The 4th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

Paradigm Shift in Advancing HFrEF Care

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What does "paradigm-shift" mean?

Some dictionary definitions

- **Cambridge: A time when the usual and accepted way of doing or thinking about something changes completely**
- **Oxford: A fundamental change in approach or underlying assumptions**
- **Merriam-Webster: An important change that happens when the usual way of thinking about or doing something is replaced by a new and different way**

Heart Failure Poses A Significant Global Disease Burden

>60 million patients worldwide have heart failure[1]

#1 reason for hospitalisation in patients aged >65 years, with 24% of patients re-hospitalised within 30 days of discharge[2,3]

Approximately **50% of patients** diagnosed with heart failure will **die within 5 years**[4]

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Lancet 2017; 390:1211;
2. Azad N et al. J Geriatr Cardiol 2014; 11:329;
3. Krumholz HM et al. Circ Cardiovasc Qual Outcomes 2009; 2:407;
4. Mozzafarian D et al. Circulation 2016; 133:e38

Global Burden of Heart Failure

Prevalence

Prevalence 1-3% in general adult population

Overall prevalence ↑

Prevalence in HFrEF ↔

Prevalence In HFpEF ↑

Incidence

Incidence 1-20 cases per 1,000 person-years or per 1,000 population

Incidence stable/ declining ↔

Incidence in HFrEF ↓

Incidence in HFpEF ↘

Mortality

Mortality remains high

30-day Mortality	~2-3%
1-year Mortality	~15-30%
3-year Mortality	~30-50%
5-year Mortality	~50-75%

CVD HFreF ↓ Non-CVD HFpeF ↑

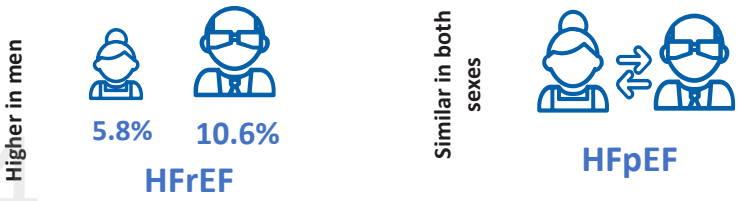
Costs

Annual health care costs up to €25,500 per year

Increasing due to major demographic changes (>65 years)

Main cost drivers:
- Directs costs (~70%)
- Non-CVD comorbidities
- Invasive procedures
- Medications/Diagnostics
- Outpatient visits

HF risk & Hospitalization



HF hospitalizations represent 1% to 2% of all hospital admissions and is the most common diagnosis in hospitalized patients aged >65 years[1]

Gianluigi Savarese, et al. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovascular Research (2022) 118, 3272–3287
Groenewegen A, et al. Eur J Heart Fail 2020;22:1342–56 2. Lippi G, Sanchis-Gomar G. AME Med J 2020;5:15

Prevalence of heart failure (HF), demographic characteristics of patients and etiology in 9 Asian countries or regions, and Europe and the USA [2,3,20,22–29,31–34].

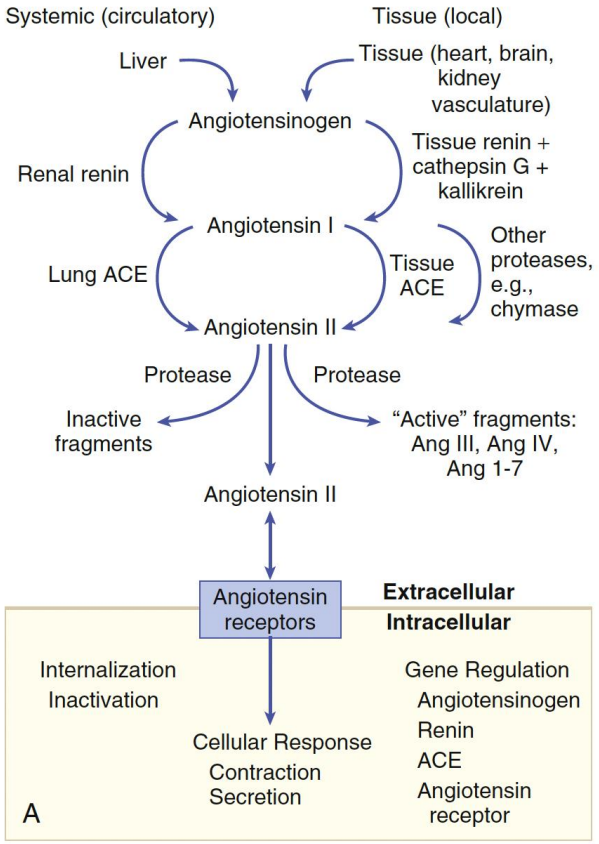
Prevalence or characteristic	Asia									Europe	USA
	Hong Kong	Indonesia	Malaysia	Philippines	Singapore	South Korea	Taiwan	Thailand	Vietnam		
Prevalence of HF	2%–3%[a]	5%	–	1%–2%	–	0.6%	6%	0.4%	–	1%–2%	2%
Demographic characteristics of HF patients											
Male	45%	66%	75%	57%	64%	55%	72%	–	59%	61%	53%
Female	55%	34%	26%	43%	36%	45%	28%	–	41%	39%	47%
Mean age at admission (years)	76.8	57.8	61.8	60	66.6	69	64	67	59	70	74
Cardiovascular risk factors											
Ischemic heart disease	29%	35%	68%	52%	37%	37%	44%	45%	32%	54%	46%
Valvular/rheumatic heart disease	6%	18%	29%	20%	–	14%	8%	19%	18%	–	–
Cardiomyopathy (non-ischemic)	1%	2%	28%	11%	–	21%	34%	14%	21%	–	–
Hypertensive heart disease	70%	8%	2%	6%	–	4%	7%	12%	21%	–	23%
Other causes[b]		2%	5%	7%	–	11%	7%	–	–	–	–
Hypertension		33%	75%	64%	69%		33%	31%	–	63%	76%
Current smoking	13%	28%	9%	54%	45%		24%	7%	31%	–	–
Diabetes mellitus	36%	37%	67%	41%	55%		43%	47%	–	33%	43%
Dyslipidemia		31%	52%	38%	65%		24%	51%	5%	–	44%
Overweight		47%	25%	21%	–		–	–	–	–	–
Renal disease		24%	31%	4%	–		31%	19%	5%	17%	50%
Atrial fibrillation		16%	24%	–	21%		26%	24%	22%	39%	31%
Coronary heart disease		35%	73%	52%	49%		43%	47%	–	54%	50%
Cerebrovascular disease		2%	7%	0%	15%		9%	12%	–	–	–
COPD		18%	13%	2%	12%		12%	8%[c]	3%	19%	–

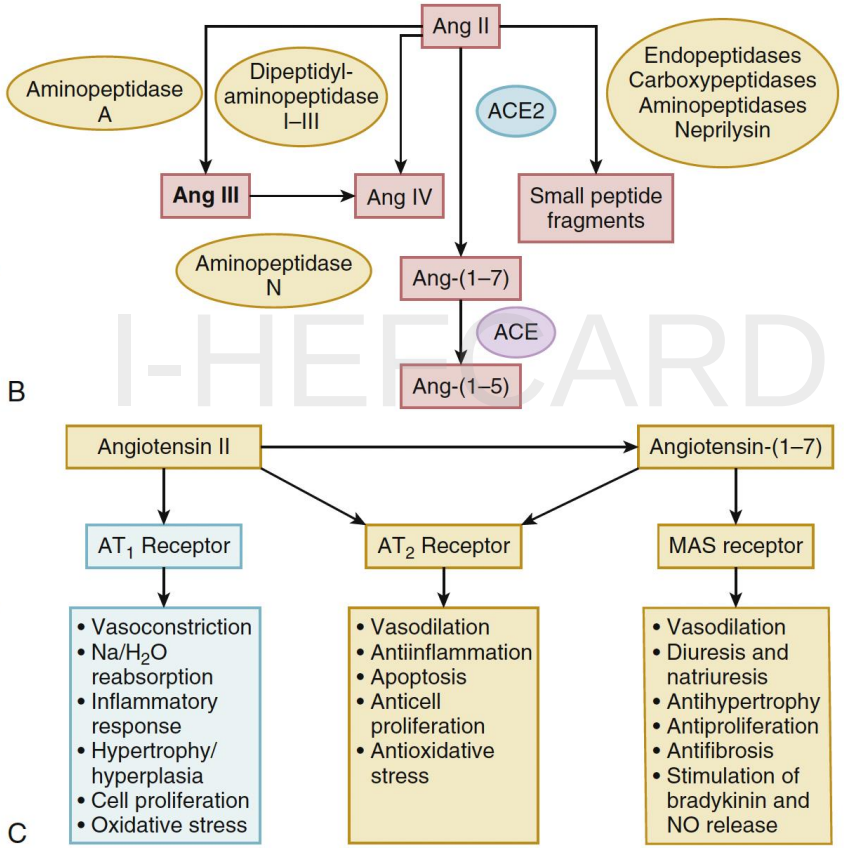
HF Prevalence in Indonesia[2]:

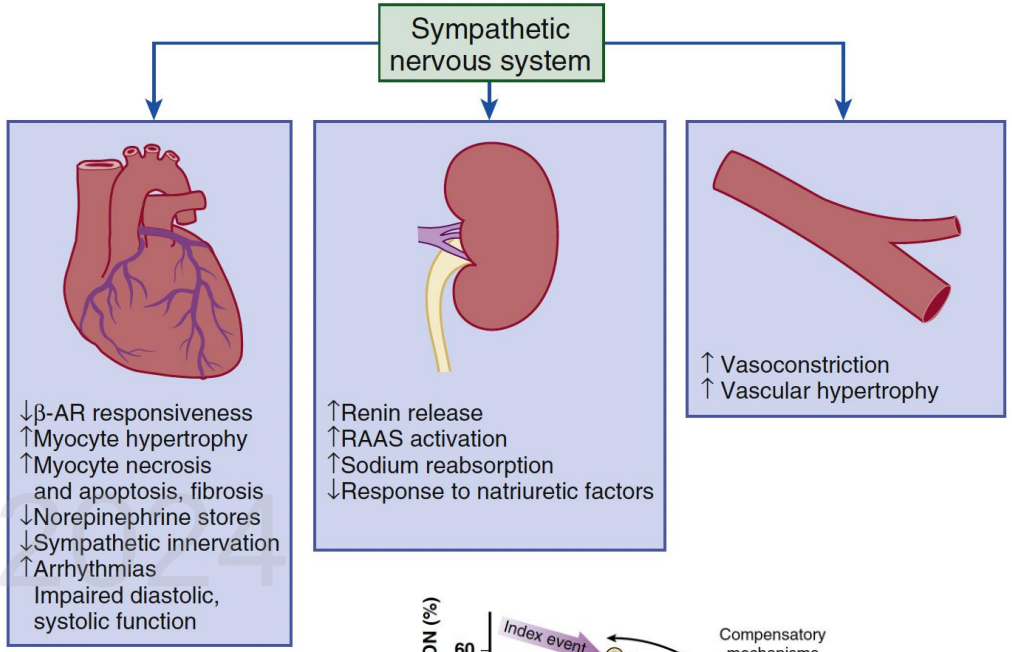
- > 5%
- Younger age
- More severe clinical presentation

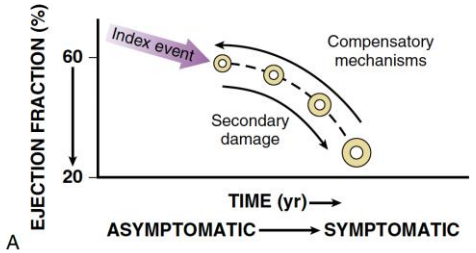
1. Reyes, E. B., Ha, J. W., Firdaus, I., Ghazi, A. M., Phrommintikul, A., Sim, D., Vu, Q. N., Siu, C. W., Yin, W. H., & Cowie, M. R. (2016). Heart failure across Asia: Same healthcare burden but differences in organization of care. International journal of cardiology, 223, 163–167. https://doi.org/10.1016/j.ijcard.2016.07.256
2. Pokja HF, 2023

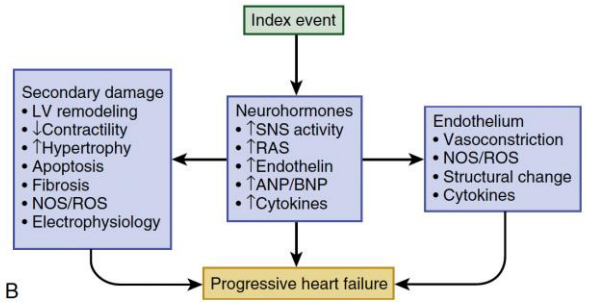
Pathophysiology of Heart Failure





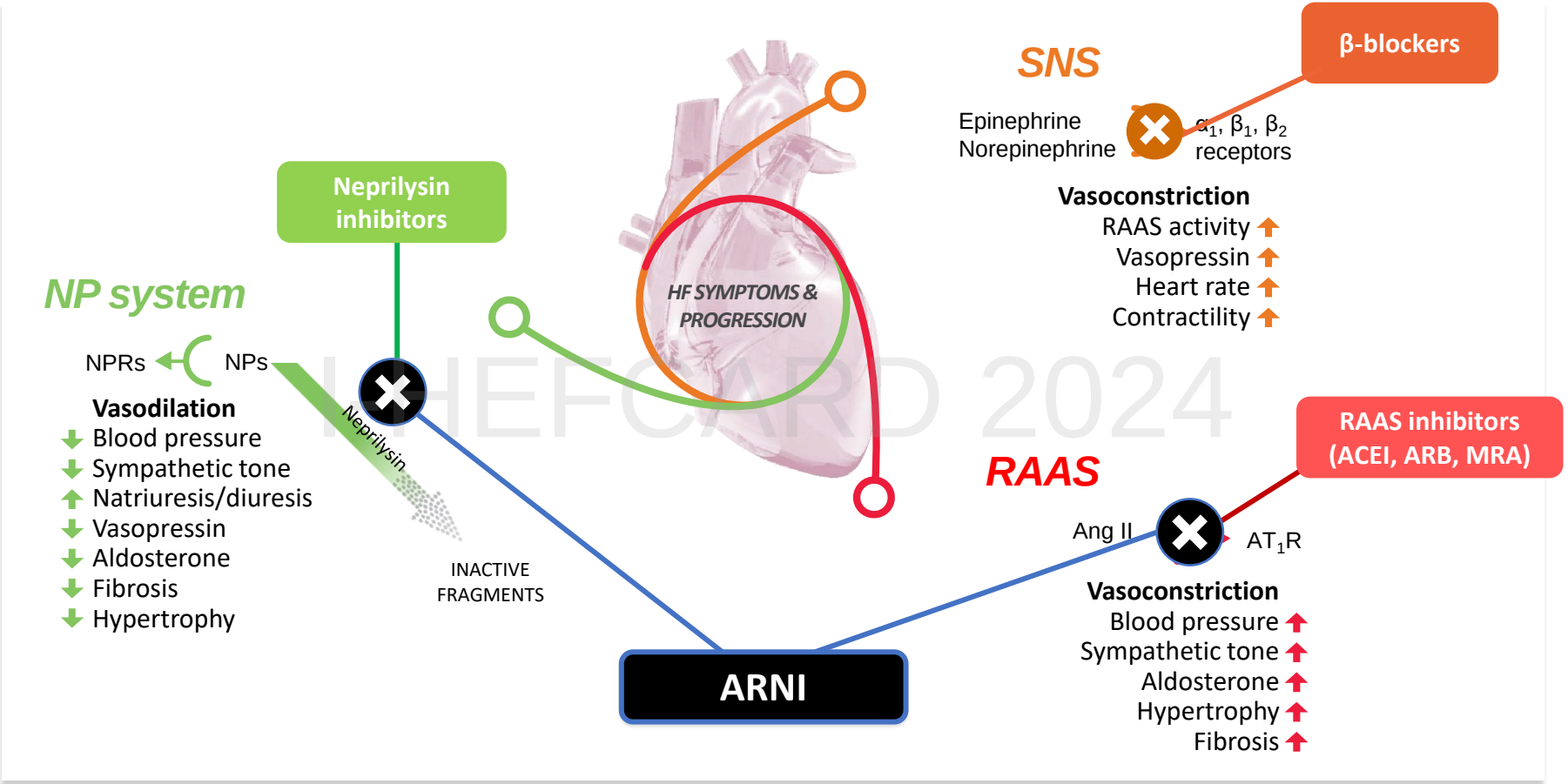






Gerd Hasenfuss and Douglas L. Mann. Pathophysiology of Heart Failure. Braunwald's Heart Disease-A Textbook Of Cardiovascular Medicine. 12th ed. 2022. 913-932.

