5th iHEF CARD

The 5th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

Indonesian Working Group on Heart Failure and Cardiometabolic Disease

WHFS World Heart Failure Society

HEART FAILURE SOCIETY (SINGAPORE)

# Hidden Complexity Behind the Myth of "Stable" HFrEF


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# Disclosure

- **This is a collaboration session with PT. NOVARTIS**
- Scientific speaker for :
  Servier, Dexa Medica, Boehringer Ingelheim (ZPT), Bayer, Astra Zeneca, Otsuka, Menarini, Medtronic, Merck, Abbott

# STABLE factual definition

GOAL SCORES LATEST COMPETITIONS INDIVISA MUNDIAL GOALSTUDIO

## Have Everton ever won the Premier League?

**Everton have won the English title nine times, but never in the Premier League era.**

Their last league triumph came in the 1986-87 season, under Howard Kendall. The Toffees finished nine points clear of second-placed Liverpool in a good season for Merseyside.

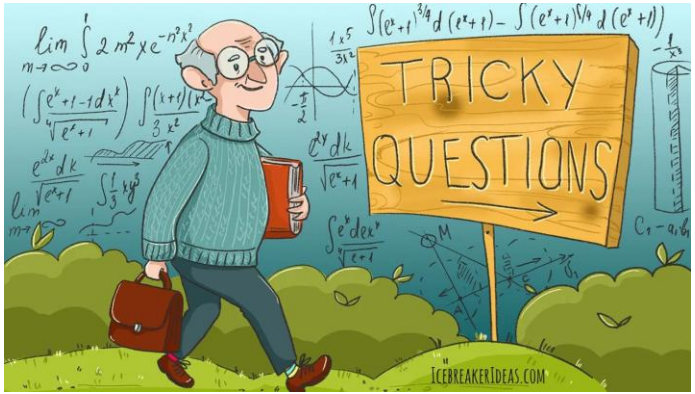


## Full list of Everton trophies & titles

| Competition | Year(s) won |
|---|---|
| First Division / Premier League | 1890-91, 1914-15, 1927-28, 1931-32, 1938-39, 1962-63, 1969-70, 1984-85, 1986-87 |
| Second Division / Championship | 1930-31 |
| FA Cup | 1905-06, 1932-33, 1965-66, 1983-84, 1994-95 |
| Charity Shield / Community Shield | 1928, 1932, 1963, 1970, 1984, 1985, 1986*, 1987, 1995 |
| European Cup Winners' Cup | 1984-85 |

**Trophy shared with Liverpool*

**30 years ago….**




- 43 years old male
- History of ACS in 2020; poor adherence
- NYHA fc III
- Crackles with pedal edema
- ECG QS anterior leads
- CXR cardiomegaly with pulmonary edema
- Lab Cr 1.34, NTproBNP 3435
- Echo EDD 58 / EF 23% / RWMA (+) / moderate MR / TAPSE 1.8

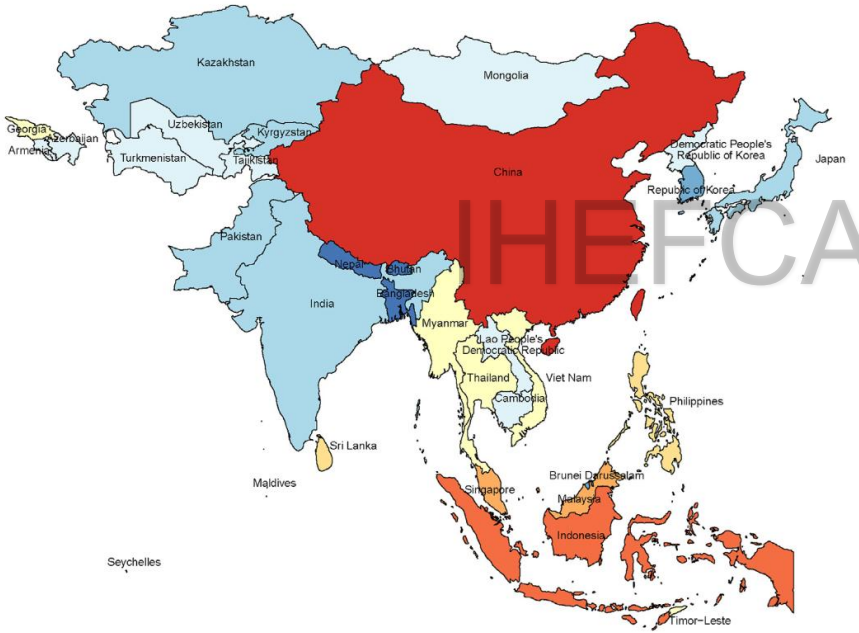


**How to initiate and optimize tx?**

- 51 years old male
- History of HF since 2021 (ICM non-revasc)
- NYHA fc III manageable to fc I-II
- BPs 108-123 mmHg; HR 68-76 bpm (monthly visit)
- No congestion; 6-mwt >300 m
- ECG SR, poor R wave V1-V5
- Echo EDD 62 / EF 32% / RWMA (+) / moderate MR / TAPSE 1.9 / E/A 1.7
- Current meds : ramipril 5 mg od, bisoprolol 5 mg od, spironolactone 25 mg od, dapa 10 mg od, statin

**Satisfy enough?**

# Age-Standardized Prevalence Rate of Heart Failure in Asia




**The 3 highest nations** in terms of ASR :

1. China (1,032.84)
2. Indonesia (900.90)
3. Malaysia (809.47)



**Indonesia:**

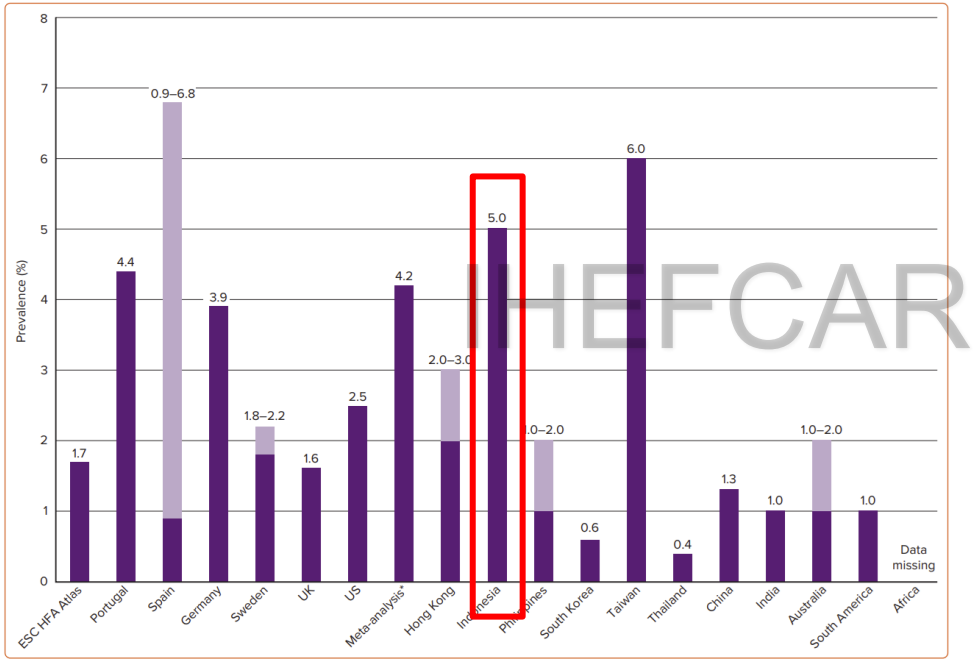
ASR 1990: 835.45

ASR 2019: 900.90

**7.83%**

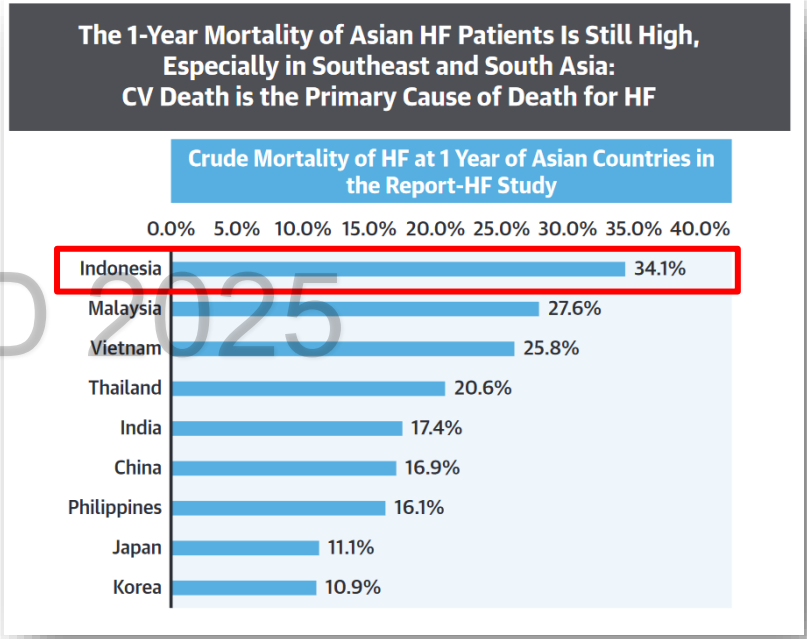
Feng J, et al. JACC: Asia. 2024;4(4):249–264.

# Prevalence of Heart Failure Worldwide




*Meta-analysis of studies from developed countries using echocardiographic case validation. ESC = European Society of Cardiology; HFA = Heart Failure Association.






Shahim et al. Cardiac Failure Review 2023;9:e11
Feng J, et al. JACC: Asia. 2024;4(4):249–264.

# Heart Failure across Asia

| 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 | | 35% | 68% | 52% | 37% | 37% | 44% | 45% | 32% | 54% | 46% |
| Valvular/rheumatic heart disease | | 18% | 29% | 20% | – | 14% | 8% | 19% | 18% | – | – |
| Cardiomyopathy (non-ischemic) | | 2% | 28% | 11% | – | 21% | 34% | 14% | 21% | – | – |
| Hypertensive heart disease | | 8% | 2% | 6% | – | 4% | 7% | 12% | 21% | – | 23% |
| Other causes[b] | | 2% | 5% | 7% | – | 11% | 7% | – | – | – | – |
| Hypertension | | 33% | 75% | | | | | | | 63% | 76% |
| Current smoking | | 28% | | | | | | | | – | – |
| Diabetes mellitus | | 37% | | | | | | | | 33% | 43% |
| Dyslipidemia | | 31% | | | | | | | | – | 44% |
| Overweight | | 47% | 25% | | | | | | | – | – |
| 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% | – |



**Indonesia: Younger, Male, *Overweight*, CAD, DM, hypertension**

Missing data are not available.

