The 3rd Indonesian Symposium on Heart Failure and Cardiometabolic Disease 2023

DELIVERING THE NEW ADVANCES IN TREATMENT OF HEART FAILURE

Silfi Pauline Sirait, MD, FIHA

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HF is a growing public health problem, with high morbidity and mortality

BURDEN

HF affects **~64 million** people worldwide[1]

HOSPITALIZATION

HF is the number one cause of hospitalization in people >65 years[2,a]

hHF is **projected to rise by ~50%** over the next 25 years[3]

MORTALITY

The 5-year mortality rate for patients with HF is **~50%**[4]

Mortality significantly increases after each HF readmission[5]

[a]In developed countries.

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Lancet. 2018;392(10159):1789-1858; 2. Cowie MR et al. ESC Heart Fail. 2014;1(2):110-145;
3. Groenewegen A et al. Eur J Heart Fail. 2020;22(8):1342-1356; 55; 4. Jones NR et al. Eur J Heart Fail. 2019;21(11):1306-1325; 5. Setoguchi S et al. Am Heart J. 2007;154(2):260-266.

Despite poor prognosis, there is a lack of urgency for early identification and initiation of guideline recommended therapies

Over 40% have HF symptoms up to 5 years prior to diagnosis[1]

~75% are diagnosed with HF following an unplanned hHF[1,2,a]

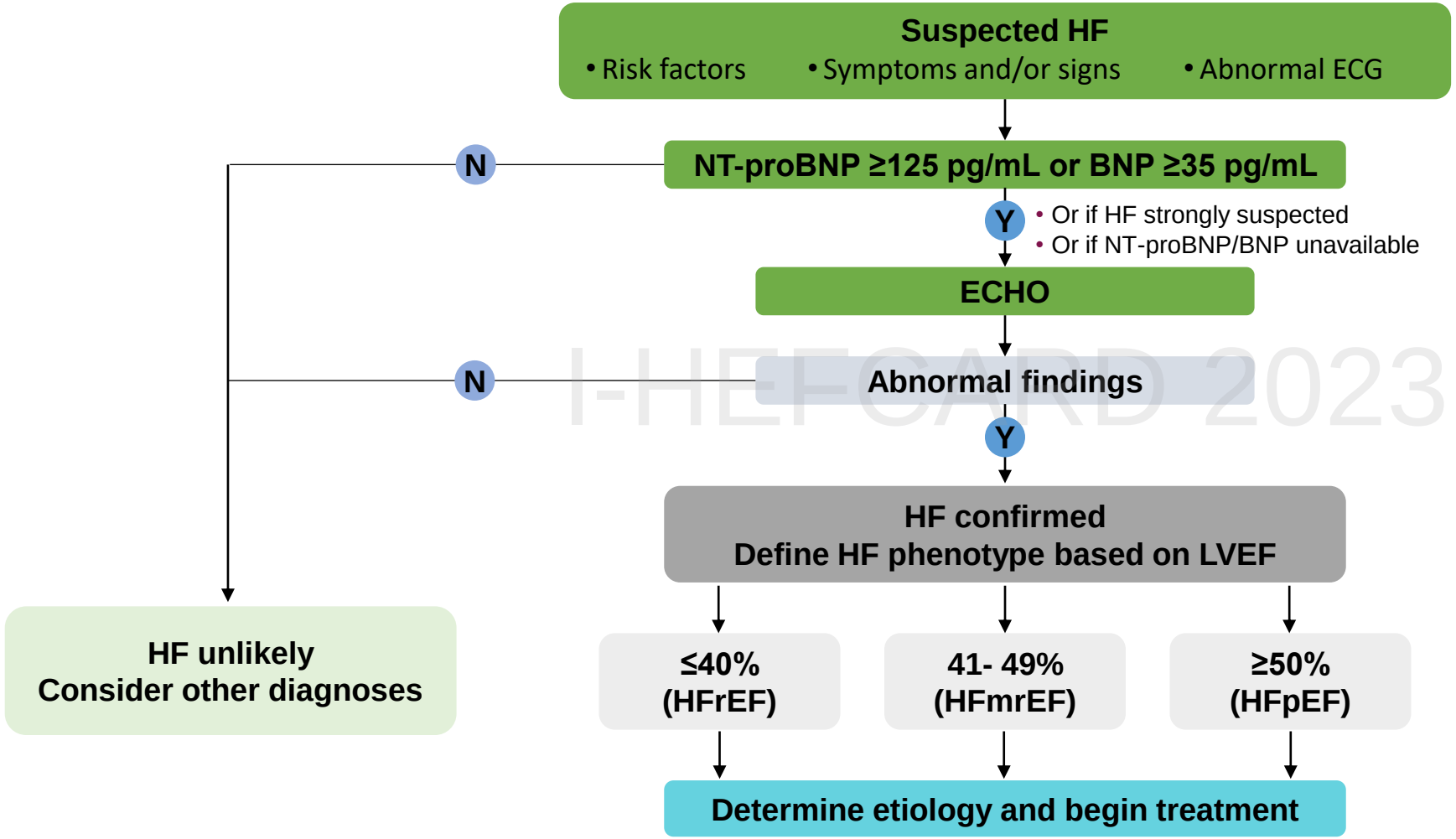
Therapy optimisation for HF is **suboptimal** for the majority of patients[3]