Evolution of Pharmacologic Approaches in HF: ARNI as a New Alternative to an ACEI or ARBs in Patients with HFrEF[1]



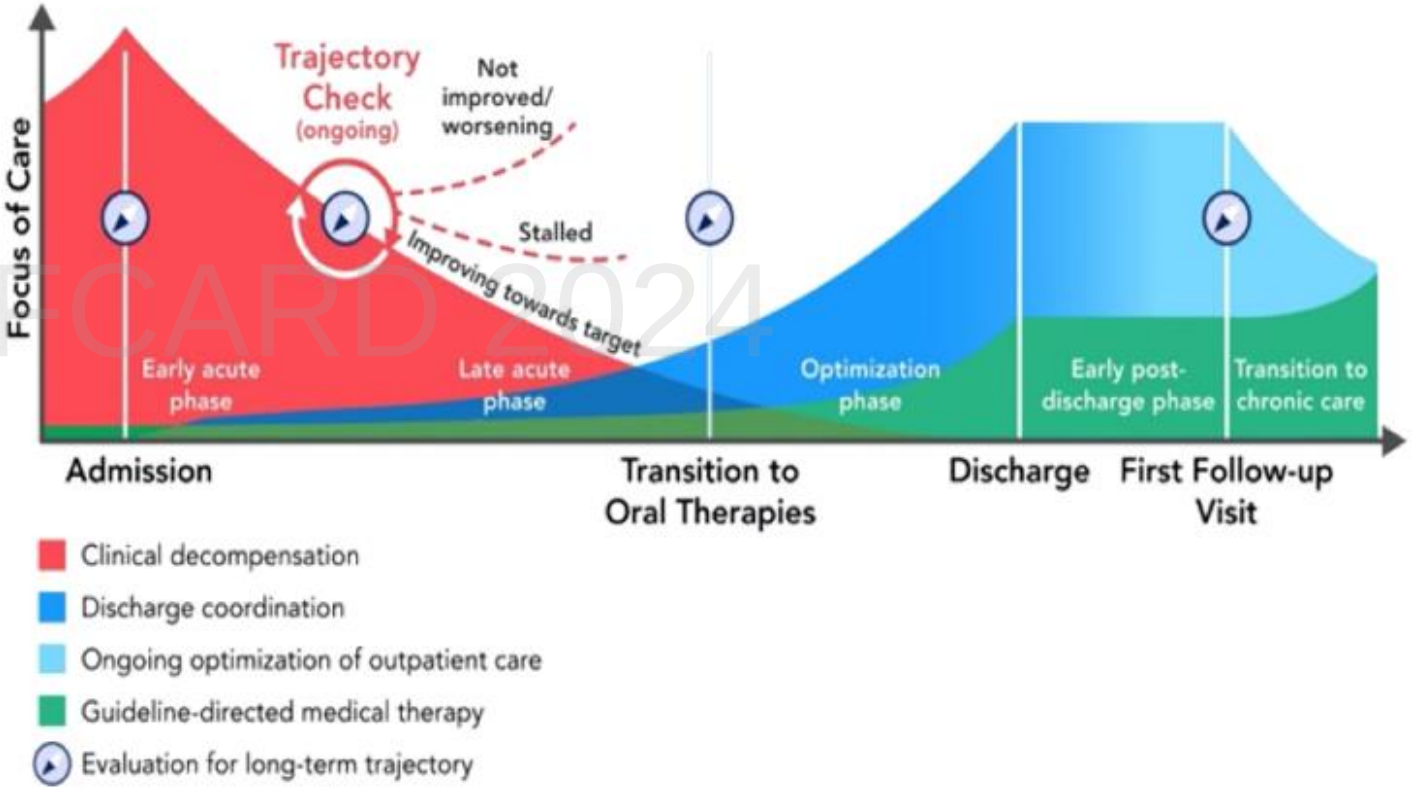
- ARNI: enhancement of natriuretic and other vasoactive peptides, with simultaneous RAAS suppression

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

Heart Failure Patients Currently Have High Rates of Readmission and Mortality After Discharge

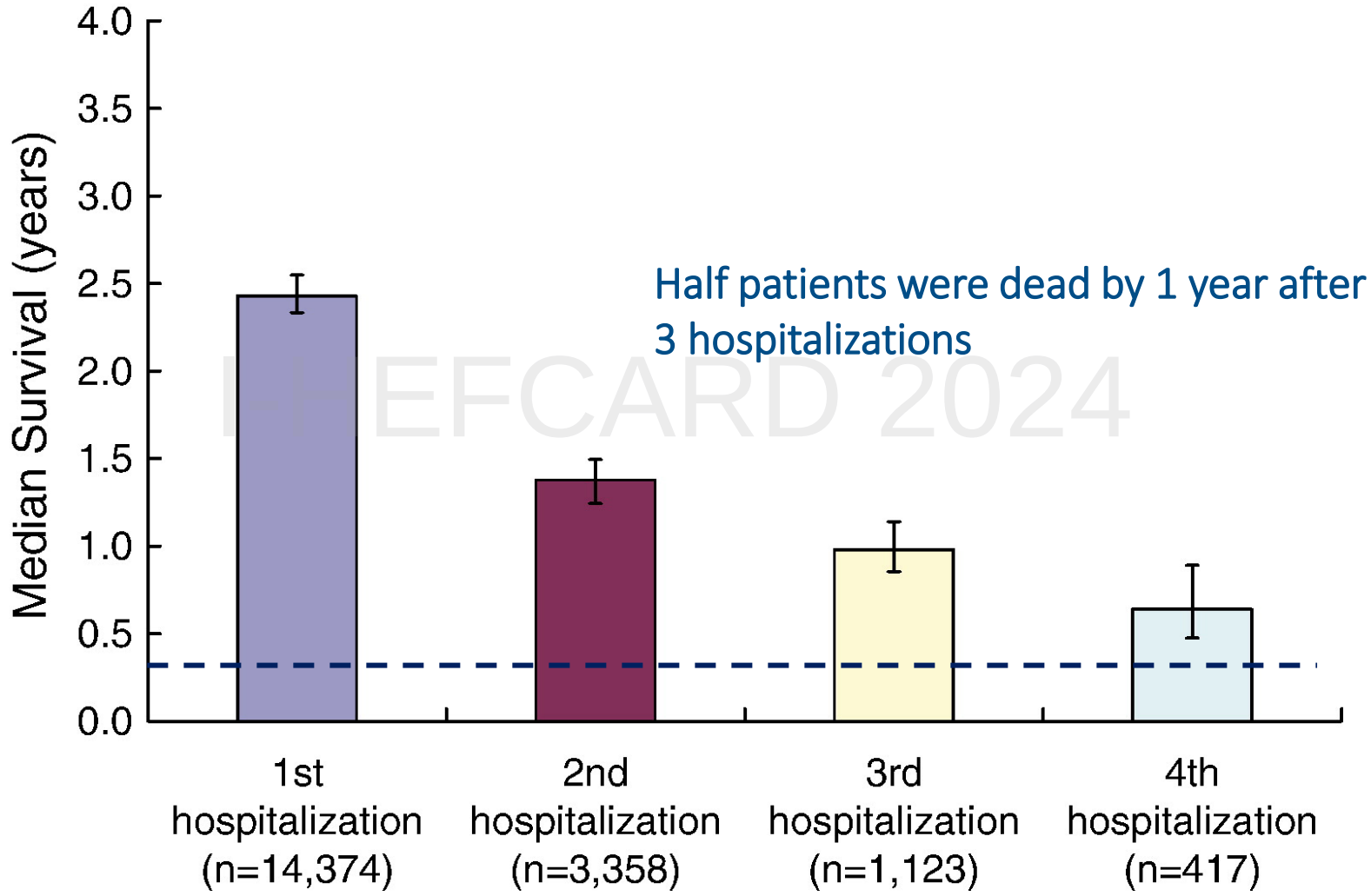
To establish best practices for inpatient drug therapy.

To optimize GDMT for the outpatient environment.



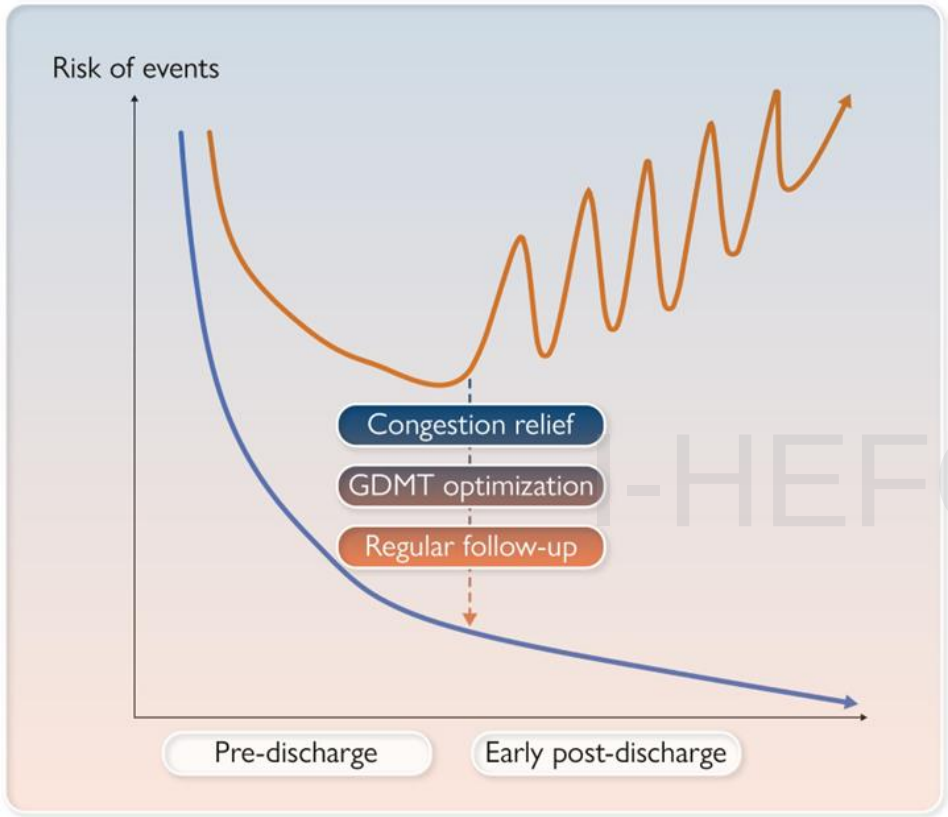
Hollenberg SM, et al. J Am Coll Cardiol. 2019;74:1966-2011

Strong Predictor for Increased Mortality



Half patients were dead by 1 year after 3 hospitalizations

Setoguchi S, et al. *Am Heart J*. 2007;154:260-266.



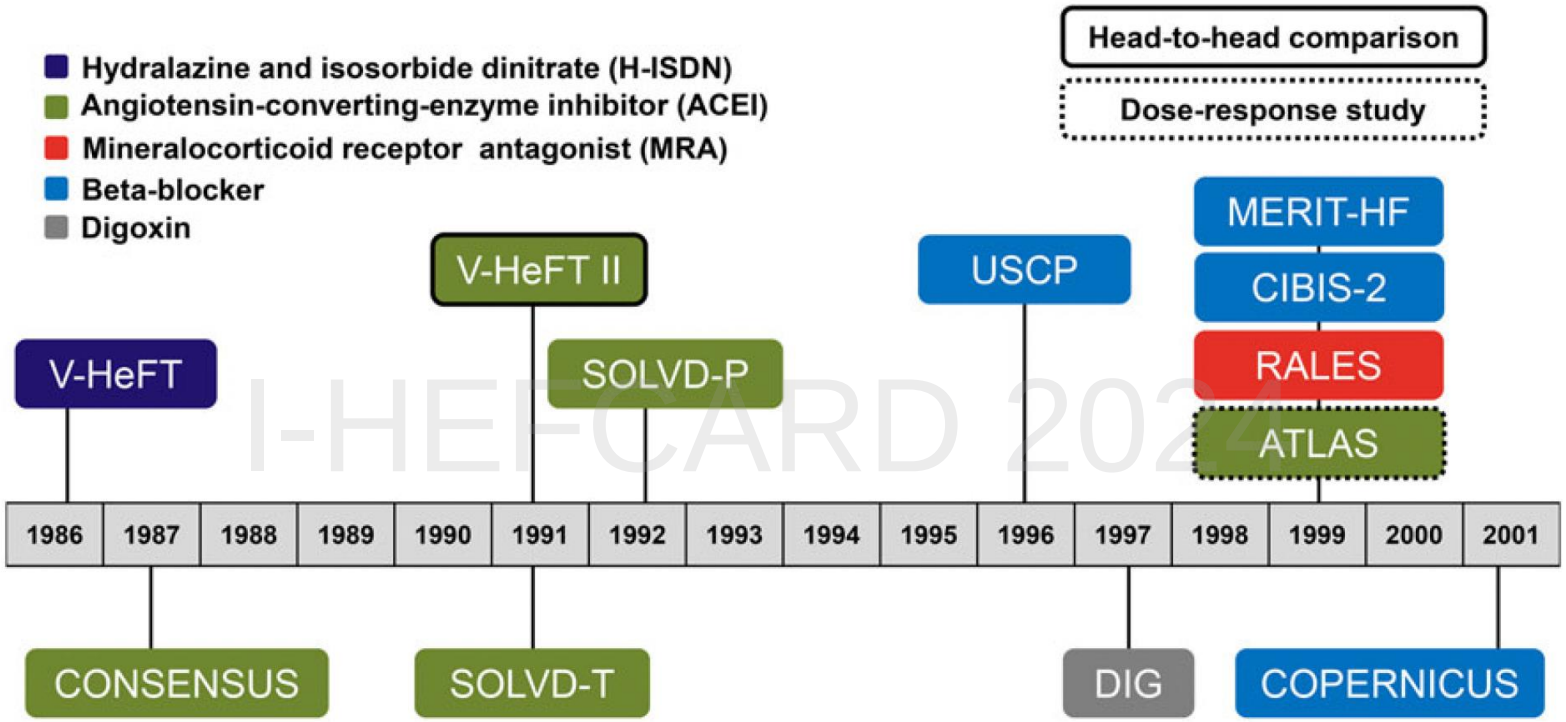
Determinants of better outcome after discharge

1. Optimal decongestion
2. Optimization GDMT
3. Intensive post-discharge monitoring reduce mortality and new heart failure events after discharge

Pre-discharge optimization of treatment

European J of Heart Fail, Volume: 25, Issue: 7, Pages: 1115-1131, First published: 18 May 2023, DOI: (10.1002/ejhf.2888)

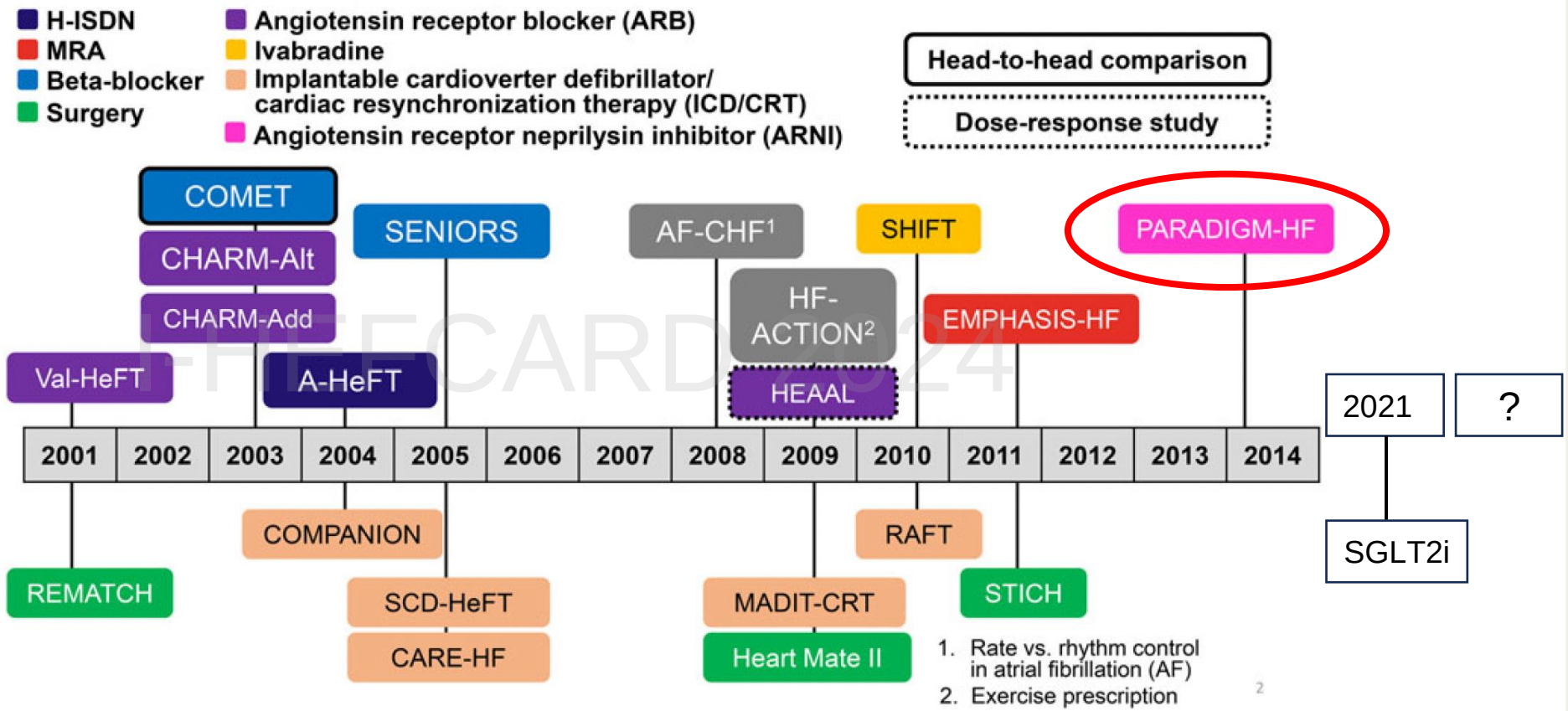
Landmark Trial of Heart Failure



HFrEF: thirty years of progress – positive drug trials 1986–2001

John J.J.V. McMurray. European Heart Journal (2015) 36, 3467–3470

Landmark Trial of Heart Failure



HFrEF: thirty years of progress - positive drug, device and other trials 2001–2014.

