The 4th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

# Addressing The Unmet Need for Patients with Heart Failure with Reduced and Preserved Ejection Fraction Meeting-In-A-Box

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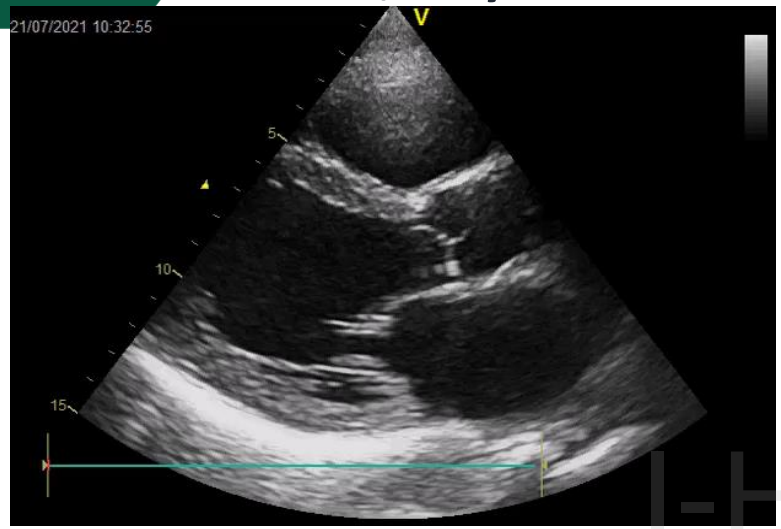
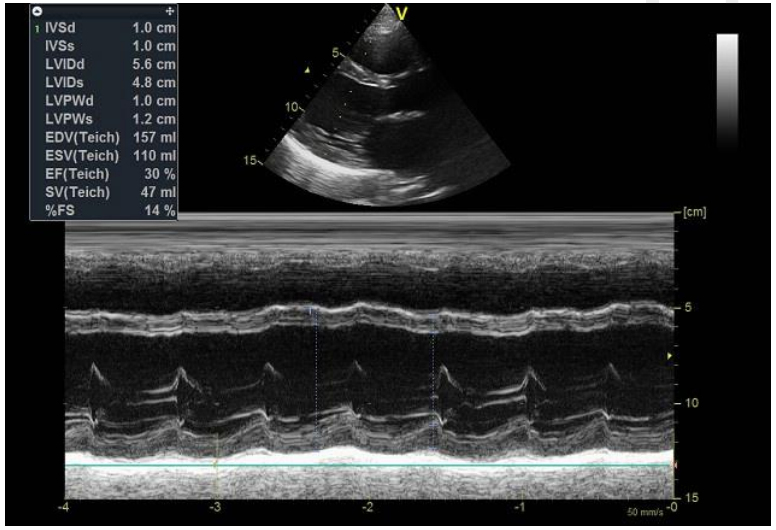
# To those who do not yet believe in the effectiveness of GDMT..



Please check this one out..

