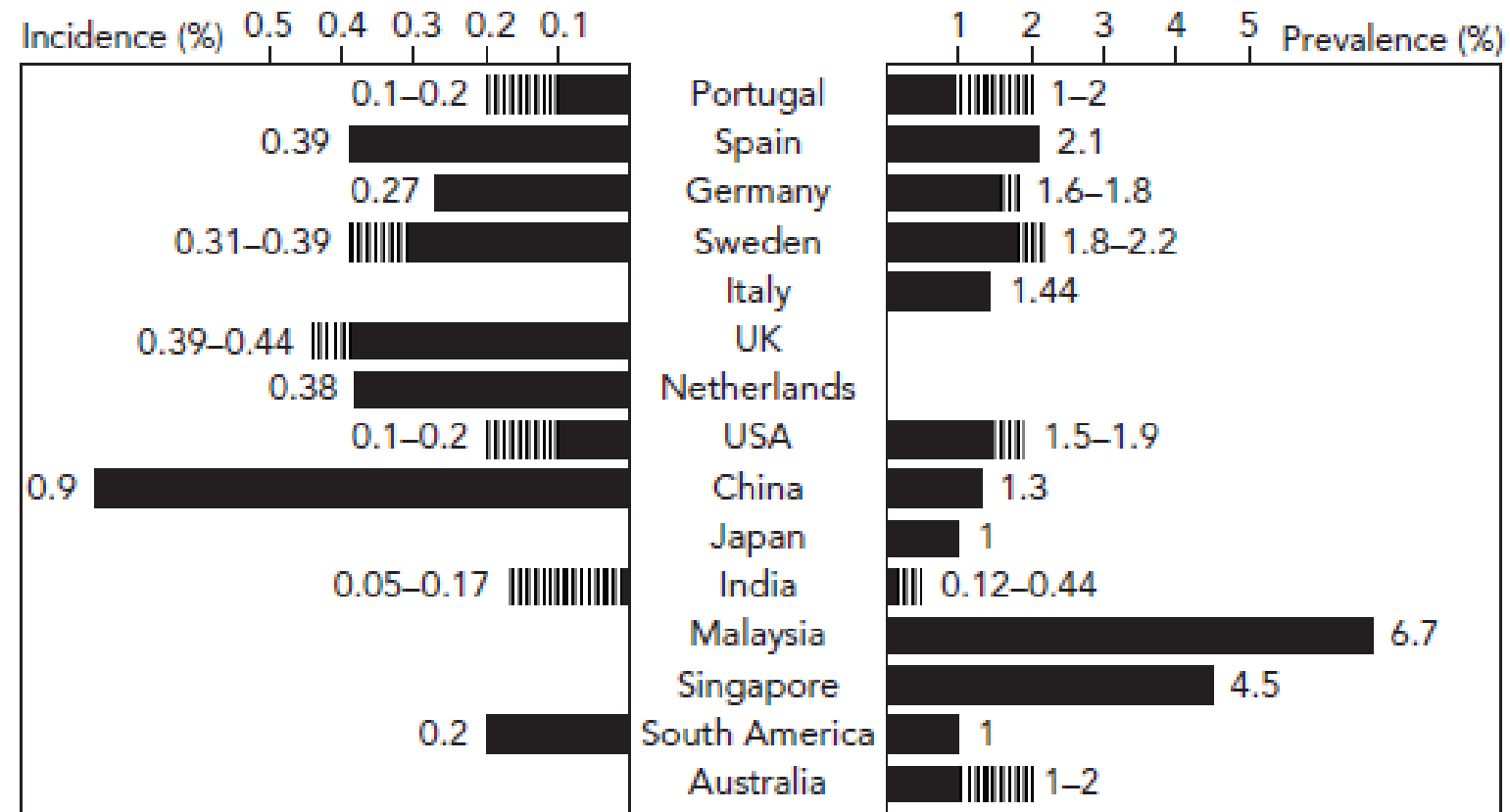
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Heart Failure, a worldwide disease

- 26 million heart failure patients worldwide
- 1-2% health care expenditure attributed to health failure in Europe and North America
- 74% Heart failure patients suffering from at least 1 comorbidity: more likely to worsen the patient's overall health status

Figure 2: Prevalence and Incidence of Heart Failure Worldwide



Main challenges: heart failure hospitalization

>1 million

Annual hospitalizations in both the United States and Europe¹

1-4%

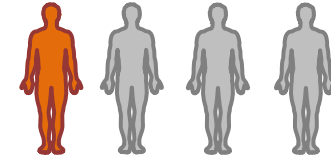
Heart failure hospitalizations as a percentage of total hospital admissions²

Up to 9/10 patients

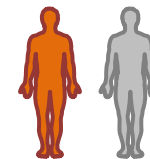
Hospitalized due to worsening chronic heart failure as compared with de novo heart failure³

5-10 days

Average length of hospital stay³

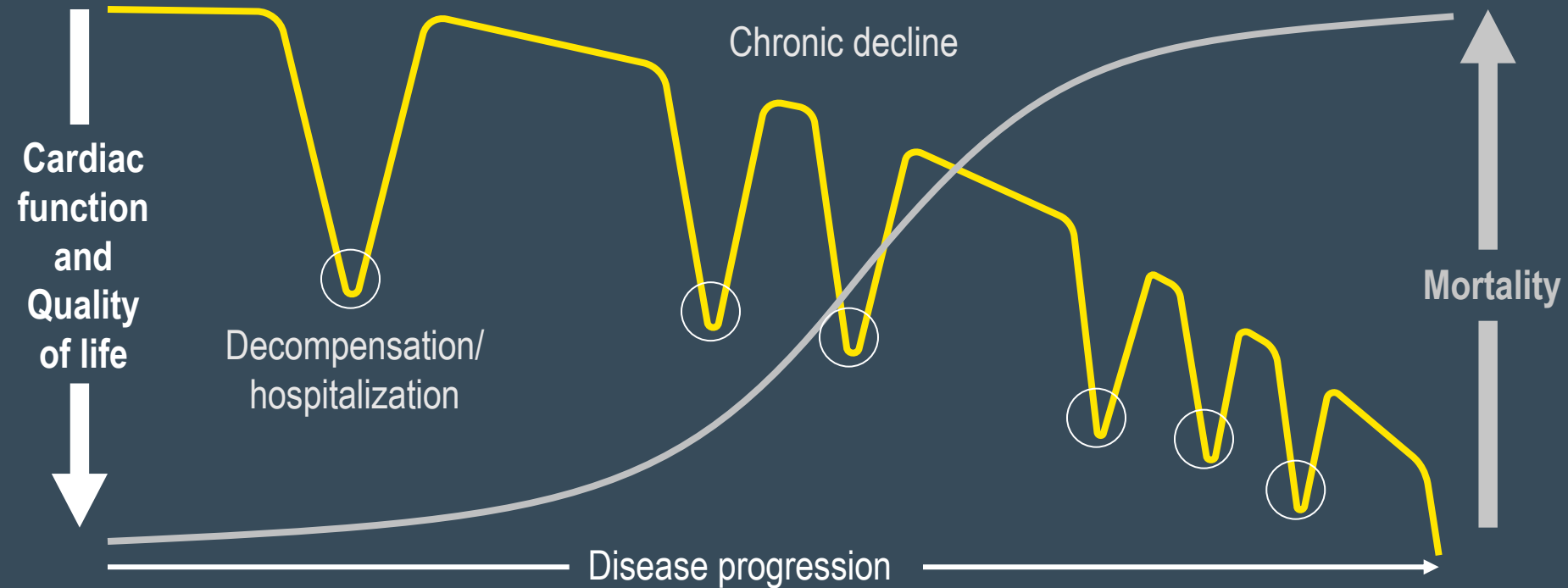


Almost 1 out of 4 hospitalized patients (24%) are rehospitalized for heart failure within the 30-day post discharge period⁴



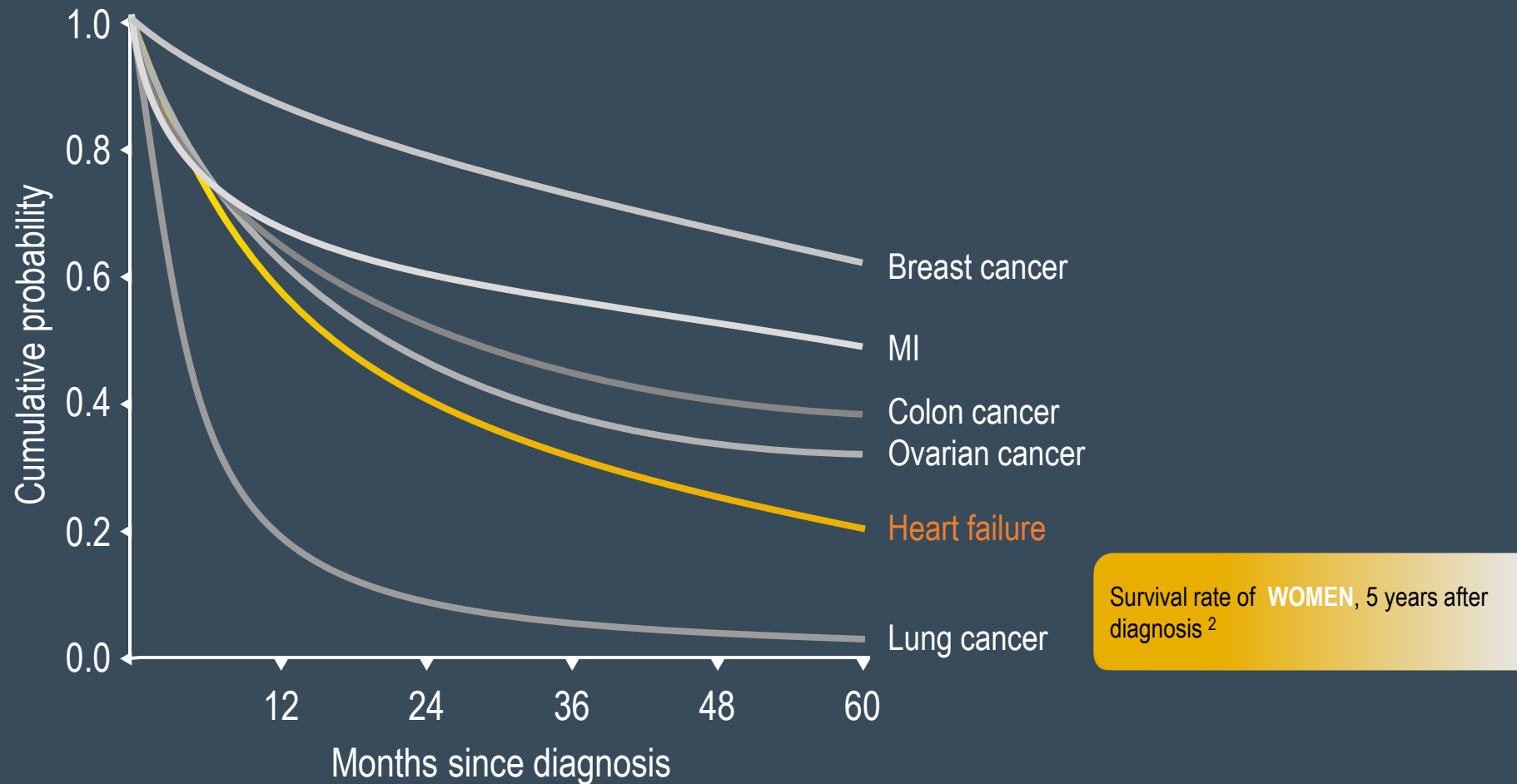
Nearly 1 out of 2 patients (46%) are rehospitalized for heart failure within the 60-day post discharge period⁴

Increasing frequency of acute events with disease progression leads to high rates of hospitalization and increased risk of mortality¹⁻⁵



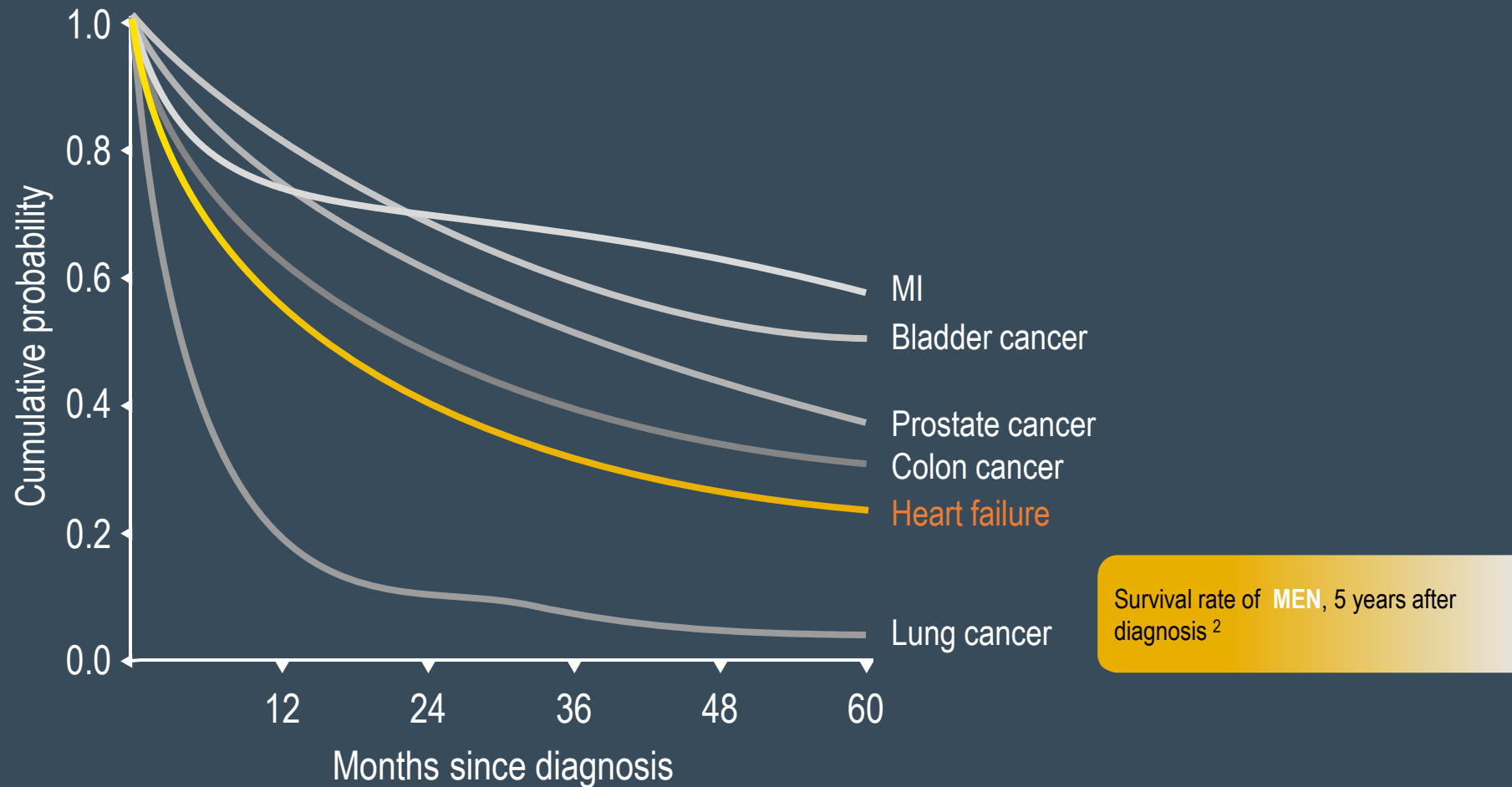
1. Ahmed et al. Am Heart J 2006;151:444–50; 2. Adapted from Gheorghiade et al. Am J Cardiol 2005;96:11G–17G; 3. Gheorghiade, Pang. J Am Coll Cardiol 2009;53:557–73; 4. Holland et al. J Card Fail 2010;16:150–6; 5. Muntwyler et al. Eur Heart J 2002;23:1861–6