John J.J.V. McMurray. European Heart Journal (2015) 36, 3467–3470

ARNI Pivotal Study : PARADIGM-HF

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

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

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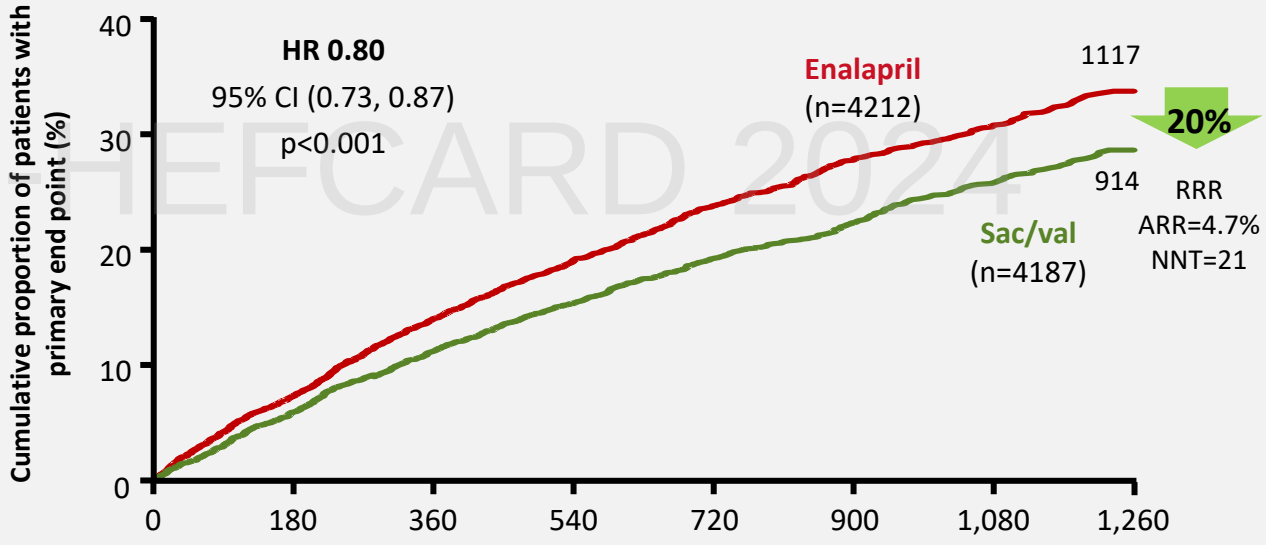
Summary from Paradigm-HF Trials: Sacubitril Valsartan was Proven Superiority Over Enalapril

20% risk reduction of CV death or first HF hospitalization[1]	20% risk reduction for sudden cardiac death[2]	16% risk reduction of death from any cause[1]	23% fewer admissions for HF[3]	18% fewer stays in intensive care[3]

PARADIGM-HF
Reduction of CV death or first HF hospitalization[1]



No. at risk

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

ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk reduction; Sac/val, sacubitril valsartan

1. McMurray JJV, et al. N Engl J Med 2014;371(11):993-1004; 2. Desai AS, et al. Eur Heart J 2015;36(30):1990-7; 3. Packer M, et al. Circulation 2015;131(1):54-61

TRANSITION

PIONEERHF

Key Questions Addressed by TRANSITION

1. Can ARNI be started shortly after an ADHF event?

ADHF hospitalized patients have

- a **more severe** clinical profile
- **higher rate** of **co-morbidities** vs. chronic HF patients[1,2,3]

PARADIGM-HF patients were **ambulatory** at the time of inclusion[2]

2. Could target dose be achieved in about 10 weeks?

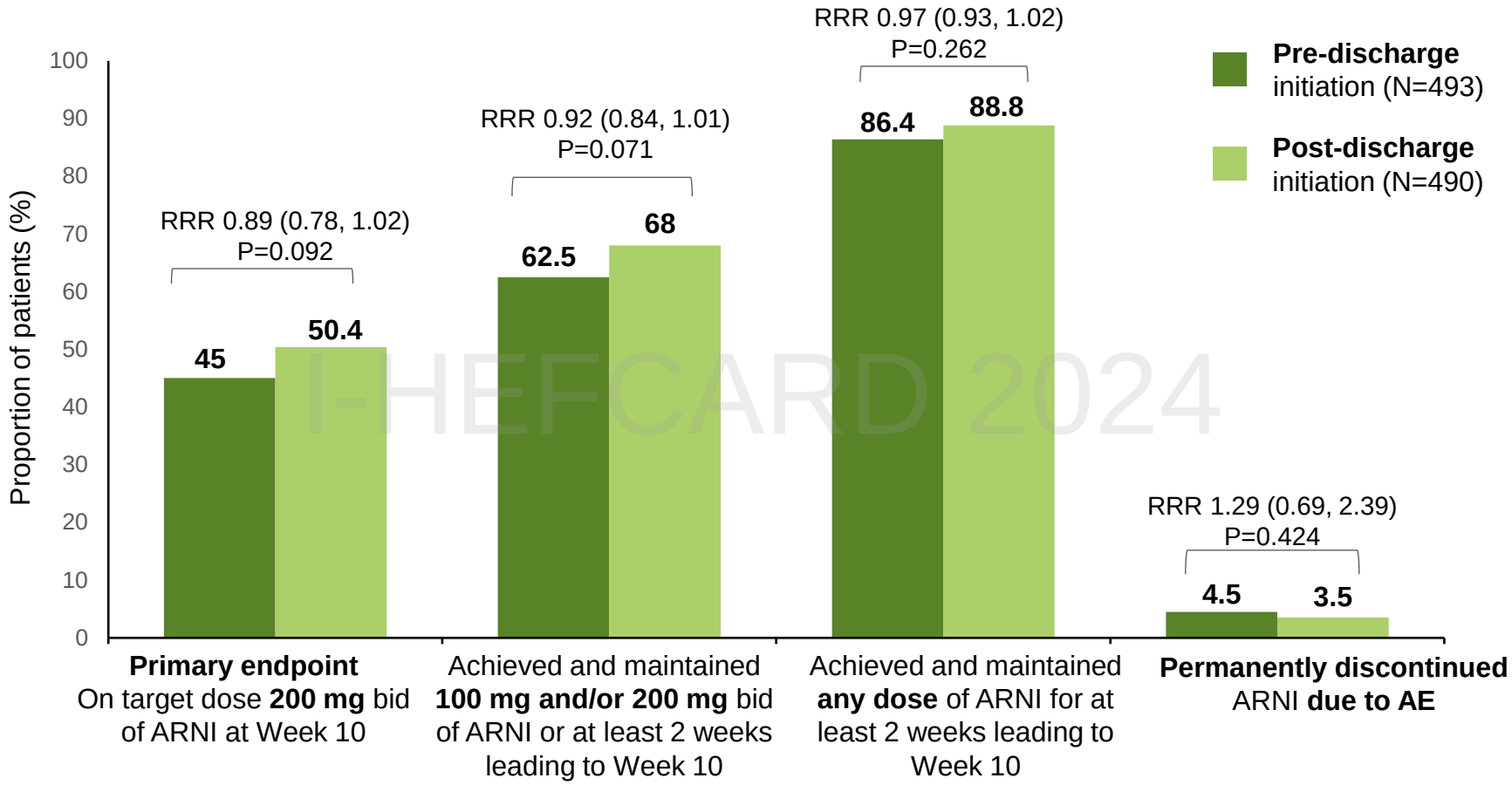
TRANSITION aims to provide evidence on ***safety and tolerability*** of ***early initiation*** of ARNI in hospitalized HFrEF patients

- **stabilized** following an ADHF episode
- with **pre-existing** or newly diagnosed (***'de novo'***) HF
- on **any** ACEI/ARB dose before admission or ACEI/ARB **naïve**

ACEI, angiotensin converting enzyme inhibitor; ADHF, acute decompensated heart failure; ARB, angiotensin receptor blocker; HF, heart failure; HFrEF, HF with reduced ejection fraction

1. McMurray et al. N Engl J Med 2014;371(11):993-1004; 2. McMurray et al. Eur J Heart Fail 2013;15:1062-73; 3. Senni et al. Eur J Heart Fail 2016;18(9):1193–1202

Primary and Secondary Endpoints



Safety analysis set

AE, adverse events; bid, twice daily; sac/val, sacubitril/valsartan; RRR, relative risk ratio

Wachter R et al., TRANSITION primary data poster presentation (P886) at ESC Congress 2018, Munich Germany

Conclusions: 10 week results

- **Comparable** proportions of patients **met** the **primary and secondary** endpoints in the pre- and post-discharge initiation groups
- About **half** of HFrEF patients stabilized after an ADHF event achieved the **target dose** of 200 mg ARNI bid within **10 week**s
- At Week 10, more than **86%** of patients in both groups were receiving **any dose** for 2 weeks or longer without interruption
- Incidence of AEs and ARNI discontinuations due to AEs was **similar** in in-hospital and ambulatory initiation groups

Initiation of sacubitril/valsartan
in a **wide range** of HFrEF patients, **early after ADHF event**
in-hospital or **shortly after discharge**,
was **feasible** and overall **well tolerated**

ADHF, acute decompensated heart failure; AE, adverse event; HFrEF, heart failure with reduced ejection fraction

Wachter R et al., TRANSITION primary data poster presentation (P886) at ESC Congress 2018, Munich Germany

The NEW ENGLAND JOURNAL of MEDICINE

Whether Initiation of sacubitril-valsartan therapy is
effective and safe among patients
who are hospitalized for acute decompensated heart failure unknown

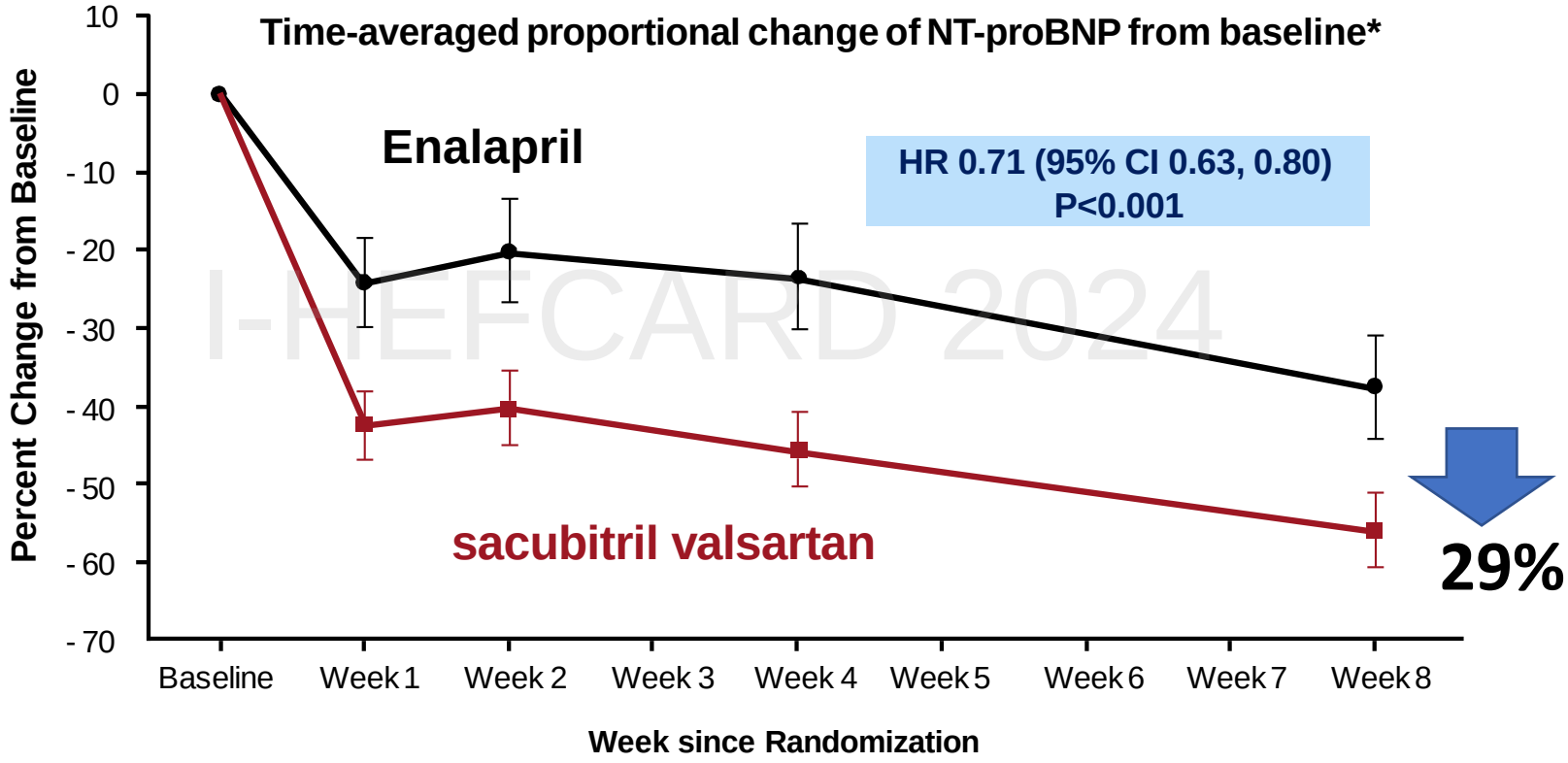
Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H., Adam D. DeVore, M.D., M.H.S., Carol I. Duffy, D.O., Andrew P. Ambrosy, M.D., Kevin McCague, M.A., Ricardo Rocha, M.D., and Eugene Braunwald, M.D., for the PIONEER-HF Investigators*

Primary Endpoint

PIONEER-HF

In-hospital Initiation of Sacubitril/Valsartan Reduce NT-pro BNP Significantly vs. Enalapril

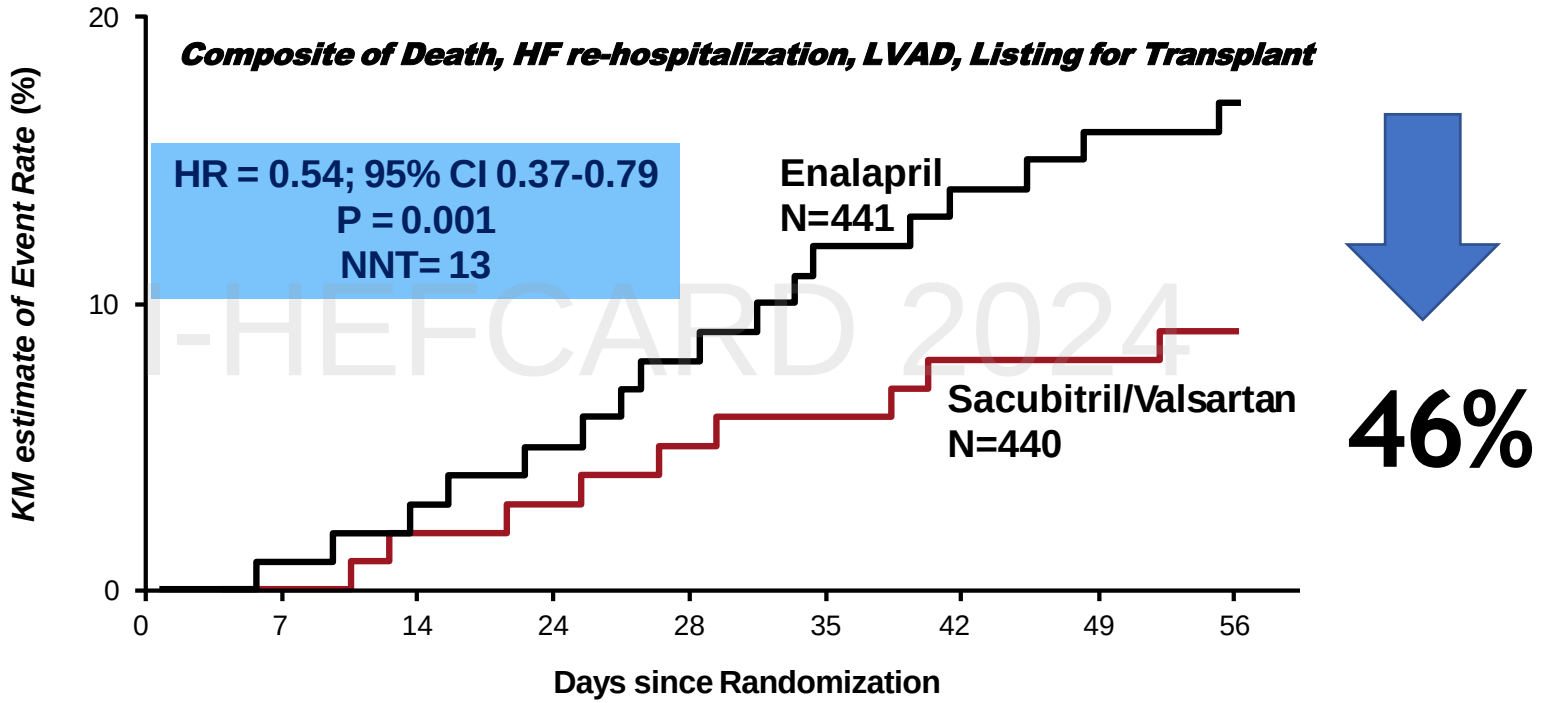


*Percentage (%) change from baseline to mean of weeks 4 and 8

Velazquez E, Morrow D, DeVore, A, et al., N Engl J Med. 2018. doi: 10.1056/NEJMoa1812851.