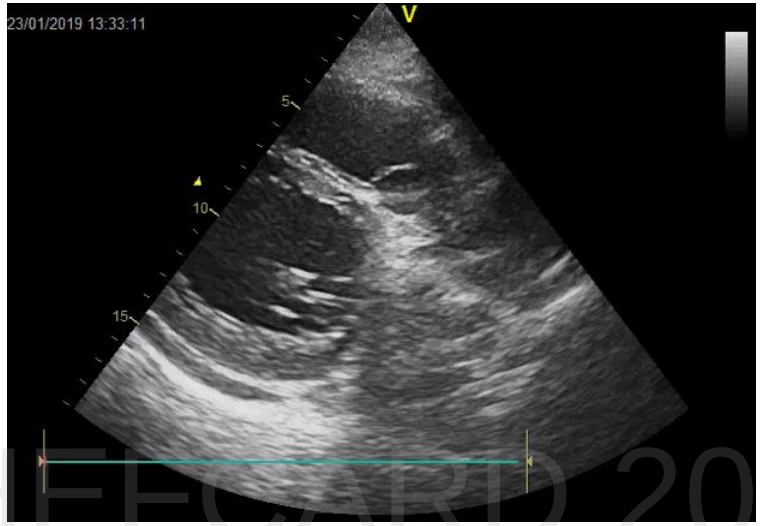
## Mr. A, 48 yo

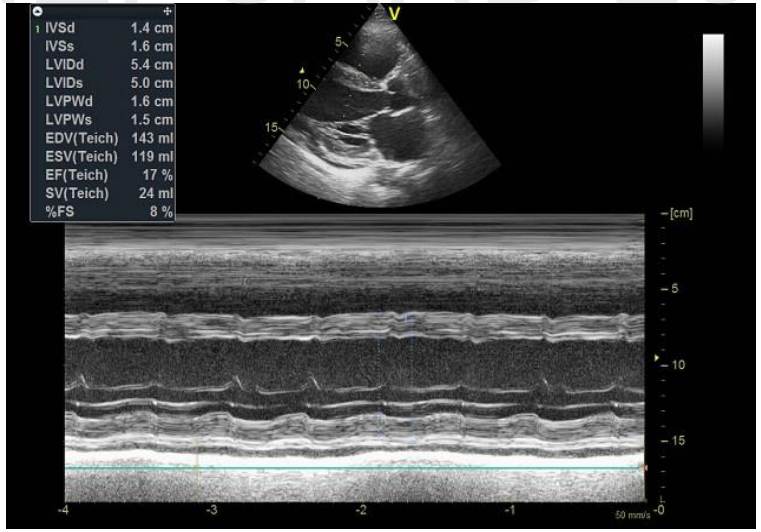


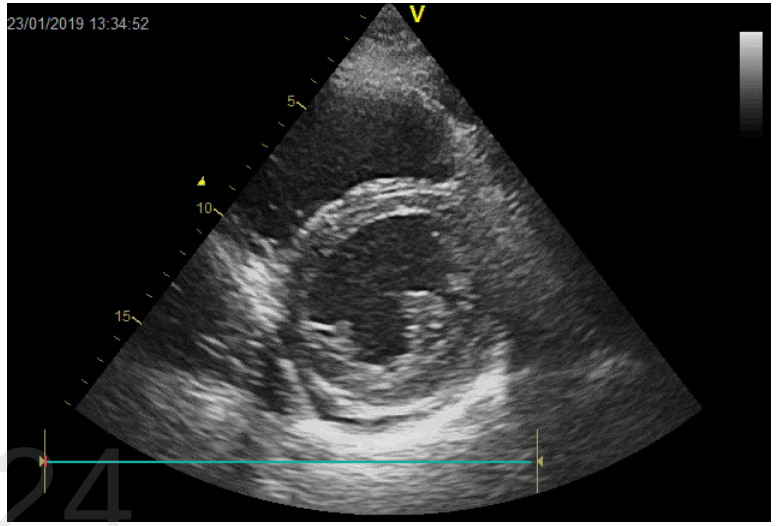

**LVEF 30%**

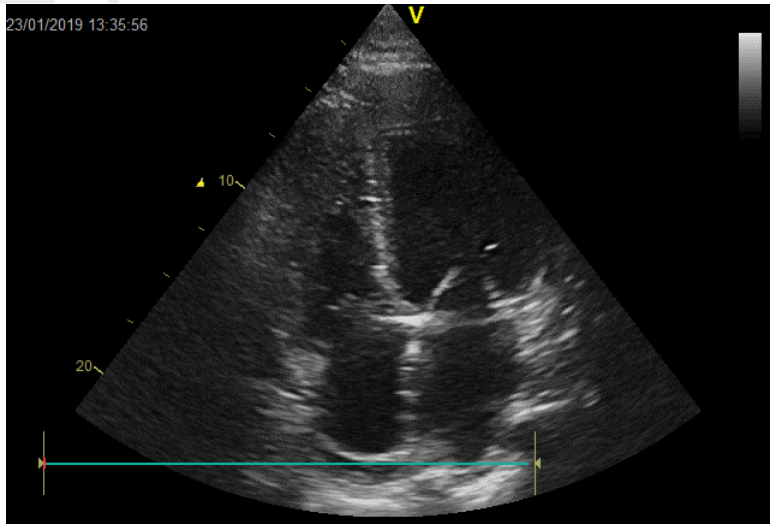
## Mr. N, 29 yo



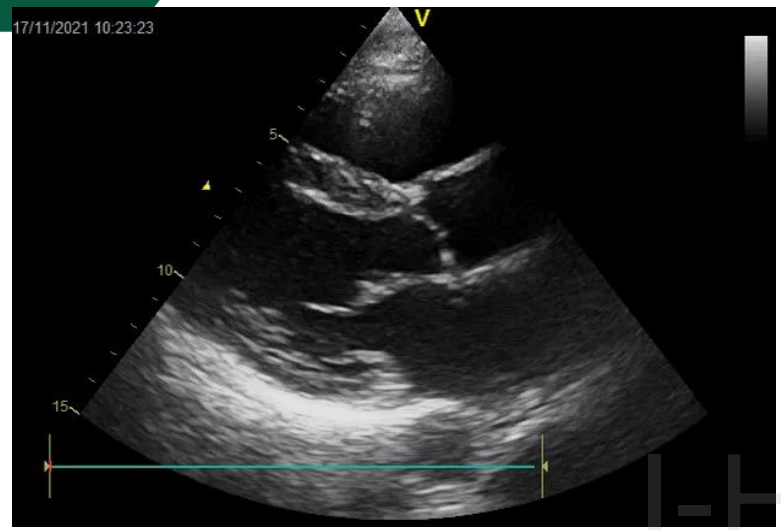



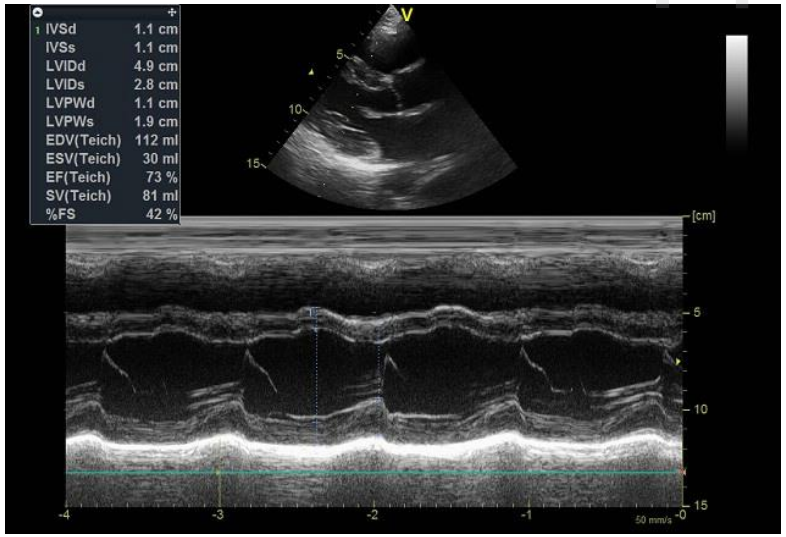

**LVEF 17%**



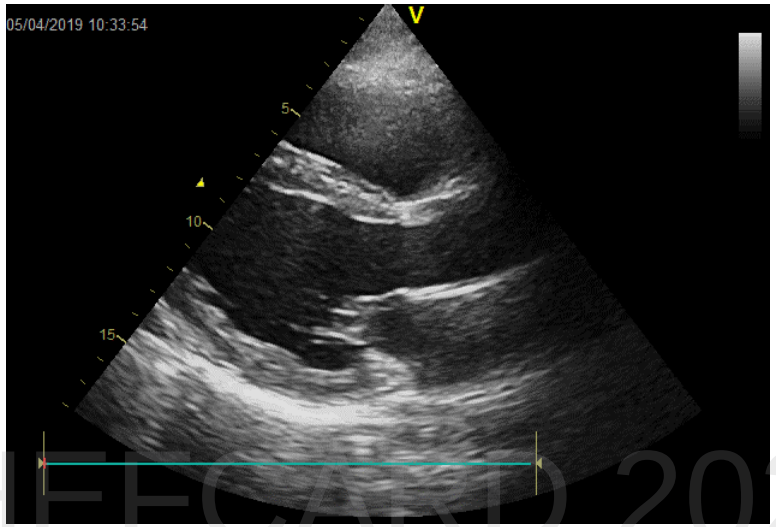
## Mr. A, 48 yo

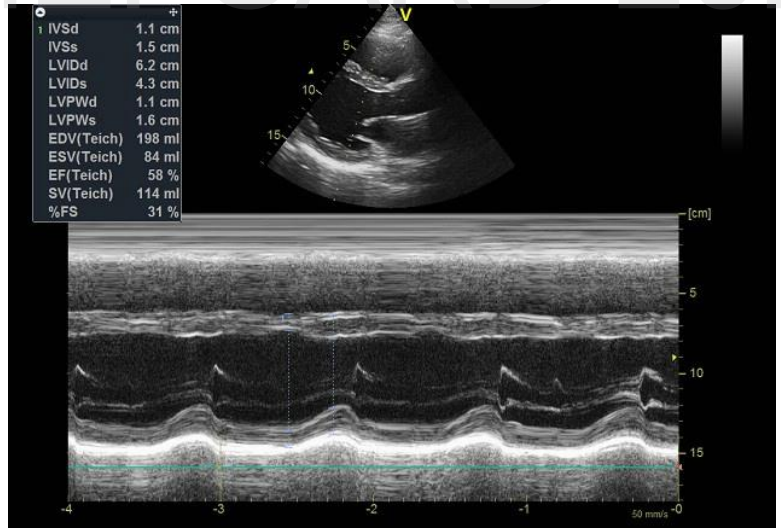


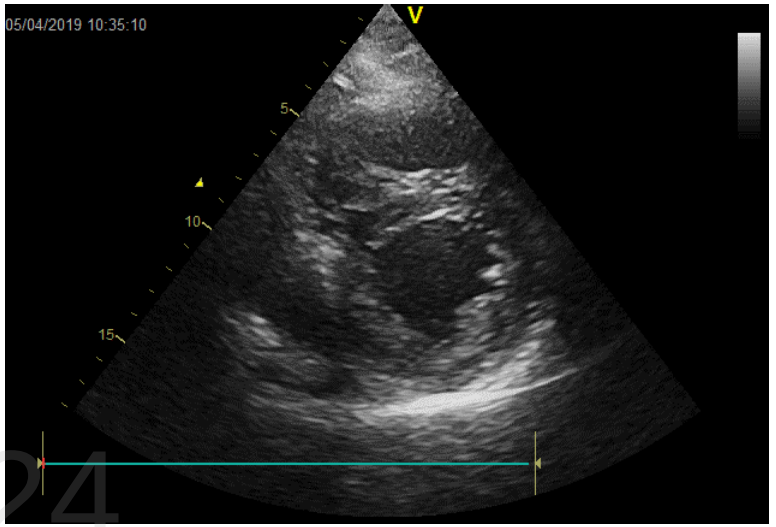



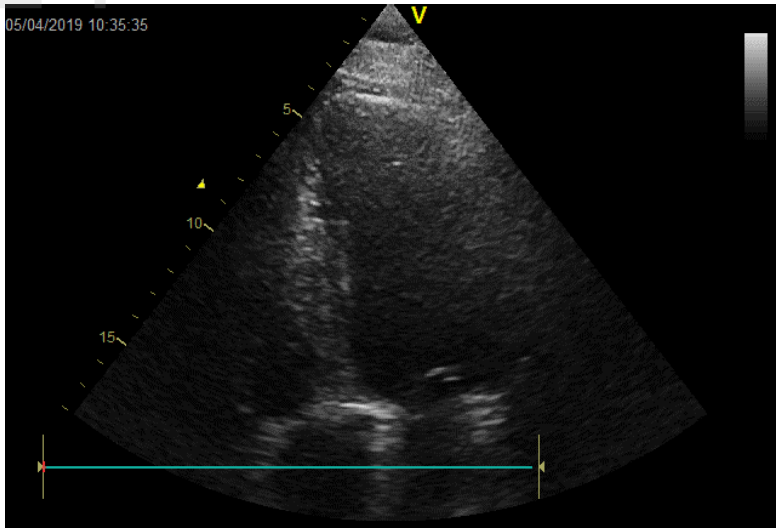

**LVEF 73%, in 4 months**

## Mr. N, 29 yo



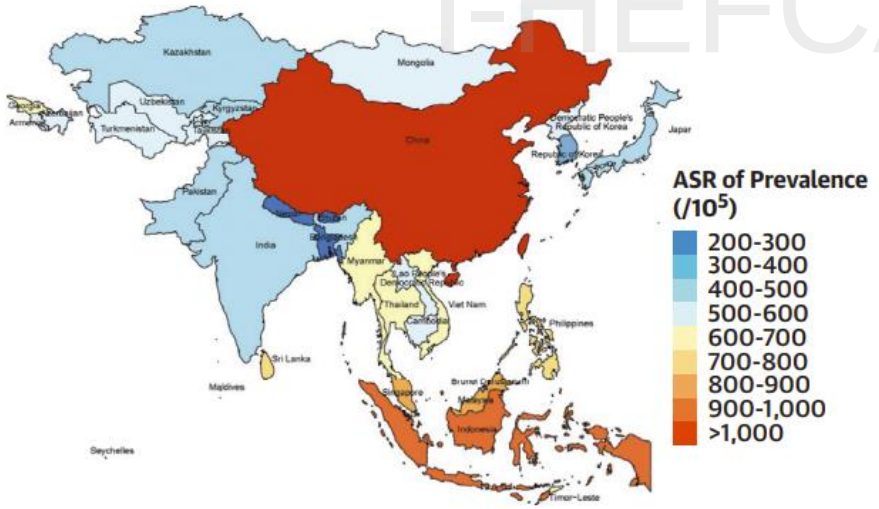

**LVEF 58% in 4 months**

# The GDMT itself..

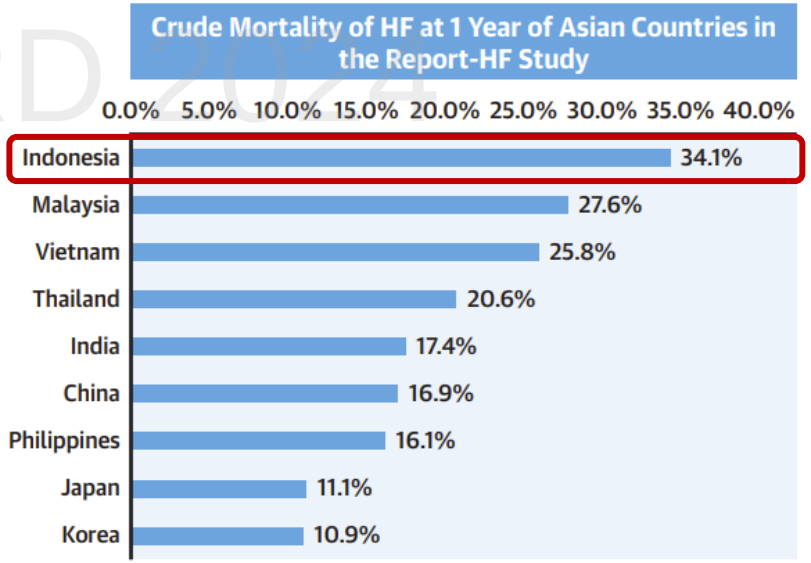
| Mr. A, 48 yo | Mr. N, 29 yo |
|---|---|
| • Sacubitril/Valsartan 50 mg bid<br>• Bisoprolol 5 mg od<br>• Spironolactone 25 mg od<br>• Empagliflozin 10 mg od<br>• No Furosemide | • Sacubitril/Valsartan 200 mg bid<br>• Bisoprolol 10 mg od<br>• Spironolactone 50 mg od<br>• Dapagliflozin 10 mg od<br>• No Furosemide |

# Indonesia is the WINNER

**The Prevalence of HF in Asia is High: China, Indonesia, and Malaysia are the 3 Highest Nations in Terms of Age-Standardized Prevalence**