[a] In patients aged >85 years.

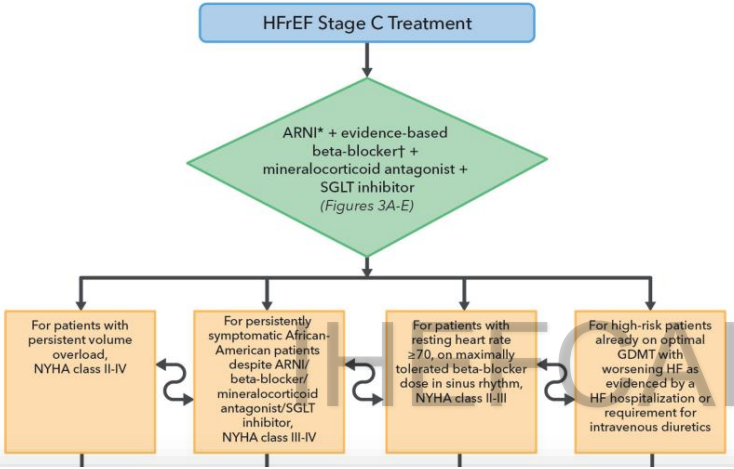
[b] Including tachycardia, congenital heart disease and cardiopulmonary heart disease.

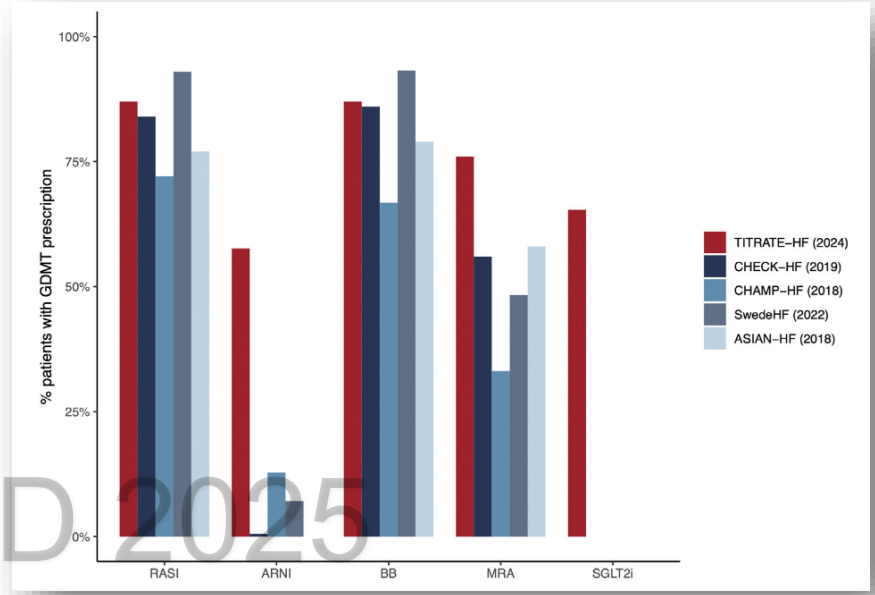
[c] COPD or asthma.



Reyes EB, et al. *Int J Cardiol*. 2016 Nov 15;223:163-167.
O'Gallagher, et al. *British Journal of Sports Medicine*. 2022

# Despite the guideline...





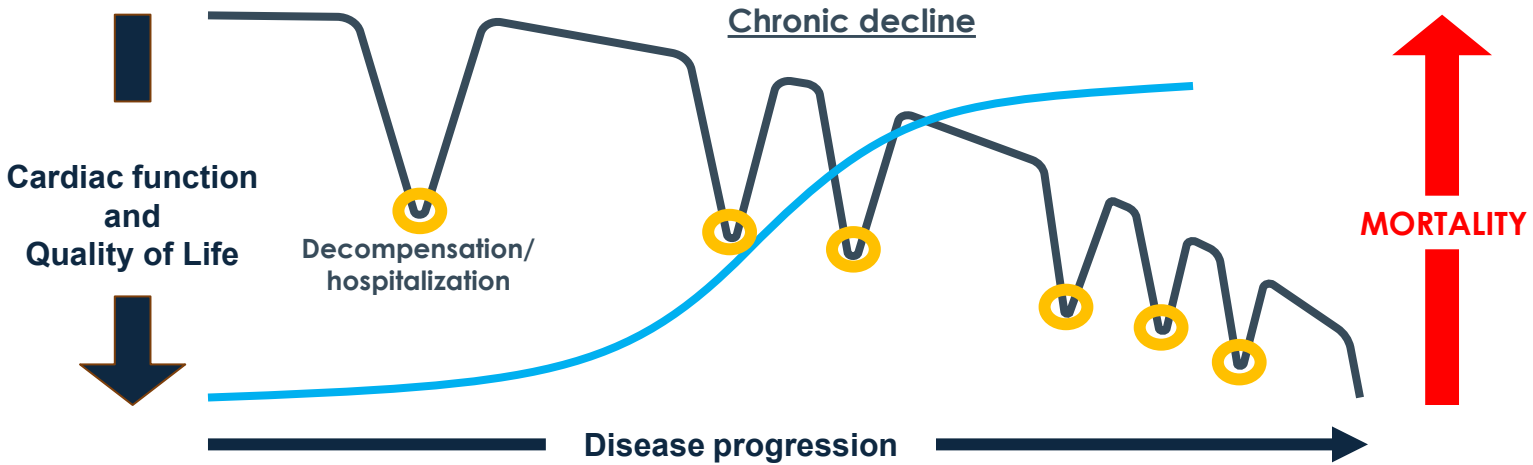

| | N | Mean age (years) | RASi | RASi td | BB | BB td | MRA | MRA td |
|---|---|---|---|---|---|---|---|---|
| CHAMP-HF | 2518 | 66.4 | 73.4% | 16.8% | 67.0% | 27.5% | 33.4% | 76.6% |
| CHECK-HF | 8360 | 72.3 | 84% | 43.6% | 86% | 18.9% | 56% | 52.0% |
| ASIAN-HF | 5276 | 59.6 | 77% | 17% | 79% | 13% | 58% | 29% |
| ESC-LT (Spanish) | 2834 | 65 | 92.6% | ACEi 16.2%/ARB 23.3% | 93.3% | 13.2% | 74.5% | 23.5% |
| QUALIFY | 7092 | 63.1 | 86.7% | ACEi 27.9%/ARB 6.9% | 86.7% | 14.8% | 69.3% | 70.8% |
| Savarese 2021 | 68,172 | 65–75 | - | ACEi 15%/ARB 10%/ARNI 30% | - | 12% | - | - |

*ACEi* angiotensin-converting enzyme inhibitor, *td* target dose, *ARB* angiotensin II receptor blocker, *ARNi* angiotensin receptor–neprilysin inhibitor, *BB* beta-blocker, *MRA* mineralocorticoid receptor antagonist

Maddox et al. JACC. 2024; 83(15)
Malgie et al. Heart Failure Reviews. 2023; 28:1221–1234
Malgie et al. European Journal of Heart Failure. 2024. doi:10.1002/ejhf.3267

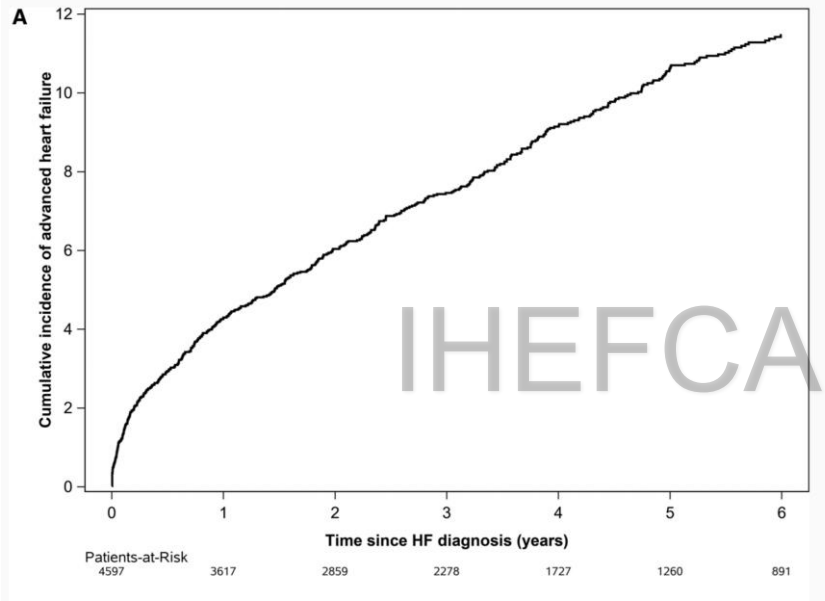
# HF is a chronic condition interspersed with acute episodes

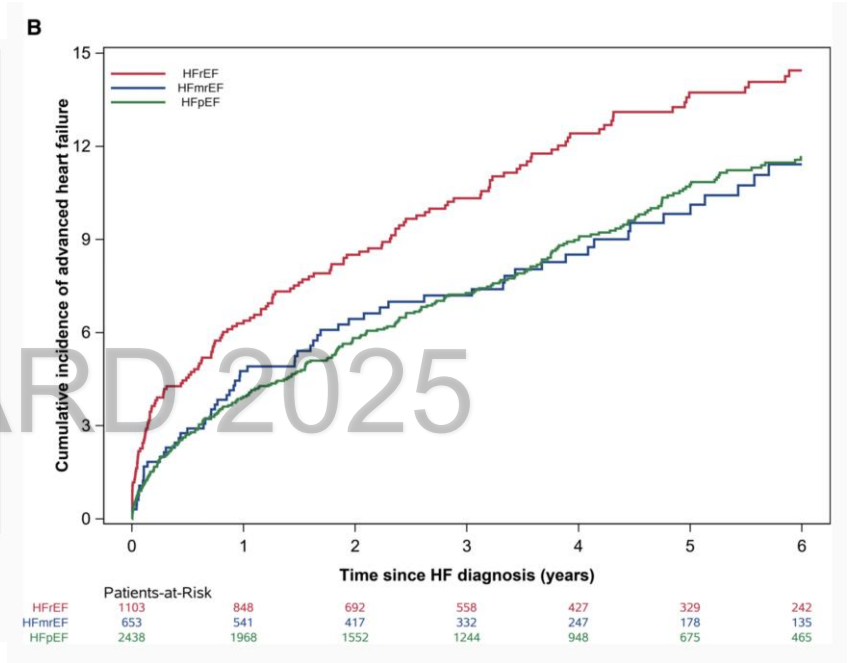
## Frequency of decompensation and risk of mortality increase, with acute events and sudden death occurring at any time