Over 30% mortality rate 1 year after hHF[2,b]

[a]Based on data from 2010-2013[1] and 2017[2]; [b]Based on patients diagnosed with HF during hHF from 2012-2015.

1. Bottle A et al. *Heart.* 2018;104(7):600-605; 2. Lawson CA et al. Article and supplementary appendix. *Lancet Public Health*. 2019;4(8):e406-e420; 3. Ghazi L et al. *J Am Coll Cardiol*. 2022;79(22):2203-2213.

ESC Diagnostic Algorithm for HF



BNP = B-type natriuretic peptide; ECG = electrocardiogram; ECHO = echocardiography; ESC = European Society of Cardiology; 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; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

McDonagh TA et al. *Eur Heart J*. 2021;42:3599-3726.

Changes in LVEF Occur Over Time and Are Associated With Specific Patient Characteristics

Factors associated with progression[b]:

Diabetes, ischemic heart disease, lack of specialized HF follow-up, higher NT-proBNP levels

Factors associated with recovery[c]:

Younger age, female, lower HF severity, shorter HF duration, fewer comorbidities

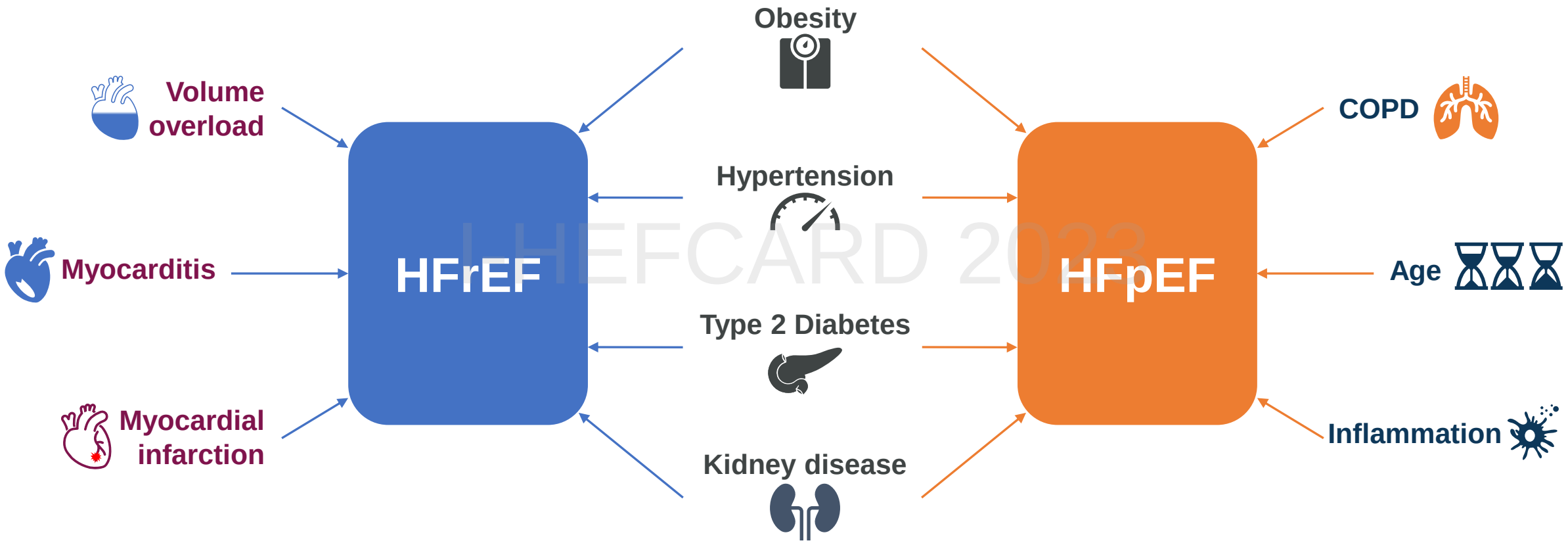
Data from patients with ≥2 EF measurements in the SwedeHF study (N=4942) between May 2000 and December 2012.