**The 1-Year Mortality of Asian HF Patients Is Still High, Especially in Southeast and South Asia: CV Death is the Primary Cause of Death for HF**




Feng J, et al. JACC: Asia. 2024

# There is an urgent unmet medical need for people living with HF

**More than 60 million** people worldwide are living with HF[1]

HF is one of the leading causes of hospitalization[2,3] and the **number 1 cause of hospitalization in patients over 65 years old**[4]

**Hospital readmission** rates after HHF are as high as ~**30%** within 90 days[5]

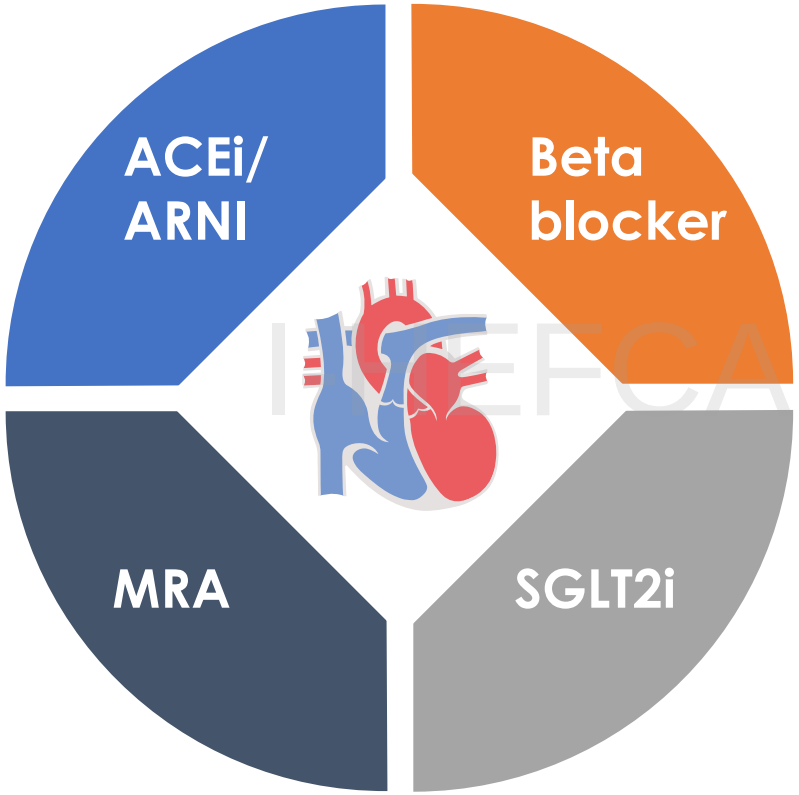
Approximately **30%** of patients who are hospitalized with HF **die within 1 year**[6]



HF, heart failure

1. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. *Lancet*. 2017;390:1211; 2. Blecker S *et al. J Am Coll Cardiol.* 2013;61:1259; 3. Ambrosy AP *et al. J Am Coll Cardiol.* 2014;63:1123; 4. Azad N, Lemay G. *J Geriatr Cardiol.* 2014;11:329; 5. Fonarow GC *et al. J Am Coll Cardiol.* 2007;50:768; 6. Shah KS *et al. J Am Coll Cardiol.* 2017;70:2476.

# There are four foundational therapies for the treatment of patients with HFrEF[1–3]




**As highlighted in recent consensus papers and guidelines from:**

AMERICAN COLLEGE of CARDIOLOGY

Canadian Cardiovascular Society

ESC European Society of Cardiology

PERKI Indonesia

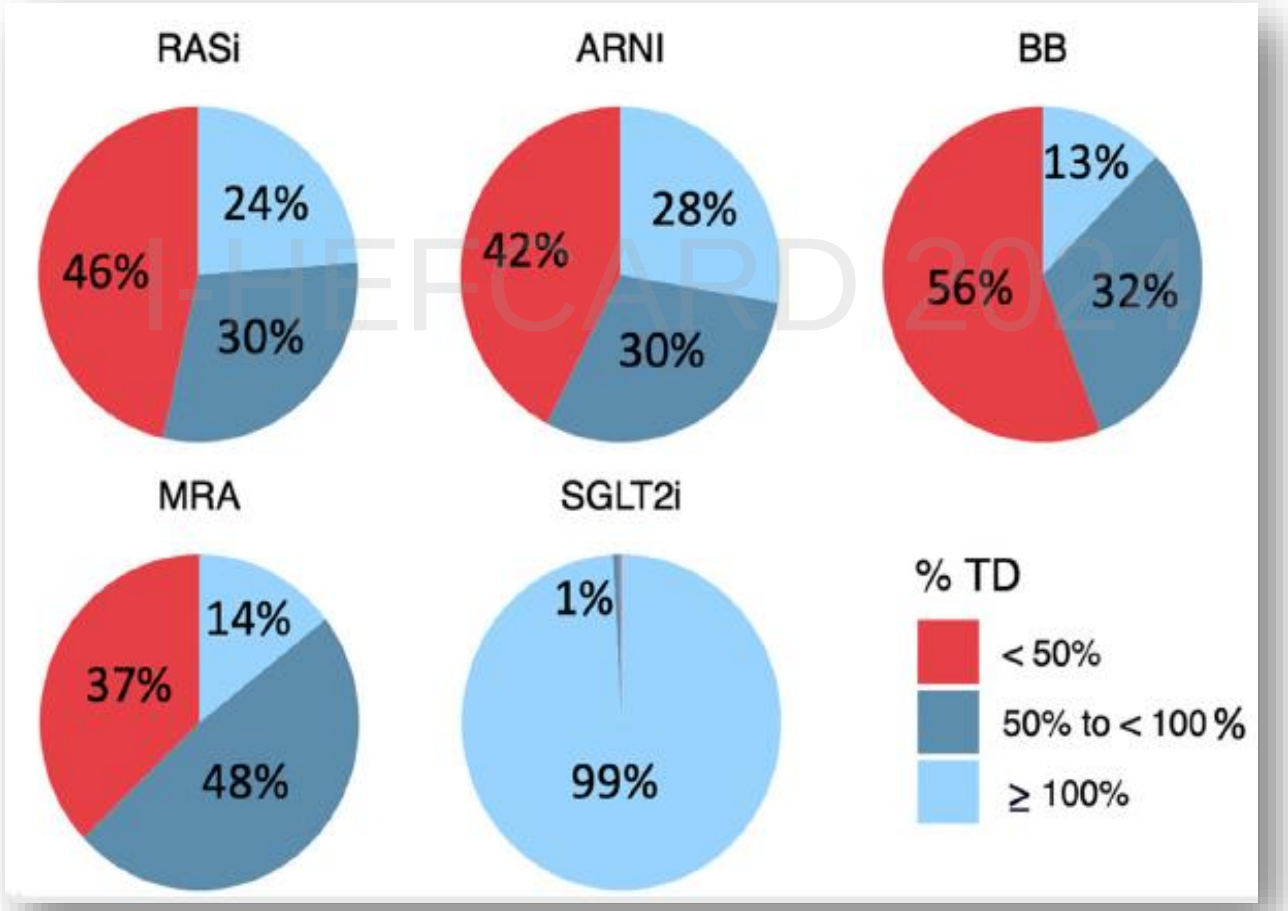


1. Maddox TM *et al. J Am Coll Cardiol.* 2021;77:772; 2. McDonald M *et al. Can J Cardiol.* 2021;37:531; 3. McDonagh TA *et al. Eur Heart J.* 2021;42:3599.

# Contemporary guideline-directed medical therapy in de novo, chronic, and worsening HF patients: First data from the TITRATE-HF study

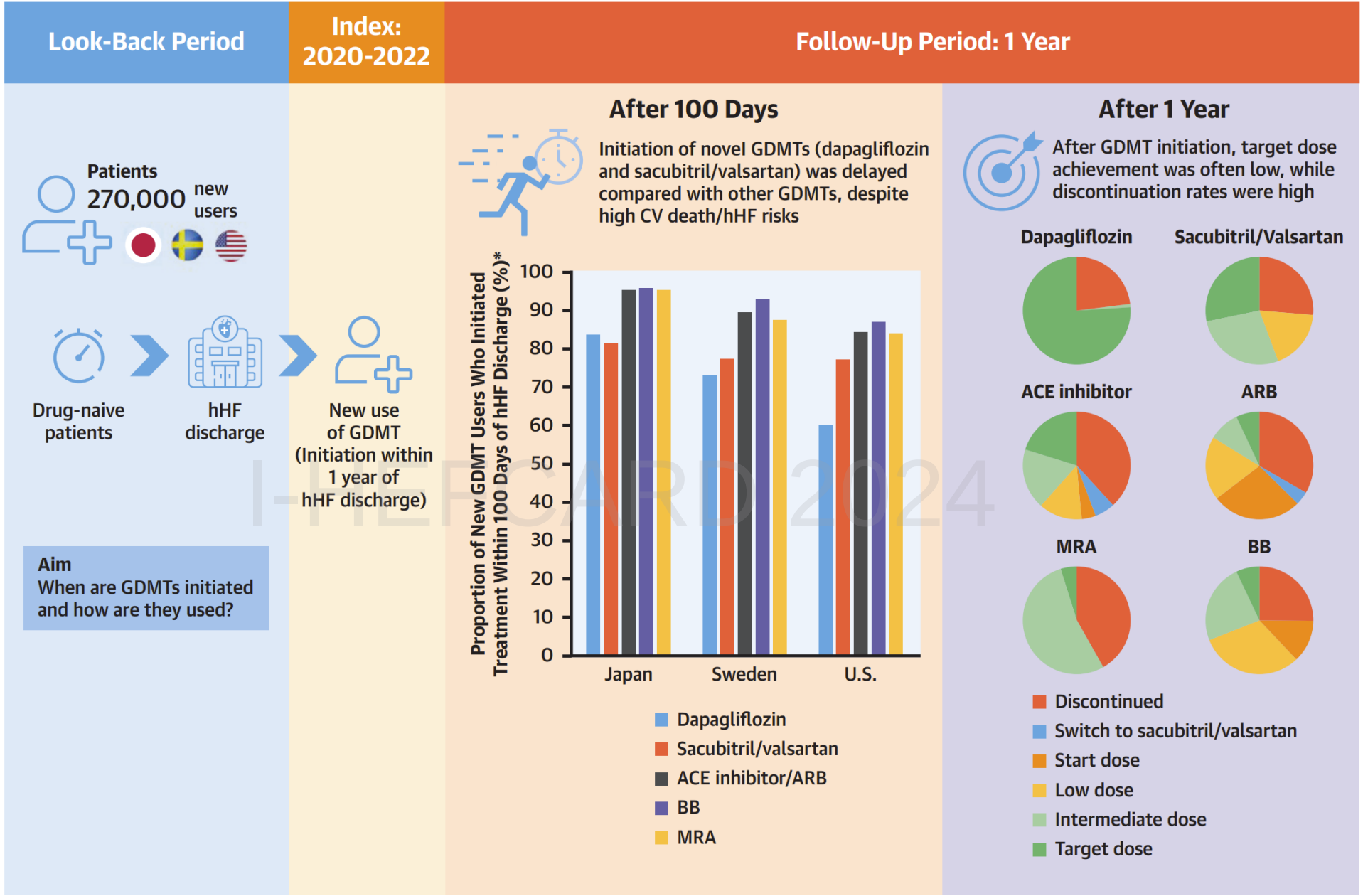
TITRATE-HF: ongoing long-term HF registry conducted in the Netherlands. Overall, 4288 patients from 48 hospitals were included; 1732 presented de novo, 2240 chronic, and 316 with worsening HF.