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

# Magnitude of the Problem

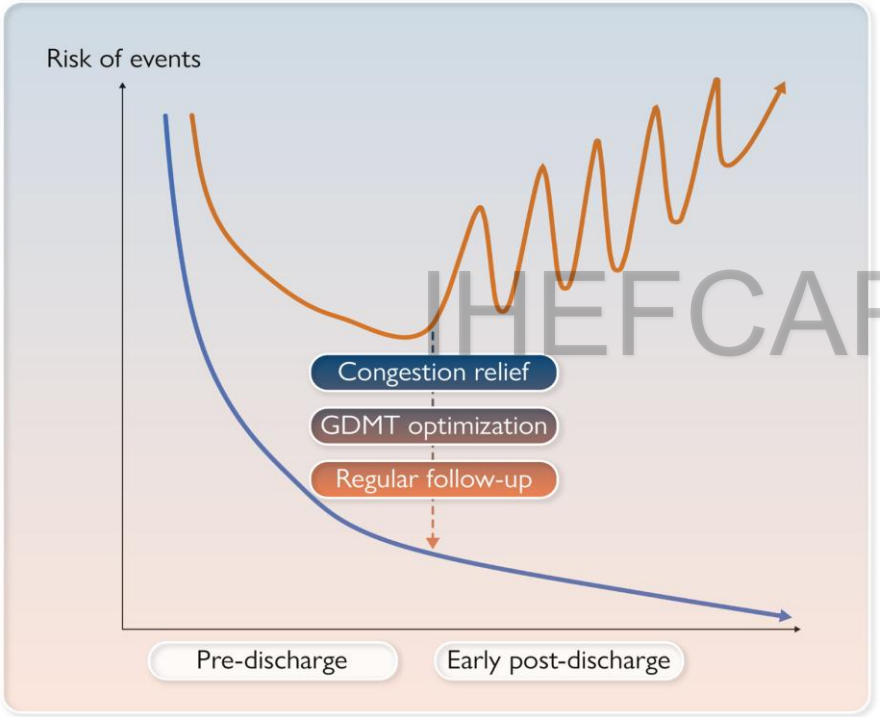





The **cumulative incidence of advanced HF** was 6.0% (5.4%–6.8%), 9.1% (8.3%–10.1%), and 11.5% (10.5%–12.5%) at 2, 4, and 6 years after incident HF diagnosis

Subramaniam AV, et al. Circulation: Heart Failure. 2022;15




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



**Key Points :**
Pre-discharge treatment
**initiation and optimization**

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

# LEARNING POINT



CORE - HF
Sebelas Maret COmprehensive Registry and rEsearch on Heart Failure

2023 Interim Analysis

# Drug Regiments

According to :

- 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure
- 2021 CCS/CHFS Heart Failure Guidelines Update
- 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

| DRUG CLASS | | | | HFrEF | | |
|---|---|---|---|---|---|---|
| | In | | t.)** | Initial | 3 Mo (Opt.)^ | 12 Mo (Opt.)^^ |
| ACE-Inhibitor | 8 | | 1%) | 86.7% | 82.6% (98.8%) | 76.0% (98.4%) |
| ARB | 1 | | 7%) | 8.9% | 11.0% (83.7%) | 17.6% (95.5%) |
| ARNI | 0.7% | 0.9% (100.0%) | 1.3% (100.0%) | 4.4% | 6.1% (54.2%) | 6.0% (93.3%) |
| Beta-Rec. Blocker | 97.1% | 99.1% (81.7%) | 98.7% (92.2%) | 98.5% | 99.5% (84.6%) | 99.6% (92.8%) |
| MRA | 23.5% | 34.5% (26.3%) | 39.7% (41.9%) | 48.7% | 65.0% (51.6%) | 70.4% (59.7%) |

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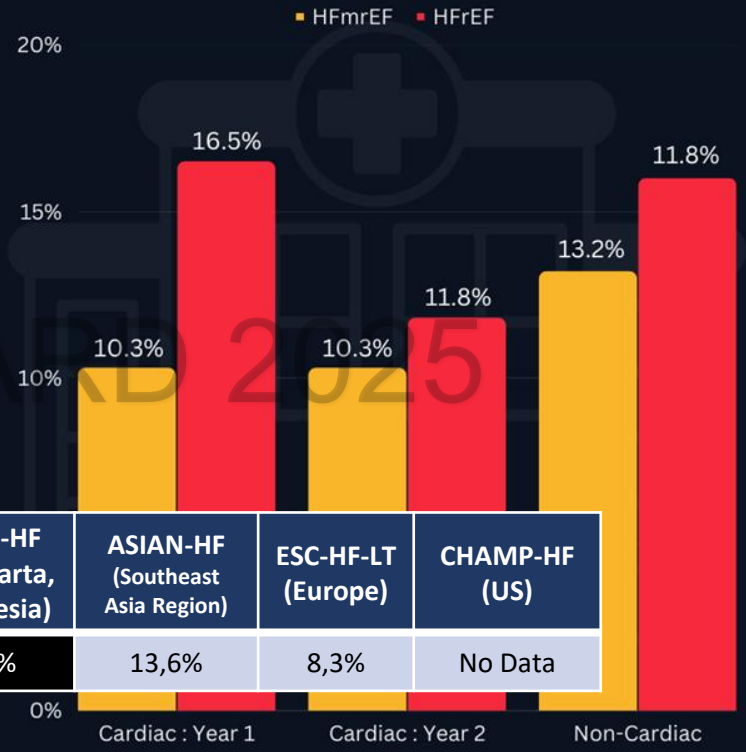
*110 Subjects ; **78 Subjects ; ^391 Subjects ; ^^250 Subjects

# Outcome

*2023 Interim Analysis*


| | CORE-HF (Surakarta, Indonesia) | ASIAN-HF (Southeast Asia Region) | ESC-HF-LT (Europe) | CHAMP-HF (US) |
|---|---|---|---|---|
| 1-y mortality | 7,2% | 13,6% | 8,3% | No Data |

Cummulative All-Cause Mortality

Rehospitalization

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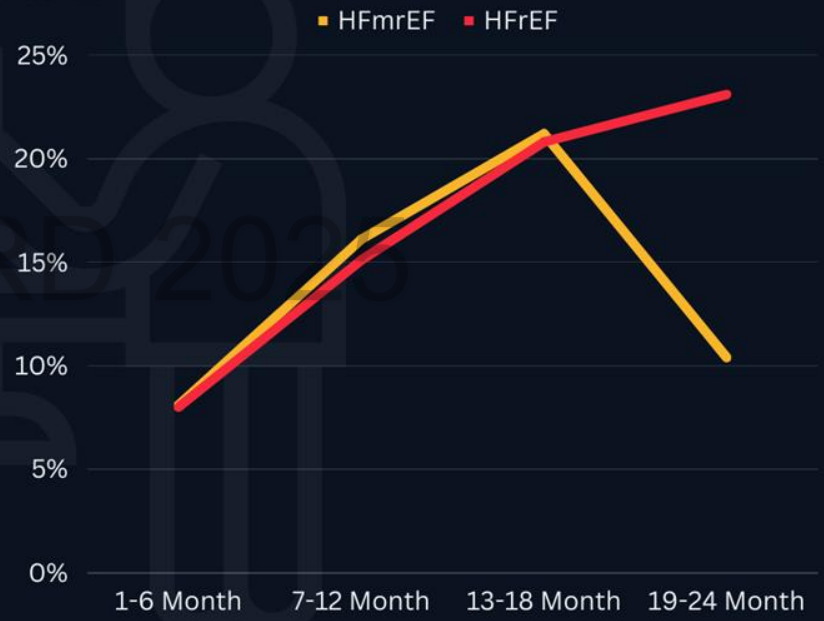
2023 Interim Analysis

# Follow-Up


Lost-to-Follow-Up

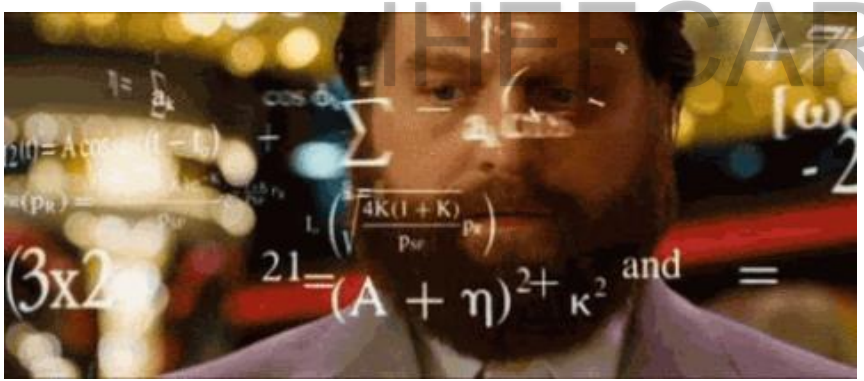
corehfrsuns@gmail.com

# Definition of clinically ‘stable’ CHF

A treated patient with **symptoms and signs** that have **remained generally unchanged** for at least 1 month is said to be **‘Chronic STABLE HF’**.

ESC Guidelines (2016) Eur Heart J; 37: 2129-2200.