Risk of mortality in systolic heart failure is higher than potentially many cancers in women ¹



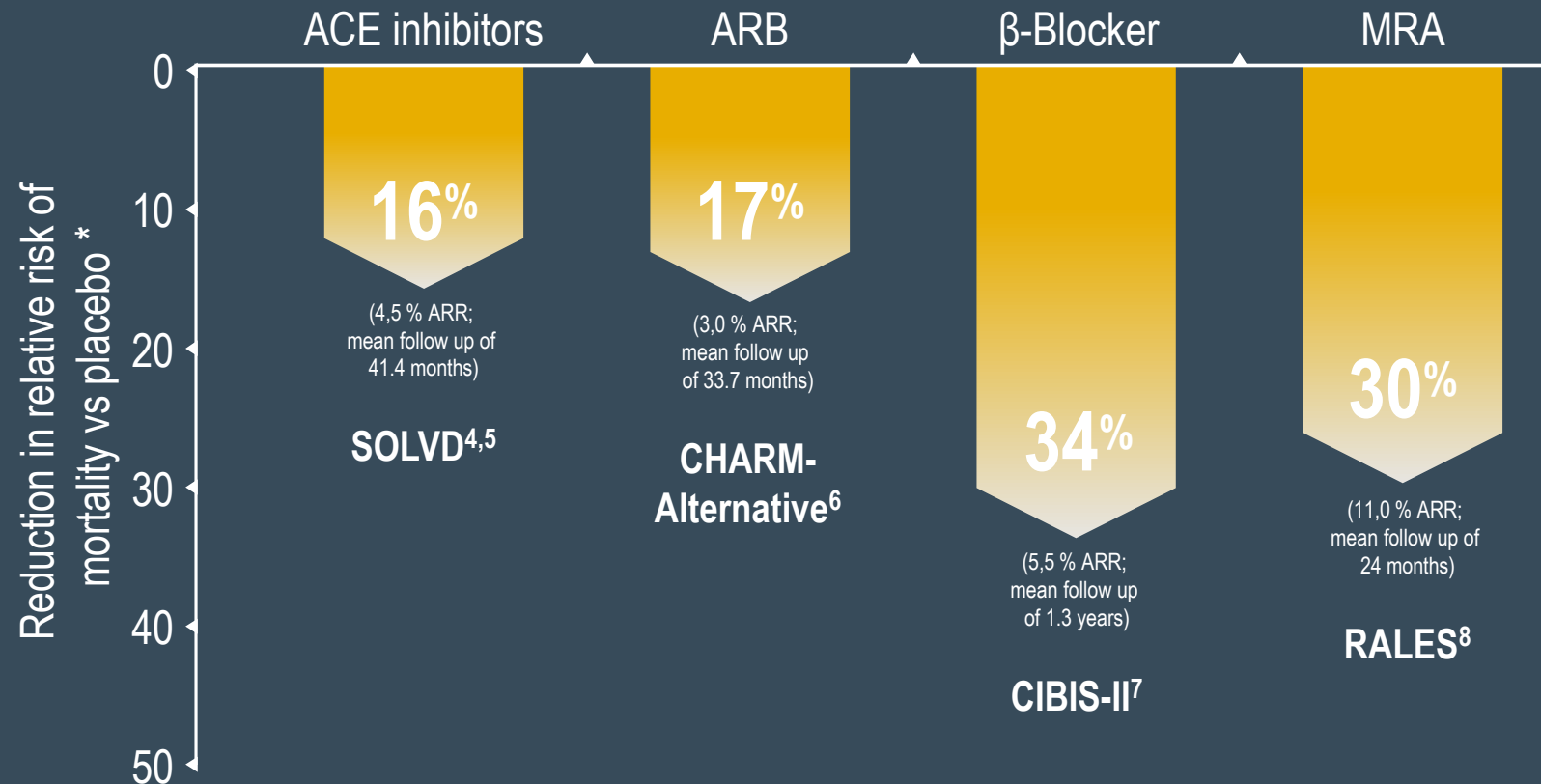
1. Roger et al. JAMA 2004;292(3):344-350; 2. Stewart et al. Eur J Heart Fail 2001;3(3):315-322

Risk of mortality in systolic heart failure is higher than potentially many cancers in men ¹



1. Roger et al. JAMA 2004;292(3):344-350; 2. Stewart et al. Eur J Heart Fail 2001;3(3):315-322

Mortality in HFrEF remains high despite the current therapies that improve survival¹⁻⁴



1. Levy et al. N Engl J Med 2002;347(18):1397–1402; 2. Go et al. Circulation 2014;129(3):e28–e292;
3. Yancy et al. Circulation 2013;128(16):e240–e327; 4. McMurray et al. Eur Heart J 2012;33(14):1787–1847;
5. SOLVD Investigators. N Engl J Med 1991;325(5):293–302; 6. Granger et al. Lancet 2003;362(9386):772–776;
7. CIBIS-II Investigators. Lancet 1999;353(9146):9–13; 8. Pitt et al. N Engl J Med 1999;341(10):709–717

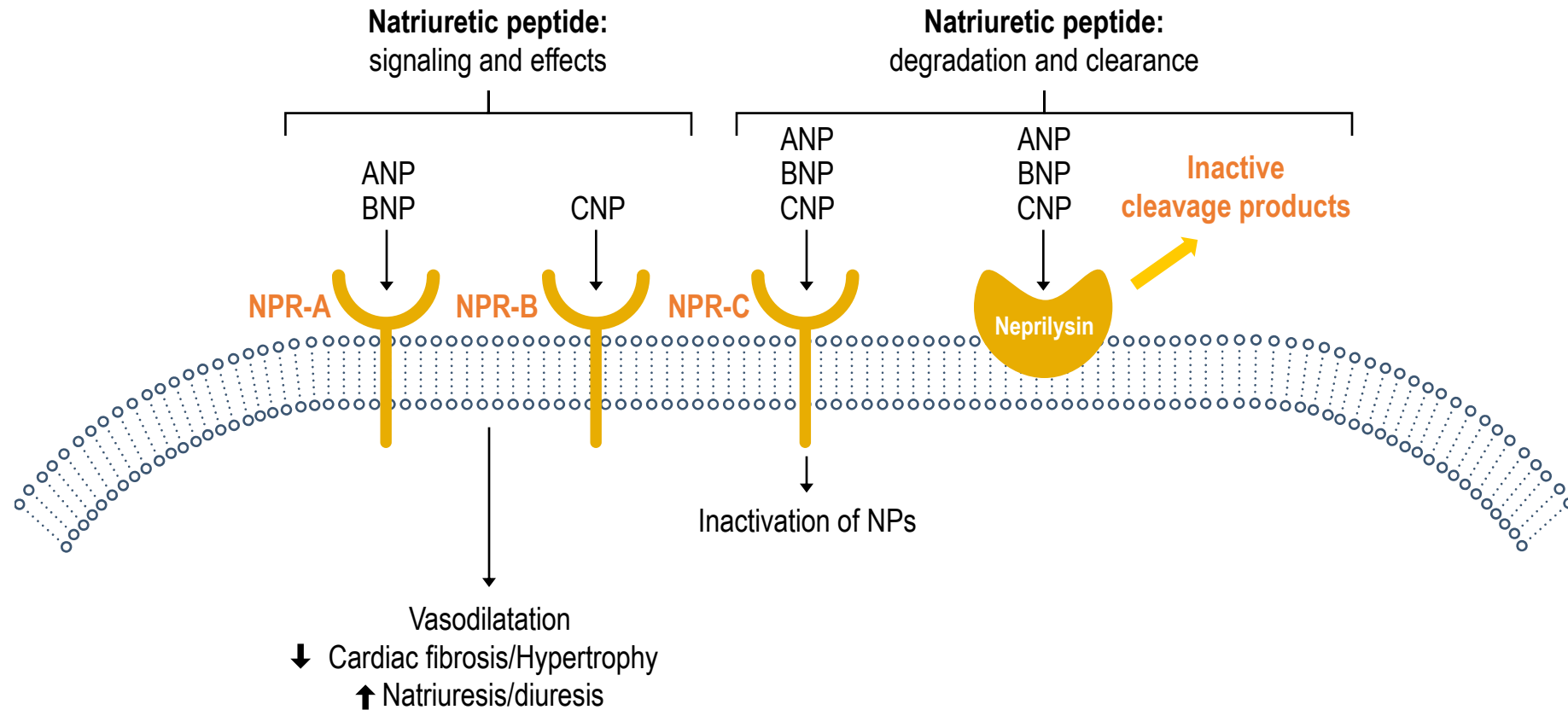
Conventional treatment

- RAAS system
 - ACEI/ARB
 - Aldosterone antagonist
- Sympathetic nervous system
 - Beta-blocker
- Heart rate
 - Ivabradine
- Device therapy



The role of natriuretic peptides in heart failure

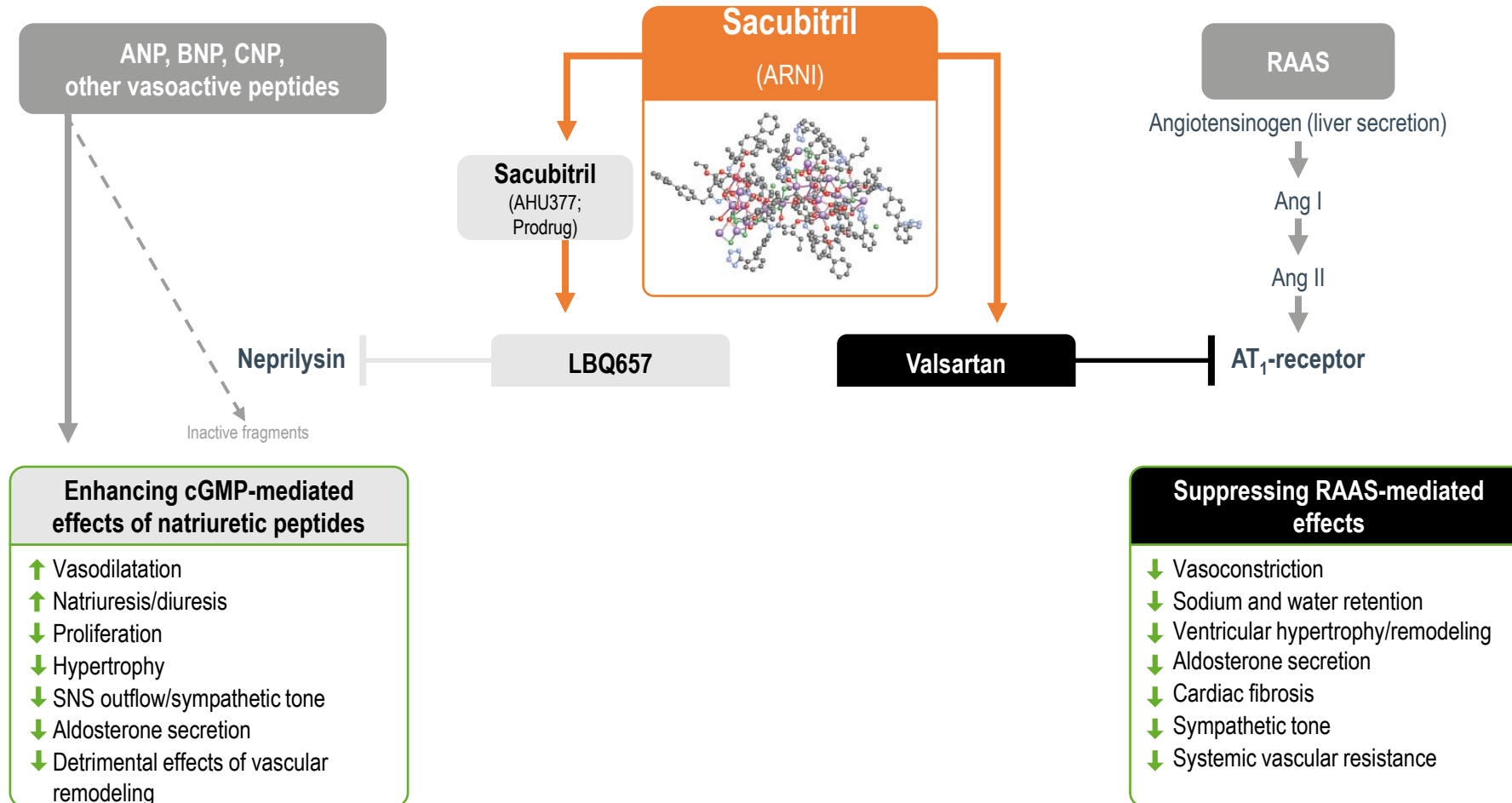
Natriuretic peptides are cleared by NPR-C and neprilysin¹⁻⁶



ANP: atrial natriuretic peptide; **BNP:** B-type natriuretic peptide; **CNP:** C-type natriuretic peptide; **NPR:** natriuretic peptide receptor