PIONEER-HF

In-hospital Initiation of Sacubitril/Valsartan Reduce Serious Clinical Outcome vs. Enalapril



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

Velazquez EJ et al. Late Breaker AHA 2018. Chicago, IL, USA November 10-12, 2018

Conclusions

PIONEER and TRANSITION showed that initiation of sacubitril/valsartan **shortly after an ADHF event** is **feasible** and **well tolerated**[2]

In-hospital initiation of sacubitril/valsartan is associated with **early and sustained improvements** in biomarkers of **cardiac wall stress** and **myocardial injury**, indicating **pathophysiological benefits** in a **wide range** of HFrEF patients [1]

ADHF, acute decompensated heart failure; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; hs-TnT, high-sensitivity-troponin-T; NT-proBNP, N-terminal pro b-type natriuretic peptide

1. Pascual-Figal D, et al. TRANSITION biomarker poster [Su2183] presented at AHA Congress 2018, Chicago, USA; 2. Wachter R, et al. Eur Heart J 2018; 39 (S):167 (presented as a poster [P886] at ESC Congress 2018, Munich Germany)

The evidence doesn't stop....

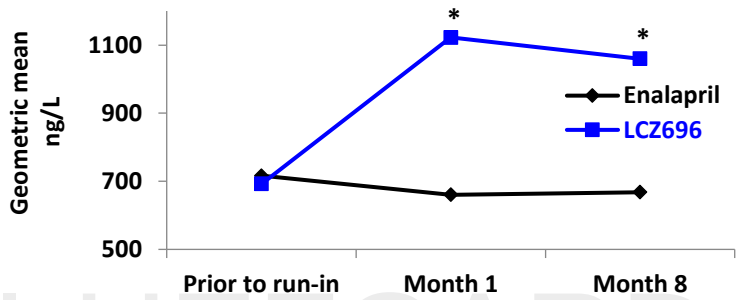
What has come after PARADIGM-HF?

Publications from PARADIGM-HF (1)

Title	Journal
Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure.	**Circulation**
A putative placebo analysis of the effects of LCZ696 on clinical outcomes in heart failure.	Eur Heart J
Effect of the angiotensin receptor neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients.	Eur Heart J
Efficacy and safety of LCZ696 (sacubitril/valsartan) according to age: Insights from PARADIGM-HF	Eur Heart J
Comparing LCZ696 with enalapril according to baseline risk using the MAGGIC and EMPHASIS-HF risk scores: an analysis of mortality and morbidity in PARADIGM-HF.	JACC
Estimating the long-term treatment benefits of sacubitril/valsartan.	NEJM letter
Influenza vaccination in patients with chronic heart failure: The PARADIGM-HF trial	JACC-HF

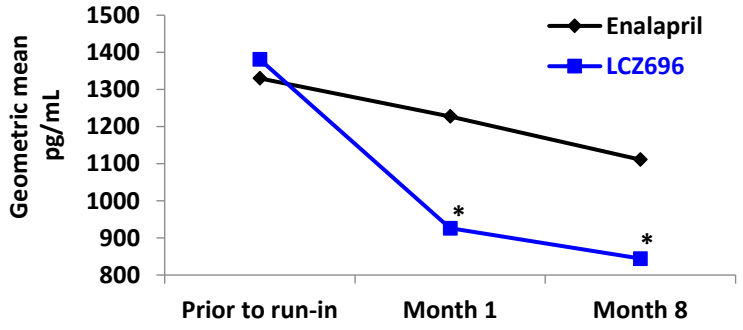
LCZ696 Increased cGMP and Reduced NT-proBNP and hs Troponin

cGMP: marker of LCZ696 drug action



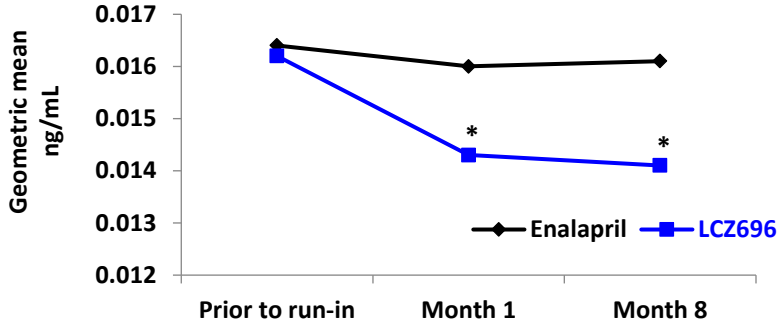
*p-value=<.0001

NT-proBNP: cardiac wall stress



*p-value=<.0001

hs Troponin T: myocardial injury



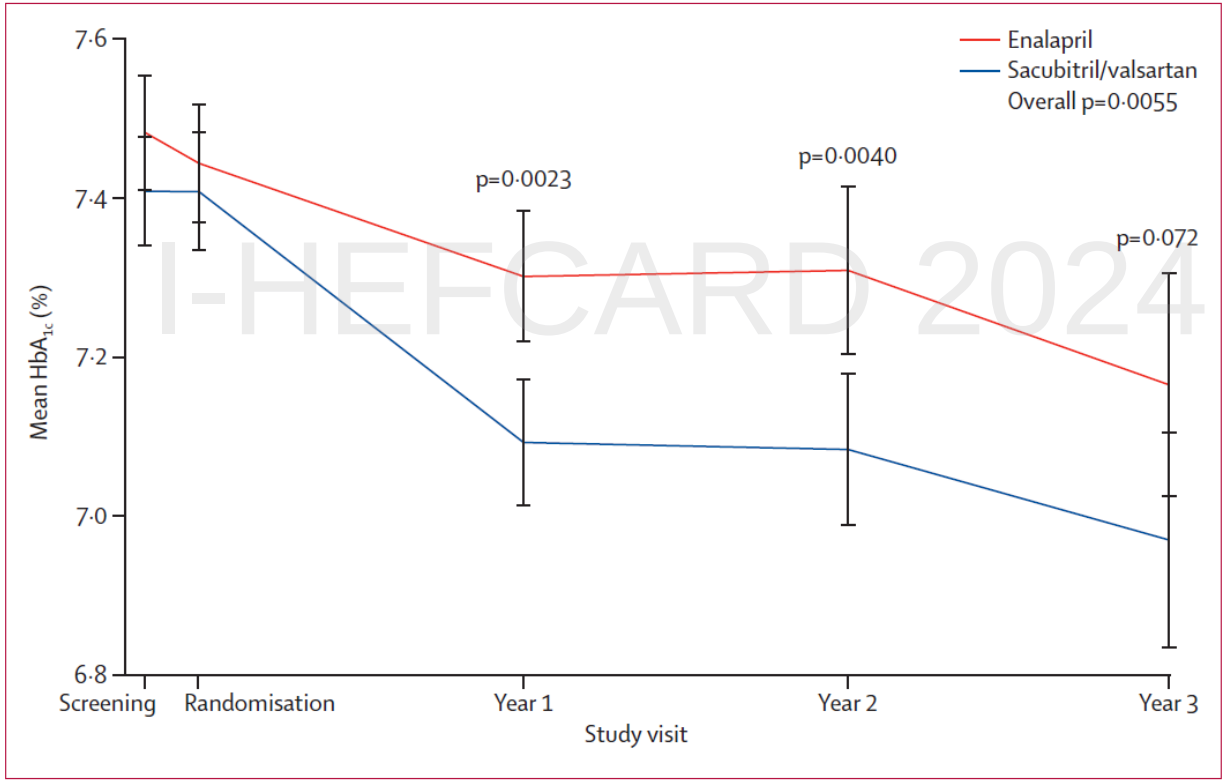
*p-value=<.0001

Data from Packer M, et al. Circulation. 2015:131:54-61

Publications from PARADIGM-HF (3)

Title	Journal
Geographic variations in the PARADIGM-HF trial.	Eur Heart J
Effects of sacubitril/valsartan in the PARADIGM-HF trial according to background therapy.	Circ-HF
Dementia-related adverse events in PARADIGM-HF and other trials in heart failure with reduced ejection fraction.	Eur J HF
Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure.	JACC
Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction.	Eur J HF
Reduced risk of hyperkalemia during treatment of heart failure with mineralocorticoid receptor antagonists by use of sacubitril/valsartan compared with enalapril.	JAMA Cardiol
Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced EF.	Eur Heart J
Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial.	**Lancet diabetes**
The effect of sacubitril/valsartan on coronary outcomes in PARADIGM-HF.	Am Heart J

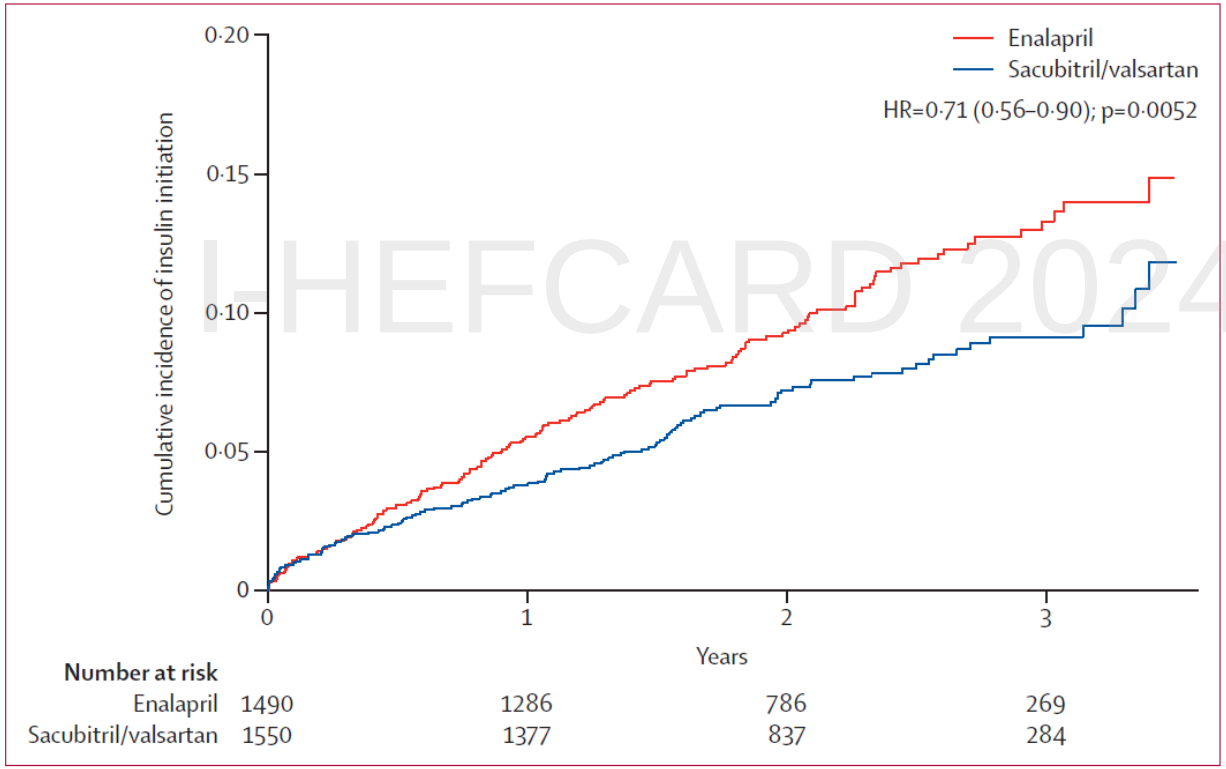
PARADIGM-HF: Change in HbA1c in patients with a baseline diabetes



*Sacubitril valsartan is indicated for symptomatic heart failure with reduced ejection fraction

Seferovic et al. Lancet Diabetes Endocrinol. 2017 May ; 5(5): 333–340.

PARADIGM-HF: Time to initiation of insulin in patients with diabetes



*Sacubitril valsartan is indicated for symptomatic heart failure with reduced ejection fraction

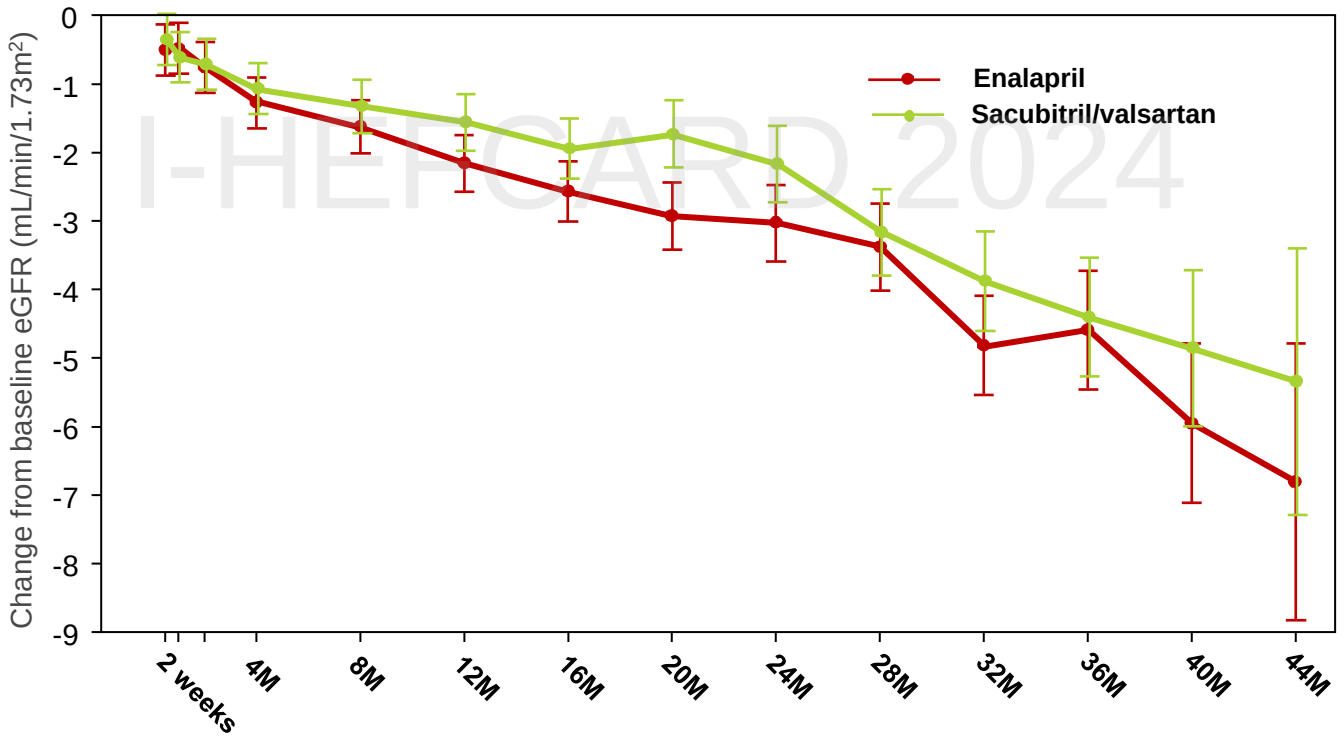
Seferovic et al. Lancet Diabetes Endocrinol. 2017 May ; 5(5): 333–340.

Publications from PARADIGM-HF 2018 to date……

Title	Journal
Sacubitril/valsartan reduces serum uric acid concentration, an independent predictor of adverse outcomes in PARADIGM-HF.	Eur J HF
Effect of sacubitril/valsartan on recurrent events in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF).	Eur J HF
Incidence, Predictors, and Outcomes Associated With Hypotensive Episodes Among Heart Failure Patients Receiving Sacubitril/Valsartan or Enalapril: The PARADIGM-HF Trial	Circ-HF
Effects of Sacubitril/Valsartan on Physical and Social Activity Limitations in Patients With Heart Failure: A Secondary Analysis of PARADIGM-HF	JAMA Cardiol
Renal Effects and Associated Outcomes During Angiotensin-Neprilysin Inhibition in Heart Failure.	**JACC-HF**
Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system	**Lancet diabetes**
Independent Prognostic Value of Serum Soluble ST2 Measurements in Patients With Heart Failure and a Reduced Ejection Fraction in PARADIGM-HF	Circ-HF
Angioedema in heart failure patients treated with sacubitril/valsartan or enalapril in PARADIGM-HF	Int J Cardiol.