Percentage of target dose for each drug class, stratified by <50% vs 50%-100% vs ≥100% of target dose





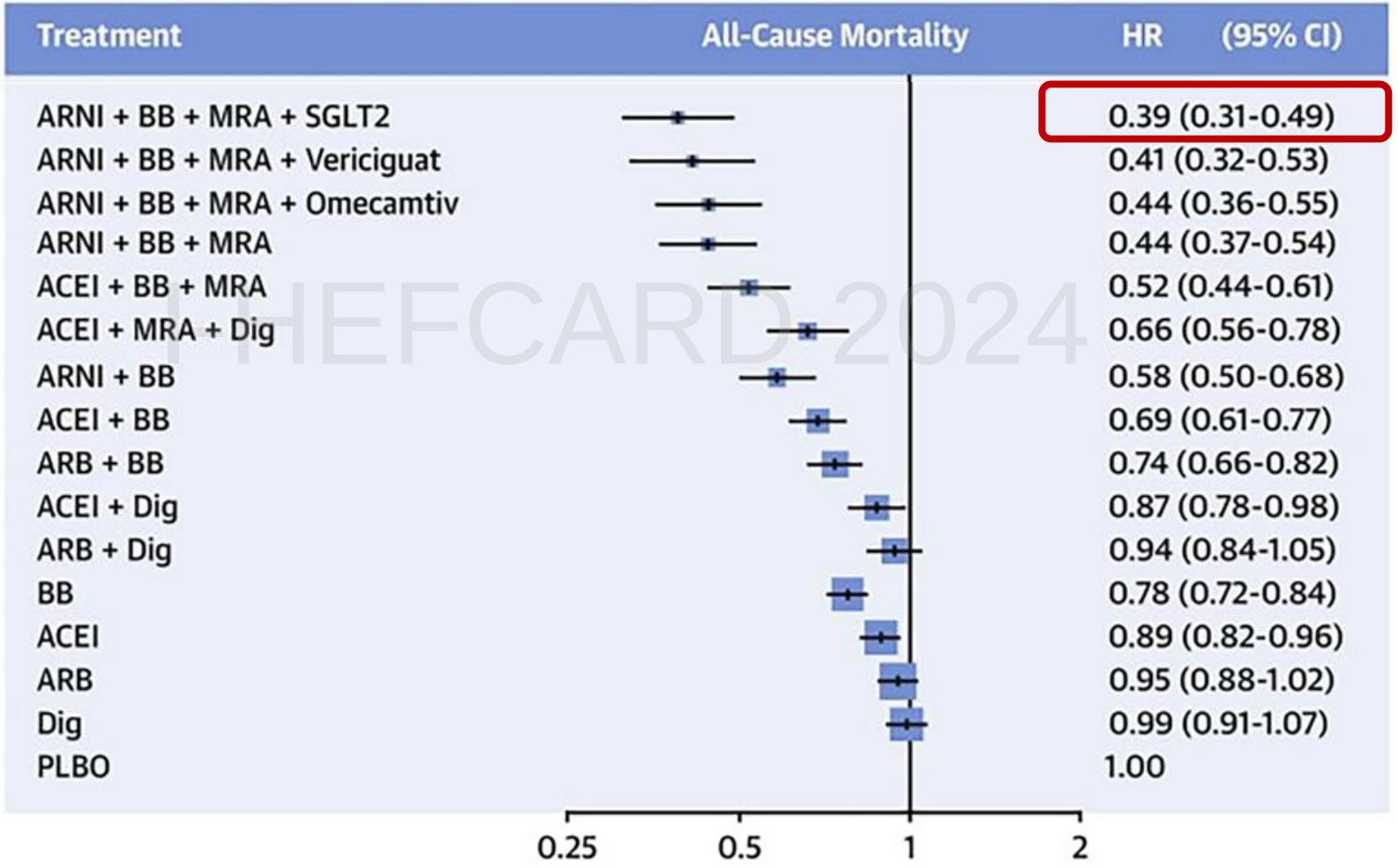

*Malgie J et al. European Journal of Heart Failure (2024) doi:10.1002/ejhf.3267*






Savarese G, et al. J Am Coll Cardiol HF. 2023;11(1):1-14.

# Relative Risk Reduction of Different Pharmacological Treatment Combinations for Heart Failure

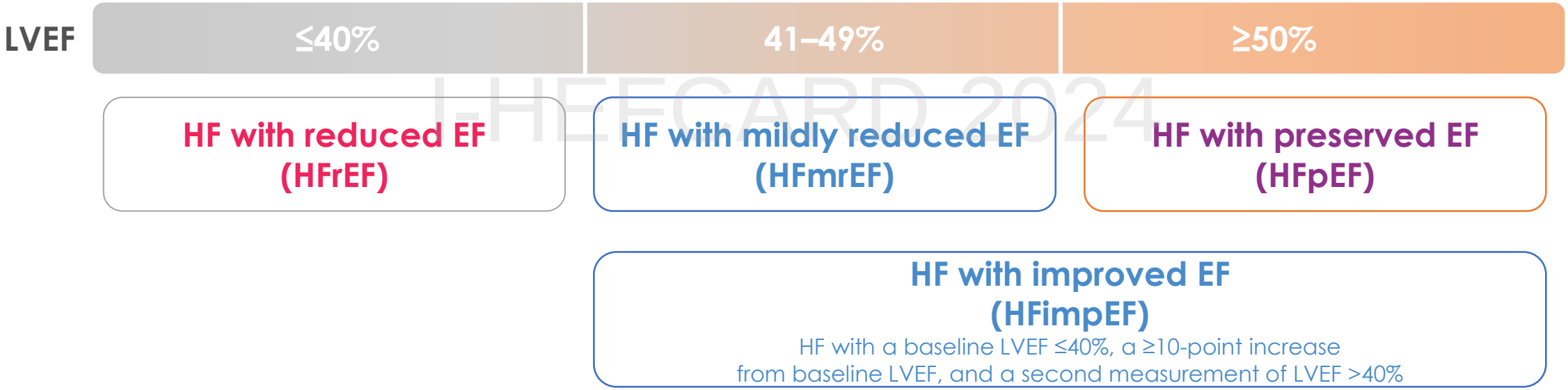







Tromp J. et al .J Am Coll Cardiol HF 2022;10:73–84

# The new universal definition of heart failure classifies the different phenotypes according to LVEF

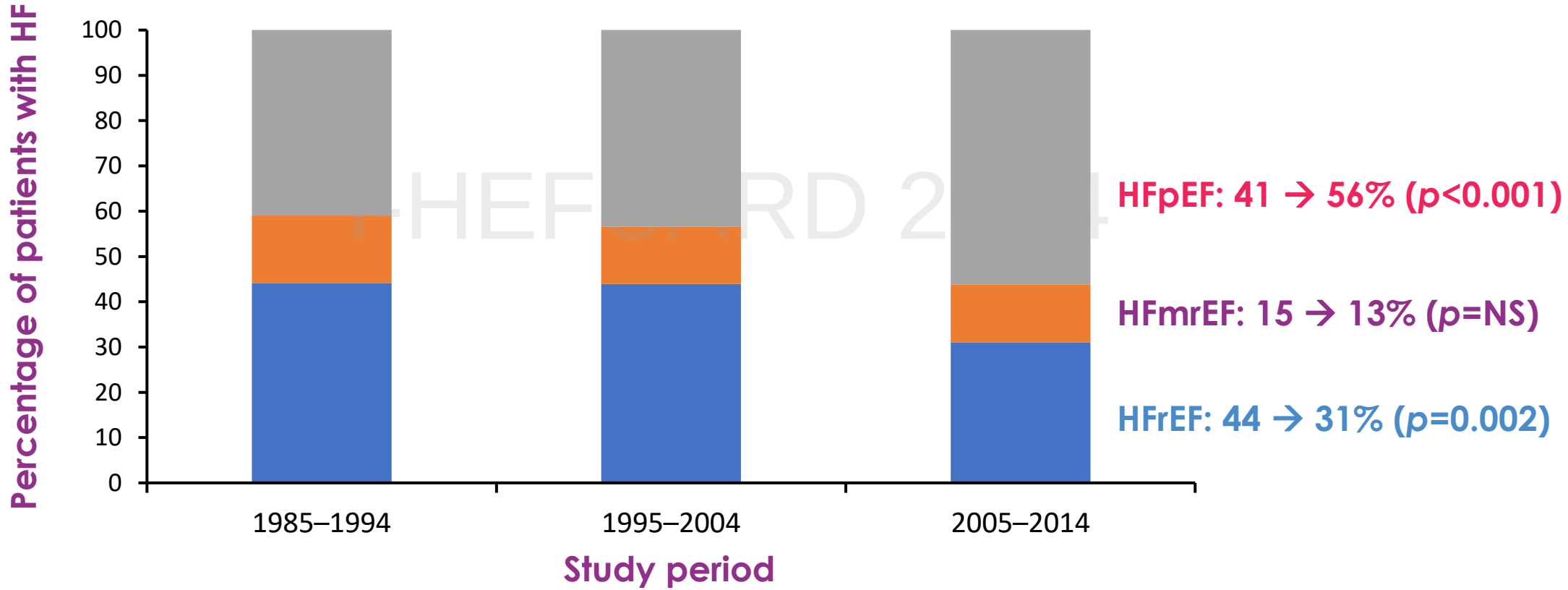





EF, ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction.
Bozkurt B *et al*. *Eur J Heart Fail*. 2021;23:352.