1. Mangiafico et al. Eur Heart J 2013;34:886-893;
2. Levin et al. N Engl J Med 1998;339:321-328;
3. Gardner et al. Hypertension 2007;49:419-426;
4. Horio et al. Hypertension 2000;35:19-24;
5. D'Souza et al. Pharmacol Ther 2004;101:113-129;
6. Cao & Gardner. Hypertension 1995;25:227-234

Sacubitril – the first angiotensin receptor neprilysin inhibitor (ARNI)¹⁻⁹



ANP: atrial natriuretic peptide; **BNP:** B-type natriuretic peptide; **CNP:** C-type natriuretic peptide; **AT₁:** angiotensin II type1; **RAAS:** renin-angiotensin aldosterone system; **ARNI:** Angiotensin-Receptor-Neprilysin-Inhibitor

1. ENTRESTO® Prescribing Information, Februar 2016; 2. Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9(4):e131–e139;
3. Gu et al. J Clin Pharmacol 2010;50(4):401–414; 4. Levin et al. N Engl J Med 1998;339 (5):321–328; 5. Gardner et al. Hypertension 2007;49(3):419–426;
6. Molkenin. J Clin Invest 2003;111(9):1275–1277; 7. Nishikimi et al. Cardiovasc Res 2006;69(2):318–328; 8. Volpe et al. Int J Cardiol 2014; 176(3):630–639;
9. Von Lueder et al. Circ Heart Fail 2013;6(3):594–605



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

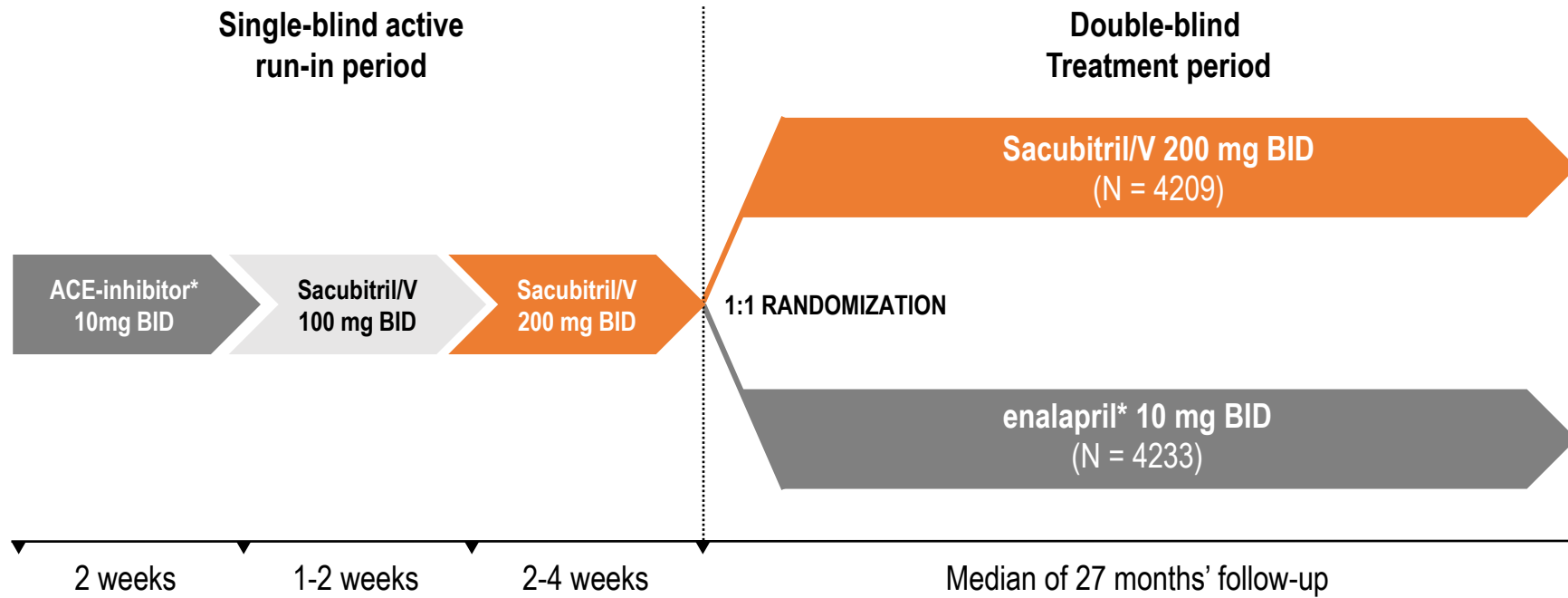
PARADIGM-HF – Key inclusion criteria

- Chronic HF NYHA FC II–IV with LVEF $\leq 40\%$ *
- 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 $\leq 35\%$ in a protocol amendment. **NYHA**: New York Heart Association; **LVEF**: left ventricular ejection fraction; **NT-proBNP**: N-terminal pro-brain natriuretic peptide; **ACE**: angiotensin-converting enzyme; **ARB**: angiotensin-receptor-blocker; **BNP**: B-type natriuretic peptide



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

ACE: angiotensin-converting enzyme; **NYHA:** New York Heart Association; **LVEF:** left ventricular ejection fraction; **ARB:** angiotensin-receptor-blocker

1. McMurray et al. Eur J Heart Fail 2013;15(9):1062–1073



PARADIGM-HF
study results

Sacubitril/V is significantly superior to enalapril* regarding mortality and morbidity ¹

Primary and secondary endpoints of the PARADIGM-HF study

	Sacubitril/V (N=4187)	enalapril (N=4212)	HR (95% CI)	RRR (%)	p-value	NNT
Primary composite endpoint N (%)						
Death from CV causes or first hospitalization for worsening of HF	914 (21.8)	1117 (26.5)	0.8 (0.73-0.87)	20%	<0.001	21
Death from CV causes	558 (13.3)	693 (16.5)	0.8 (0.71-0.89)	20%	<0.001	32
First hospitalization for worsening of HF	537 (12.8)	658 (15.6)	0.79 (0.71-0.89)	21%	<0.001	
Secondary endpoints N (%)						
All-cause mortality	711 (17.0)	835 (19.8)	0.84 (0.76-0.93)	16%	<0.001	-
Change in KCCQ clinical summary score at 8 months, mean ± SD**	-2.99 ±0.36	-4.65 ±0.36	1.64 (0.63-2.65)	-	0.001	-
New onset atrial fibrillation¶, n (%)	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	-	0.83	-
Decline in renal function§, n (%)	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	-	0.28	-

- enalapril 10 mg 2x daily as comparator vs. ENTRESTO® 200 mg 2x daily in the PARADIGM-HF study (in addition of standard therapy). **§KCCQ scores range from 0 to 100 – higher scores indicate fewer symptoms and physical limitations associated with HF; **ACE**: angiotensin-converting enzyme; **HF**: heart failure; **ARR**: absolute risk reduction; **HR**: Hazard Ratio; **RRR**: relative risk reduction

¶2670 patients in the ENTRESTO® and 2638 in the enalapril group who did not have atrial fibrillation at randomization were evaluated

§Defined as: (a) ≥ 50% decline in eGFR from randomization; (b) > 30 mL/min/1.73 m² decline in eGFR from randomization or to a value of <60 mL/min/1.73 m², or (c) progression to end-stage renal disease

Sacubitril/V reduced the frequency and severity of hospitalization compared to enalapril*

30%

**LESS VISITS
TO THE EMERGENCY UNIT
FOR HEART FAILURE ¹**

p=0.017



18%

**SHORTER STAYS
IN INTENSIVE CARE UNITS ¹**

p=0,005



16%

**LOWER RISK
FOR ALL-CAUSE
HOSPITALIZATION ¹**

p<0,001



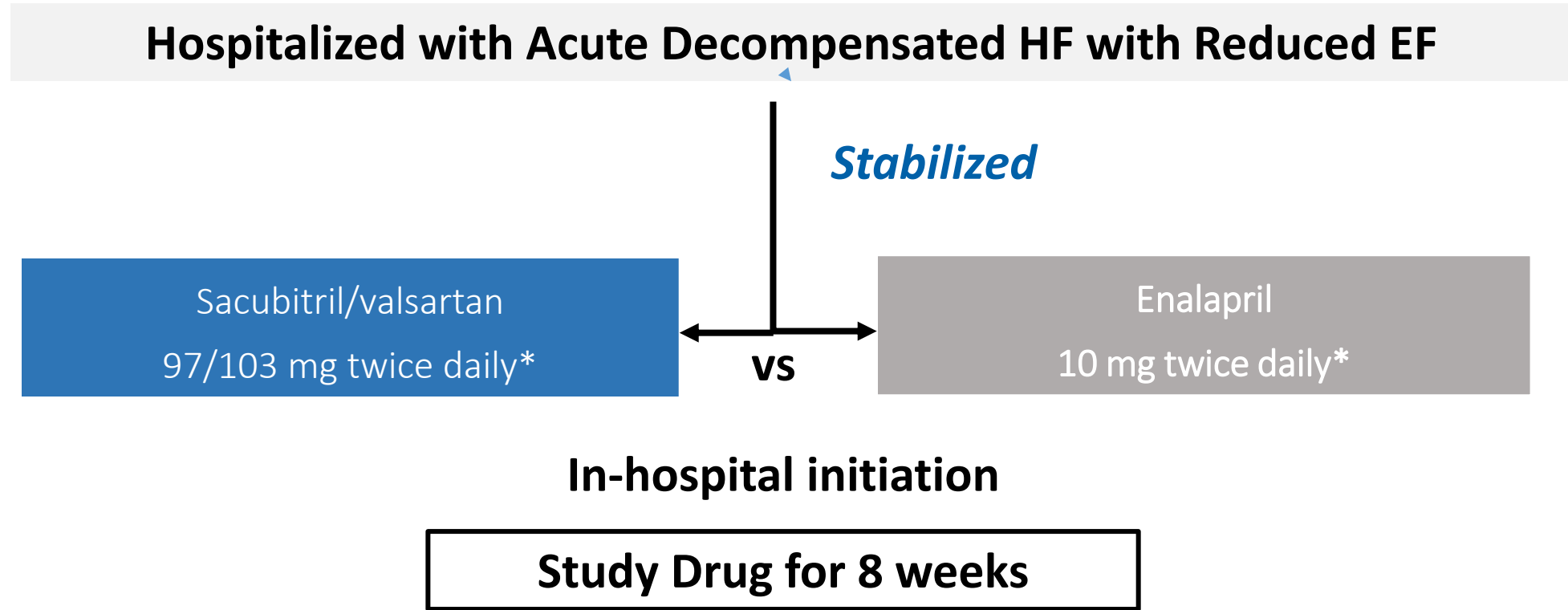
* enalapril 10 mg 2x daily as comparator vs. ENTRESTO[®] 200 mg 2x daily in the PARADIGM-HF study (in addition of standard therapy).

1. Packer et al. Circulation 2015;131(1):54–61

ACUTE HEART FAILURE

PIONEER-HF

Study Design



- Evaluate biomarker surrogates of efficacy
- Evaluate safety and tolerability
- Explore clinical outcomes

*Target Dose
HF, Heart Failure. EF, Ejection Fraction

PIONEER-HF

Key Entry Criteria

- Hospitalized for **Acute Decompensated Heart Failure (ADHF)**
- LVEF $\leq 40\%$ within the last 6 months
- NT-proBNP ≥ 1600 pg/mL or BNP ≥ 400 pg/mL*
- Stabilized while hospitalized
 - SBP ≥ 100 mmHg in prior 6h; no symptomatic hypotension
 - No increase in IV diuretics in prior 6h
 - No IV vasodilators in prior 6h
 - No IV inotropes in prior 24h

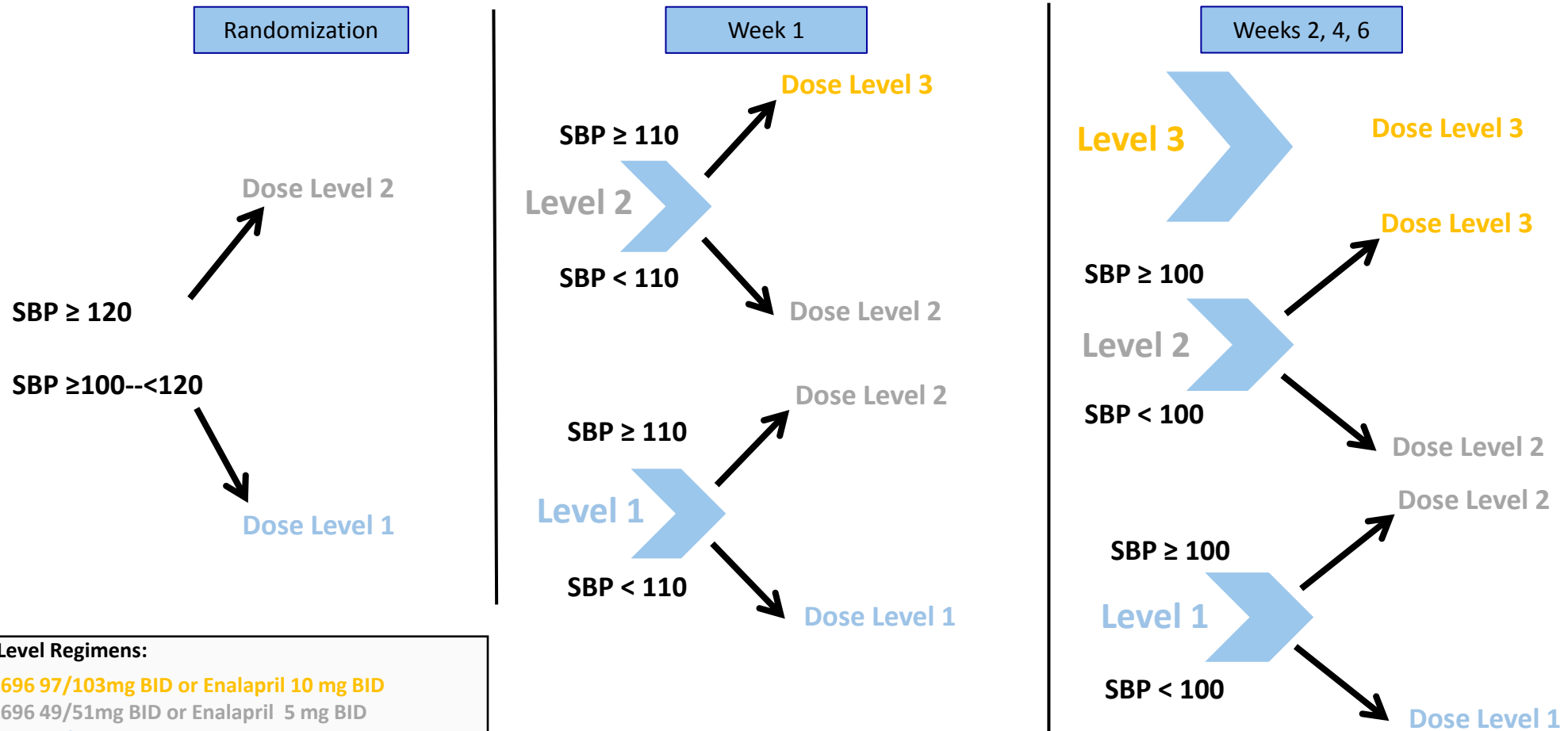
*At screening

A complete list of inclusion and exclusion criteria has been previously published at Velazquez et al. Am Heart J 198 (2018) 145-151