**But it is not that simple!**



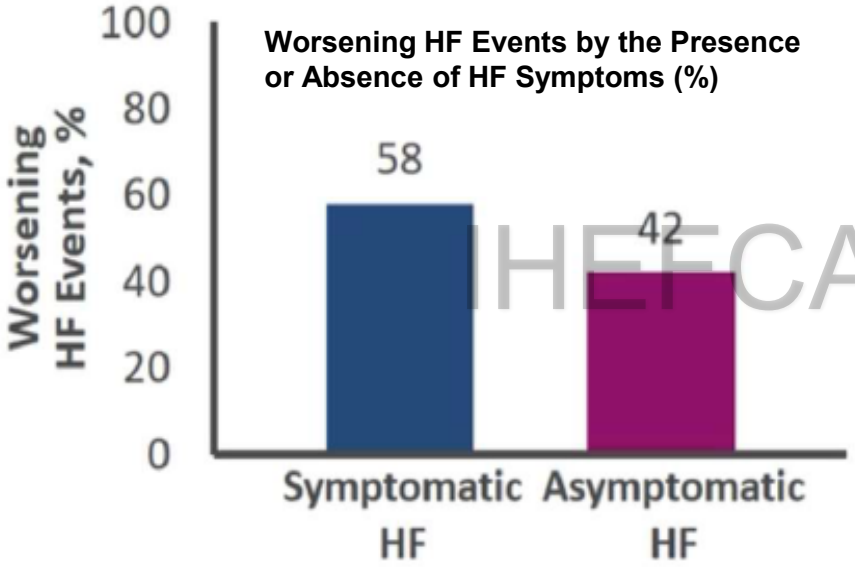



## Stability condition?

$$\kappa T\left(1+\frac{2B(1-u)}{(1-u)\sigma^2+uv^2}\right)<\frac{1}{e}$$

- Easier to meet stability condition the larger the volume $u$ or the infinitesimal variance $v^2$ of the short transfers

# Asymptomatic Worsening of HF




**Asymptomatic worsening was defined as :**
an event indicative of fluid retention by a clinician despite the absence of symptoms*

All events except one case, both in symptomatic and asymptomatic **worsening HF demonstrated elevated serum BNP**



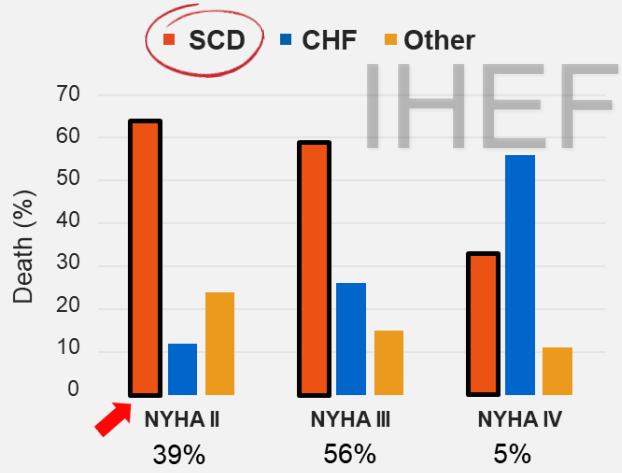
*Symptoms of worsening HF included dyspnea on exertion or at rest, orthopnea, paroxysmal nocturnal dyspnea, or inappropriate fatigue. In this study, appearance of moderate to severe leg edema without any other HF-related symptoms was included to be one of the HF-related symptoms.

Kataoka, Congest Heart Fail. 2012;18:37–42.

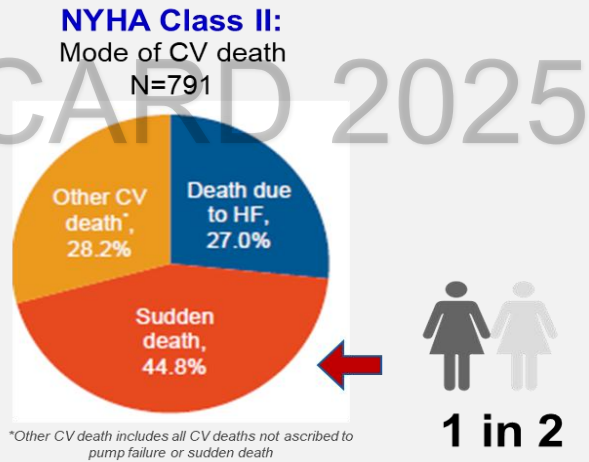
# NYHA class II : high risk of sudden cardiac death

- **MERIT HF** post hoc analysis: the **incidence of SCD is higher in patients with less severe HF (NYHA class II)**, although total mortality rates increase with higher NYHA class
- **PARADIGM-HF** analysis: 70% of patients were NYHA II  **44.8% of NYHA class II HF CV deaths were SCDs**






A post-hoc analysis from **MERIT-HF** (n=3991)[1]
**Mean follow up, 1 year**




An analysis from **PARADIGM-HF** (n=8399)[2]
**Median follow up, 2.3 years**

CV, cardiovascular; HF, heart failure; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in-Congestive Heart Failure; NYHA, New York Heart Association; PARADIGM-HF, Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure;SCD, sudden cardiac death; CHF, congestive heart failure

MERIT-HF Study Group. Lancet. 1999;353(9169):2001–7
Desai AS et al. Eur Heart J. 2015;36:1990–7

## Factors influencing limited adherence to GDMT (Guideline Directed Medical Therapy)[13]





**Physician:**

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

**Get Back to the GUIDELINES…!**

**-medical:**

gh costs
nited access

3. Intolerance and contraindications

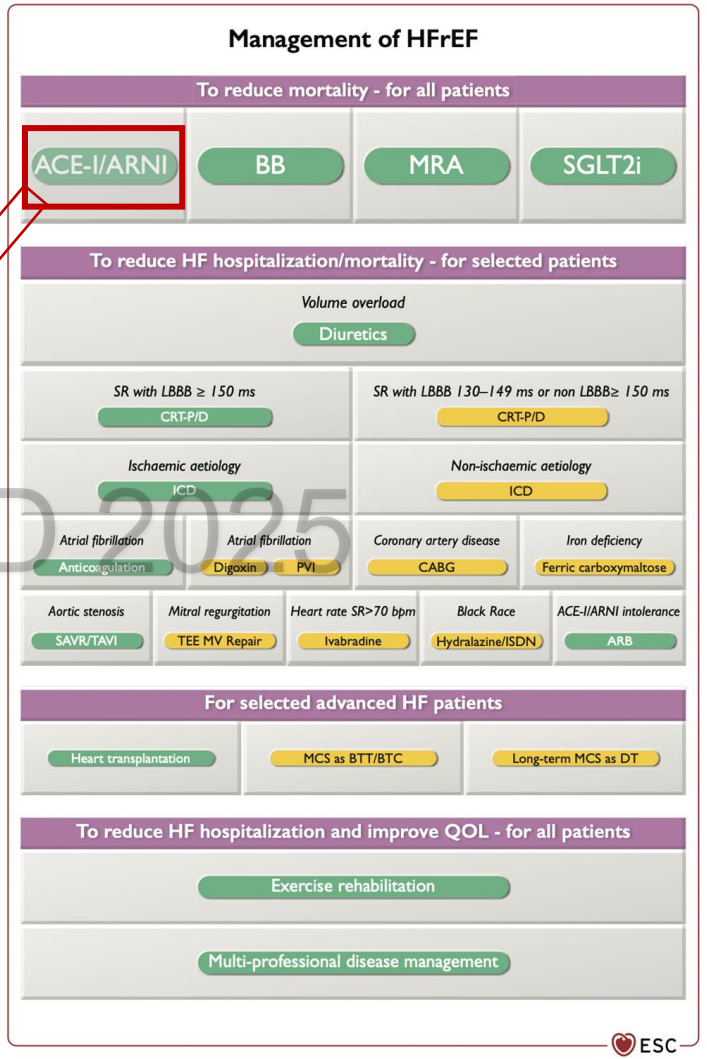
Komajda M, et al. Eur J Heart Fail. 2016;18(5):514-22

# InaHF guideline...


**Download Link :**
**https://inahfcarmet.org/**




Gambar 4. 1 Algoritma tatalaksana HFrEF



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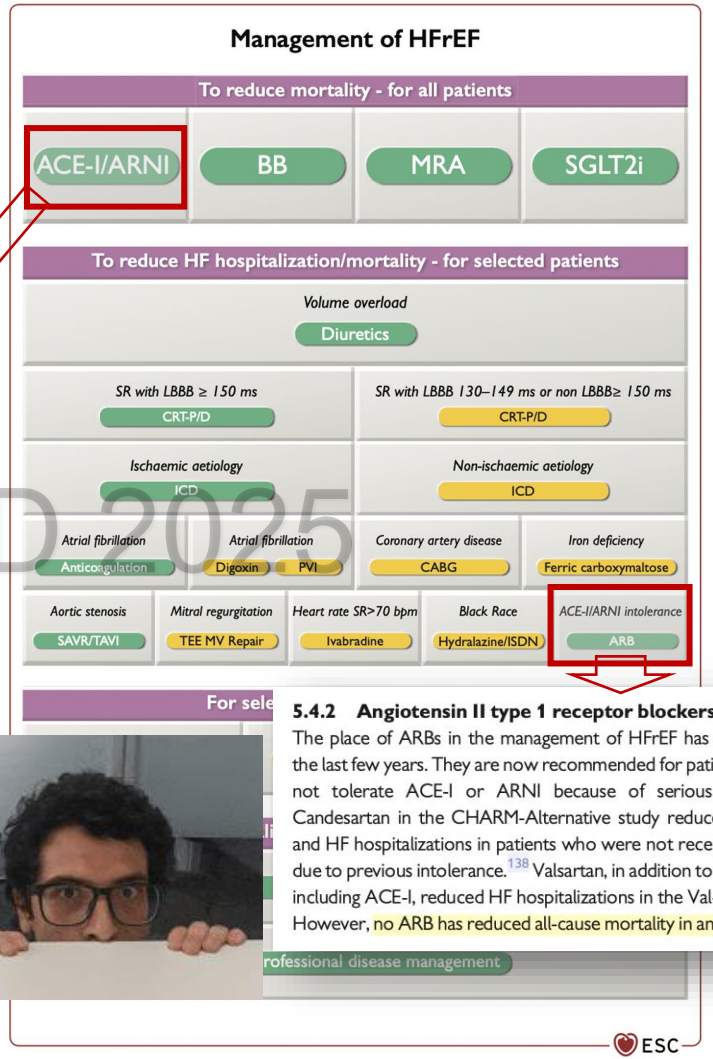
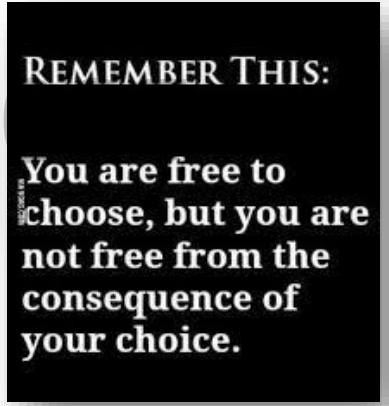


# ARNI vs ACEi

*which one is better?*

Rattanavipanon et al. BMC Cardiovasc Disord (2021) 21:324
https://doi.org/10.1186/s12872-021-02145-9

BMC Cardiovascular Disorders

RESEARCH Open Access

# Real-world experience of angiotensin receptor/neprilysin inhibitor (ARNI) usage in Thailand: a single-center, retrospective analysis

Wipharak Rattanavipanon[1], Thanyaluck Sotananusak[2], Fairus Yamaae[1], Arisa Chandrsawang[1], Pitchapa Kaewkan[3], Surakit Nathisuwan[1] and Teerapat Yingchoncharoen[3*]



**Conclusions**

In real-world practice, ARNI use was associated with a **significant reduction in both clinical outcomes and symptom improvement**, while **orthostatic hypotension was more common** in patients in the ARNI group than in patients in the standard treatment group.