# The proportion of HF patients with HFpEF has significantly increased over time

## Framingham study participants with new-onset HF (n=894) over 3 decades




HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NS, not significant.

Vasan R *et al. JACC Cardiovasc Imaging.* 2018;11:1.

Cureus
Open Access Original Article
DOI: 10.7759/cureus.38086

# Heart Failure With Preserved Ejection Fraction: Current Status of Daily Clinical Practice in Indonesia

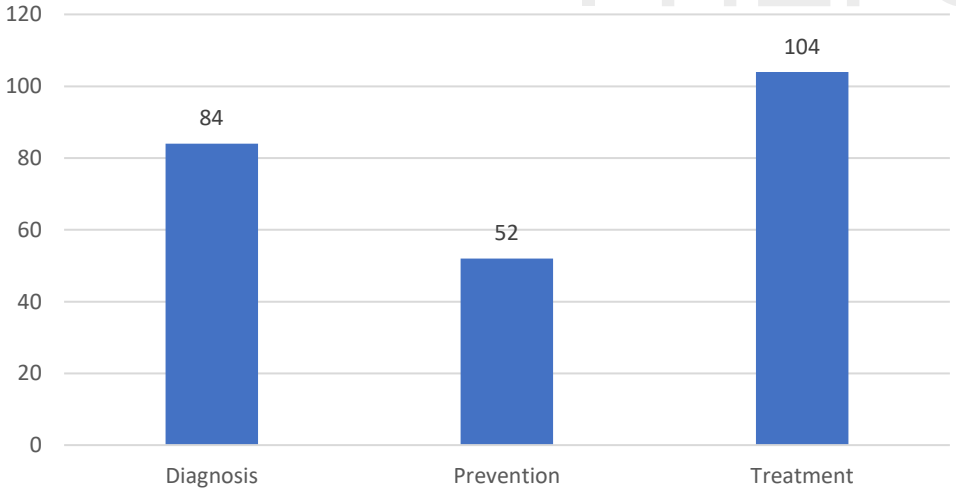
Review began 03/28/2023
Review ended 04/15/2023
Published 04/24/2023

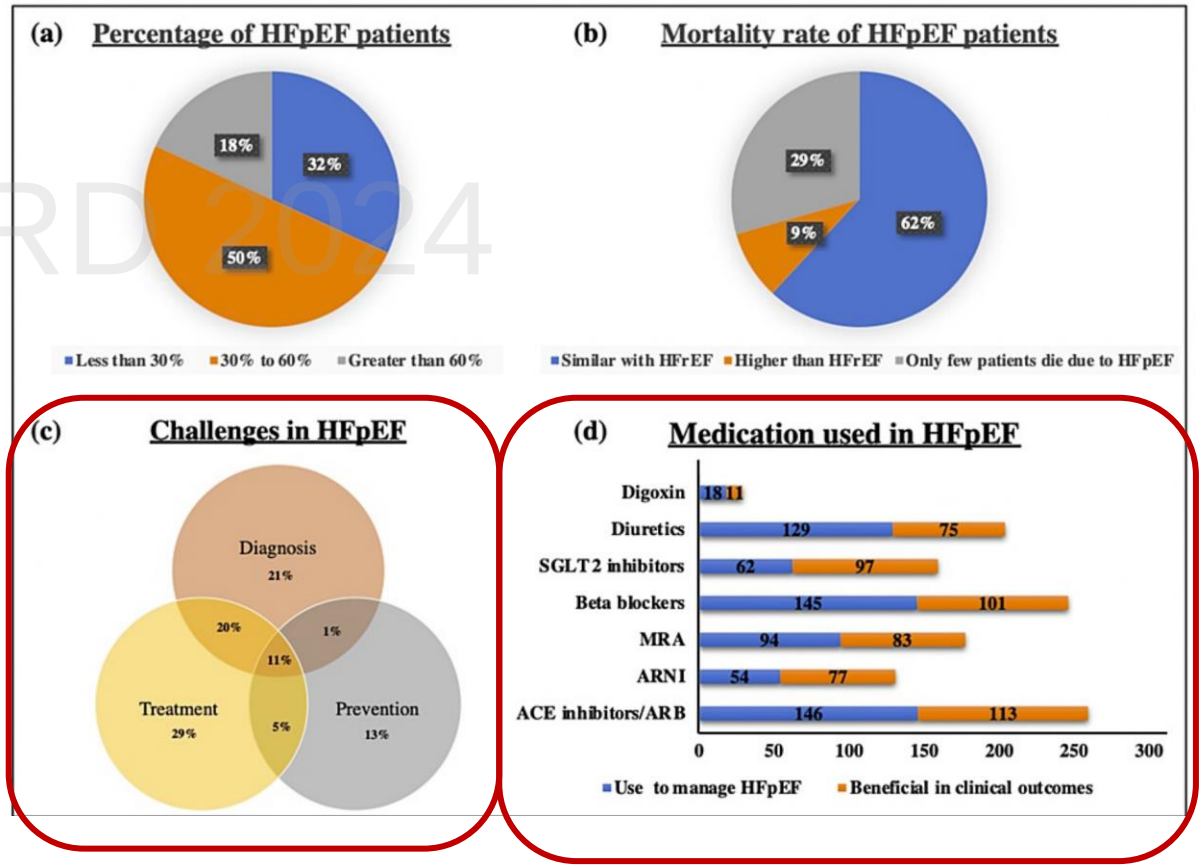


Siti E. Nauli [1, 2], Vebiona K. Prima Putri [3, 2], Habibie Arifianto [4, 2], Hawani S. Prameswari [5, 2], Anggia C. Lubis [6, 2], Edrian Zulkarnain [7, 2], Dian Y. Hasanah [8, 2], Paskariatne P. Dewi Yamin [9, 2], Triwedya I. Dewi [5, 2], Irnizarifka . [10, 2]

What are the challenges in HFpEF based on your opinion?





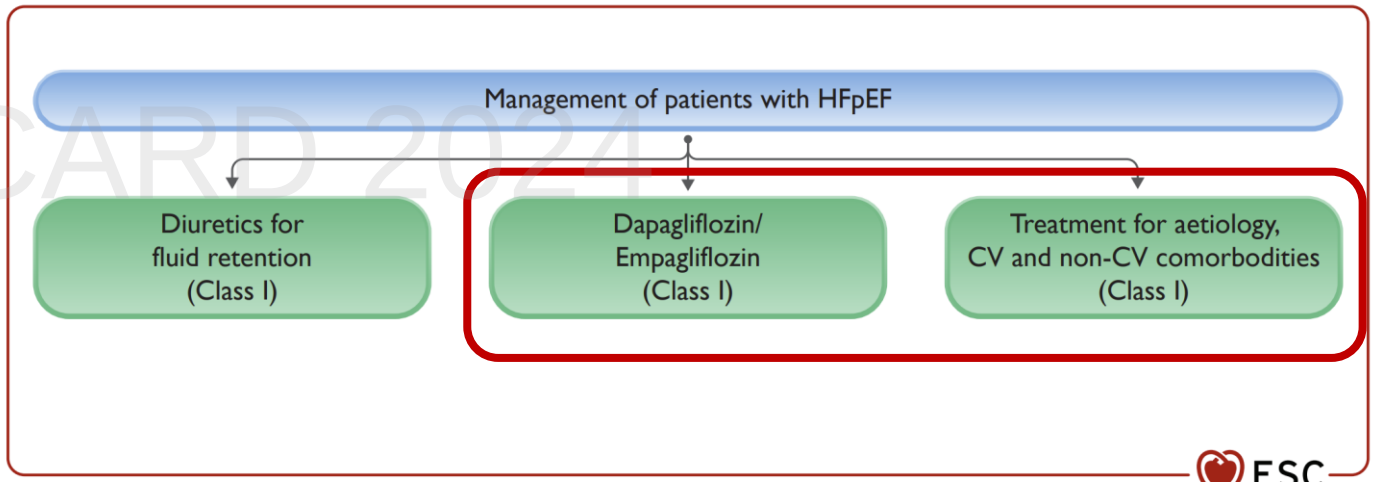
# HFpEF before SGLT2-I Era

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

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.[137] | I | C |
| An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[11] | IIb | C |
| An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[245] | IIb | C |
| A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[12,119] | IIb | C |
| An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[246] | IIb | C |
| Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.[13,247] | IIb | C |