LVEF, Left Ventricular Ejection Fraction. NT-proBNP N-terminal pro-Brain Natriuretic Peptide. BNP, Brain Natriuretic Peptide. SBP, Systolic Blood Pressure. IV, Intravenous

PIONEER-HF

Patient Treatment – Dose Titration



Dose Level Regimens:

- 3) LCZ696 97/103mg BID or Enalapril 10 mg BID
- 2) LCZ696 49/51mg BID or Enalapril 5 mg BID
- 1) LCZ696 24/26mg BID or Enalapril 2.5 mg BID

Patients taking low dose or no ACEI/ARB at randomization were initiated on Entresto 49/51 mg if their SBP was ≥ 120 . Similarly, patients were up-titrated as early as Week 1 and again at Week 2 based on their blood pressure. Follow label dosing recommendations

PIONEER-HF

*Study Endpoints**

Primary endpoint:

- Time-averaged proportional change in NT-proBNP from baseline at 4 and 8 weeks

Safety

- Worsening renal function
- Hyperkalemia
- Symptomatic hypotension
- Angioedema

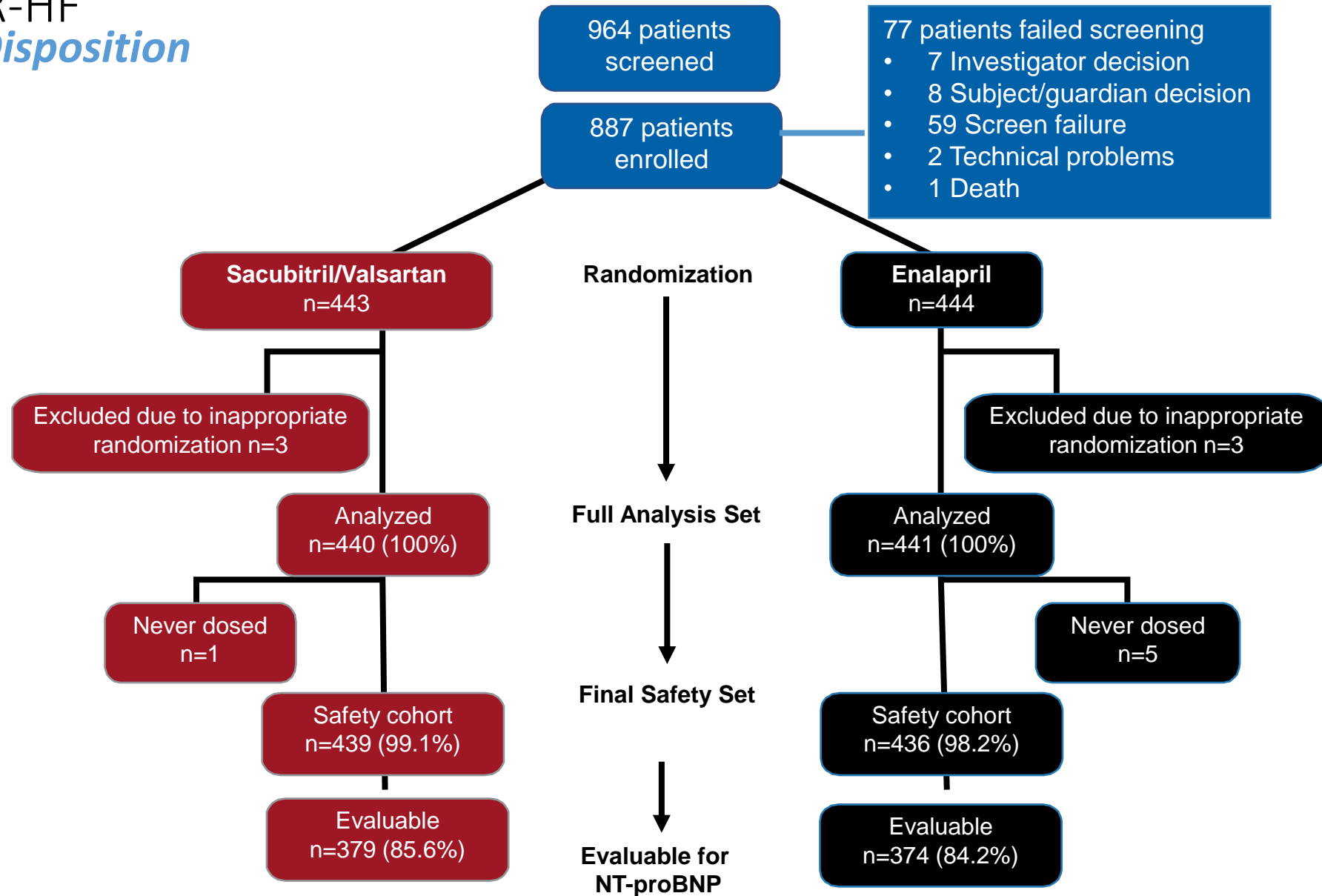
Exploratory Clinical Outcomes

- Serious Clinical Composite: Death, Hospitalization for HF, LVAD or listing for cardiac transplant

*A more complete list of PIONEER study endpoints has been previously published at Velazquez et al. Am Heart J 198 (2018) 145-151
NT-proBNP N-terminal pro-Brain Natriuretic Peptide. HF, Heart Failure. LVAD, Left Ventricular Assist Device. HF, Heart Failure
Data on File: PIONEER-HF Protocol, Novartis Pharmaceutical Corp; October 2018

PIONEER-HF

Patient Disposition



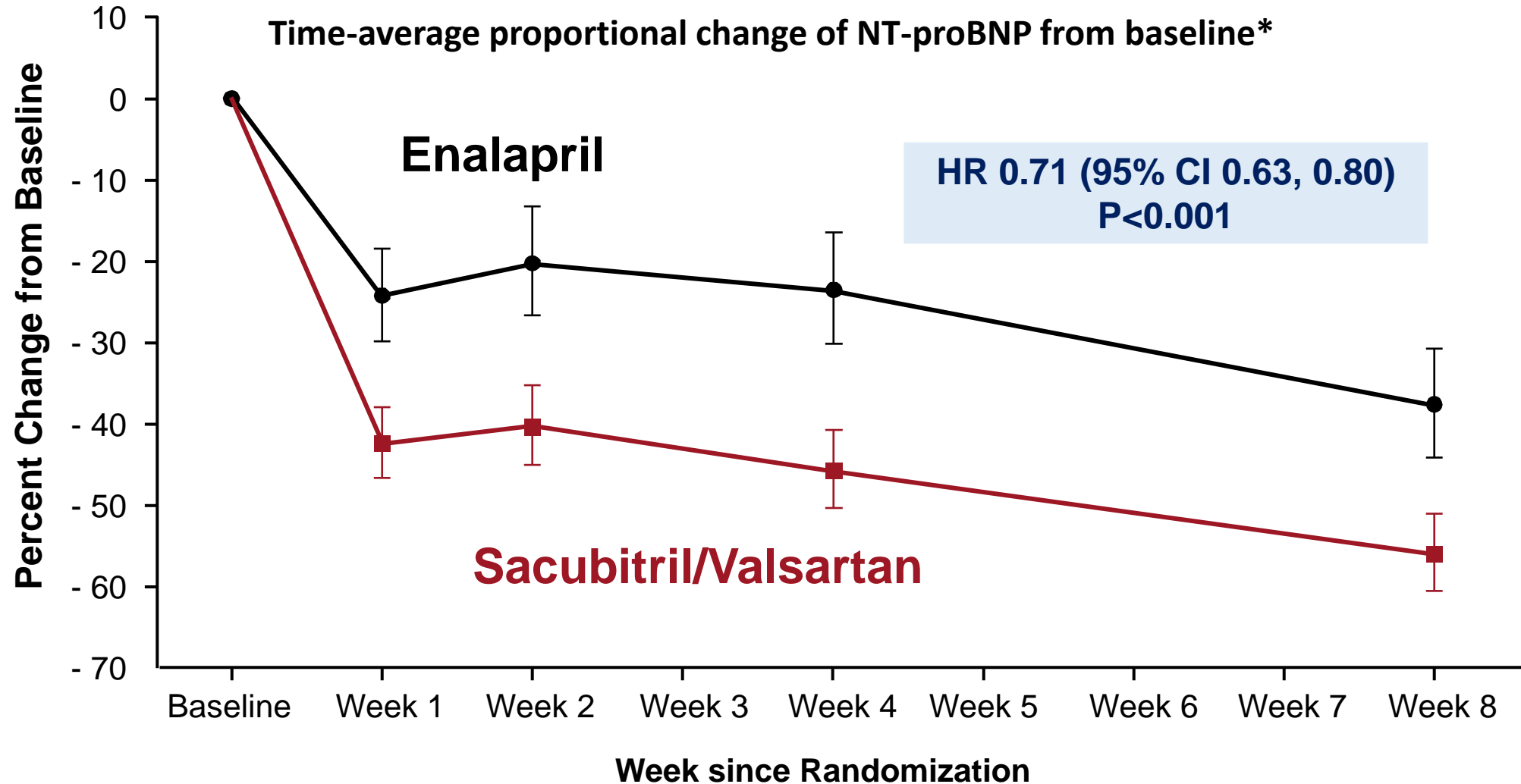
PIONEER-HF

Baseline Characteristics

	Sacubitril/Valsartan (n=440)	Enalapril (n=441)
Age (years)	61 (50.5, 71)	63 (54, 72)
Women (%)	25.7	30.2
Black (%)	35.9	35.8
Prior HF diagnosis (%)	67.7	63.0
LVEF, median (25th, 75th)	0.24 (0.18, 0.30)	0.25 (0.20, 0.30)
Systolic pressure, median (25th, 75th) mm Hg	118 (110, 133)	118 (109, 132)
NT-proBNP median (25th, 75th) pg/mL at randomization	2883 (1610, 5403)	2536 (1363, 4917)
ACEi/ARB therapy (%)	47.3	48.5
Beta-adrenergic blockers (%)	59.6	59.6

PIONEER-HF

Primary Endpoint



*Percentage (%) change from baseline to mean of weeks 4 and 8

PIONEER-HF

Safety

Safety Events (%)	Sacubitril/ Valsartan (n=440) (%)	Enalapril (n=441) (%)	RR (95% CI)
Worsening renal function^a	13.6	14.7	0.93 (0.67-1.28)
Hyperkalemia	11.6	9.3	1.25 (0.84-1.84)
Symptomatic hypotension	15.0	12.7	1.18 (0.85-1.64)
Angioedema events^b	0.2	1.4	0.17 (0.02-1.38)

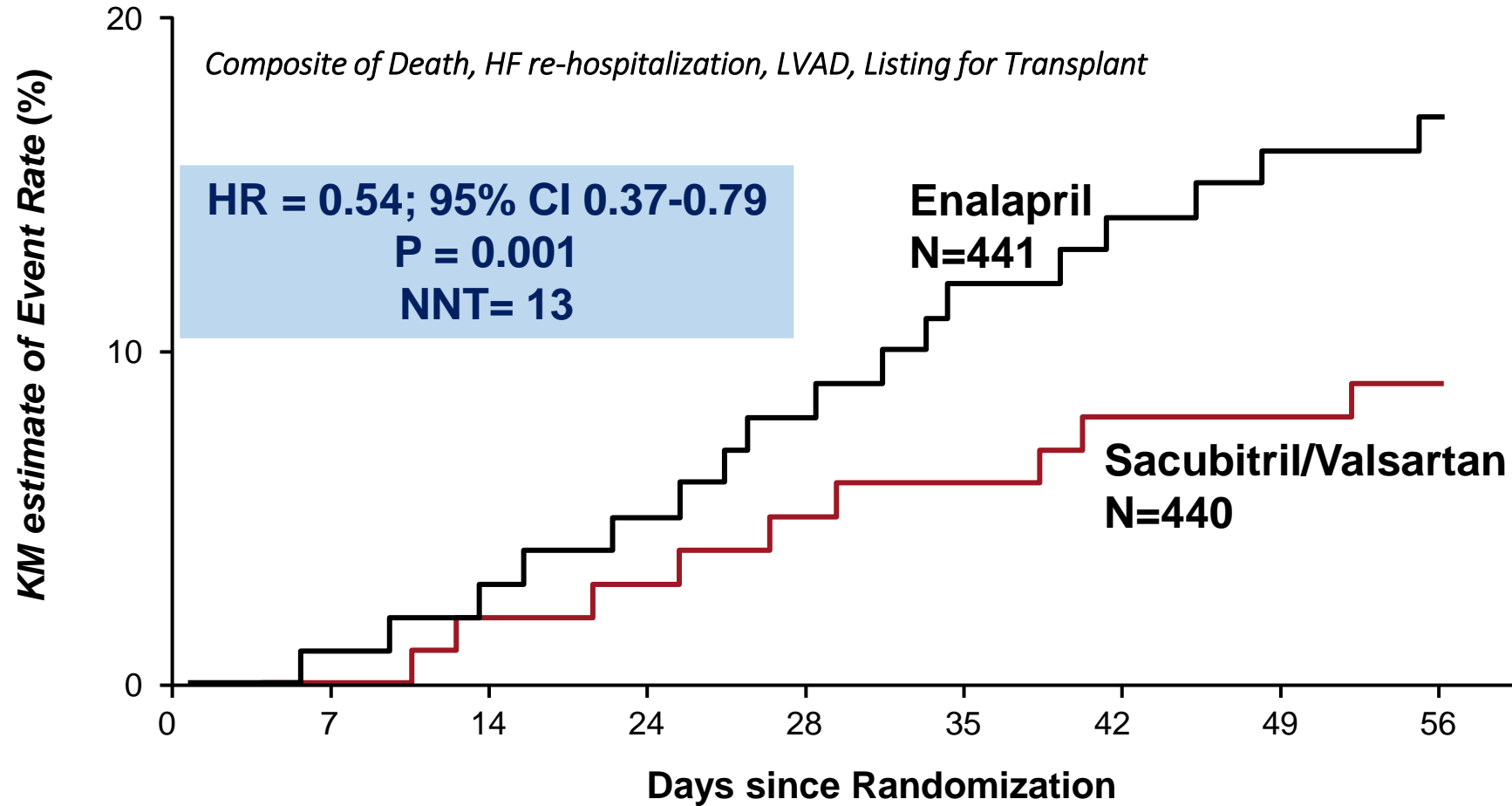
^a SCr ≥ 0.5 with simultaneous eGFR reduction of $\geq 25\%$

^b Positively adjudicated angioedema cases.