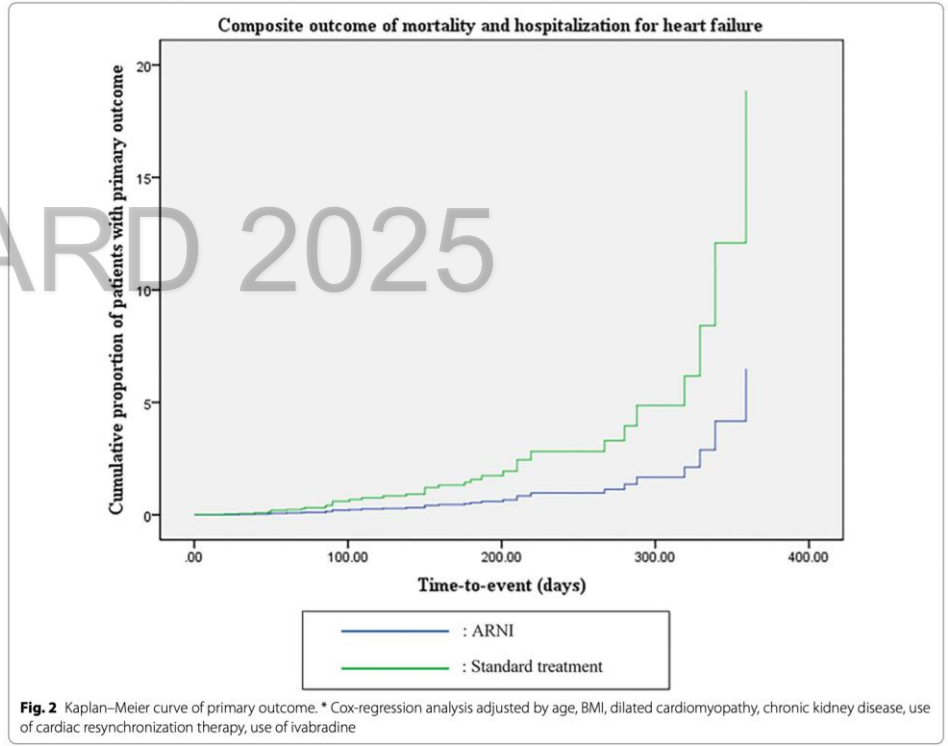



**Fig. 2** Kaplan–Meier curve of primary outcome. * Cox-regression analysis adjusted by age, BMI, dilated cardiomyopathy, chronic kidney disease, use of cardiac resynchronization therapy, use of ivabradine

Cardiol Ther (2022) 11:113–127
https://doi.org/10.1007/s40119-021-00252-4

ORIGINAL RESEARCH

# Hospitalization Rates in Patients with Heart Failure and Reduced Ejection Fraction Initiating Sacubitril/Valsartan or Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers: A Retrospective Cohort Study

Emma Houchen · Emil Loefroth · Raymond Schlienger · Clare Proudfoot · Stefano Corda · Sibasish Saha · Sarvesh K. Satwase · Rachel Studer



**Conclusions**

In real-world clinical practice, RAASi-naïve patients with HFrEF initiating SAC/ VAL were **less likely to be hospitalized** than those initiating ACEi/ARB, suggesting a potential for a **reduced clinical and economic burden** in these patients.

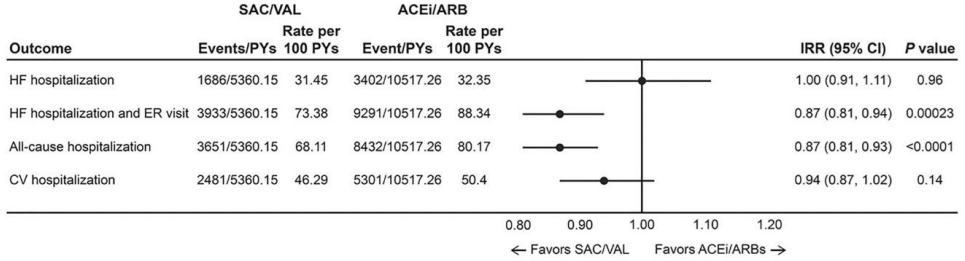



**Fig. 3** Comparison of rate of events between new SAC/VAL users and new ACEi/ARB users. *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CI* confidence interval, *CV* cardiovascular, *ER* emergency room, *HF* heart failure, *IRR* incidence rate ratio, *PY* patient-year, *SAC/VAL* sacubitril/valsartan

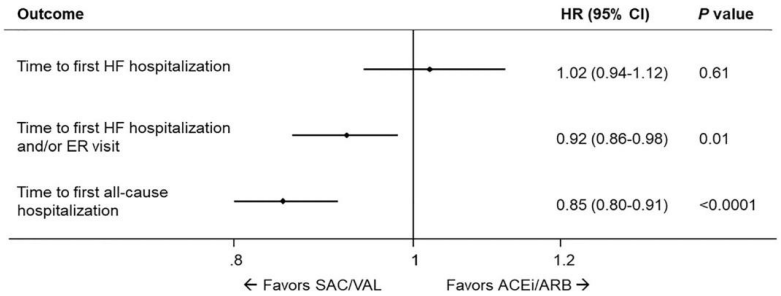



**Fig. 4** Comparison of time to event between new SAC/VAL users and new ACEi/ARB users. *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CI* confidence interval, *ER* emergency room, *HF* heart failure, *HR* hazard ratio, *SAC/VAL* sacubitril/valsartan

Clinical Research in Cardiology (2023) 112:167–174
https://doi.org/10.1007/s00392-022-02124-w

ORIGINAL PAPER

# Real-world comparative effectiveness of ARNI versus ACEi/ARB in HF with reduced or mildly reduced ejection fraction

Michael Fu[1] · Aldina Pivodic[2,3] · Oskar Käck[4] · Madlaina Costa-Scharplatz[4] · Ulf Dahlström[5,6] · Lars H. Lund[7]

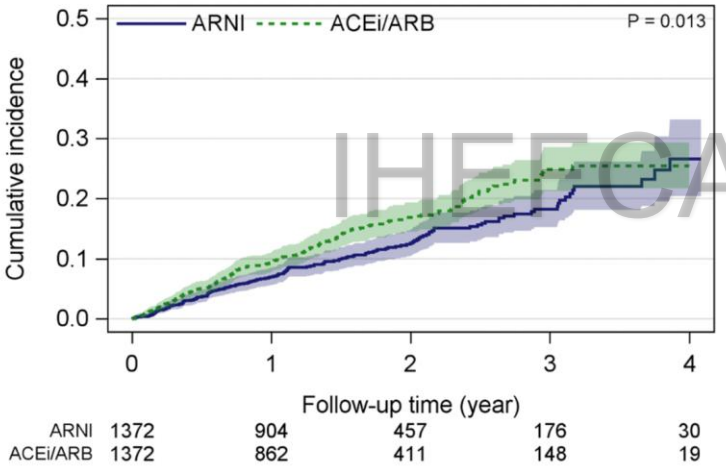


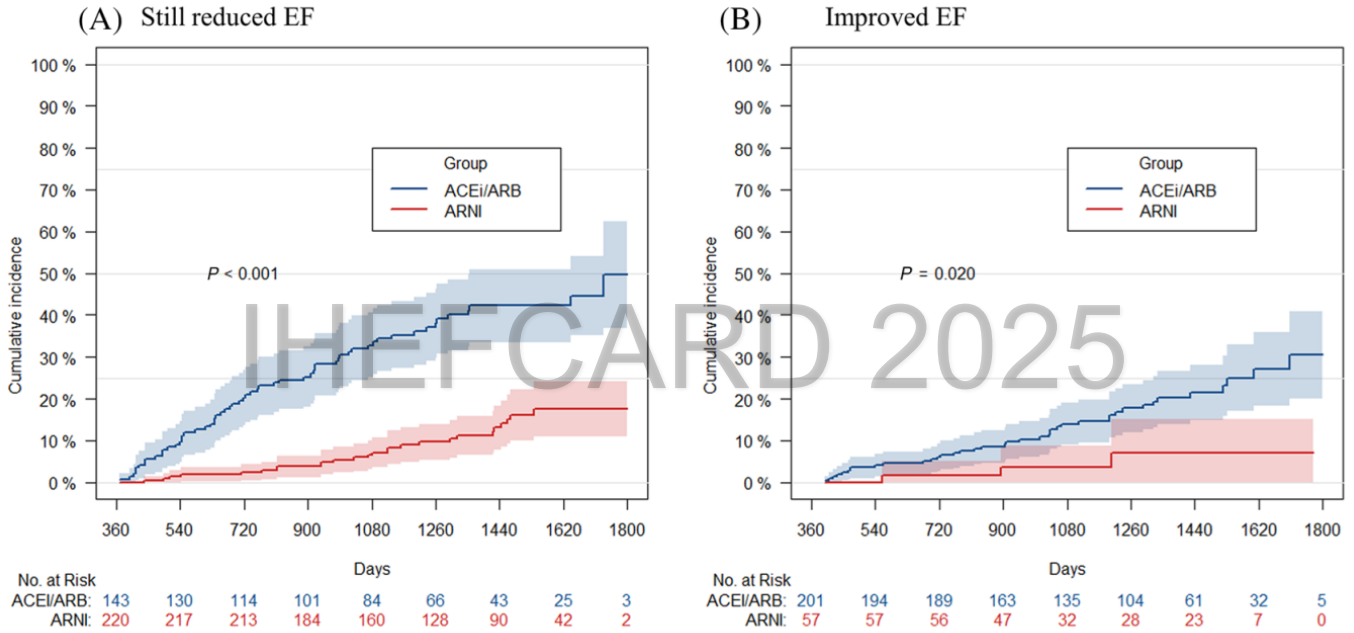

**Fig. 2** Cumulative incidence estimates with 95% confidence intervals for all-cause mortality for ARNI versus ACEi/ARB groups matched 1:1 ratio using propensity score matching including clinical variables. *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blockers, *ARNI* angiotensin receptor–neprilysin inhibitor



**Conclusions**

In this nationwide real-world study including a population of patients with HF with **reduced or mildly reduced EF**, ARNI as part of guideline-led Swedish clinical practice was associated with a statistically significant relative risk reduction in **all-cause mortality** compared with ACEi/ARB.