Slower progression of renal dysfunction with sacubitril/valsartan compared with enalapril

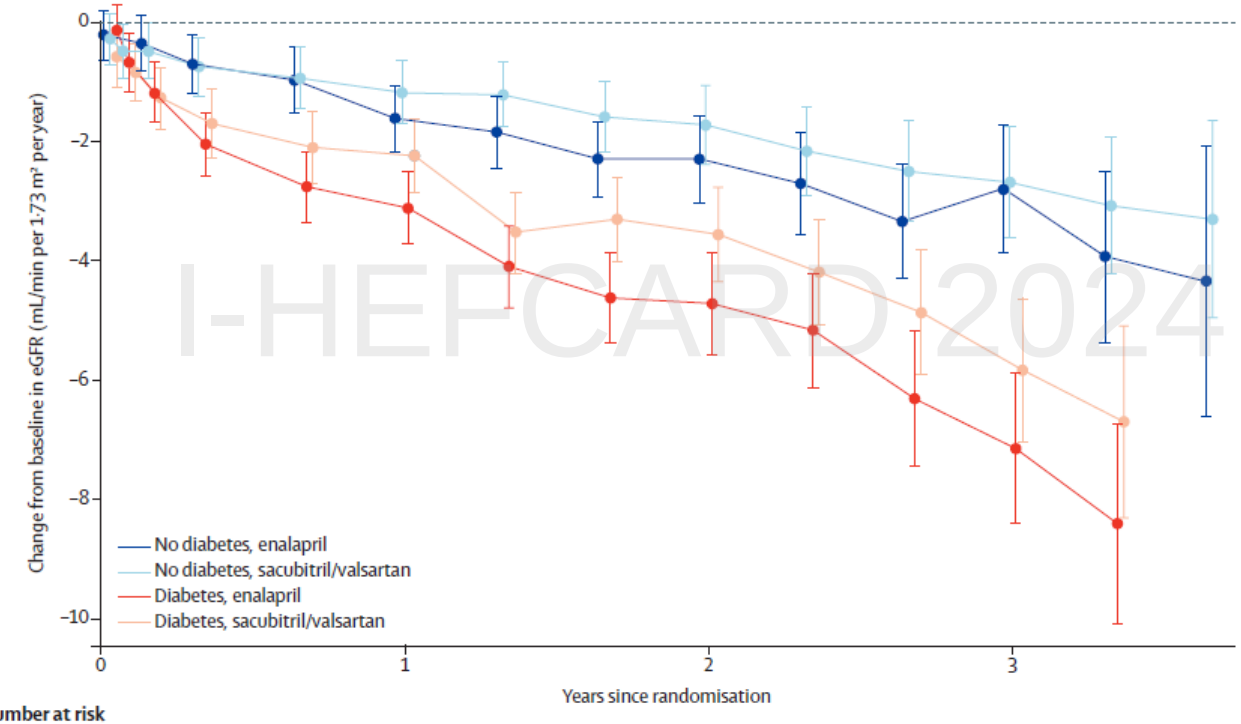
- Rate of decline in eGFR was slower with sacubitril/valsartan than enalapril, over a period of 44 months (sacubitril/valsartan -5.4 ±1.0 vs. enalapril -6.8±1.0 mL/min/1.73 m^2
- Slope of eGFR: sacubitril/valsartan -1.14 vs. enalapril -1.53 mL/min/1.73 m^2/year (P=0.0047)



Damman et al. JACC:HEART FAILURE 2018;6(6):489-98

ARNI : Slower eGFR progression in HFrEF patient with Diabetes Mellitus vs. ACEi

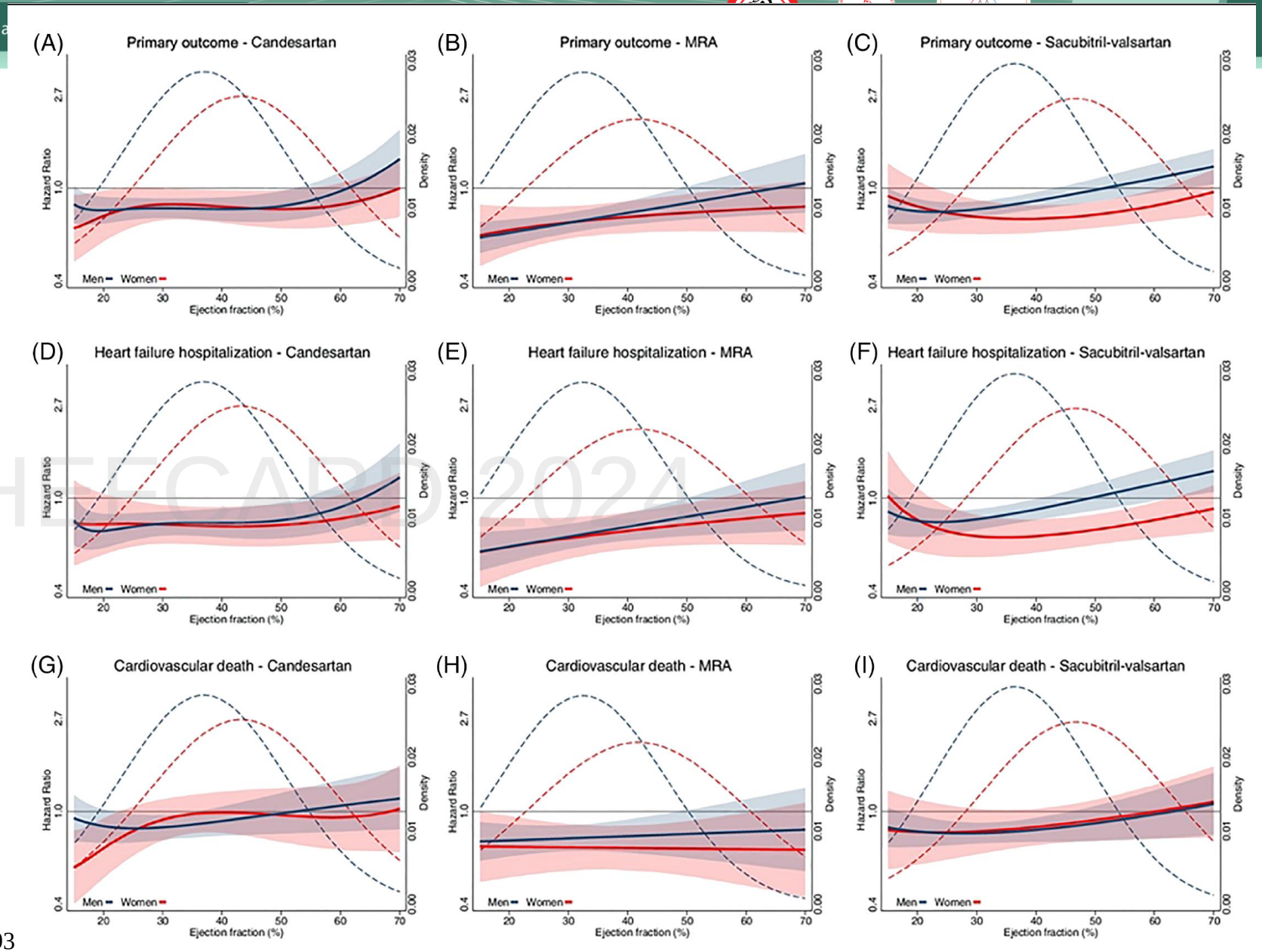
Change in eGFR in patients with and those without diabetes based on treatment assignment



Number at risk			
No diabetes, sacubitril/valsartan	1969	1425	672
No diabetes, enalapril	1937	1344	667
Diabetes, sacubitril/valsartan	1566	1101	504
Diabetes, enalapril	1557	1086	502

Packer, et al. Lancet Diabetes Endocrinol 2018.
http://dx.doi.org/10.1016/S2213-8587(18)30100-1

Variation of Treatment Effect with LVEF in Heart Failure



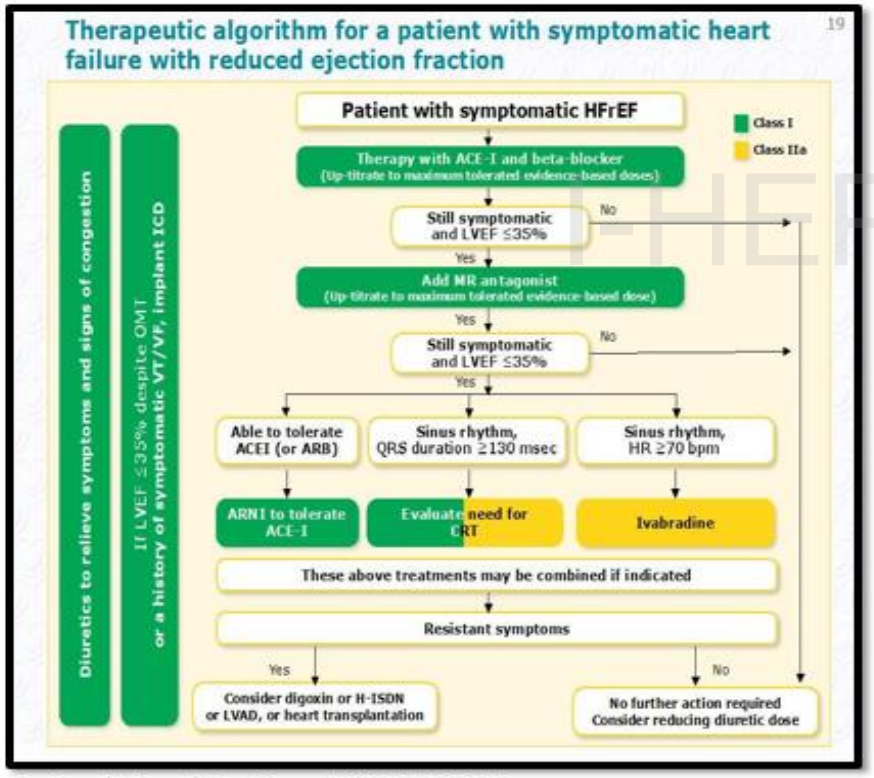
Lorenzo Stretti et al. ESC Heart Failure 2021; 8: 4370–4393

New Sequencing Approach: From Stepwise to Comprehensive 4 Pillars Heart Failure Treatment

European Heart Journal (2016) 37, 2129–2200
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

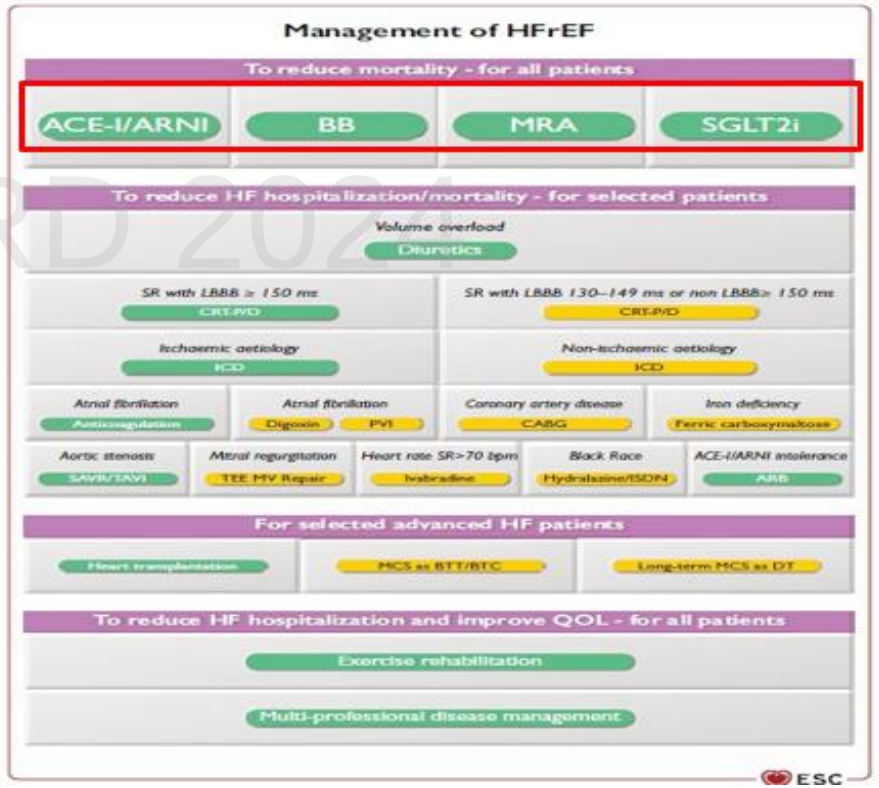
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure



ESC European Society of Cardiology
European Heart Journal (2021) 00, 1–128
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure



1. Ponikowski P et al. Eur J Heart Fail 2016;18:891
2. ESC HF Guideline 2021, European Heart Journal (2021) 00, 1128

The 4th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

Review Article OPEN ACCESS

In-hospital Initiation and Up-titration of Guideline-directed Medical Therapies for Heart Failure with Reduced Ejection Fraction

Zachary L Cox, Shuktika Nandkeolyar, Andrew J Johnson, JoAnn Lindenfeld, Aniket S Rali

Table 1: Common Initiation and Goal Doses of Guideline-directed Medical Therapy

Medication	Initial Dose	Goal Dose	Titration Comments*	All-cause Mortality, HR [95% CI]†	Mortality Relative Risk Reduction[81]
Angiotensin-Converting Enzyme Inhibitors					
Captopril	6.25 mg 3 times daily	50 mg 3 times daily	Titrate every few days in-hospital and weekly as an outpatient	0.89 [0.82–0.96]	17%
Enalapril	2.5 mg twice daily	10 mg twice daily			
Lisinopril	2.5 mg daily	40 mg daily			
Ramipril	1.25 mg daily	10 mg daily			
Angiotensin Receptor Blocker					
Candesartan	4 mg daily	32 mg daily	Titrate every few days in-hospital and weekly as an outpatient	0.95 [0.88–1.02]	17%
Losartan	25 mg daily	150 mg daily			
Valsartan	40 mg twice daily	160 mg twice daily			
Angiotensin Receptor–Neprilysin Inhibitor					
Sacubitril/valsartan	24/26 mg–49/51 mg twice daily	97/103 mg twice daily	Titrate every week	0.75 [0.66–0.85]	16%‡
β-blockers					
Bisoprolol	1.25–2.5 mg daily	10 mg daily	Titrate every 2 weeks	0.78 [0.72–0.84]	35%
Carvedilol	3.125 mg twice daily	25–50 mg twice daily			
Metoprolol XL	25 mg daily	200 mg daily			
Mineralocorticoid Receptor Antagonists					
Spironolactone	12.5–25 mg daily	25–50 mg daily	Titration often not required	0.76 [0.67–0.85]	30%
Eplerenone	25 mg daily	25–50 mg daily			
Sodium–Glucose Cotransporter 2 Inhibitors					
Empagliflozin	10 mg daily	10 mg daily	Titration not required	0.88 [0.78–0.99]	17%
Dapagliflozin	10 mg daily	10 mg daily			
ARNI + BB + MRA + SGLT2I Quadruple Therapy					
ARNI + BB + MRA + SGLT2I				0.39 [0.31–0.49]	74%

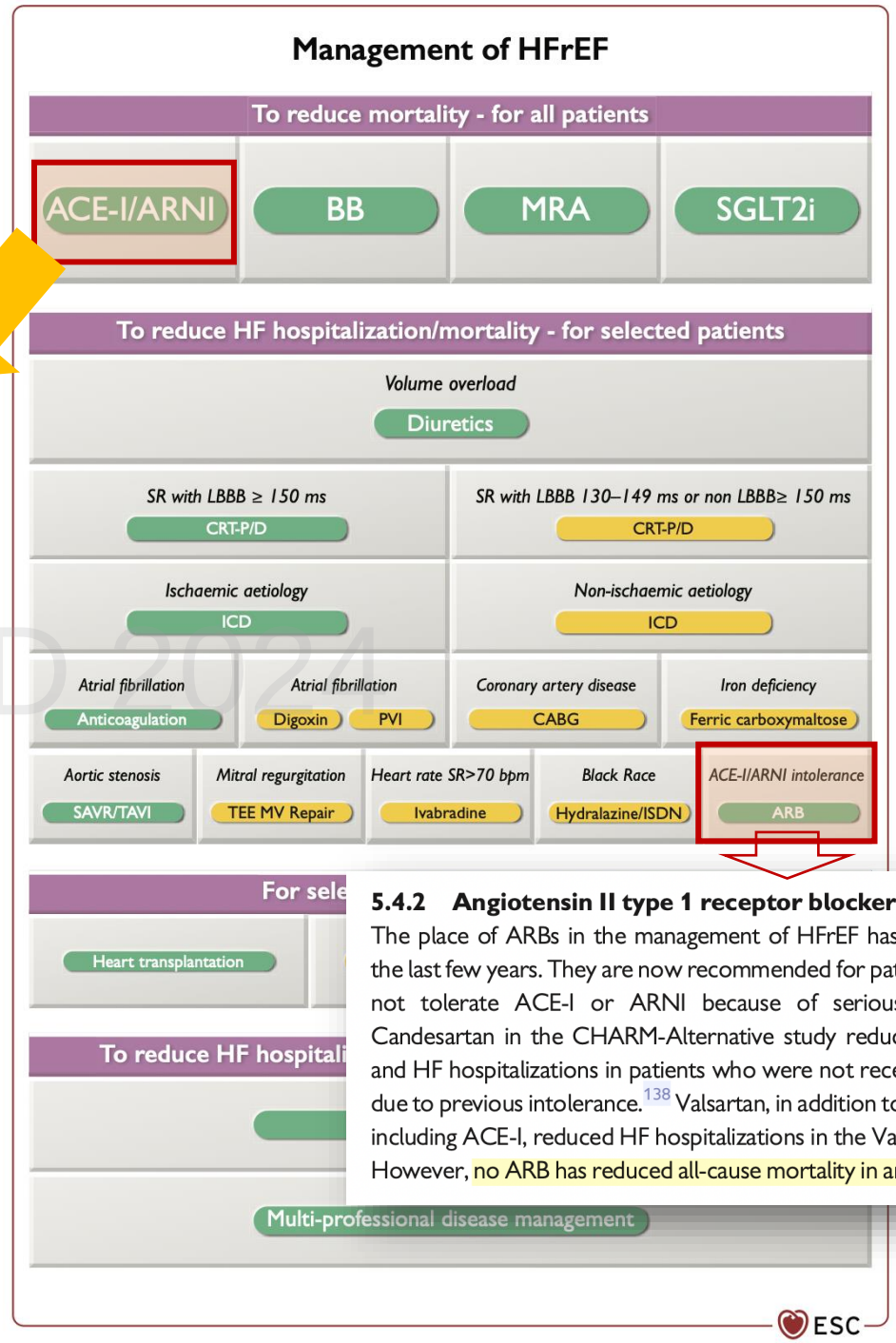
*Titration should be as tolerated and guided by clinical parameters. †HR for all-cause mortality relative risk reduction compared with placebo from source: Tromp et al.[82] ‡Replacing ACEI/ARB.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; BB = β-blocker; MRA = mineralocorticoid receptor antagonist; SGLT2I = sodium–glucose cotransporter 2 inhibitor.