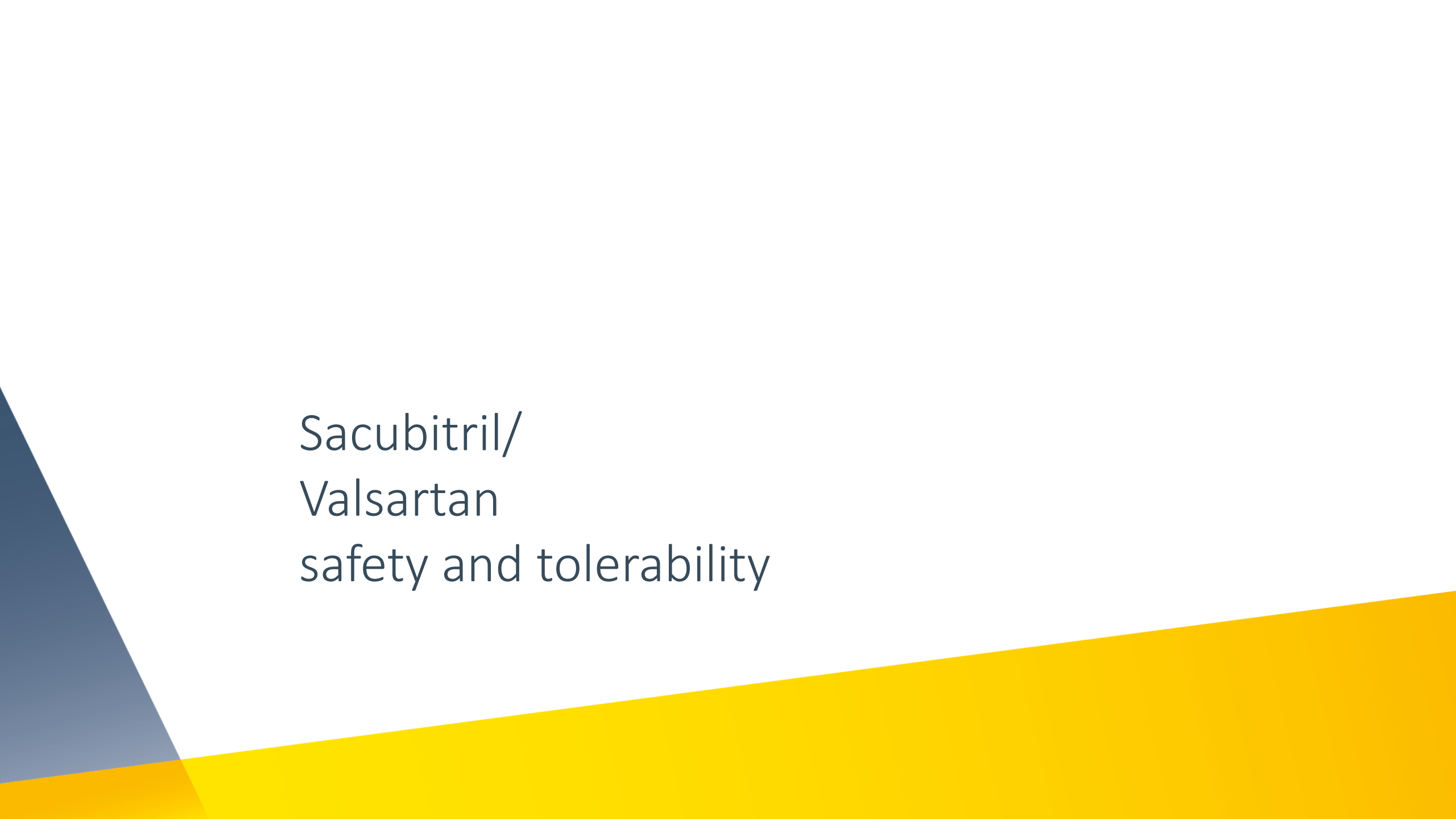
RR, Relative risk

PIONEER-HF

Exploratory Serious Clinical Composite Endpoint

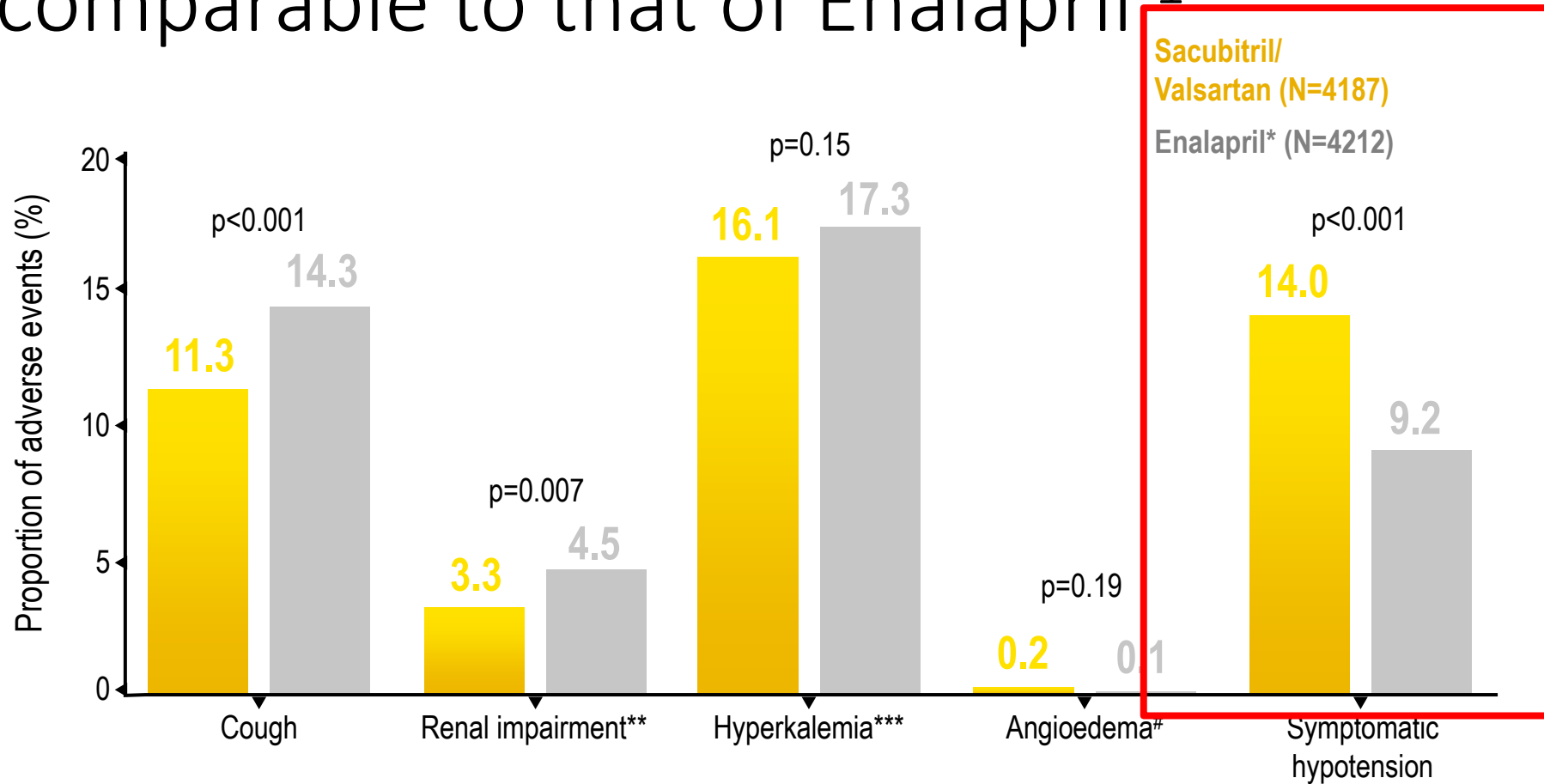


- Exploratory Serious Clinical Composite endpoint was driven by the reduction of risk of death and HF re-hospitalizations



Sacubitril/
Valsartan
safety and tolerability

Sacubitril/Valsartan has a safety and tolerability profile comparable to that of Enalapril¹



* enalapril 10 mg 2x daily as comparator vs. ENTRESTO[®] 200 mg 2x daily in the PARADIGM-HF study (in addition of standard therapy).

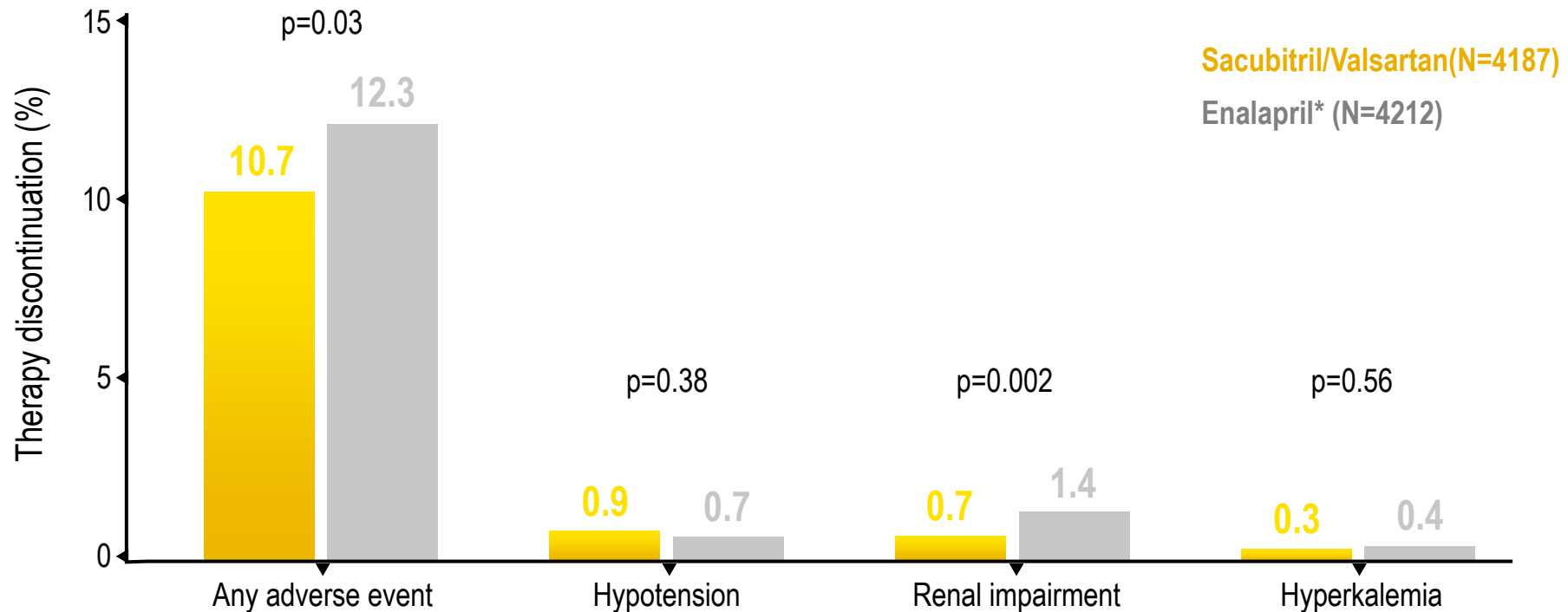
Elevated serum creatinine $\geq 2,5$ mg/dl. *Elevated serum potassium $> 5,5$ mmol/l. #Angioedema with no treatment or use of antihistamines only.

ACE: angiotensin-converting enzyme

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

Sacubitril/Valsartan had less adverse events leading to permanent study drug discontinuation¹

76 % of patients stayed until the end of the study with the 200 mg 2x daily target dose of ENTRESTO®



* enalapril 10 mg 2x daily as comparator vs. ENTRESTO® 200 mg 2x daily in the PARADIGM-HF study (in addition of standard therapy).