# Real-world long-term impact of ARNI - according to changes in LVEF





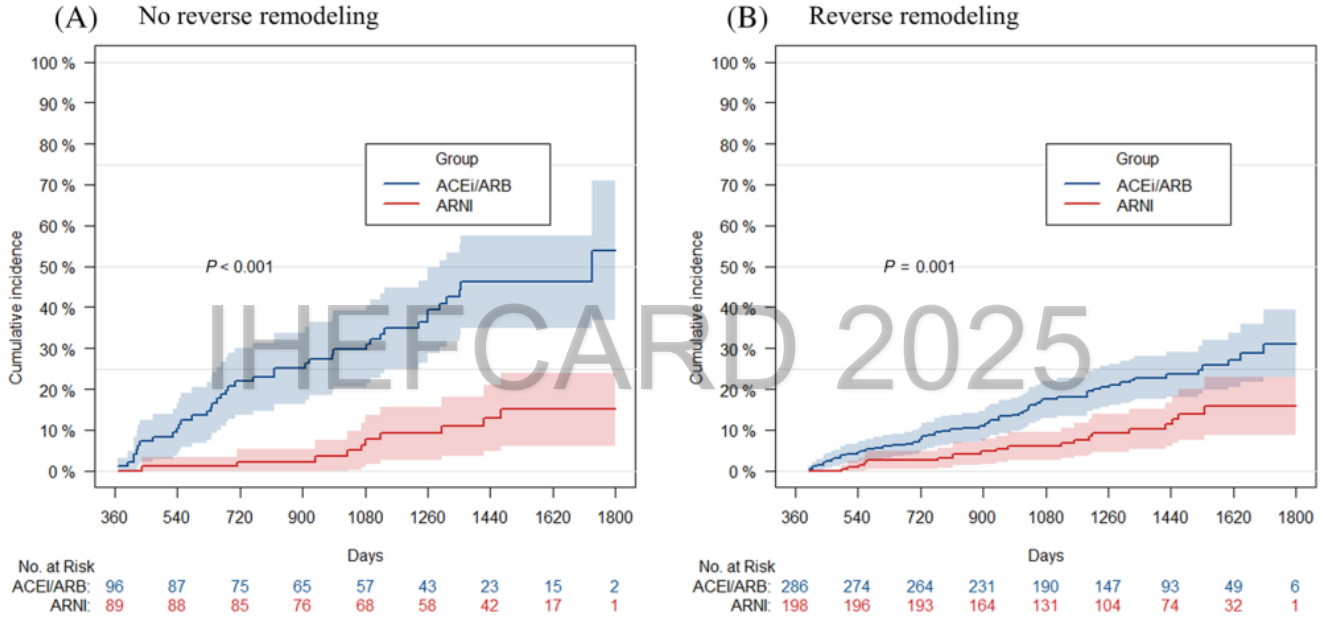

*Composite event : all-cause mortality and HF hospitalization

Prolonged use of ARNI **can be superior** to ACEIs/ARBs in HFrEF patients who:

A. Patients with **persistent reduced EF** following 1 year of treatment (ARNI vs. ACEIs/ARBs, 17.6% vs. 49.7%, **P < 0.001**)
B. Patients with **HFimpEF following 1 year of treatment** (ARNI vs. ACEIs/ARBs, 7.0% vs. 30.4%, **P = 0.020**)

Park et al. ESC Heart Failure 2023; 10: 3430–343

# Real-world long-term impact of ARNI
## - according to changes in LV reverse remodeling in HFrEF





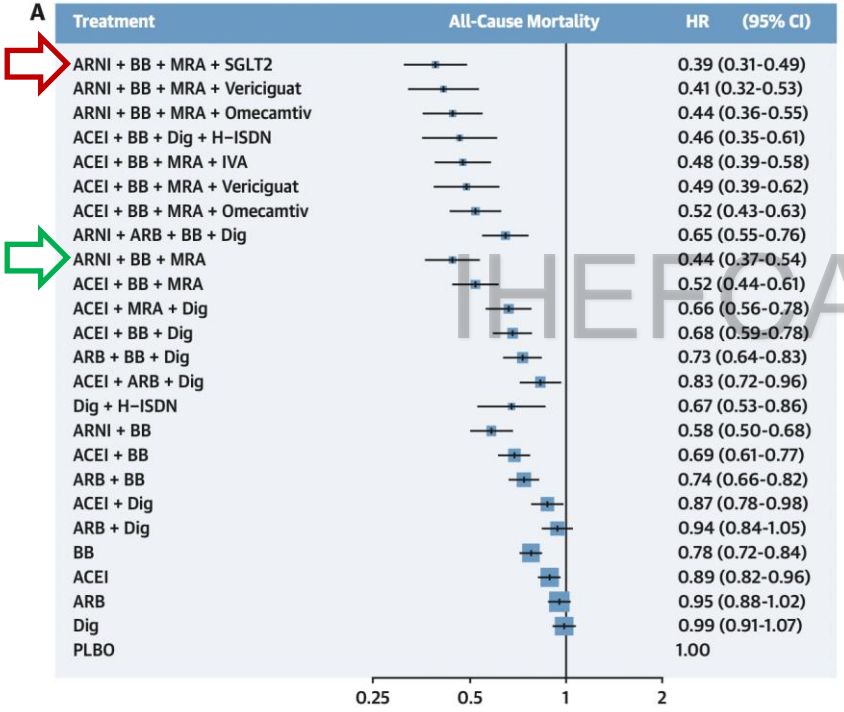

*Composite event : all-cause mortality and HF hospitalization

Prolonged use of ARNI can be superior to ACEIs/ARBs in patients with HFrEF:

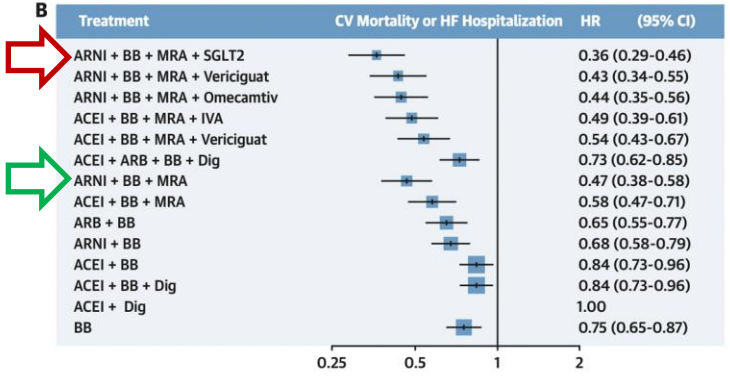
A. Patients without LV reverse remodeling following 1 year of treatment (ARNI vs. ACEIs/ARBs; 15.0% vs. 54.9%, P < 0.001)
B. Patients with LV reverse remodeling after 1 year of treatment (ARNI vs. ACEIs/ARBs, 15.8% vs. 31.1%, P = 0.001).