# HFpEF NOW

## 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure




# Pharmacotherapy



## HFrEF

Not initiated

Unoptimized

Discontinued

## HFpEF

Not initiated

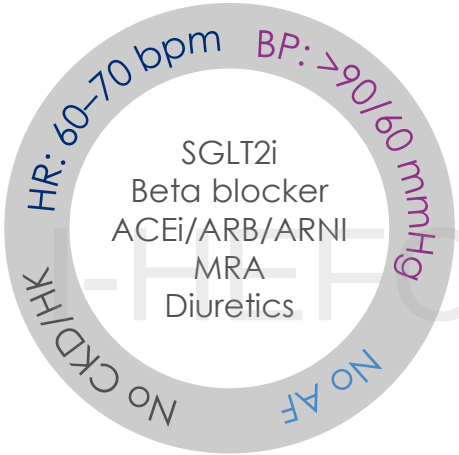
Discontinued

# Sequencing in HFrEF: Guidelines tell us *what* to do, but not *how* to do it

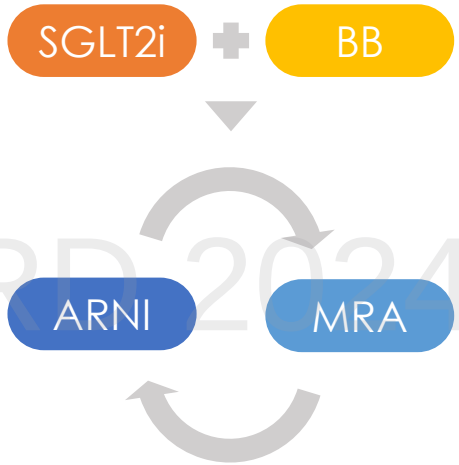
## Traditional sequencing

ARNI → BB → MRA → SGLT2i

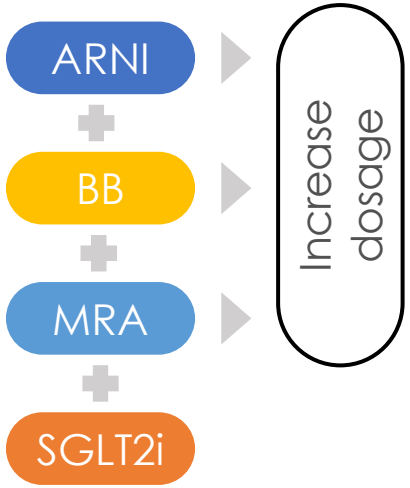
## Rosano *et al.*




## Packer, McMurray

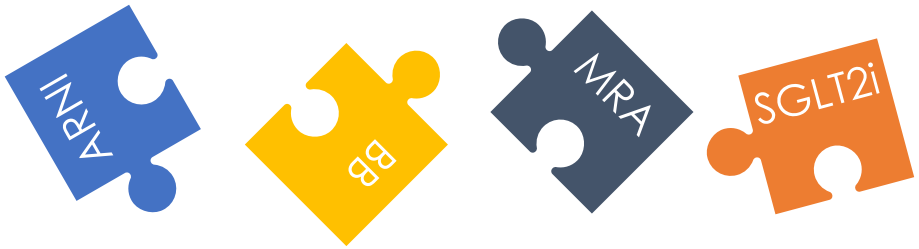



## Greene *et al.*






## GDMT



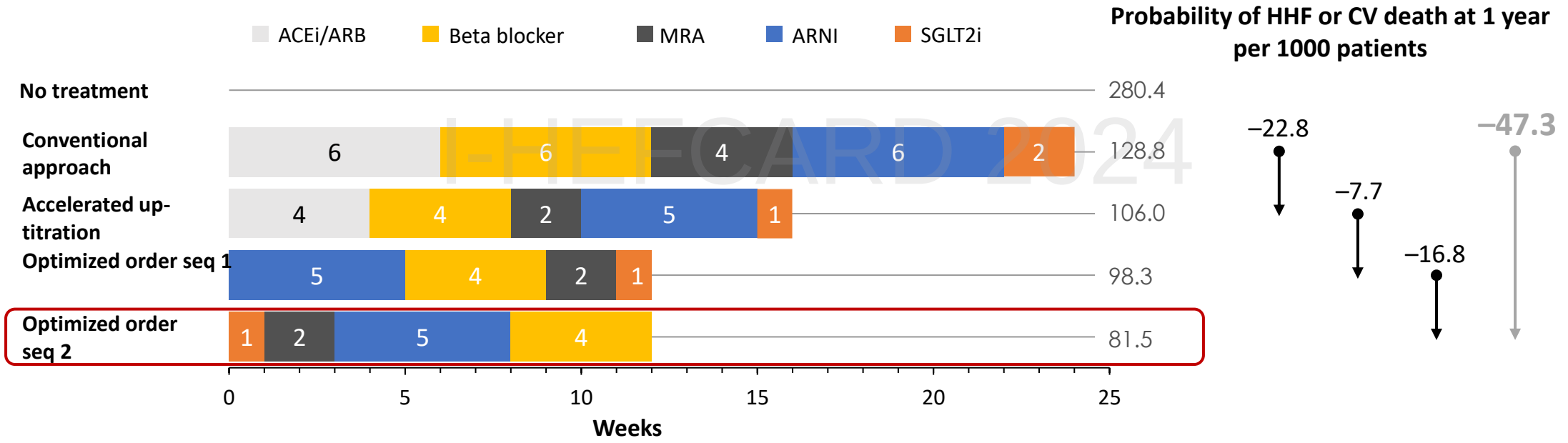

Urgency of implementation



Rosano GMC *et al. Eur J Heart Fail.* 2021;23:872; Packer M, McMurray JJV. *Eur J Heart Fail.* 2021;23:882; Greene SJ *et al. JAMA Cardiol.* 2021;6:743.

# Speed matters: Models of optimized treatment sequencing in HFrEF

**Initiating an SGLT2 inhibitor and an MRA first in the treatment sequence* achieves quadruple therapy faster and may prevent more deaths and hospital admissions**

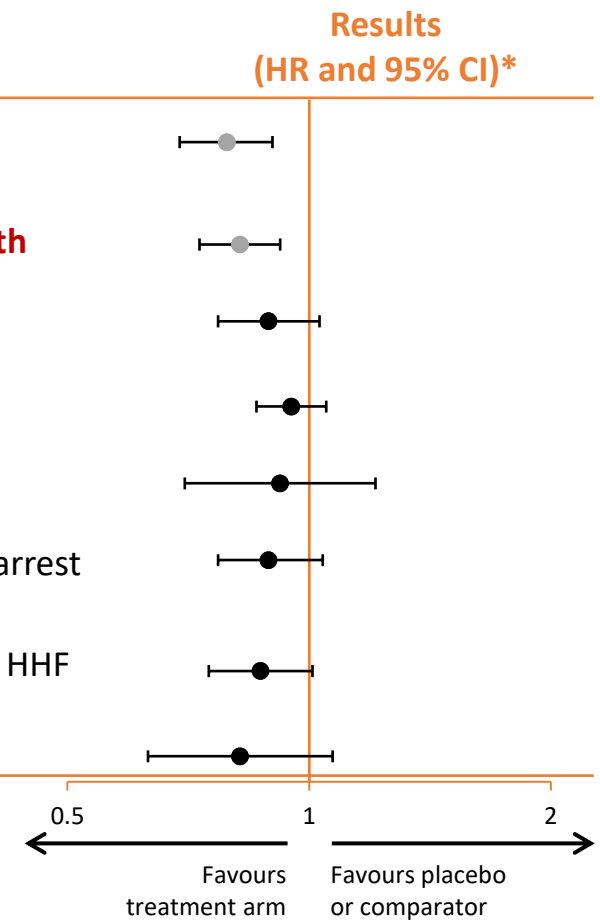





*Vs conventional approach.
Efficacy data from randomized controlled trials were used to model the impact of more rapid up-titration of therapy used in conventional order, and of using the life-saving treatments in different orders. The numbers in the bars denote the duration of up-titration periods in weeks. These findings should be tested in clinical trials.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; MRA, mineralocorticoid receptor antagonist; SGLT2(i), sodium-glucose co-transporter-2 (inhibitor). Shen L *et al. Eur Heart J.* 2022;43:2573.

# In HFpEF, SGLT2i is the only medication proven to improve outcomes

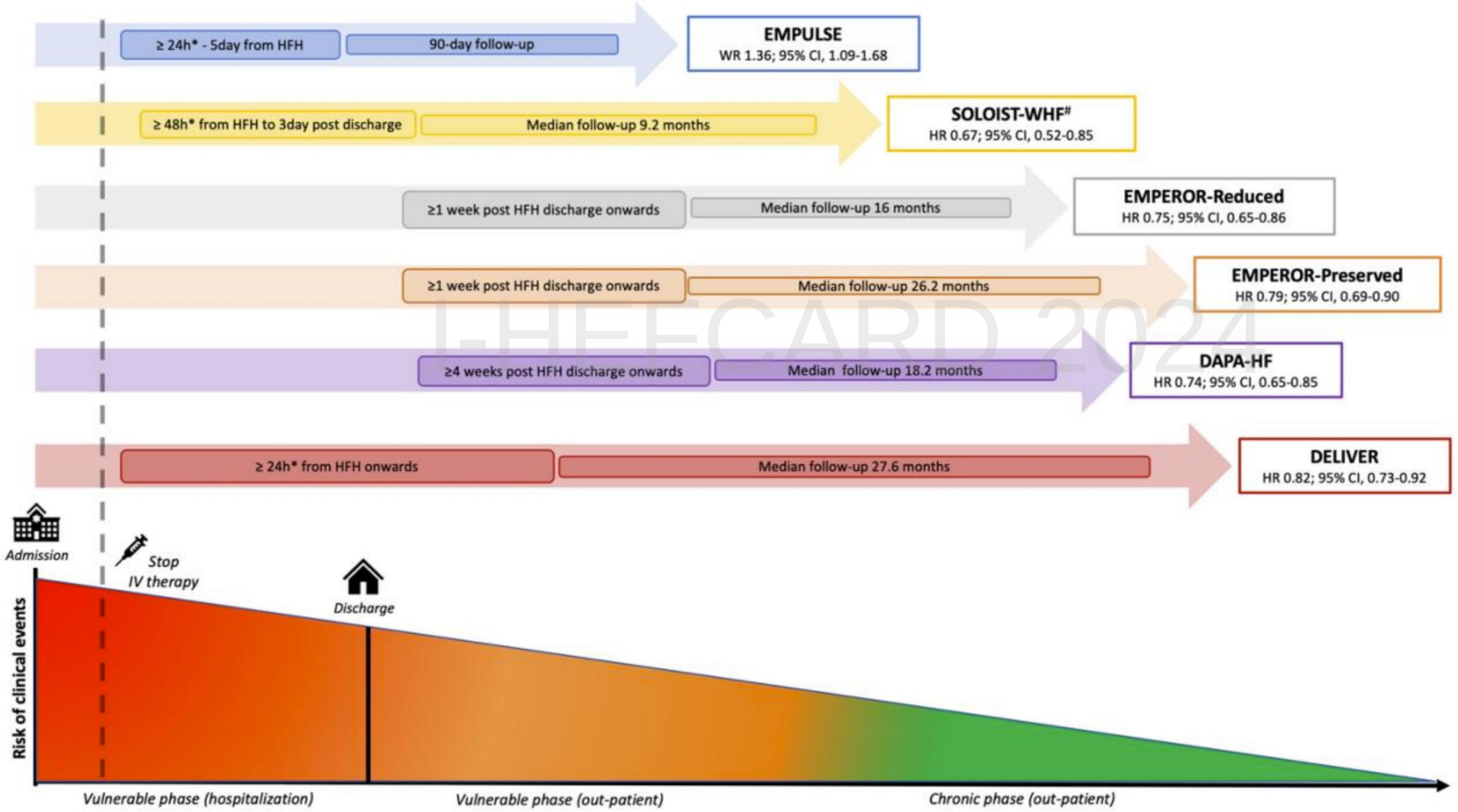
| Drug class | Trial | Treatment arms | Primary endpoint definition |
|---|---|---|---|
| **SGLT2i** | **EMPEROR-Preserved[1] (2021)** | **Empagliflozin vs placebo** | **HHF or CV death** |
| | **DELIVER[2] (2022)** | **Dapagliflozin vs placebo** | **HHF or urgent visit for HF or CV death** |
| ARB | CHARM-Preserved[3] | Candesartan vs placebo | HHF or CV death |
| | I-PRESERVE[4] | Irbesartan vs placebo | Hospitalization for CV cause or all-cause mortality |
| ACEi | PEP-CHF[5] | Perindopril vs placebo | All-cause mortality or HHF |
| MRA | TOPCAT[6] | Spironolactone vs placebo | HHF or CV death or aborted cardiac arrest |
| ARNI | PARAGON-HF[7] | Sacubitril/valsartan vs valsartan | CV death + total (first and recurrent) HHF |
| Digoxin | DIG ancillary[8] | Digoxin vs placebo | HHF or HF mortality |