ACE: angiotensin-converting enzyme

1. McMurray et al. N Engl J Med 2014;371(11):993–1004

PIONEER-HF

Additional Clinical Endpoints

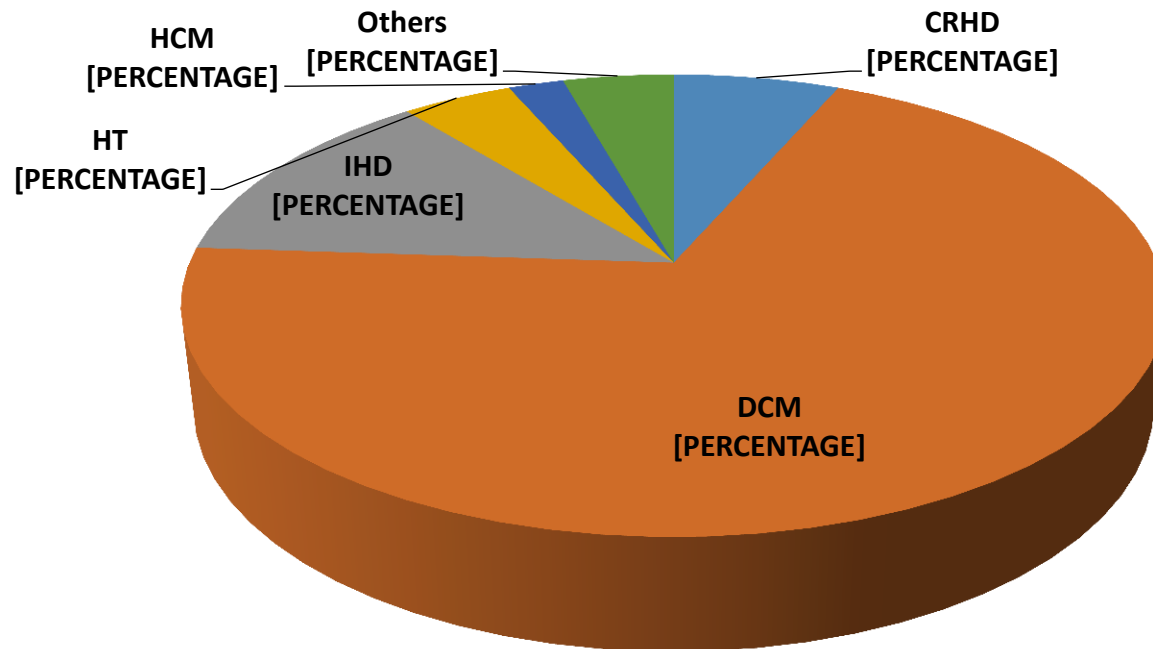
	Sacubitril/ Valsartan (n=440)	Enalapril (n=441)	HR	P-value
<i>Serious Composite, %</i>	9.3	16.8	0.54	0.001
Death, %	2.3	3.4	0.66	0.311
Re-hospitalization for HF, %	8.0	13.8	0.56	0.005
Requirement of LVAD, %	0.2	0.2	0.99	0.999
Cardiac Transplant, %	0	0	-	-

- Exploratory Serious Clinical Composite endpoint was driven by the reduction of risk of death and HF

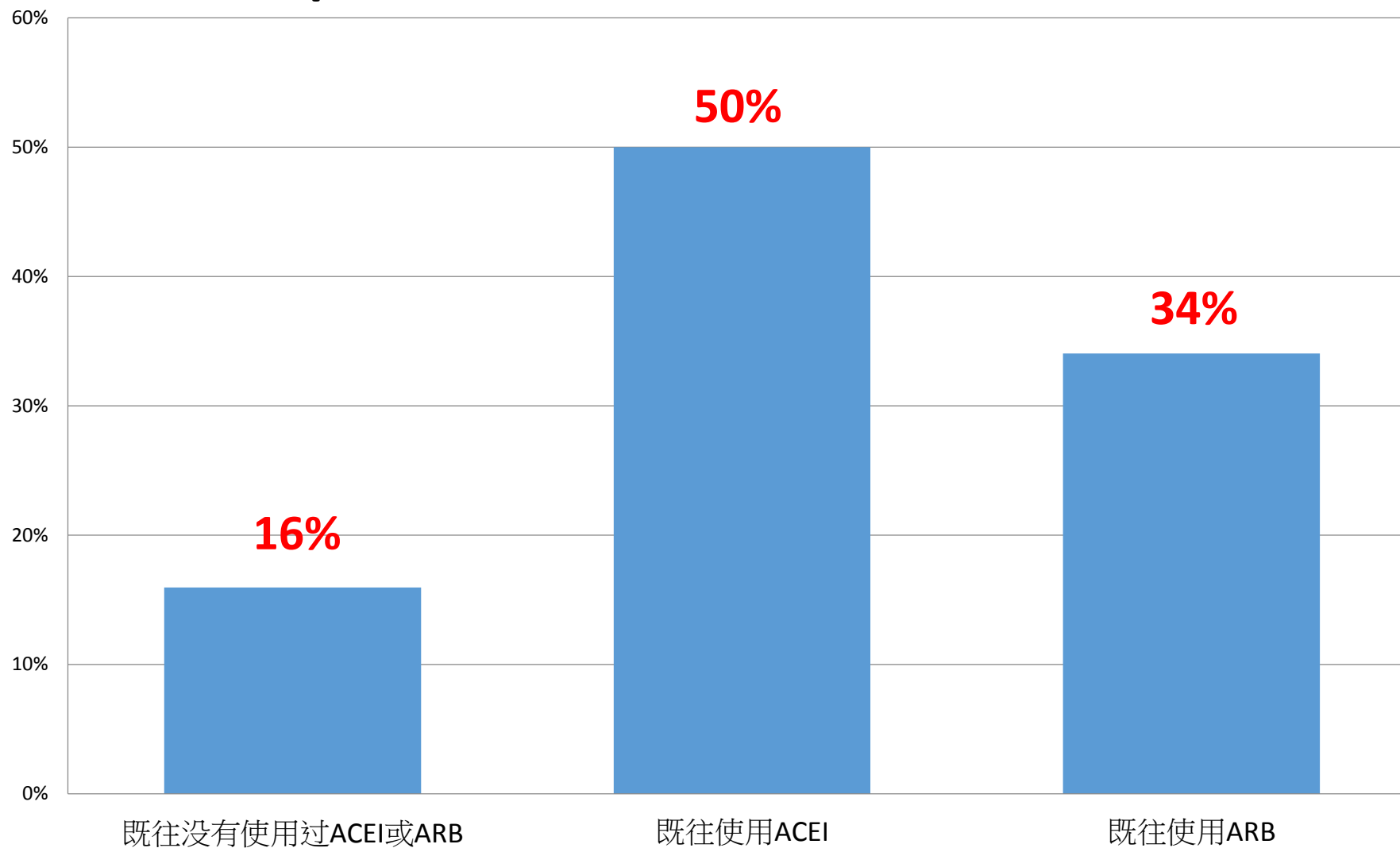
Our experience sharing

Sacubitril/Valsartan at the HKUSZH

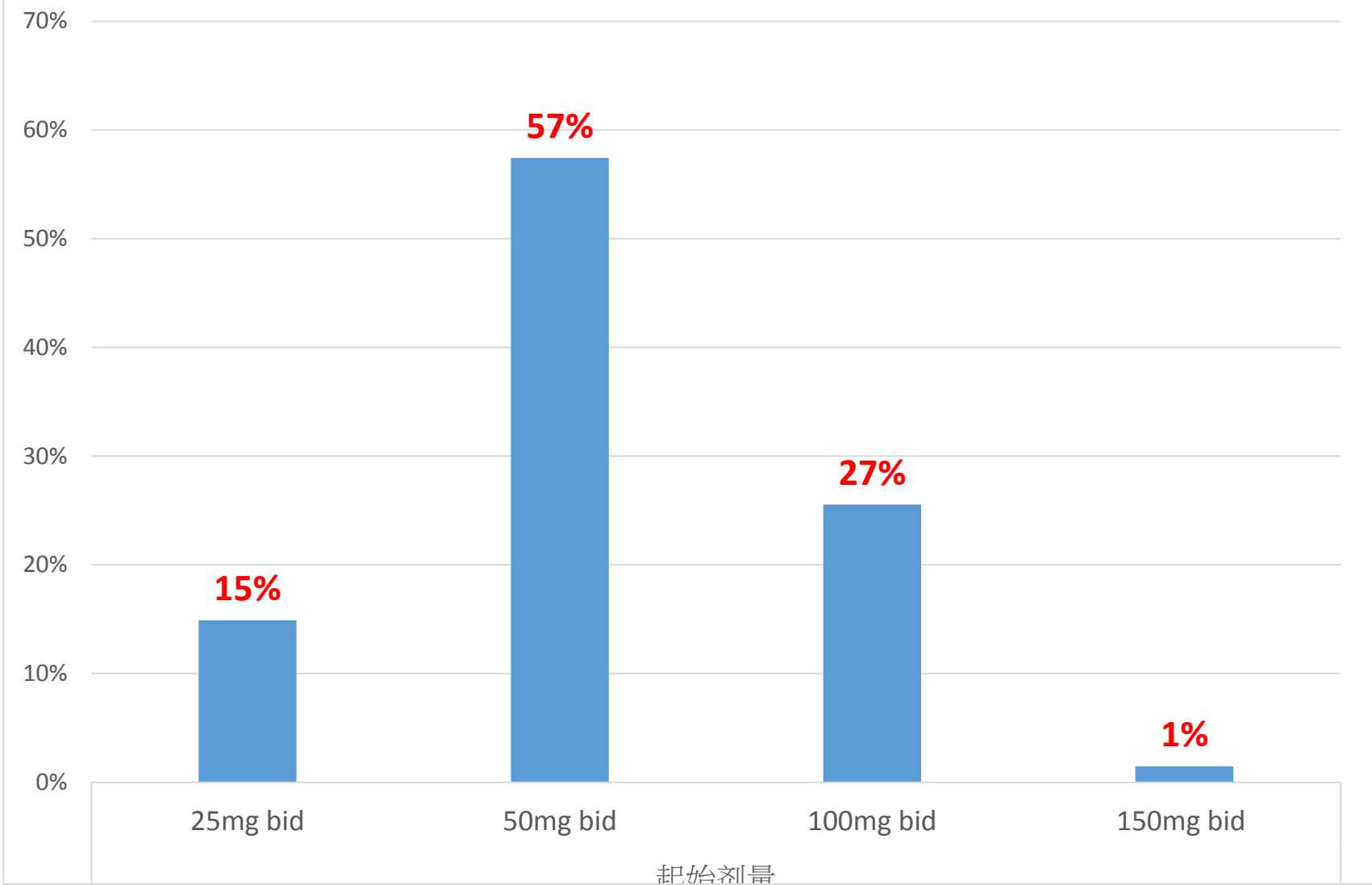
- Started from Jan 2017
- N=94 , Male 63% , Mean age 56



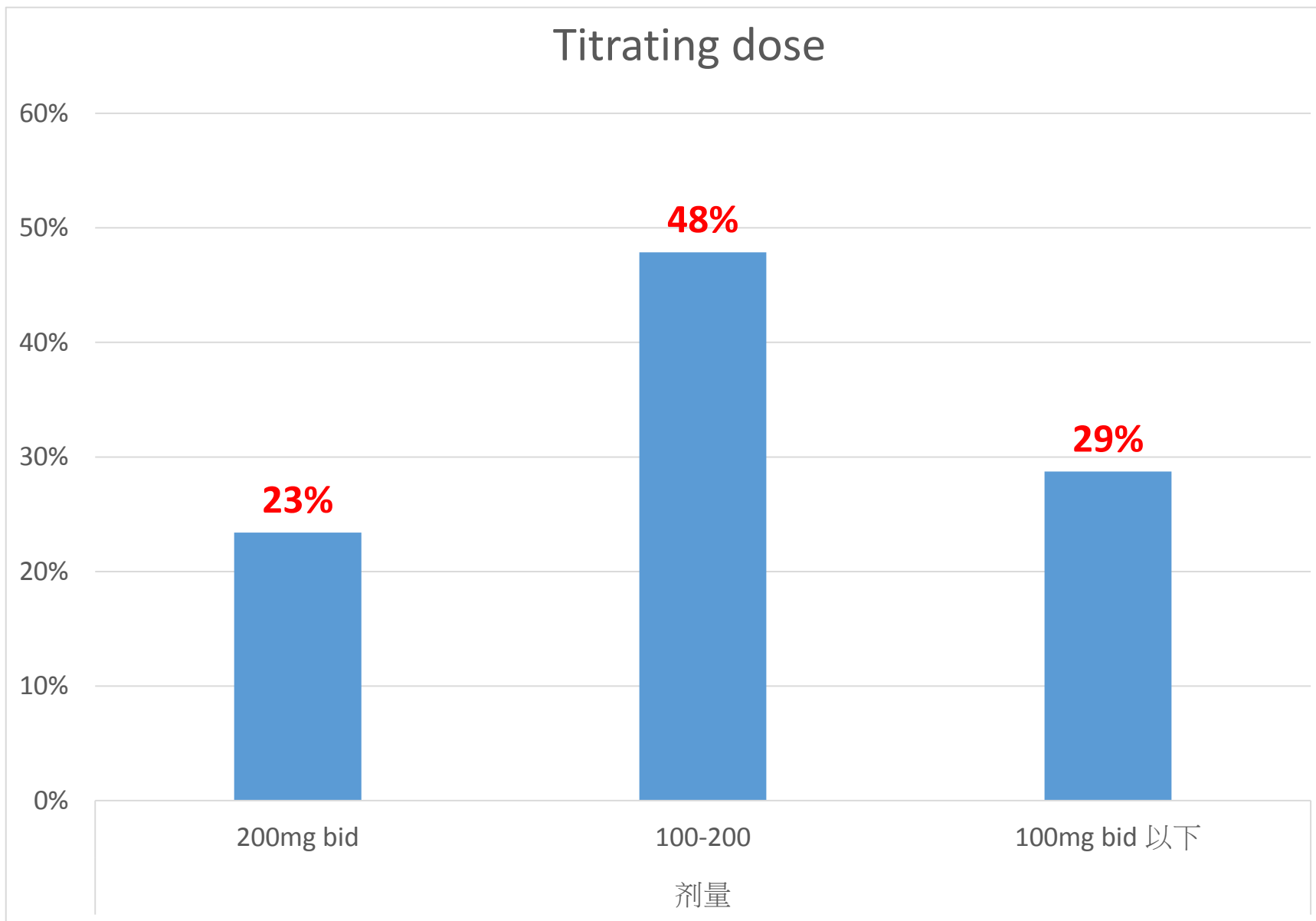
Prescription Before Sacubitril/Valsartan use