Park et al. ESC Heart Failure 2023; 10: 3430–343

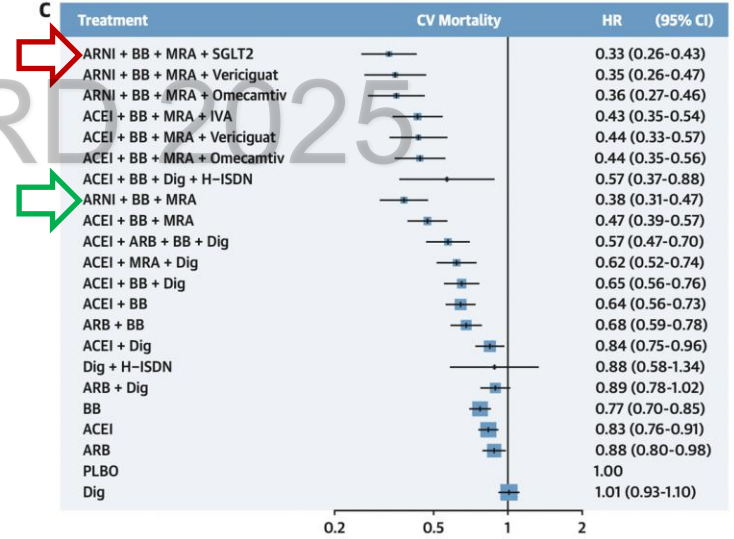
**A**




**B**



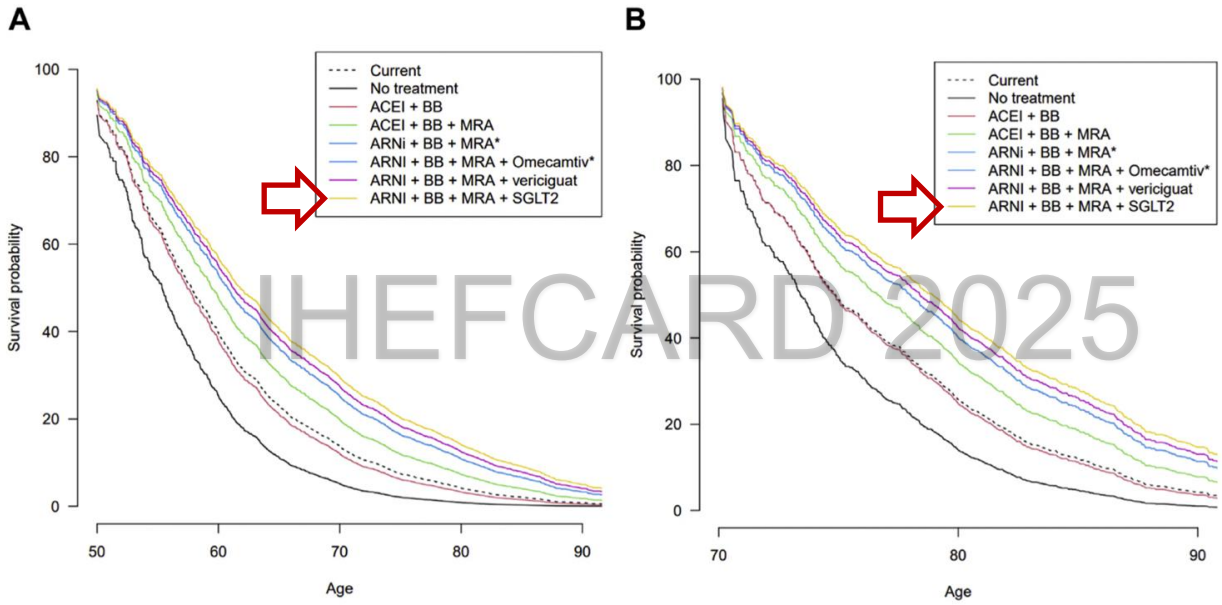

**C**






Tromp et al. JACC: HEART FAILURE VOL. 10, NO. 2, 2022

**FIGURE 3** **Estimated Average Lifetime Graphs**

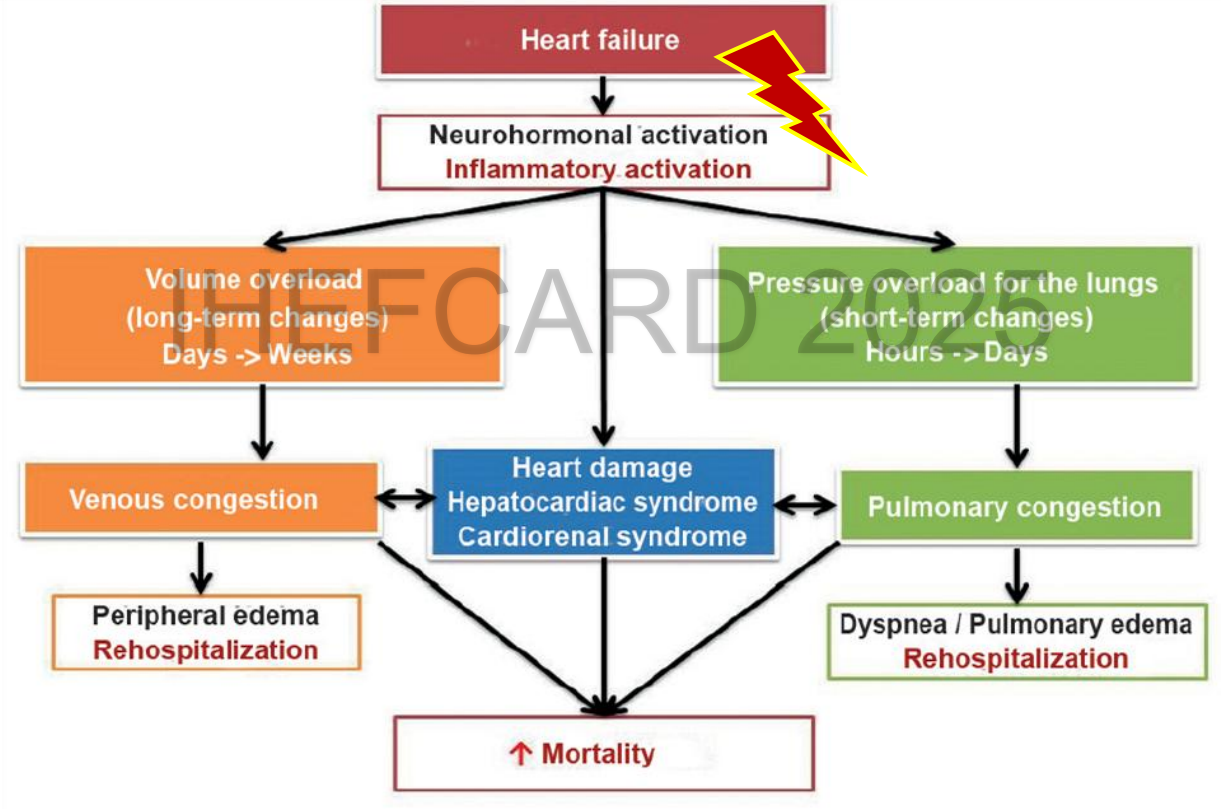





Estimated average lifetime benefit for selected treatment combinations in BIOSTAT-CHF and ASIAN-HF at age 50 years **(A)** and age 70 years **(B)**. Survival curves overlap for combinations with a *. Abbreviations as in Figure 2.

Tromp et al. JACC: HEART FAILURE VOL. 10, NO. 2, 2022

# Mechanisms of increased risk of death and rehospitalization in patients hospitalized for HF



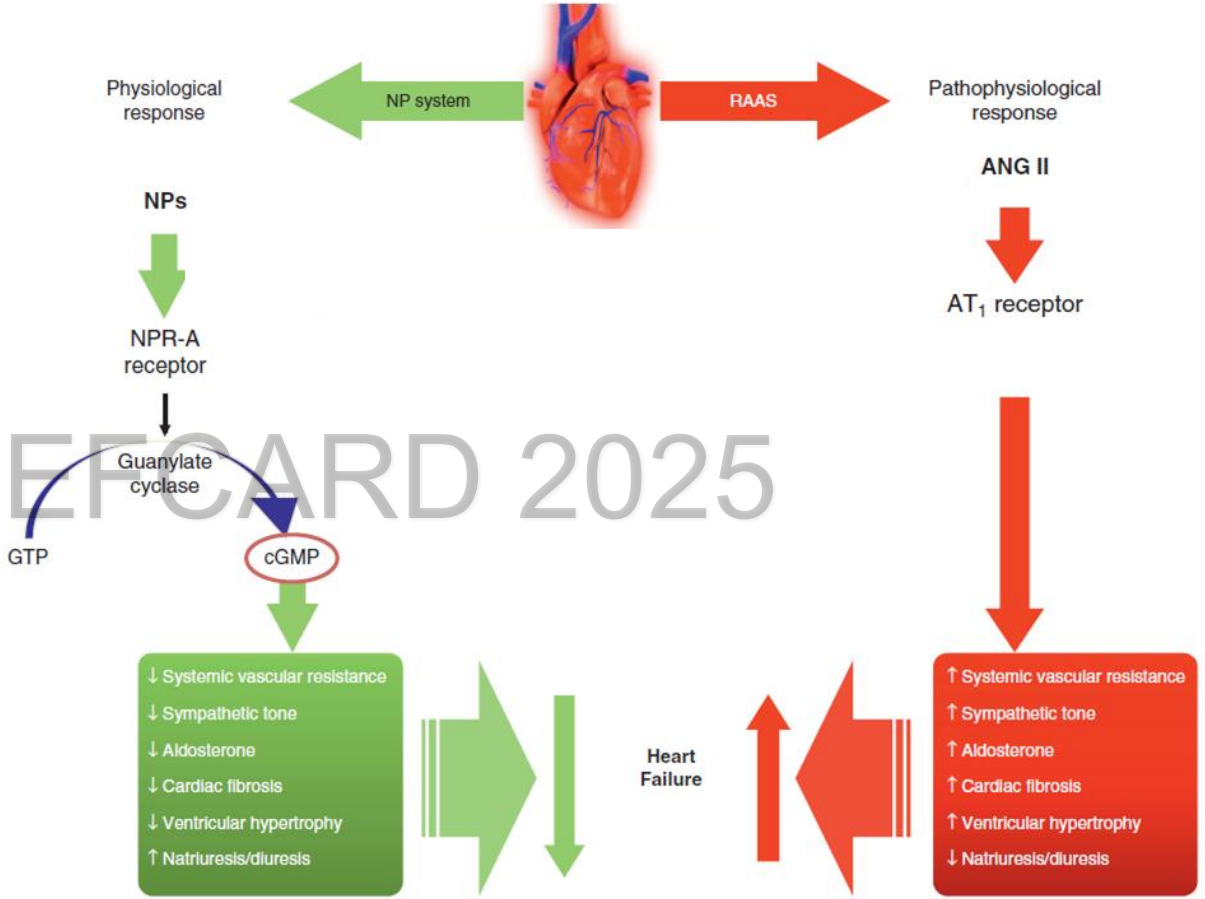



Mesquita et al. Int J Cardiovasc Sci. 2017;30(1):81-90

# ARNI :

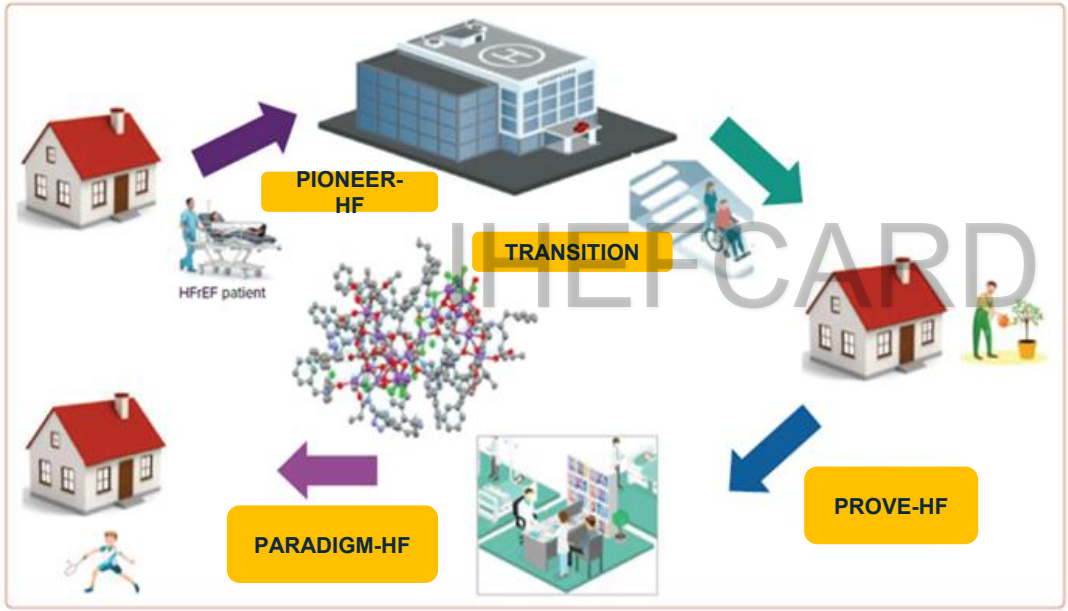
**modulates two counter-regulatory neurohormonal systems in HF**






Langenickel TH, Dole WP. 2014. Angiotensin receptor-neprilysin inhibition with LCZ696, Drug Discov Today: Ther Strategies
Fabris et al. Drugs 2019. https://doi.org/10.1007/s40265-019-01181-2