**Comparison of studies should be interpreted with caution because of differences in study design, populations and methodology.**
*For PARAGON-HF, the primary endpoint is given as rate ratio (95% CI).[7] ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter-2 inhibitor. See slide notes for references.

# Timeline of SGLT2 inhibitor trials targeting patients with heart failure






Monzo L, et al. Eur Heart J Supplements (2023) 25 (Supplement C), C309–C315

# SGLT2 inhibitors are a foundational disease-modifying treatment in HF recommended across the LVEF spectrum[1–3]

| HFrEF (LVEF ≤40%) | HFmrEF (LVEF 41–49%) | HFpEF (LVEF ≥50%) |
|---|---|---|
| **2021 ESC Guidelines[1]** | **2021/2023 ESC Guidelines[1,2]** | **2021/2023 ESC Guidelines[1,2]** |
| Diuretics, as needed (1) | Diuretics, as needed (1) | Diuretics, for fluid retention (1) |
| **SGLT2i* (1)** | **SGLT2i* (1)** | **SGLT2i* (1)** |
| ARNI/ACEi† (1) | ACEi, ARB, ARNI (2b) | Treatment for aetiology, CV and non-CV comorbidities (1) |
| MRA (1) | MRA (2b) | |
| Beta blocker (1) | Beta blocker (2b) | |
| **2022 AHA/ACC/HFSA Guideline[3]** | **2022 AHA/ACC/HFSA Guideline[3]** | **2022 AHA/ACC/HFSA Guideline[3]** |
| Diuretics, as needed (1) | Diuretics, as needed (1) | Diuretics, as needed (1) |
| **SGLT2i (1)** | **SGLT2i (2a)** | **SGLT2i (2a)** |
| NYHA II–III: ARNI NYHA II–IV: ACEi, ARB (1) | ACEi, ARB, ARNI (2b) | ARNI‡ (2b) |
| MRA (1) | MRA (2b) | MRA‡ (2b) |
| Beta blocker (1) | Evidence-based beta blocker for HFrEF (2b) | ARB‡ (2b) |



1. McDonagh TA *et al. Eur Heart J.* 2021;42:3599; 2. McDonagh TA *et al. Eur Heart J.* 2023;44:3627; 3. Heidenreich PA *et al. J Am Coll Cardiol.* 2022;79:e263.

# Guideline recommendations for SGLT2 inhibitors are based on clinical trial data

## HFrEF (LVEF ≤40%)

### EMPEROR-Reduced[1,2]

3730 patients with HFrEF (LVEF ≤40%); empagliflozin vs placebo; median follow-up: 16 months

RRR 25%

**CV death or first HHF**

HR: 0.75 (95% CI: 0.65, 0.86); *p*<0.001; NNT=19; ARR: 5.2%

### DAPA-HF[3]

3744 patients with HFrEF (LVEF ≤40%); dapagliflozin vs placebo; median follow-up: 18.2 months

RRR 26%

**Composite of worsening HF* or death from CV causes**

HR: 0.74 (95% CI: 0.65, 0.85); *p*<0.001; NNT=21

## HFmrEF (LVEF 41–49%) HFpEF (LVEF ≥50%)

### EMPEROR-Preserved[4]

5988 patients with HFmrEF and HFpEF (LVEF >40%); empagliflozin vs placebo; median follow-up: 26.2 months

RRR 21%

**CV death or first HHF**

HR: 0.79 (95% CI: 0.69, 0.90); *p*<0.001; NNT=31; ARR: 3.3%

### DELIVER[5]

6263 patients with HFmrEF and HFpEF (LVEF >40%); dapagliflozin vs placebo; median follow-up: 2.3 years

RRR 18%

**Composite of time to first occurrence of CV death, HHF, urgent HF visit**

HR: 0.82 (95% CI: 0.73, 0.92); *p*<0.001†

## Hospitalized after HFE

### EMPULSE[6]

530 patients hospitalized after a heart failure event; empagliflozin vs placebo

36%

**More likely to experience clinical benefit‡ vs placebo**

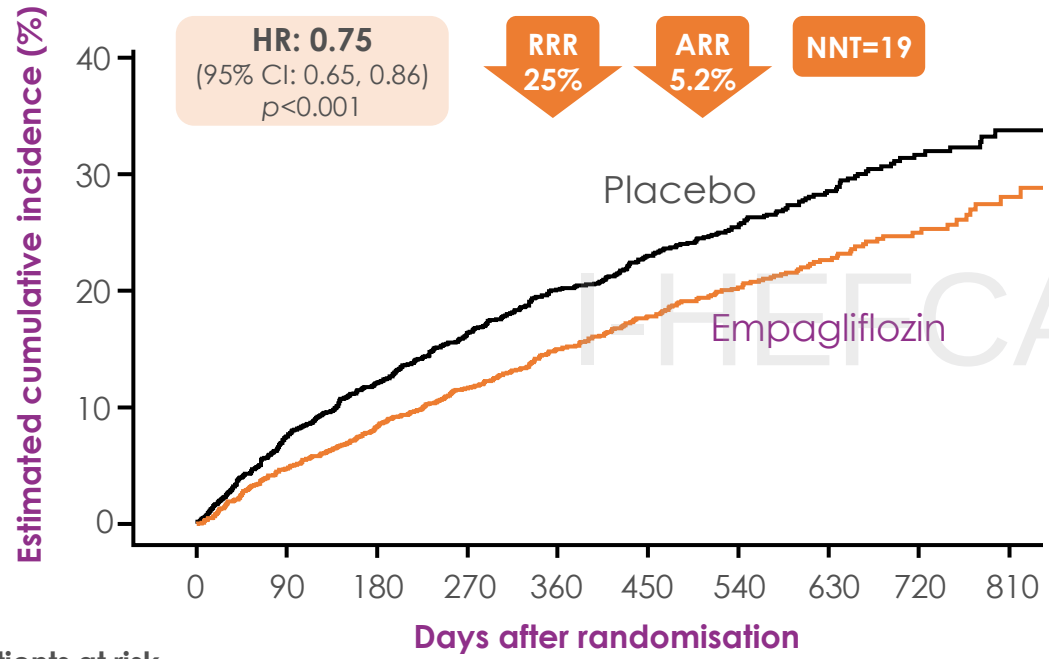
Win ratio: 1.36 (95% CI: 1.09, 1.68); *p*=0.0054



1. Packer M *et al. N Engl J Med.* 2020;383:1413; 2. Butler J *et al. Eur J Heart Fail.* 2020;22:1991; 3. McMurray JJV *et al. N Engl J Med.* 2019;381:1995; 4. Anker SD *et al. N Engl J Med.* 2021;385:1451; 5. Solomon SD *et al. N Engl J Med.* 2022;387:1089; 6. Voors AA *et al. Nat Med.* 2022;28:568.