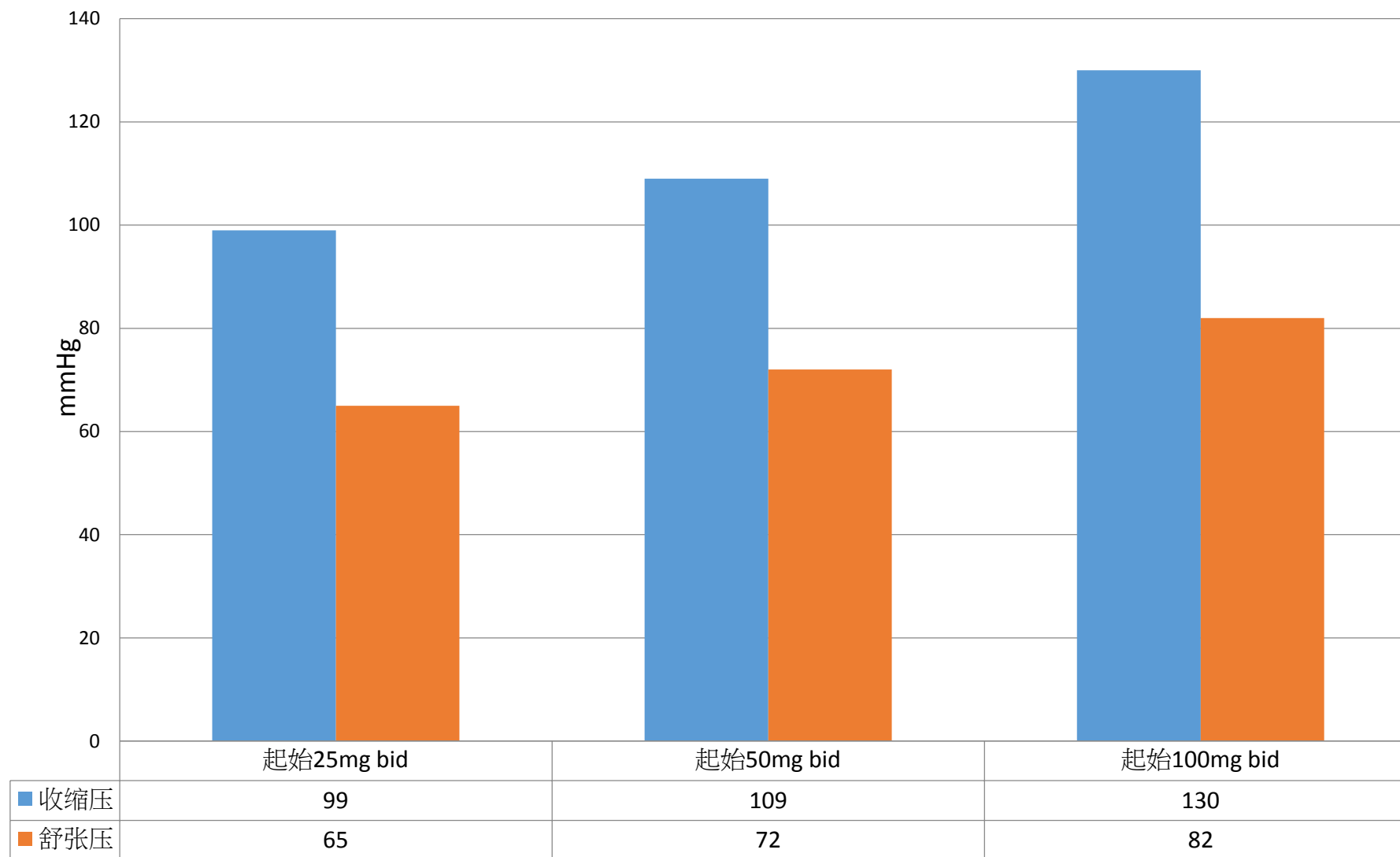
Initial dose of Sacubitril/Valsartan

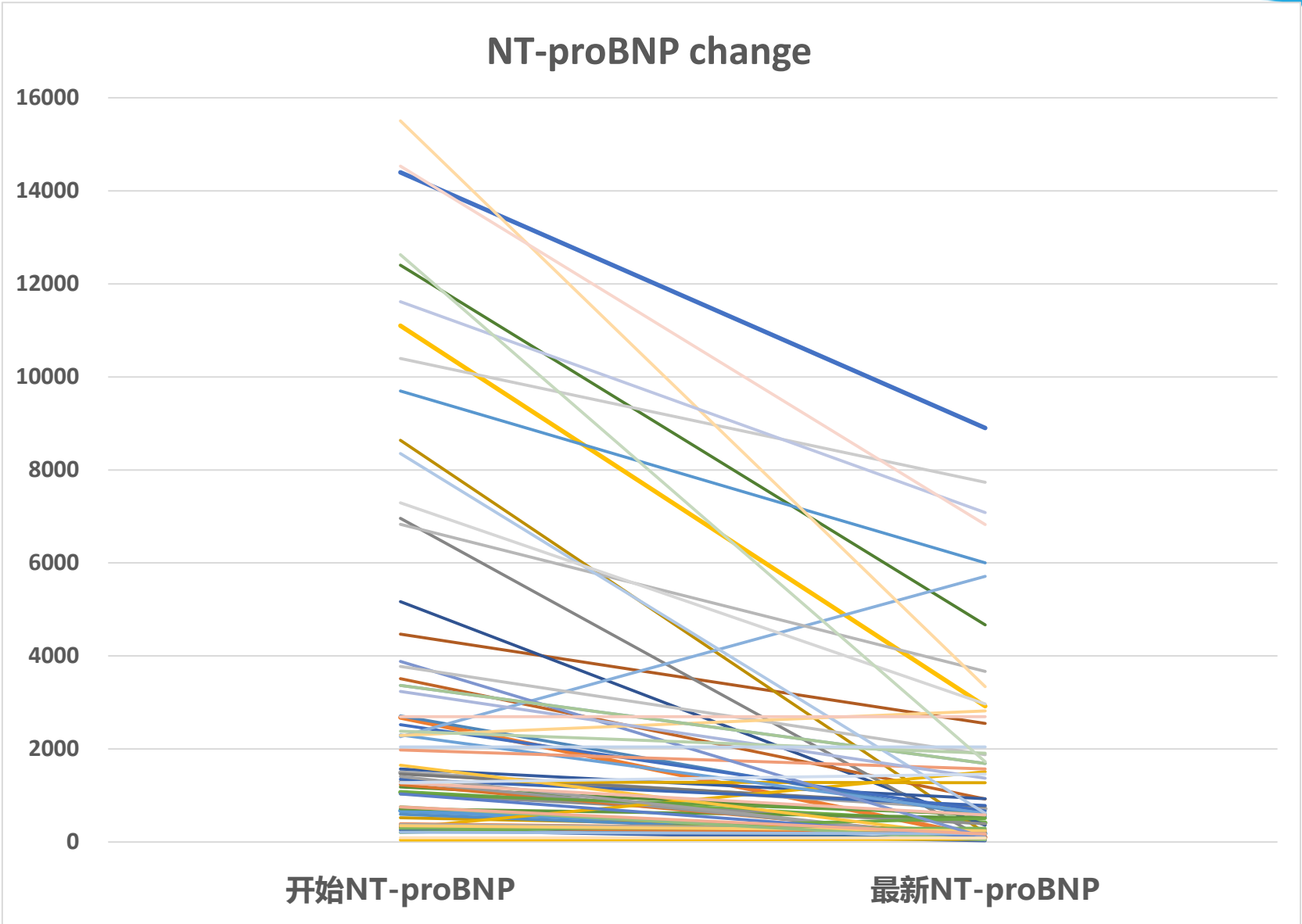


Titrating dose

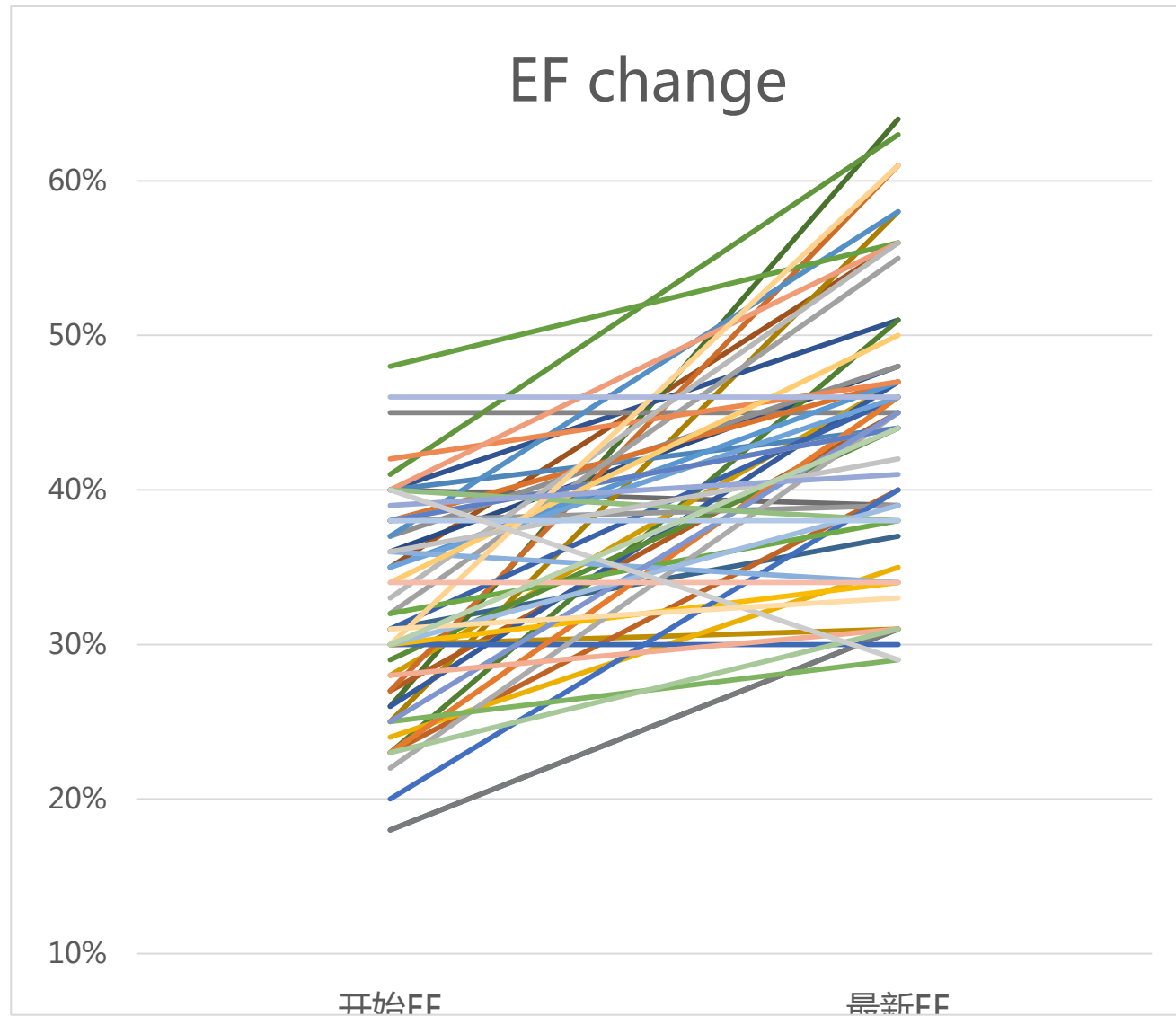


Initial blood pressure





EF change



When to use Sacubitril/Valsartan

- Newly diagnosed HFrEF
- Symptomatic patients despite ACEI/ARB
- Low EF despite ACEI/ARB

What follows discharge?

Health Care team

The primary care doctor

A cardiologist diagnoses and treats heart problems.

Other doctors include surgeons and other specialists, if recommended by the primary care doctor or cardiologist.

Clinical nurse specialists, nurse practitioners and physician assistants may perform tests and provide care, education and counseling.

Physical and occupational therapists assist with cardiac rehabilitation and help develop an appropriate plan for regular physical activity.

Dietitians share heart-healthy eating guidelines and help develop meal plans.

Mental health professionals help patients and families deal with emotional stress, anxiety or depression.

Social workers and case managers can help with complex financial, legal and other issues, such as insurance coverage, developing an advance directive and finding social support services.

Pharmacists are an excellent resource for information about your medications. They can advise you if one of your drugs interacts badly with certain foods or with other drugs, including nonprescription ones.

Transition Care

Designed to prevent readmissions among populations transitioning from one care setting to another

- Home visit
- Telemonitoring
- Telephone call
- Multidisciplinary clinic

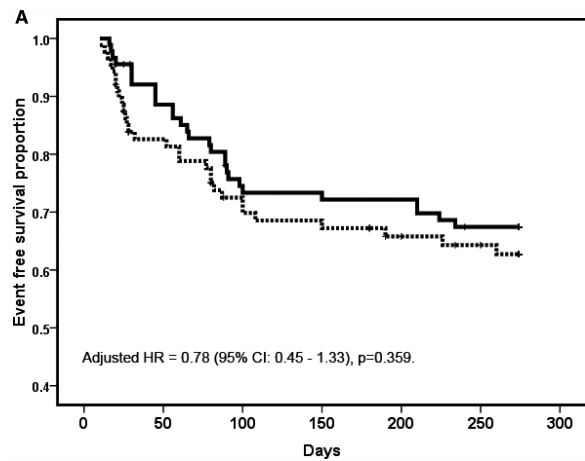
Effect of Nurse-Implemented Transitional Care for Chinese Individuals with Chronic Heart Failure in Hong Kong: A Randomized Controlled Trial

Doris S. F. Yu, RN, PhD, Diana T. F. Lee, RN, RM, PhD,* Simon Stewart, RN, PhD,^{†‡} David R. Thompson, RN, PhD, MBA,[§] Kai-Chow Choi, PhD,* and Cheuk-Man Yu, MD^{||}*

Table 1. Details of Nurse-Implemented Transitional Care (TC) Program

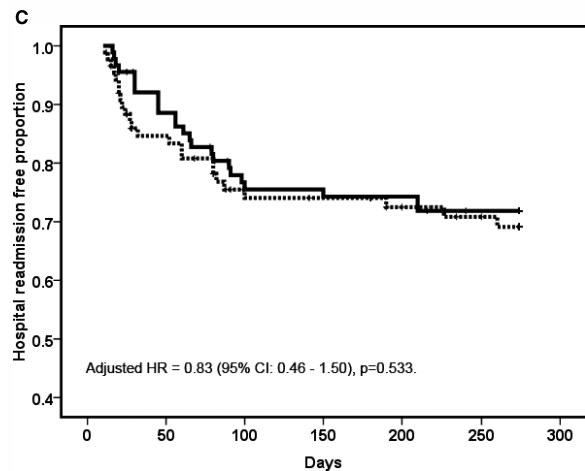
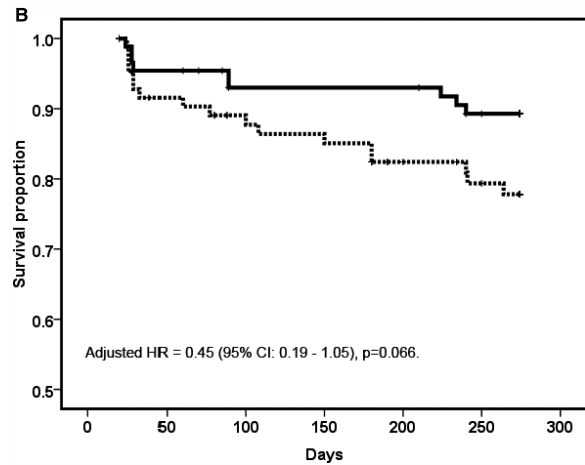
TC Program Component	Nursing Activities
Predischarge visit	Assessing health status (past and current medical history, reasons for admission, treatment regimen), cultural beliefs and self-care practices, and personal concerns about impending discharge
Two weekly home visits after discharge	Assessing disease progress (blood pressure, body weight, heart and lung auscultation, symptom assessment) and psychosocial assessment
	Assessing self-care implementation at home and identifying environmental barriers, if any
	Conducting customized educational and supportive interventions
	Developing partnership relationships
	Providing education and skill training on disease monitoring and management
	Creating personal self-care goals and action plan that best match participant cultural and personal preferences
	Matching community support service to participant needs according to an algorithm, (developed in a way to match the potential problems of individuals with CHF to the most relevant and accessible community support services)
Intensive telephone follow-up	Monitoring CHF symptom severity (e.g., dyspnea, fatigue, activity level) and providing advice on self-care decision-making
	Conducting health counseling for goal attainment
	Assessing implementation of action plan
	Identifying environmental, psychosocial, cultural barriers to self-care and related methods to resolve
	Providing positive reinforcement
	Reviewing and adjusting self-care goal if necessary
Telephone access to cardiac nurse	Providing prompt advice to participant inquiries

CHF = congestive heart failure.