ESC Heart Failure Guideline 2021

Recommendations	Class	Level
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B

ACE-I = angiotensin-converting enzyme inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA= New York Heart Association.



5.4.2 Angiotensin II type 1 receptor blockers

The place of ARBs in the management of HFrEF has changed over the last few years. They are now recommended for patients who cannot tolerate ACE-I or ARNI because of serious side effects. Candesartan in the CHARM-Alternative study reduced CV deaths and HF hospitalizations in patients who were not receiving an ACE-I due to previous intolerance.[138] Valsartan, in addition to usual therapy, including ACE-I, reduced HF hospitalizations in the Val-HeFT trial.[147] However, no ARB has reduced all-cause mortality in any trial.

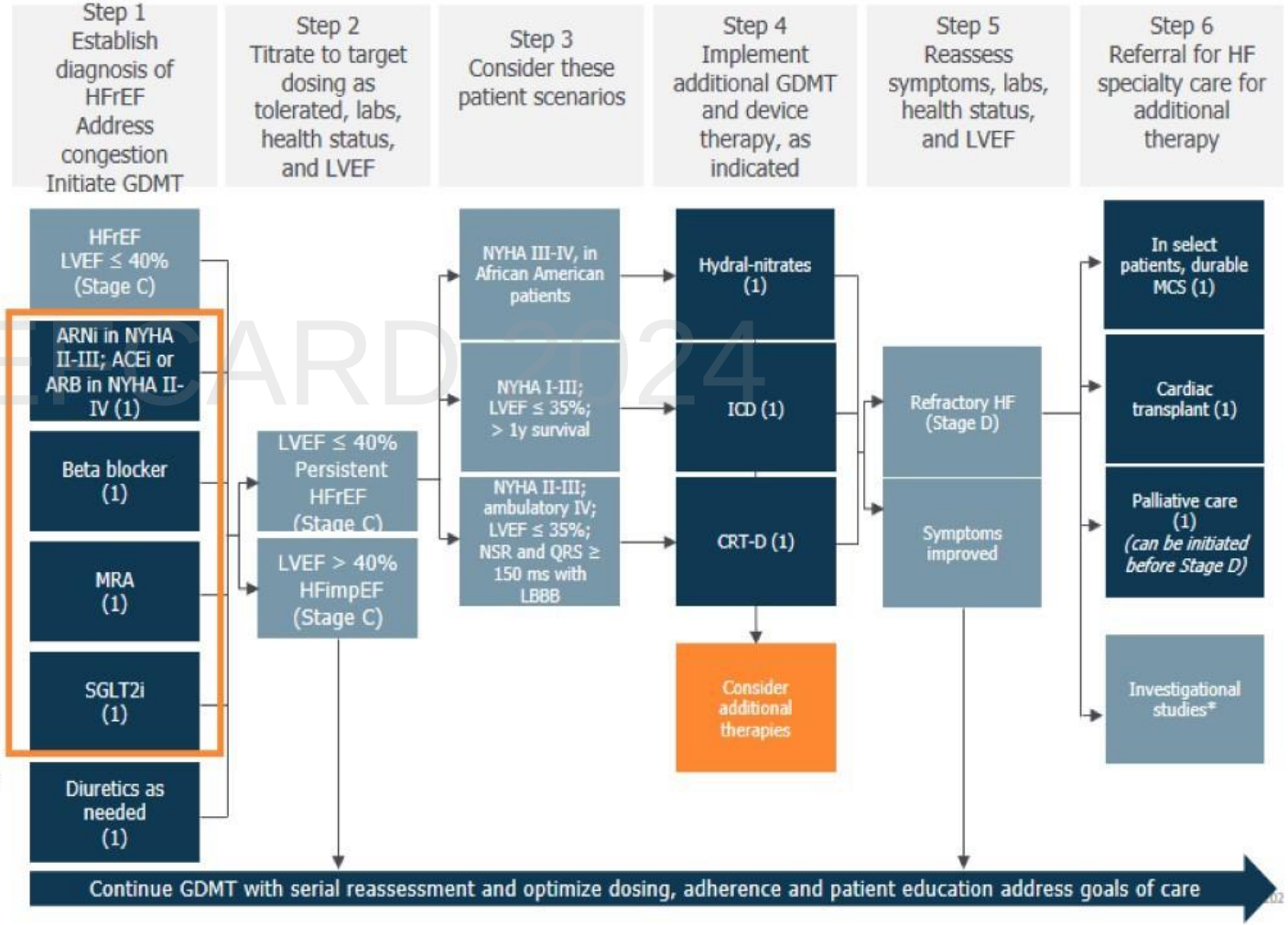
ESC HF Guideline 2021, European Heart Journal (2021) 00, 1128

HFrEF Management
2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

Step 1 medications may be started simultaneously at initial (low) doses recommended for HFrEF.

Alternatively, these medications may be started sequentially, with sequence guided by clinical or other factors, without need to achieve target dosing before initiating next medication.

Medication doses should be increased to target as tolerated.



CRT-D, Cardiac resynchronization therapy with a pacemaker and an ICD; ICD, implantable cardioverter-defibrillator; MCS, Mechanical circulatory support; MRA, aldosterone receptor antagonists; NSR, normal sinus rhythm; NYHA, New York Heart Association.

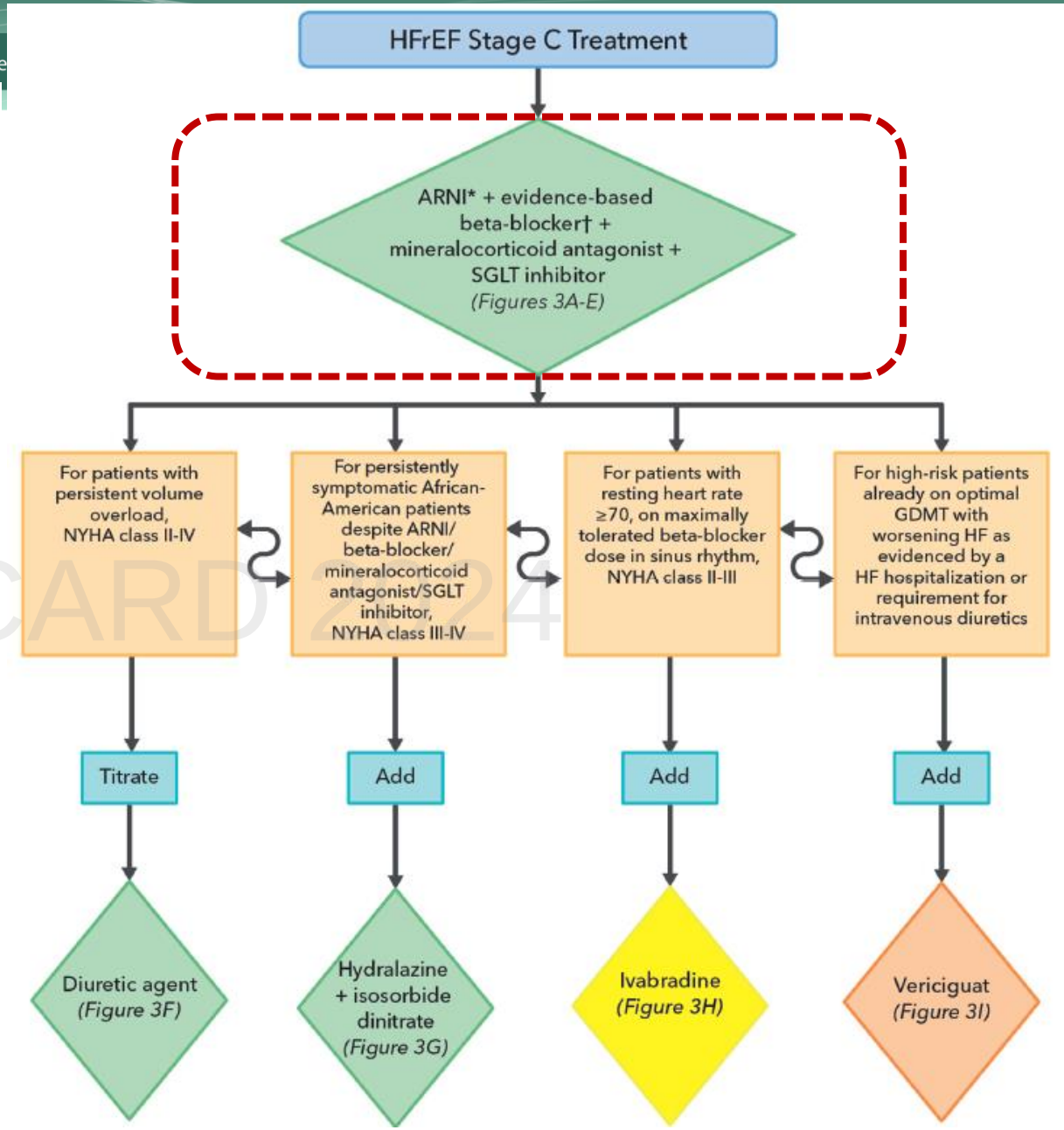
Heidenreich P, Bozkurt B, et al. Circulation. 2022;145:e895-e1032.

2024 ACC Expert Consensus Decision Pathway for Treatment of Heart Failure With Reduced Ejection Fraction

Treatment Algorithm for Guideline-Directed Medical Therapy

ACE inhibitors/ARBs should only be considered in patients with contraindications, intolerance, or inaccessibility to ARNI

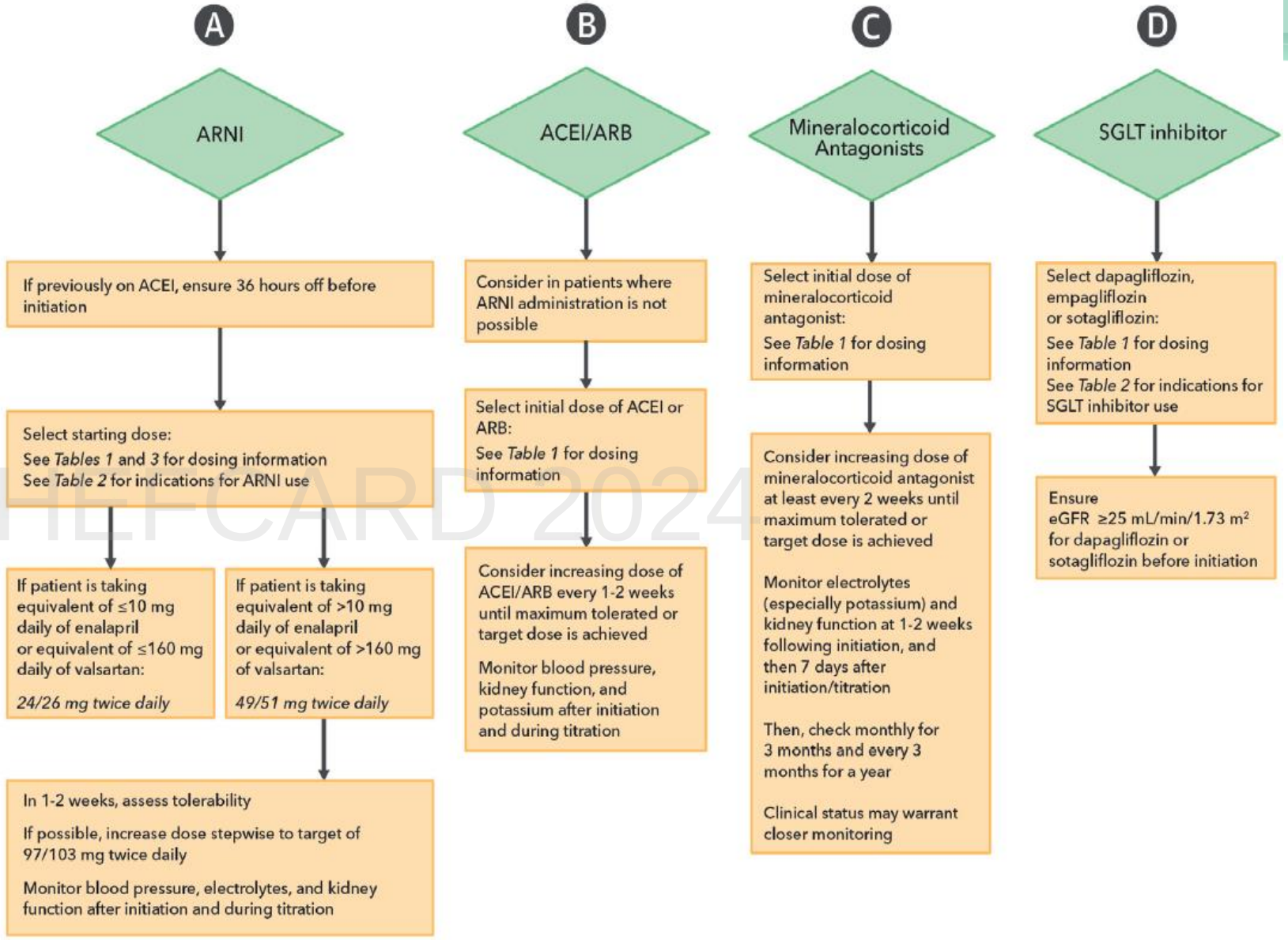
Colors correspond to ACC/AHA Class of Recommendation. Green = Class 1 (strong); Yellow = Class 2a (moderate); Orange = Class 2b (weak).



Maddox et al. ACC Expert Consensus Decision Pathway for Treatment of HFrEF

2024 ACC Expert Consensus Decision Pathway for Treatment of Heart Failure With Reduced Ejection Fraction

GDMT in the ECDP for Chronic HF



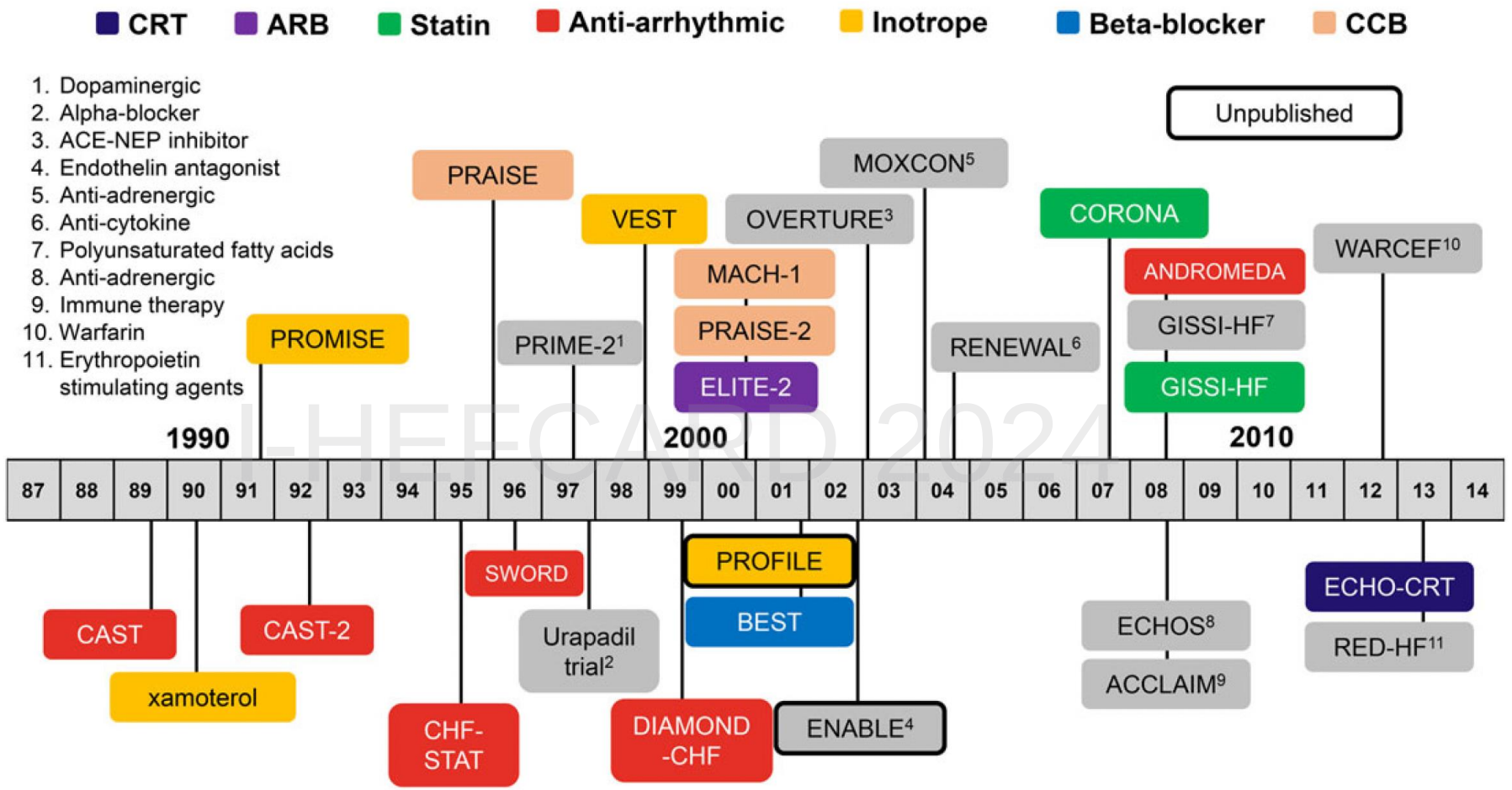
- ARNIs are the preferred renin-angiotensin system inhibitor and should be used as first-line therapy whenever possible.
- For patients in whom ARNI administration is not possible, an ACE inhibitor/ARB is recommended