# Empagliflozin showed a clinically meaningful RRR in the composite primary endpoint of CV death or HHF in both EMPEROR-Reduced and EMPEROR-Preserved[1,2]

## EMPEROR-Reduced[1]



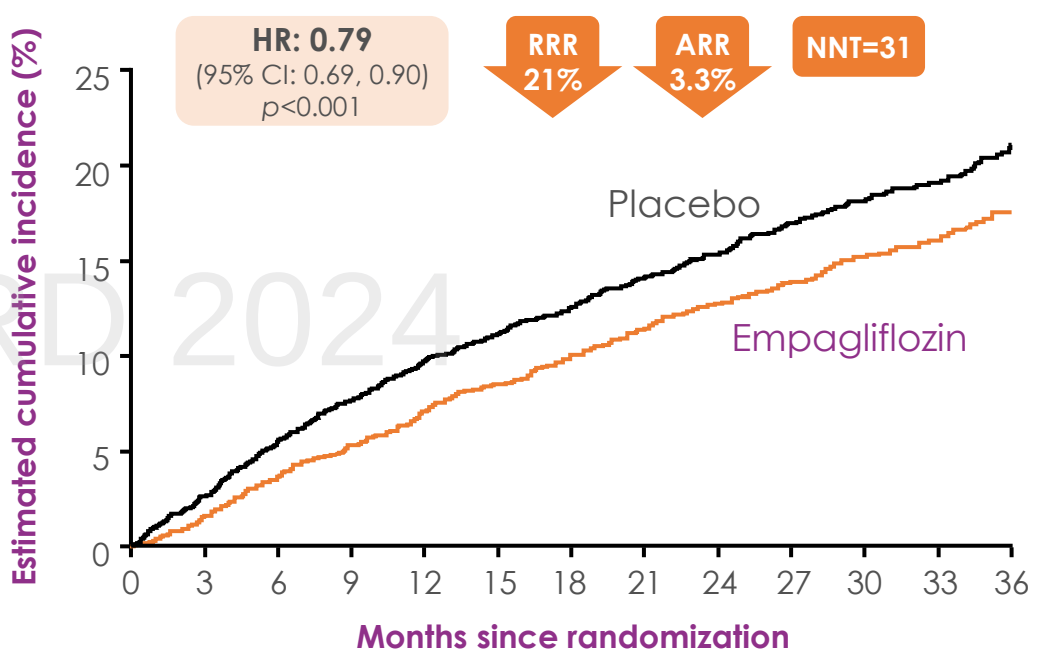

**Patients at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 1867 | 1715 | 1612 | 1345 | 1108 | 854 | 611 | 410 | 224 | 109 |
| Empagliflozin | 1863 | 1763 | 1677 | 1424 | 1172 | 909 | 645 | 423 | 231 | 101 |

361 (19.4%) patients with event
Rate: 15.8/100 patient-years

462 (24.7%) patients with event
Rate: 21.0/100 patient-years

## EMPEROR-Preserved[2]




| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2991 | 2888 | 2786 | 2706 | 2627 | 2424 | 2066 | 1821 | 1534 | 1278 | 961 | 681 | 400 |
| 2997 | 2928 | 2843 | 2780 | 2708 | 2491 | 2134 | 1858 | 1578 | 1332 | 1005 | 709 | 402 |

415 (13.8%) patients with event
Rate: 6.9/100 patient-years

511 (17.1%) patients with event
Rate: 8.7/100 patient-years

ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk reduction.

1. Packer M *et al. N Engl J Med.* 2020;383:1413; 2. Anker S *et al. N Engl J Med*. 2021;385:1451.

# Early benefits with empagliflozin were observed in both EMPEROR-Reduced and EMPEROR-Preserved[1,2]

## EMPEROR-Reduced[1]

*Combined risk of death, HHF or an emergent/urgent heart failure visit requiring intravenous treatment*

Statistical significance was reached **12 days after randomization** and was sustained from day 34

## EMPEROR-Preserved[2]

*Time to CV death or first HHF (primary endpoint)*

Statistical significance was reached **18 days after randomization** and was sustained for the duration of the follow-up period



CV, cardiovascular; HHF, hospitalization for heart failure.

1. Packer M *et al. Circulation.* 2021;143:326; 2. Butler J *et al. Eur J Heart Fail.* 2022;doi:10.1002/ejhf.2420.

# EMPEROR-Preserved and EMPEROR-Reduced both met their key prespecified endpoints

| | EMPEROR-Reduced[1] | EMPEROR-Preserved[2] |
|---|---|---|
| Primary endpoint: Adjudicated **CV death or HHF** | ✓ | ✓ |
| Key secondary endpoint: Adjudicated **first and recurrent HHF** | ✓ | ✓ |
| Key secondary endpoint: **eGFR slope** | ✓ | ✓ |



In Indonesia, Empagliflozin is not yet indicated for the treatment of Kidney Disease

1. Packer M et al. N Engl J Med. 2020;383:1413; 2. Anker S et al. N Engl J Med. 2021; doi:10.1056/NEJMoa2107038.

# Clear practical guidance on SGLT2 inhibitor use can facilitate successful GDMT

## Dosing

## How should SGLT2 inhibitors be started?

- Single dose[1,2] ✓
- Once daily[1,2] ✓
- No titration[1,2] ✓
- With or without food[1,2] ✓
- Any time of day, but regularly[1,2] ✓



GDMT, guideline-directed medical therapy; SGLT2, sodium-glucose co-transporter-2.

1. Jardiance® Summary of Product Characteristics. Boehringer Ingelheim International GmbH; 2. Forxiga® Summary of Product Characteristics. AstraZeneca AB.

# Practical guide to initiation of SGLT2 inhibitors in patients with heart failure

**Eligible patients**
- All symptomatic HF patients, regardless of LVEF, diabetic status and care setting

**Contraindications**
- Type 1 diabetes mellitus or history of ketoacidosis
- Hypotension (caution if SBP <100 mmHg)
- Severe CKD (dapagliflozin: eGFR <25 ml/min/1.73m$^2$; empagliflozin: eGFR <20 ml/min/1.73m$^2$)[a]
- Pregnancy/risk of pregnancy and breastfeeding period
- Caution in patients with history of recurrent genital or urinary tract infections
- In AHF, use of inotropes within the last 24h or use of IV vasodilators or LD escalation within the last 6h

**Dose**
- 10 mg once daily for both dapagliflozin and empagliflozin (irrespective of food)

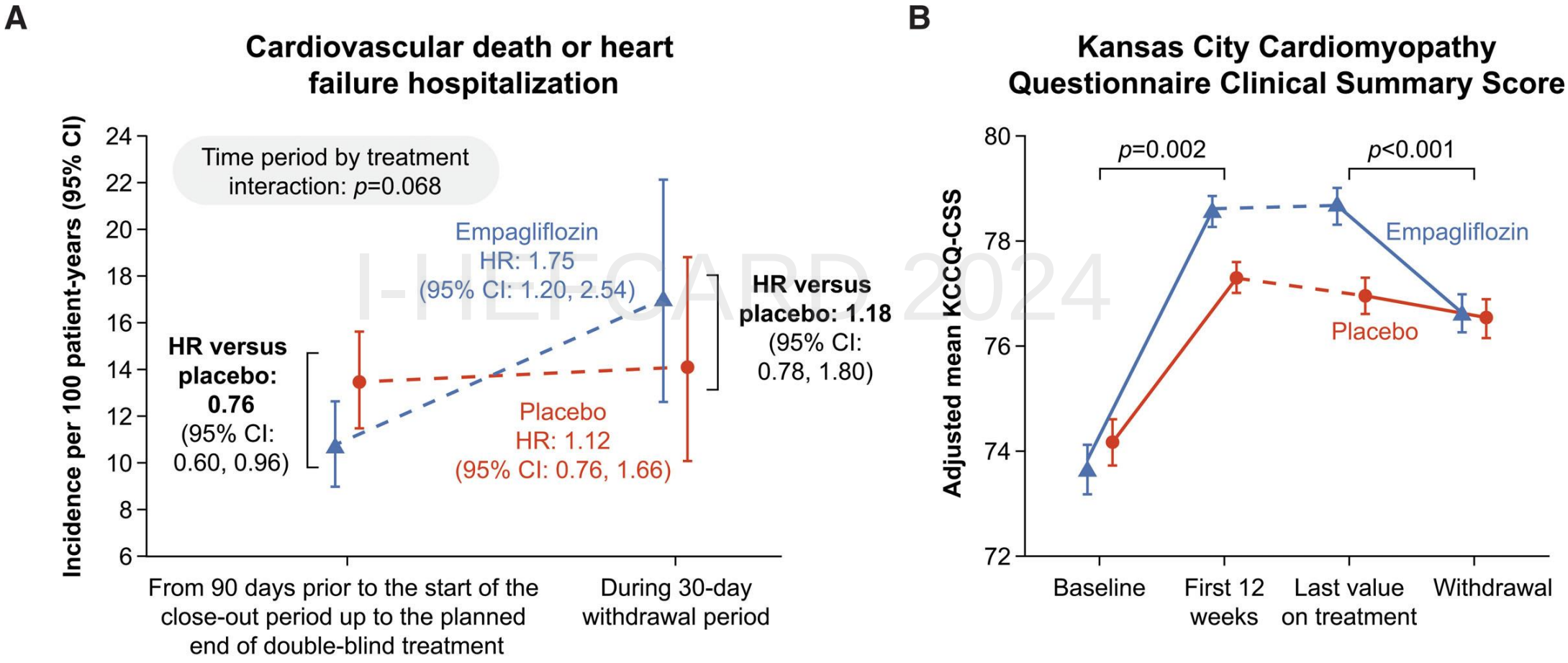


**Monitoring**
- Check renal function when starting the therapy and then after 1-2 weeks[a,b]
- Blood glucose (if SGLT2 inhibitors are used in association with anti-diabetic drugs – mainly insulin and insulin secretagogues)
- Acute illness or major surgery[c]

**Patient/caregiver counselling**
- Ensure adequate daily genital hygiene
- Watch for symptoms of volume depletion[d], uro-genital infections[e] and diabetic ketoacidosis[f]
- Avoid dehydration, low carbohydrate (ketogenic) diet and excessive alcohol consumption

Monzo L, et al. Eur Heart J Supplements (2023) 25 (Supplement C), C309–C315

# Blinded withdrawal of long-term randomized treatment with empagliflozin or placebo in patients with heart failure






Placebo 163/3623 (4.5%)
Empagliflozin 132/3670 (3.6%)

Placebo 40/3381 (1.2%)
Empagliflozin 49/3418 (1.4%)

Values for KCCQ in the same cohort of 3900–4000 patients who provided data at the end of the planned withdrawal period

Packer M et al. Circulation 2023;148:1011-22.

# Take home messages

SGLT2-inhibitors have been shown to reduce risks of clinical events in patients with heart failure, with early and sustained benefits regardless of ejection fraction.



Their clinical benefit has been demonstrated early and sustained, without any major safety concern.

Unless contraindicated, SGLT2 inhibitors should be rapidly initiated as part of the foundational therapy in all patients with HF