Transition care group

- had a lower hospital readmission rate at 6 weeks
- had a lower mortality at 9 months (4.1% vs. 13.8%)
- had a shorter hospital stay
- had better self-care and health related quality of life



Transitional Care Interventions to Prevent Readmissions for Persons With Heart Failure

A Systematic Review and Meta-analysis

Cynthia Feltner, MD, MPH; Christine D. Jones, MD, MS; Crystal W. Cené, MD, MPH; Zhi-Jie Zheng, MD, PhD, MPH; Carla A. Sueti, MD, PhD; Emmanuel J.L. Coker-Schwimmer, MPH; Marina Arvanitis, MD; Kathleen N. Lohr, PhD, MPhil, MA; Jennifer C. Middleton, PhD; and Daniel E. Jonas, MD, MPH

Background: Nearly 25% of patients hospitalized with heart failure (HF) are readmitted within 30 days.

Purpose: To assess the efficacy, comparative effectiveness, and harms of transitional care interventions to reduce readmission and mortality rates for adults hospitalized with HF.

Data Sources: MEDLINE, Cochrane Library, CINAHL, ClinicalTrials.gov, and World Health Organization International Clinical Trials Registry Platform (1 January 1990 to late October 2013).

Study Selection: Two reviewers independently selected randomized, controlled trials published in English reporting a readmission or mortality rate within 6 months of an index hospitalization.

Data Extraction: One reviewer extracted data, and another checked accuracy. Two reviewers assessed risk of bias and graded strength of evidence (SOE).

Data Synthesis: Forty-seven trials were included. Most enrolled adults with moderate to severe HF and a mean age of 70 years. Few trials reported 30-day readmission rates. At 30 days, a high-intensity home-visiting program reduced all-cause readmission and the composite end point (all-cause readmission or death; low SOE). Over 3 to 6 months, home-visiting programs and multidisciplinary

heart failure (MDS-HF) clinic interventions reduced all-cause readmission (high SOE). Home-visiting programs reduced HF-specific readmission and the composite end point (moderate SOE). Structured telephone support (STS) interventions reduced HF-specific readmission (high SOE) but not all-cause readmissions (moderate SOE). Home-visiting programs, MDS-HF clinics, and STS interventions produced a mortality benefit. Neither telemonitoring nor primarily educational interventions reduced readmission or mortality rates.

Limitations: Few trials reported 30-day readmission rates. Usual care was heterogeneous and sometimes not adequately described.

Conclusion: Home-visiting programs and MDS-HF clinics reduced all-cause readmission and mortality; STS reduced HF-specific readmission and mortality. These interventions should receive the greatest consideration by systems or providers seeking to implement transitional care interventions for persons with HF.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. 2014;160:774-784.

www.annals.org

For author affiliations, see end of text.

This article was published online first at www.annals.org on 27 May 2014.

Table 1. Transitional Care Interventions

Category	Definition
Home-visiting programs	Home visits by clinicians, such as a nurse or pharmacist, who educate, reinforce self-care instructions, perform physical examination, or provide other care (e.g., physical therapy or medication reconciliation). These interventions are often referred to as nurse case management interventions, but they also can include home visits by a pharmacist or multidisciplinary team.
STS	Monitoring, education, or self-care management (or various combinations) using simple telephone technology after discharge in a structured format (e.g., series of scheduled calls with a specific goal, structured questioning, or use of decision-support software).
Telemonitoring	Remote monitoring of physiologic data (e.g., electrocardiogram, blood pressure, weight, pulse oximetry, or respiratory rate) with digital, broadband, satellite, wireless, or Bluetooth transmission to a monitoring center, with or without remote clinical visits (e.g., video monitoring).
Outpatient clinic-based	Services provided in one of several types of outpatient clinics: multidisciplinary HF, nurse-led HF, or primary care. The clinic-based intervention can be managed by a nurse or other provider and may also offer unstructured telephone support (e.g., patient hotline) outside clinic hours.
Primarily educational	Patient education (and self-care training) delivered before or at discharge by various personnel or methods: in person, interactive CD-ROM, or video education. Interventions in this category do not feature telemonitoring, home visits, or STS and are not delivered primarily through a clinic-based intervention. Follow-up telephone calls may occur to ascertain outcomes (e.g., readmission rates) but not to monitor patients' physiologic data.
Other	Unique interventions or interventions that do not fit into any of the other categories (e.g., individual peer support for patients with HF).

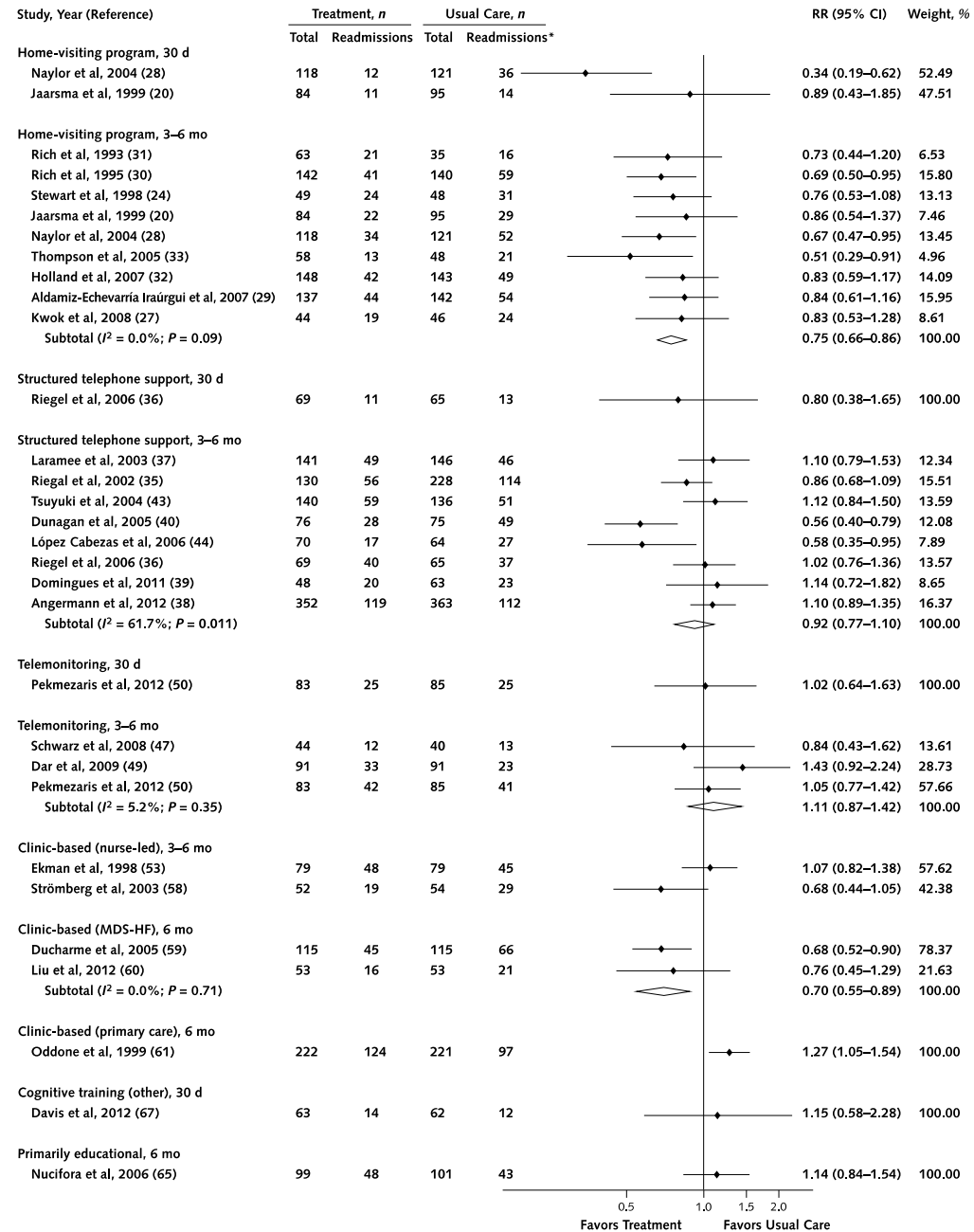
Figure 1. All-cause readmissions for transitional care interventions compared with usual care, by intervention category and outcome timing.

Home-visiting program

Telephone support

Telemonitoring

Clinic-based



Comparative effectiveness of transitional care services in patients discharged from the hospital with heart failure: a systematic review and network meta-analysis

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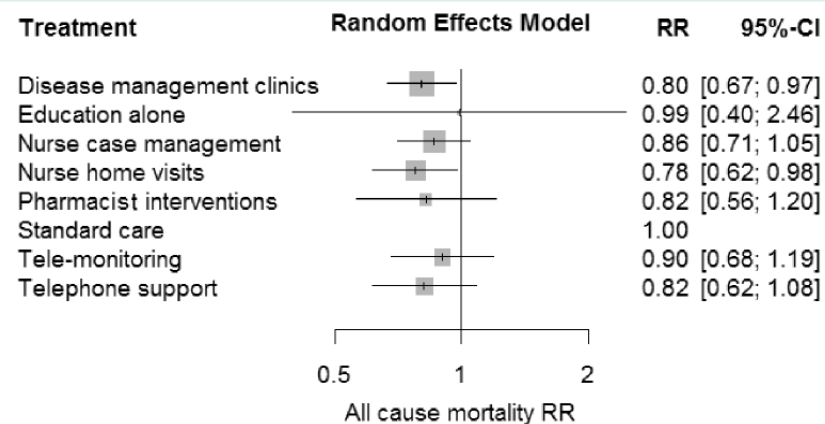


Figure 2 Comparative effectiveness of transitional care services in reducing all-cause mortality after hospitalization for heart failure. Results of the network meta-analysis are depicted in the forest plot. CI, confidence interval; RR, relative risk.

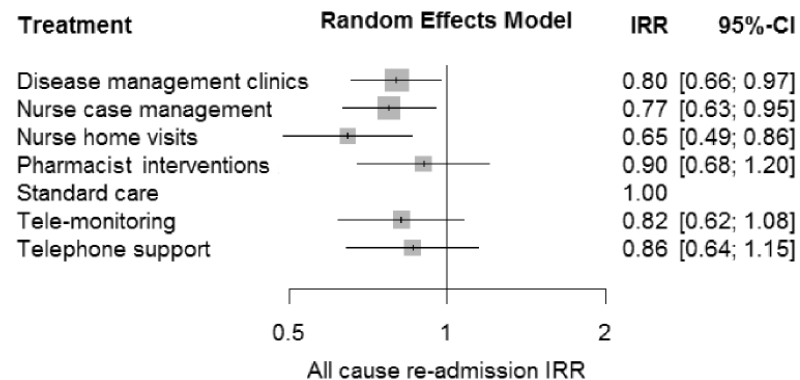
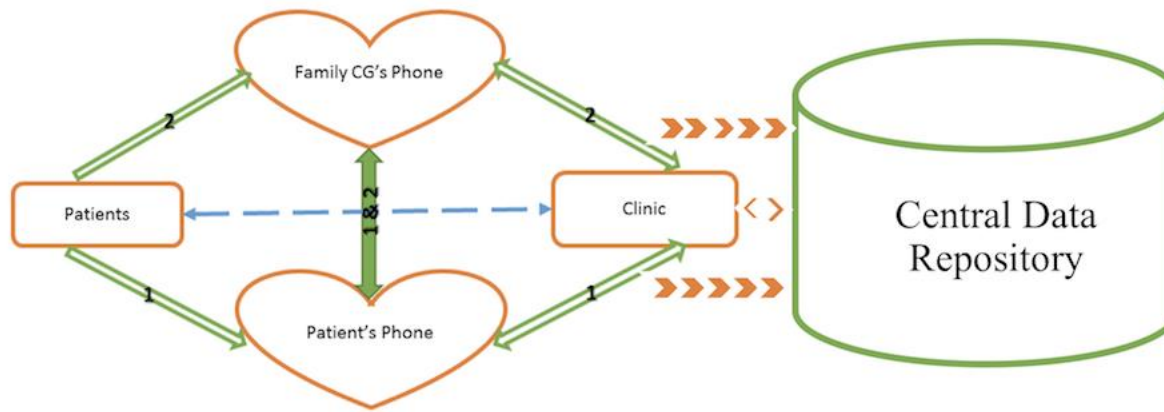


Figure 3 Comparative effectiveness of transitional care services in reducing all-cause readmissions after hospitalization for heart failure. Results of the network meta-analysis are depicted in the forest plot. CI, confidence interval; IRR, incident rate ratio.

Elements of interventions

- A multidisciplinary approach, recurrent face-to-face contact, education of patients, with an emphasis on self-care, weight monitoring, and pharmacotherapy, and proactive optimization of medications rather than sole reliance on patient triggers.
- Face-to-face assessments may be more effective than remote monitoring at addressing non-cardiovascular conditions that account for approximately 40% of readmissions .



Conclusion

- **HEART FAILURE** remains a chronic disease with unmet needs despite current available treatments.
- “...angiotensin receptor–neprilysin inhibition was superior to ACE inhibition alone in reducing the risks of death and of hospitalization for HF”
- “This robust finding provides strong evidence that combined inhibition of the angiotensin receptor and neprilysin is superior to inhibition of the RAS alone in patients with *acute and chronic HF*.”
- Transitional intervention is useful for reducing hospitalization burden in patients with HF.