Maddox et al. ACC Expert Consensus Decision Pathway for Treatment of HFrEF

Take Home Messages

- Heart failure (HF) is a progressive condition with intermittent acute decompensation leading to poor prognosis despite established GDMT.
- A paradigm of HF therapy has been shifted over last four decades.
- Until the early 1970s, HF was empirically managed, then was managed with the hemodynamic concept until the early 1980s and has been shifted to the neurohormonal paradigm since the late 1980s until recently.
- From PARADIGM-HF, Transition, Pioneer HF study and multiple publication that relate to ARNI have proved to strengthening our understanding that ARNI was superior to Enalapril in:
  - Reducing 20% CV mortality and first hospitalization of HF
  - Well tolerated safety profile
  - Reducing of intensive care burden
  - Positive effect on biomarker
  - Superiority of sub-optimal dose efficacy compared to equal dose of enalapril
  - Effect on blood glucose level in HFrEF patient with diabetes
  - Slowing the progression of renal dysfunction
- From latest guidelines, ARNIs are the preferred RAAS Blocker and should be used as first-line therapy whenever possible

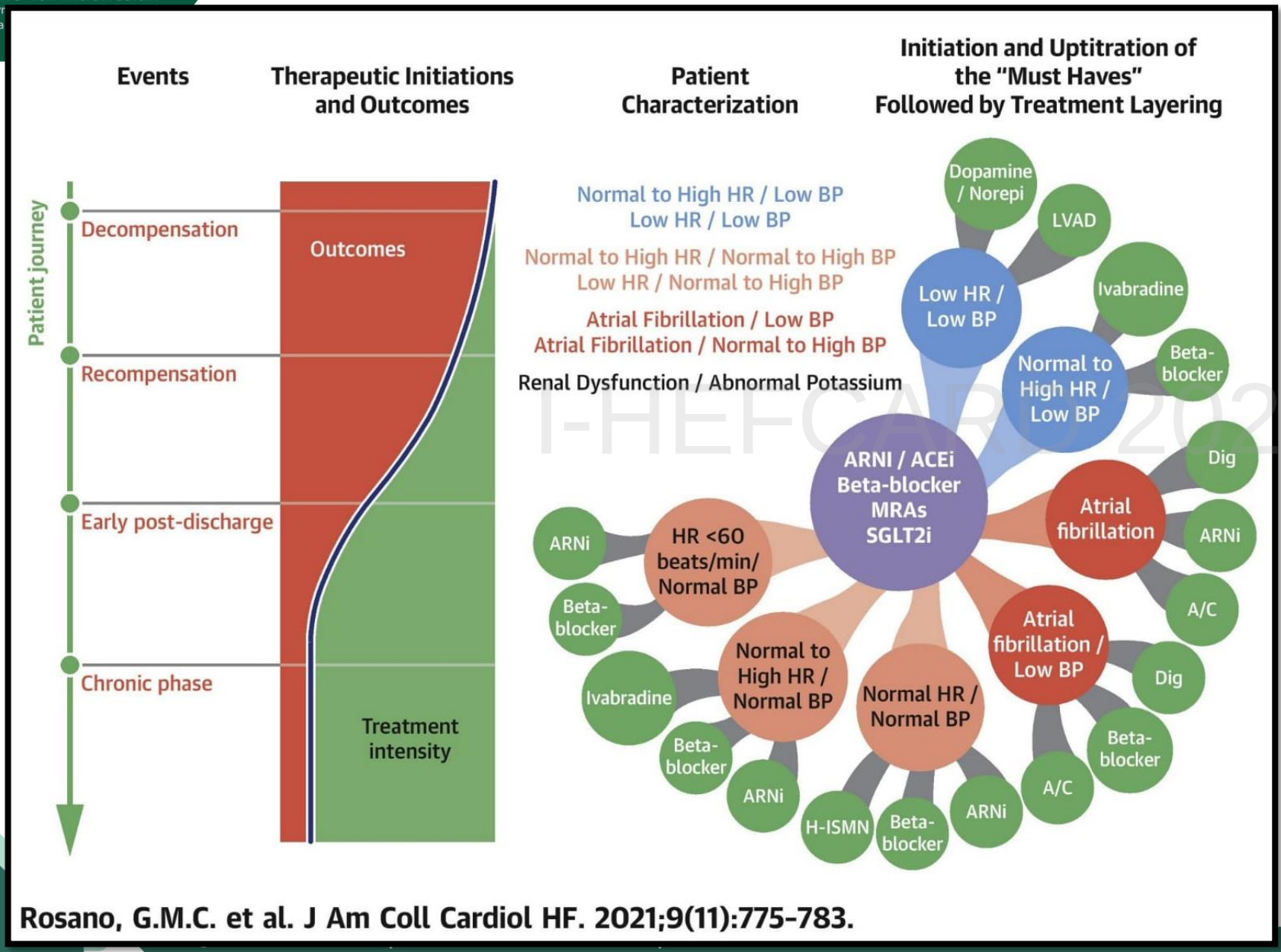
Thank You



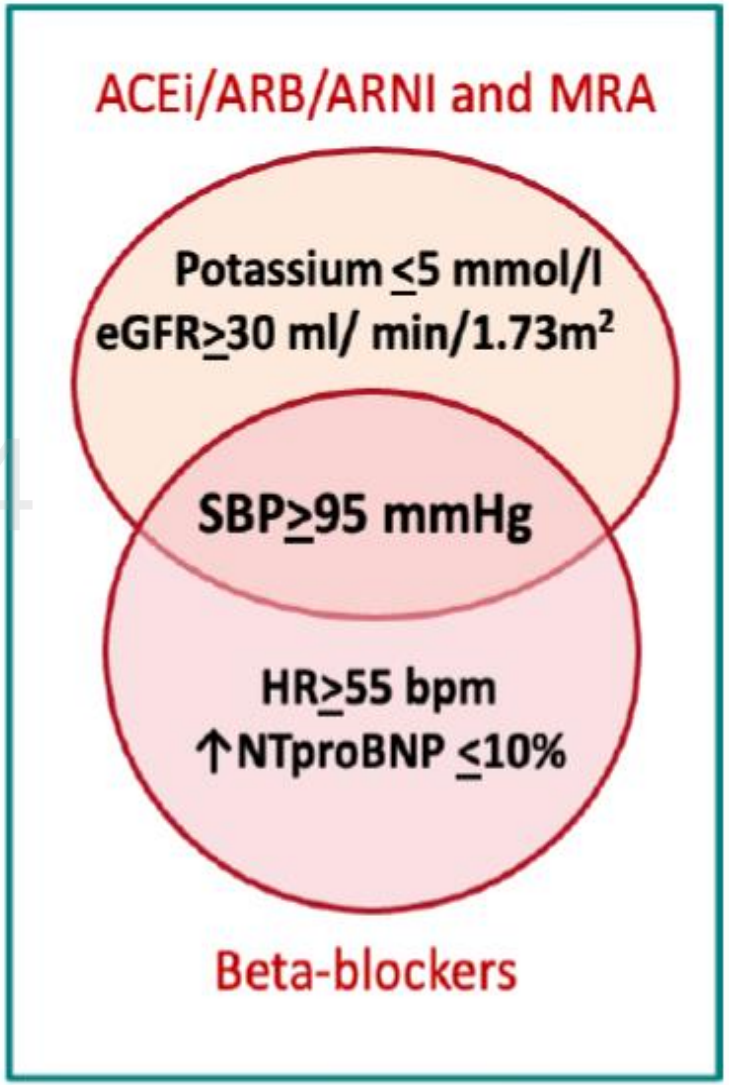
Heart Failure Trials: the disappointments: 1987–2013

John J.J.V. McMurray. European Heart Journal (2015) 36, 3467–3470

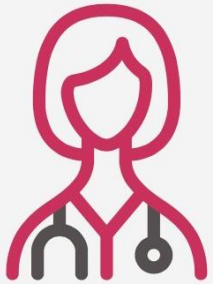
Patient Profiling in Heart Failure for Tailoring Medical Therapy



Rosano, G.M.C. et al. J Am Coll Cardiol HF. 2021;9(11):775-783.

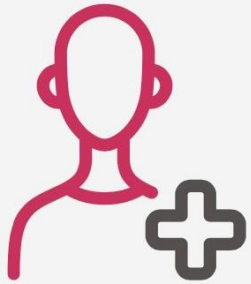


Factors Influencing Limited Adherence To GDMT



Physician:

1. Lack of awareness
2. Focus on treating symptoms
3. Fear of adverse effects



Patient:

1. Age
2. Frailty and sensitivity
3. Intolerance and contraindications

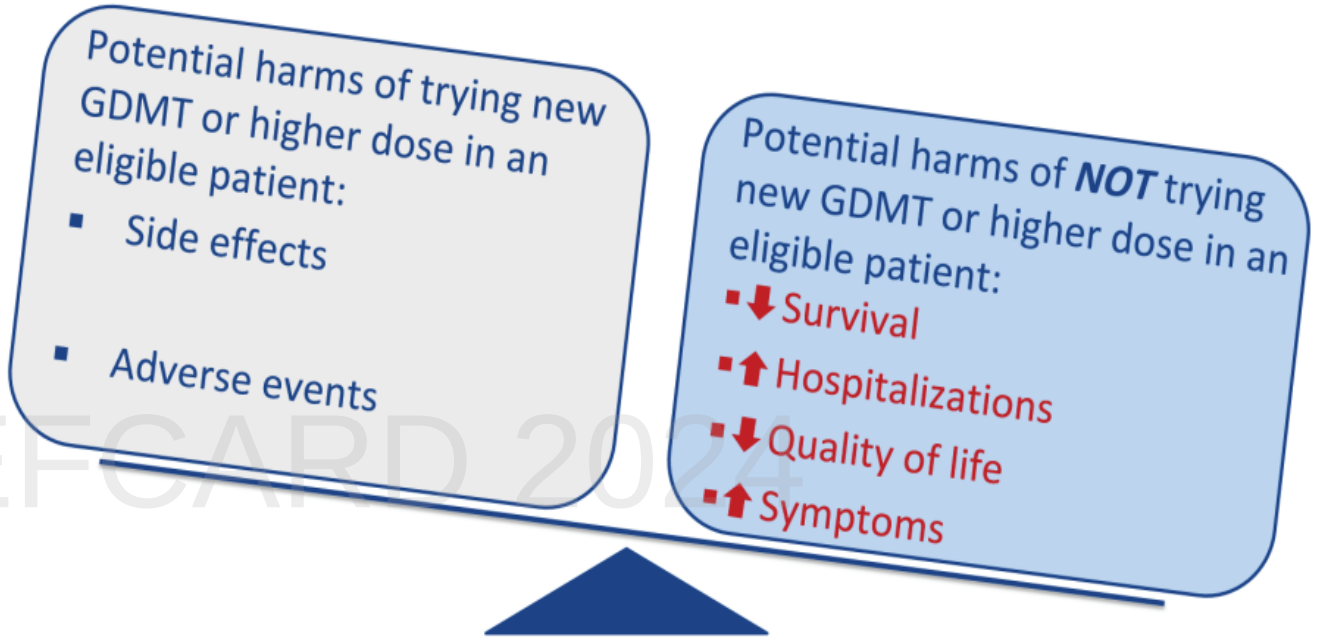
Non-medical:

1. High costs
2. Limited access

Komajda M, et al. Eur J Heart Fail. 2016;18(5):514-22

HOW SOON and HOW FAST

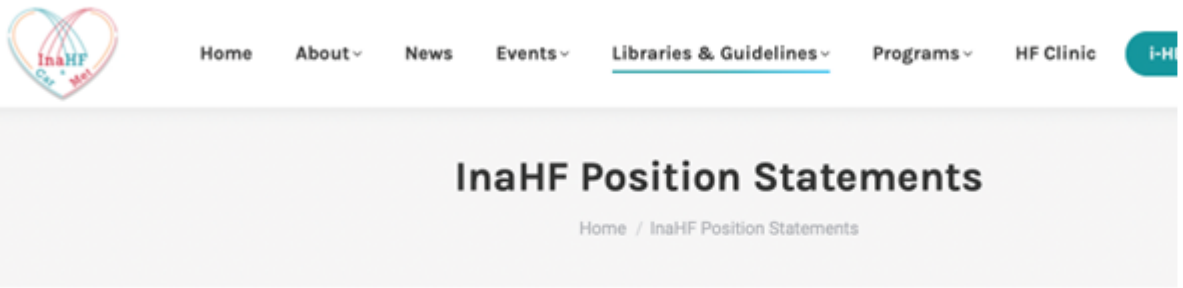
The Risks of Guideline-Directed Medication Changes in HFrEF



Every visit/every setting is an opportunity to initiate and escalate GDMTs, as tolerated

- New-onset heart failure ≠ "low risk"
- "Stable" outpatient heart failure ≠ "low risk"
- Hospitalized heart failure ≠ "low risk"

Greene SJ, Fonarow GC. European Journal of Heart Failure (2021) 23, 1343–1345



2022; ARNI Restriction in National Coverage (JKN)

Link : https://inahfcarmet.org

WORKING GROUP ON HEART FAILURE AND CARDIOMETABOLIC DISEASE
INDONESIAN HEART ASSOCIATION
Kelompok Kerja Gagal Jantung dan Penyakit Kardiometabolik
Pengurus Pusat Perhimpunan Dokter Spesialis Kardiovaskular Indonesia
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Jl. Letjen S Parman Kav 87 Jakarta, 11420 – INDONESIA
Phone : +6221-5684085, 5684093, 5684111 (Ext 2409) Fax : +6221- 5684130, 5684230
E-mail : pokjahf@gmail.com website : www.inahfcarmet.org

REKOMENDASI PENGGUNAAN ARNI (Sacubitril-Valsartan) 2022

Berdasarkan Rekomendasi Tatalaksana Gagal Jantung 2020 Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI), salah satu pilihan terapi untuk pasien gagal jantung adalah *Angiotensin Receptor-Neprilysin Inhibitor* (ARNI) yang merupakan molekul tunggal Sacubitril-Valsartan yang telah terbukti dapat menurunkan morbiditas dan mortalitas pada gagal jantung dengan penurunan fraksi ejeksi ventrikel kiri (*HFrEF*, *Heart Failure reduced Ejection Fraction*, EF ≤ 40%).

Efisiensi dapat dilakukan melalui pembatasan penggunaan ARNI berdasarkan penerapan rekomendasi tersebut sehingga tidak akan terjadi utilisasi berlebih. Maka Kelompok Kerja Gagal Jantung PERKI memberikan usulan restriksi sebagai berikut:

a. ARNI dapat diinisiasi pada pasien gagal jantung fraksi ejeksi ventrikel kiri ≤ 40% dengan penggunaan ACEI/ARB yang telah mencapai dosis optimal sebelumnya, namun tetap bergejala (kelas fungsional) NYHA II-IV
b. Dosis inisial yang dianjurkan adalah 2x50 mg dan dapat ditingkatkan hingga dosis target 2x200 mg (yang merupakan dosis maksimal) sesuai studi PARADIGM
c. Dosis inisial yang lebih rendah yakni 2x25 mg dianjurkan untuk pasien dengan gangguan fungsi ginjal berat (eGFR < 30 ml/min/1.73 m^2), gangguan hepar derajat sedang (Kelas B Child-Pugh), serta pada tekanan darah sistolik < 100 mmHg. Naikkan dosisnya tiap 2-4 minggu hingga mencapai dosis target 2x200 mg bila pasien dapat mentoleransi
d. Evaluasi ekokardiografi dilakukan dalam 6 bulan pertama setelah inisiasi ARNI kemudian selanjutnya dilakukan setiap 1 tahun, kecuali jika pasien mengalami perburukan gejala atau penurunan kelas fungsional NYHA maka evaluasi ekokardiografi dapat dilakukan lebih cepat
e. Pada pasien dimana evaluasi ekokardiografi menunjukkan perbaikan fraksi ejeksi menjadi > 40%, dianjurkan untuk tetap memberikan ARNI (bila memungkinkan). Tetapi bila tidak memungkinkan (dimana ARNI harus diganti kembali menjadi ACEI/ARB), maka evaluasi ekokardiografi ulang dalam waktu minimal 6 bulan berikutnya atau jika pasien mengalami perburukan gejala atau penurunan kelas fungsional NYHA maka evaluasi ekokardiografi dapat dilakukan lebih cepat guna mengevaluasi apakah pasien memiliki rekomendasi yang kuat untuk mendapatkan ARNI kembali
f. Diberikan di fasilitas kesehatan (Faskes) tingkat 2 dan 3

Link : https://inahfcarmet.org

Pasien dengan FEVKi ≤40%

Obat utama, lakukan inisiasi dan titrasi hingga dosis optimal/toleransi

- Penghambat SRAA (urutan sesuai prioritas)*
  1. ACE-I
  2. ARNI
  3. ARB
- Penyekat reseptor beta
- Antagonis aldosteron
- Penghambat SGLT2**
- Diuretik loop (bila ada tanda dan gejala kongesti)

Obat/alat tambahan digunakan sesuai indikasi komorbiditas

- Irama sinus & laju jantung > 70 per menit: ivabradine
- Fibrilasi atrium: antikoagulan
- Defisiensi besi: *ferric carboxymaltose*
- Etiologi iskemik: revaskularisasi
- Penyakit jantung katup: perbaikan/penggantian katup
- Lebar kompleks QRS > 120ms: terapi resinkronisasi jantung
- Menurunkan kejadian henti jantung mendadak: defibrillator intrakardiak

- Rehabillitasi Jantung
- Penanganan tim multidisiplin untuk kontrol faktor risiko dan komorbiditas