# Clinical trials of Sacubitril/Valsartan (S/V) in HFrEF patient journey



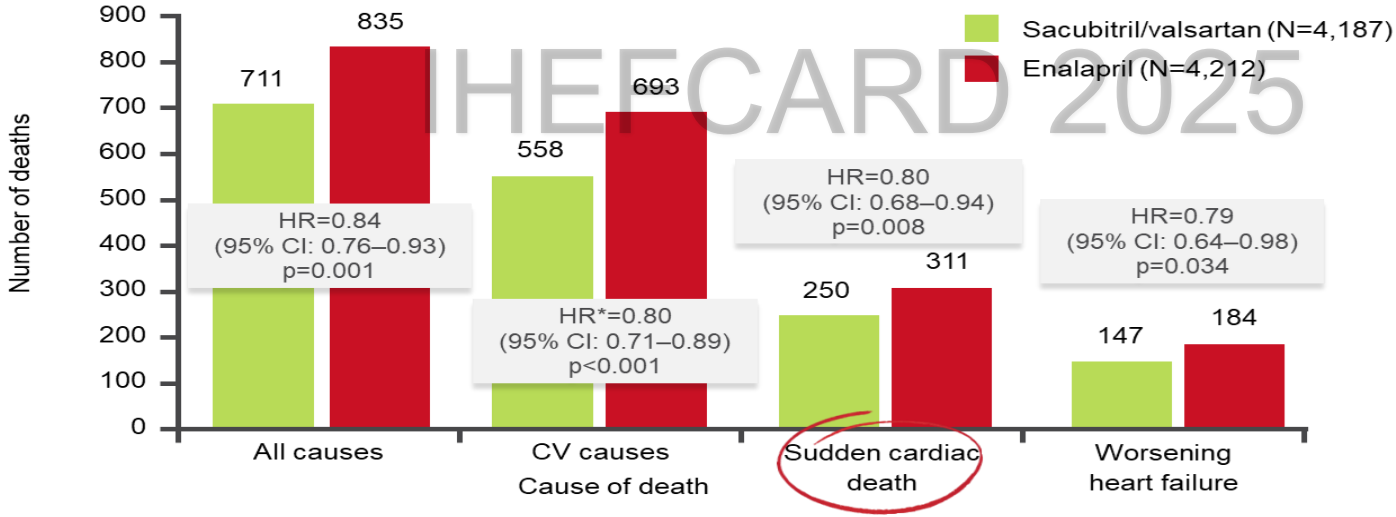



1. Once the patient with HFrEF is admitted to hospital, the **PIONEER** trial shows a significant reduction in NT-proBNP associated with the use of S/V in the acute setting; moreover, a significant reduction in HF re-hospitalization is documented.
2. After discharge, the **TRANSITION** trial shows that S/V is safe and well-tolerated in acute HFrEF patients after hemodynamic stabilization.
3. In the ambulatory setting, the **PROVE-HF** trial document a beneficial effect of S/V on reverse remodeling.
4. In stable HFrEF patients at home, the **PARADIGM-HF** trial shows a 20% reduction in CV death and HF hospitalization with S/V vs enalapril.

Cardiac Failure Review 2021;7:e06.

# Sacubitril/valsartan significantly reduced death from CV causes or first hospitalization for HF*

- More than 80% of deaths in PARADIGM-HF had a CV cause
- Sacubitril/valsartan is related to the observed reduction in sudden cardiac death and death due to worsening heart failure





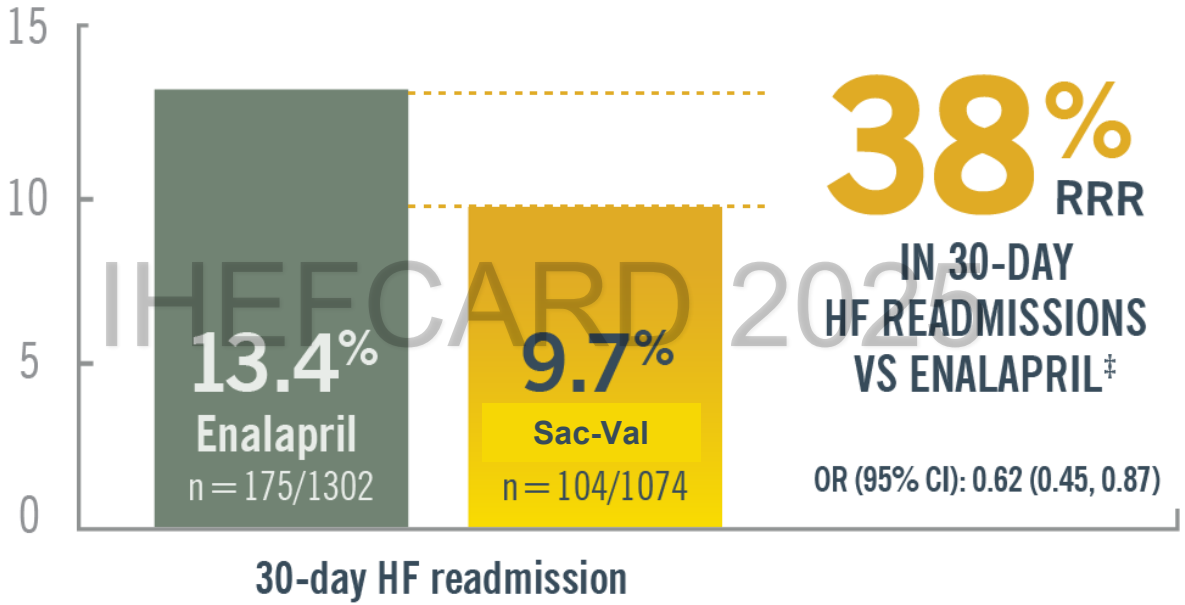

ACEI, angiotensin-converting-enzyme inhibitor; ARNI, angiotensin receptor neprilysin inhibitor; CI, confidence interval; CV, cardiovascular; HFrEF, heart failure with reduced ejection fraction; HR, Hazard ratio; PARADIGM-HF, Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

*Results from death from CV causes as per those reported by McMurray et al. Note that the hazard ratio reported by Desai et al. was HR=0.80 (95%CI: 0.72–0.89); p<0.001

Desai et al. Eur Heart J 2015;36(30):1990-7
O'Connor et al. Am J Cardiol 1998;82:881–7

# Sacubitril-Valsartan reduced 30-day HF readmissions vs enalapril

(post hoc analysis)






CI=confidence interval; HF=heart failure; OR=odds ratio; RRR=relative risk reduction.

*The primary unit of analysis was hospitalisations, including repeat hospitalisations, rather than patients.
†Among patients hospitalised at least once for HF, patient characteristics were similar at baseline between treatment groups.
‡Data are from a PARADIGM-HF post hoc analysis (hospital readmission rate was not a primary end point).

Desai AS, et al. *J Am Coll Cardiol*. 2016;68(3):241-248.

# IN-PARALLEL approach better than STRICT SEQUENTIAL approach*

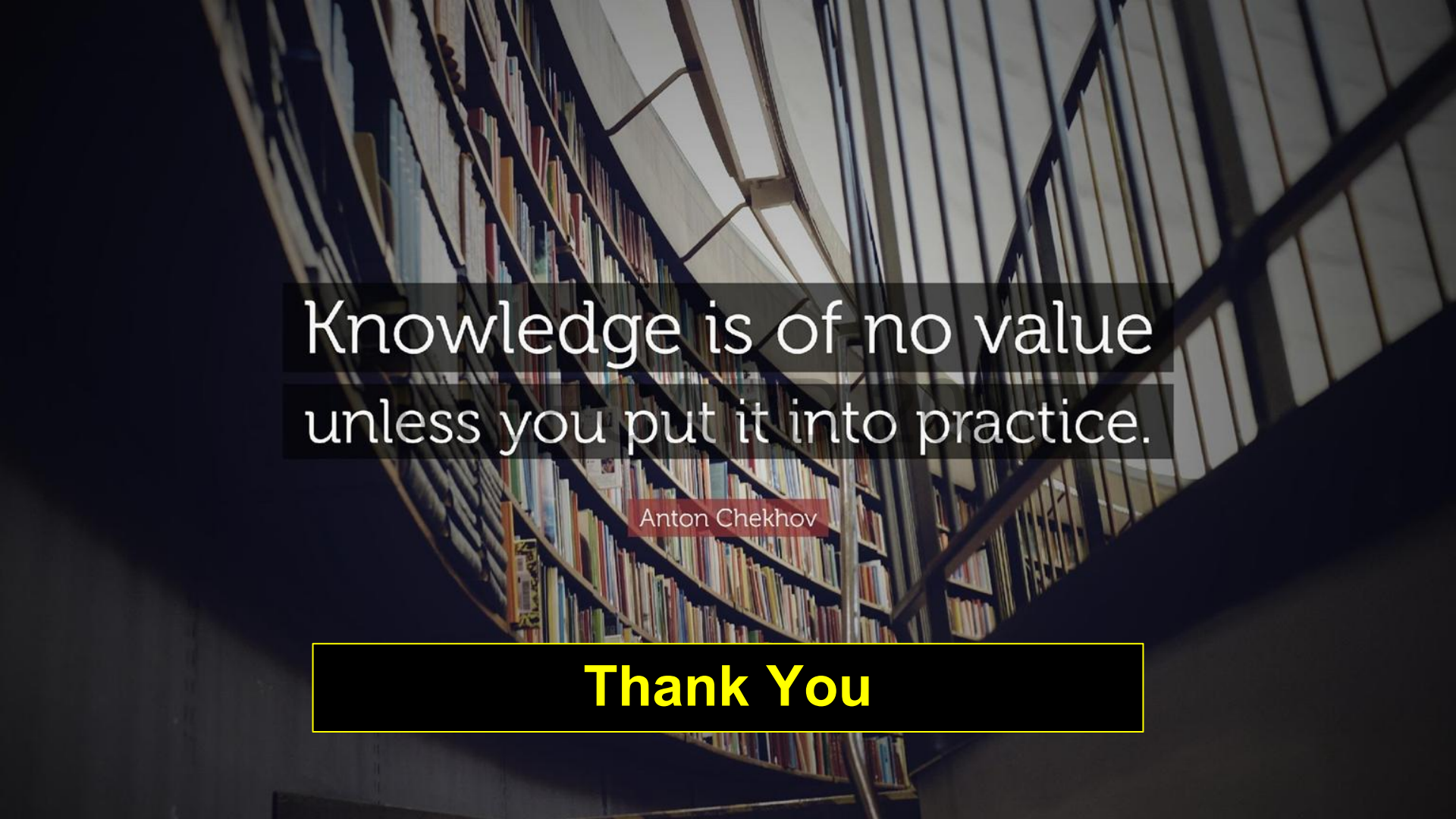
**The point is : Always keep this family TOGETHER**




*CCS HF Guideline. 2021; 531-46.

# Take Home Points

- Stable HF Myth?
  - ✓ Is almost always progressive, even if patients appear stable
  - ✓ High risk of SCD in NYHA II
  - ✓ Risk of non-compliance in stable-felt patient
  - ✓ Persistent myocardial stress and fibrosis : subtle but progressive ventricle dysfunction
- The Facts :
  - ✓ The guidelines is there....,
  - ✓ But the GDMT initiation and optimization are not there!
- Solutions :
  - ✓ Early initiation of 4-pillars in HFrEF, keep optimize the dose
  - ✓ Evidence of benefit and superiority of ARNI (decrease risk of SCD by 20%)
  - ✓ ARNI addresses multiple pathways simultaneously
  - ✓ Assure the compliance through simple medications regiment and...



Knowledge is of no value
unless you put it into practice.
Anton Chekhov

# Thank You