Evaluasi klinis (tanda dan gejala kongestif) & ekokardiografi (dalam 6 bulan)[a]

Tidak terdapat perbaikan klinis/perburukan gagal jantung:
- Optimalisasi diuretik (penambahan dosis atau penggantian menjadi sediaan injeksi)
- Optimalisasi dosis obat gagal jantung
- Evaluasi dan kontrol faktor risiko serta komorbiditas
- Vericiguat**

Perbaikan klinis & fraksi ejeksi:
- Terapi dilanjutkan

*Pilih salah satu, sesuai prioritas ketersediaan
**Apabila tersedia
[a]Ekokardiografi evaluasi dilakukan dalam 6 bulan paska inisiasi pada pasien yang stabil secara klinis untuk mengevaluasi perbaikan klinis, evaluasi ekokardiografi selanjutnya dilakukan sesuai dengan kondisi klinis pasien

Gambar 4. 1 Algoritma tatalaksana HFrEF

Take Home Messages

Optimal management of patients with acute heart failure before discharge and in the early post- discharge phase is critical

Acute heart failure hospitalization presents an opportunity for implementation of therapy

Beneficial effects of GDMT start early after their initiation

All four fundamental GDMTs must first be started and then titrated to target doses as early as possible in patients with HF

In JKN era can cover 3 of 4 pillars of HF treatment: ARNI (or ACEi/ARB), BB, MRA

PIONEER is Complementary
to other Sac-Val studies in HFrEF patients

Patients at baseline	Hospitalized post-ADHF		Ambulatory CHF	
Study	LCZ696BUS01 PIONEER-HF	LCZ696B2401 TRANSITION	LCZ696B2314 PARADIGM-HF	LCZ696B2228 TITRATION
No. of Patients	N=887	N=1002	N=8442	N=498
Primary endpoint	Effects of S/V vs enalapril on changes in NT-proBNP levels	% of Patients achieving target dose in PRE- vs POST-discharge	Morbidity and mortality vs enalapril	Safety and tolerability 3-week vs 6-week up-titration S/V
Treatment duration	12 weeks	10 weeks + 16 weeks FU	27 months	11 weeks
Outpatients n (%)	0	0	8442 (100%)	442 (89%)
In-patients n (%)	887 (100%)	1002 (100%)	0	56 (11%)
ACEI/ARB naïve n (%)	459 (52%)	242 (24%)	0	33 (7%)
De novo n (%)	303 (34%)	286 (29%)	0	0

- **PIONEER-HF** reconfirms the **superiority** of **Sacubitrril/Valsartan over ACEi** as shown in PARADIGM-HF, now demonstrated in the **hospital setting** in a **wide range** of HFrEF patients **hemodynamically stabilized** after an acute decompensated HF event**,** including ACEi/ARB naive and newly diagnosed (*de novo*) patients
- In-hospital initiating of Sacubitril/Valsartan compared to enalapril leads to:
  - Significantly **greater** and **more rapid reductions in NT-proBNP**, an established biomarker for HF severity and prognosis
  - Significantly **greater reduction** of the risk of **serious clinical outcomes** soon after discharge: In a pre-specified, exploratory, *serious clinical composite endpoint*, risk of **death, HF rehospitalization**, **LVAD implantation, or listing for cardiac transplant** was reduced by **46%** compared with enalapril over 8 weeks. The risk reduction was driven by the reduction of risk of death and HF re-hospitalizations
- Complementary evidence from **PIONEER-HF** and **TRANSITION** reconfirms that **in-hospital initiation** of Sacubitril/Valsartan shortly after hemodynamic stabilization is **safe** and **well tolerated**
- **Both trials** establish **Sacubitril/Valsartan** as (new) **standard of care** for HFrEF patients after an acute decompensated HF event, irrespective of prior ACEi/ARB use, or prior HF diagnosis
- **Start Sacubitril/Valsartan prior to discharge / soon after stabilizatio**, and keep your patients with HFrEF home and better protected

TRANSITION & PIONEER-HF

*In-hospital / shortly after discharge ARNI initiation**

TRANSITION
ARNI open label (n=1'002)
PRE- vs POST-discharge Entresto initiation

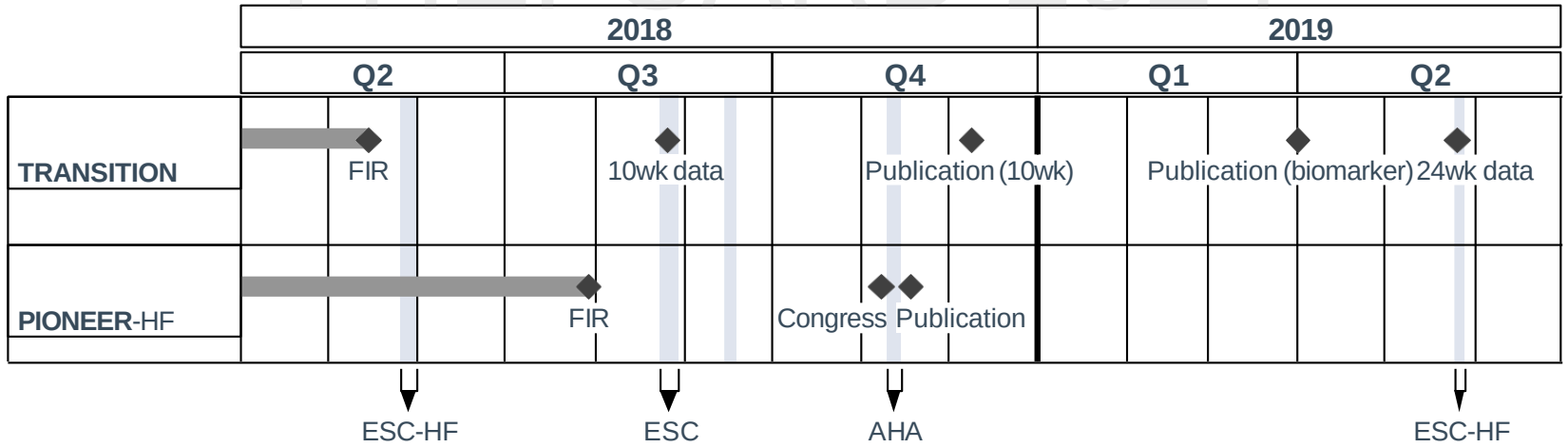
Primary endpoint: % patients achieving the target dose 200 mg b.i.d. 10 weeks after randomization

Key secondary endpoints: % pts achieving the 2 highest and any ARNI dose; % patients permanently discontinued due to AE during 10 weeks treatment

PIONEER-HF
ARNI vs. enalapril PRE-discharge initiation (n=887)

Primary endpoint: Change from baseline in NT-proBNP

Key secondary endpoint: Proportional change in NT-proBNP; Change in biomarkers of myocardial stress, cardiac fibrosis/remodeling, inflammation and tissue perfusion/injury; safety; exploratory composite clinical EP

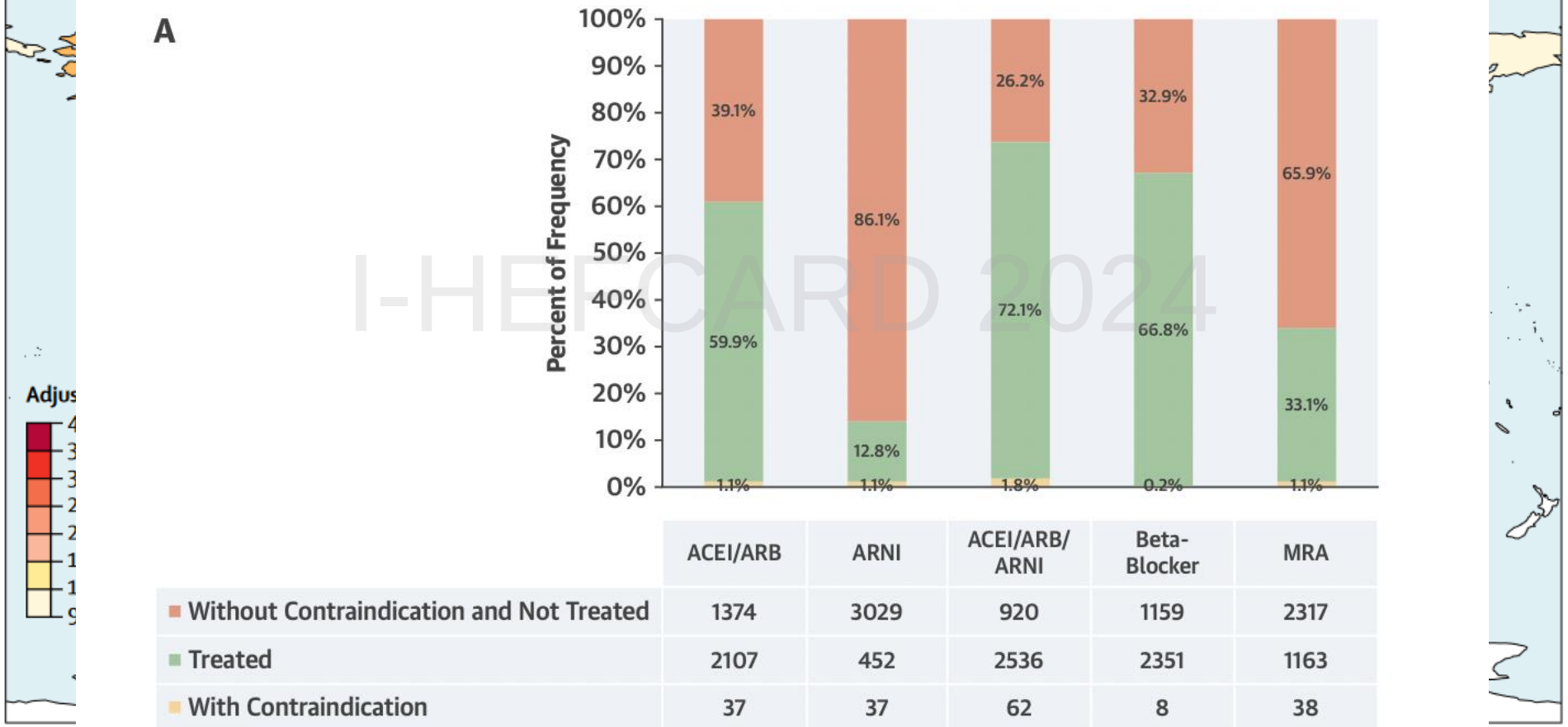


*after stabilization

Note: Publication timings are directional

The Facts are... Mortality Remains High

CENTRAL ILLUSTRATION Use and Dosing of Guideline-Directed Medical Therapy Among Patients With Chronic HFrEF in Contemporary U.S. Outpatient Practice



	ACEI/ARB	ARNI	ACEI/ARB/ ARNI	Beta-Blocker	MRA
Without Contraindication and Not Treated	1374	3029	920	1159	2317
Treated	2107	452	2536	2351	1163
With Contraindication	37	37	62	8	38

Figure 1: World map showing age, heart failure diagnosis, and New York Heart Association class-adjusted percentage of patients who died within 1 year

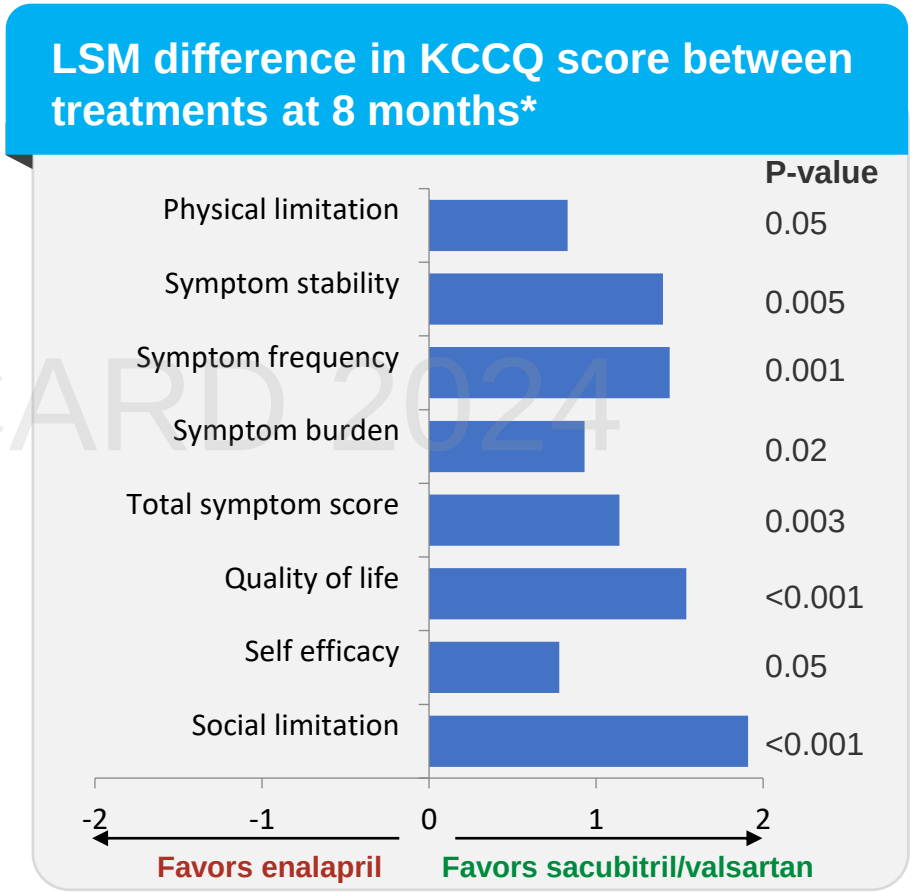
Lancet Glob Health 2020;8: e411–22

Publications from PARADIGM-HF 2018 to date……

Title	Journal
Sacubitril/valsartan reduces serum uric acid concentration, an independent predictor of adverse outcomes in PARADIGM-HF.	Eur J HF
Effect of sacubitril/valsartan on recurrent events in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF).	Eur J HF
Incidence, Predictors, and Outcomes Associated With Hypotensive Episodes Among Heart Failure Patients Receiving Sacubitril/Valsartan or Enalapril: The PARADIGM-HF Trial	Circ-HF
Effects of Sacubitril/Valsartan on Physical and Social Activity Limitations in Patients With Heart Failure: A Secondary Analysis of PARADIGM-HF	**JAMA Cardiol**
Renal Effects and Associated Outcomes During Angiotensin-Neprilysin Inhibition in Heart Failure.	JACC-HF
Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system	Lancet diabetes
Independent Prognostic Value of Serum Soluble ST2 Measurements in Patients With Heart Failure and a Reduced Ejection Fraction in PARADIGM-HF	Circ-HF
Angioedema in heart failure patients treated with sacubitril/valsartan or enalapril in PARADIGM-HF	Int J Cardiol.

Sacubitril/valsartan vs enalapril significantly improved most KCCQ domains* in surviving patients

- Differences between the treatments in score changes from baseline at 8 months favored sacubitril/valsartan vs enalapril for all KCCQ domains
- Improvements in all scores with sacubitril/valsartan treatment
- Decline# in most of the KCCQ domains were observed in the enalapril treatment group



A prespecified HRQoL efficacy measure of PARADIGM-HF in surviving patients
*Improvements were noted in all the KCCQ domains except in symptom stability
#Decline in symptom stability scores observed in both treatment groups was significantly higher in the enalapril treatment group (a 4.3-point decline) than that observed in sacubitril/valsartan group (2.9-point decline)

KCCQ, Kansas City Cardiomyopathy Questionnaire,
LSM, least squares mean

Lewis E et al. *Circ Heart Fail*. 2017;10:e003430

Link : https://inahfcarmet.org

Pasien dengan FEVKi ≤40%

Obat utama, lakukan inisiasi dan titrasi hingga dosis optimal/toleransi

- Penghambat SRAA (urutan sesuai prioritas)*
  1. ACE-I
  2. ARNI
  3. ARB
- Penyekat reseptor beta
- Antagonis aldosteron
- Penghambat SGLT2**
- Diuretik loop (bila ada tanda dan gejala kongesti)

Obat/alat tambahan digunakan sesuai indikasi komorbiditas

- Irama sinus & laju jantung > 70 per menit: ivabradine
- Fibrilasi atrium: antikoagulan
- Defisiensi besi: *ferric carboxymaltose*
- Etiologi iskemik: revaskularisasi
- Penyakit jantung katup: perbaikan/penggantian katup
- Lebar kompleks QRS > 120ms: terapi resinkronisasi jantung
- Menurunkan kejadian henti jantung mendadak: defibrillator intrakardiak

- Rehabillitasi Jantung
- Penanganan tim multidisiplin untuk kontrol faktor risiko dan komorbiditas

Evaluasi klinis (tanda dan gejala kongestif) & ekokardiografi (dalam 6 bulan)[a]

Tidak terdapat perbaikan klinis/perburukan gagal jantung:
- Optimalisasi diuretik (penambahan dosis atau penggantian menjadi sediaan injeksi)
- Optimalisasi dosis obat gagal jantung
- Evaluasi dan kontrol faktor risiko serta komorbiditas
- Vericiguat**

Perbaikan klinis & fraksi ejeksi:
- Terapi dilanjutkan

*Pilih salah satu, sesuai prioritas ketersediaan
**Apabila tersedia
[a]Ekokardiografi evaluasi dilakukan dalam 6 bulan paska inisiasi pada pasien yang stabil secara klinis untuk mengevaluasi perbaikan klinis, evaluasi ekokardiografi selanjutnya dilakukan sesuai dengan kondisi klinis pasien

Gambar 4. 1 Algoritma tatalaksana HFrEF