[a]Reference uses the term HF with midrange EF (EF 40-49%) for this group; [b]EF decrease; [c]EF increase.

EF = ejection fraction; 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; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Savarese G et al. *JACC Heart Fail.* 2019;7:306-317.

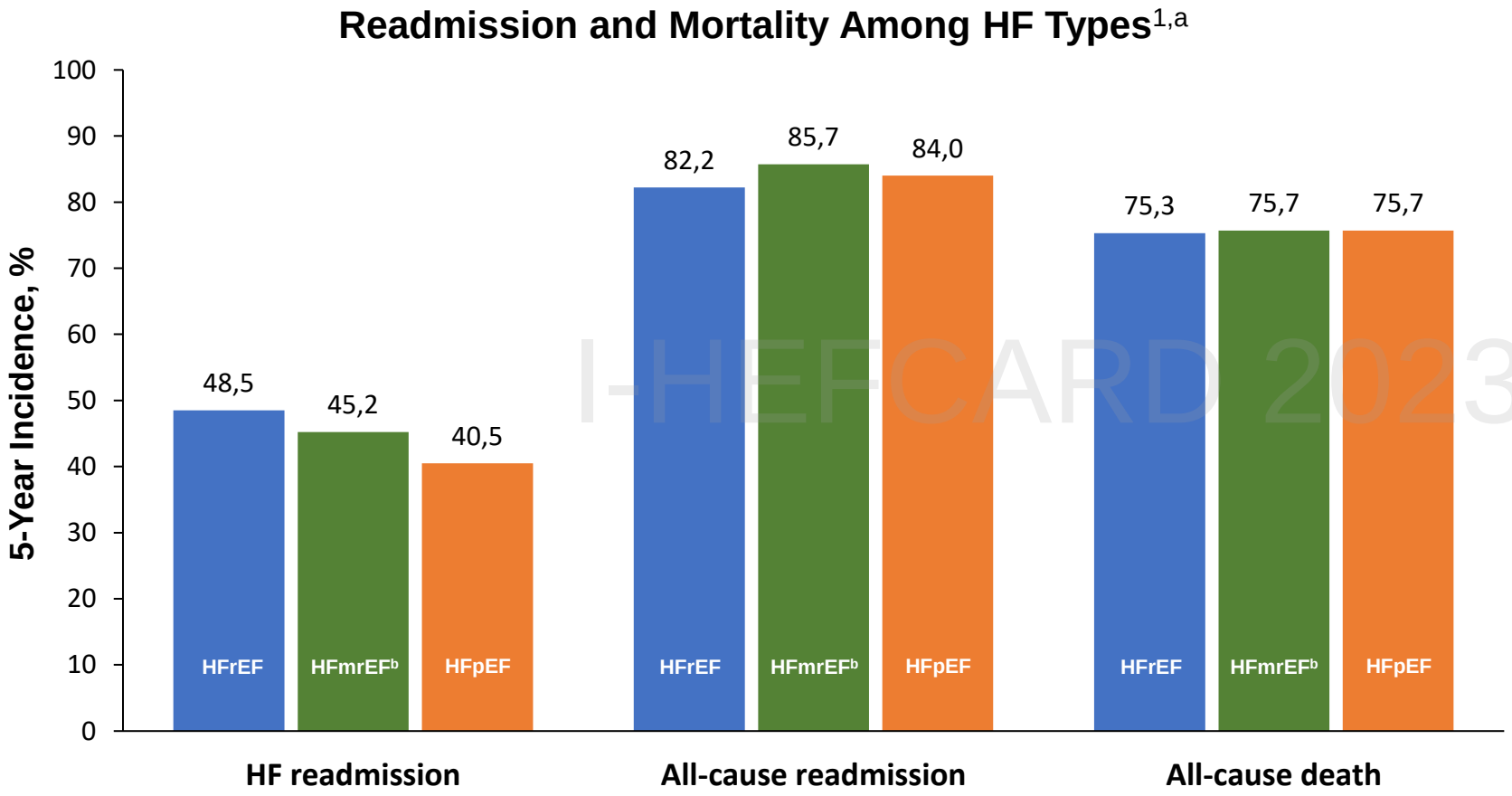
HFrEF and HFpEF share many co-morbidities and risk factors, yet are also associated with many differing factors



COPD = chronic obstructive pulmonary disease; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

Simmonds SJ et al. *Cells*. 2020;9:242.

Readmissions and Mortality Are Common Among All Types of HF



HF has the highest 30-day readmission rates compared to other diagnoses[2]

~50% of patients are readmitted at least once within 1 year of diagnosis[2]

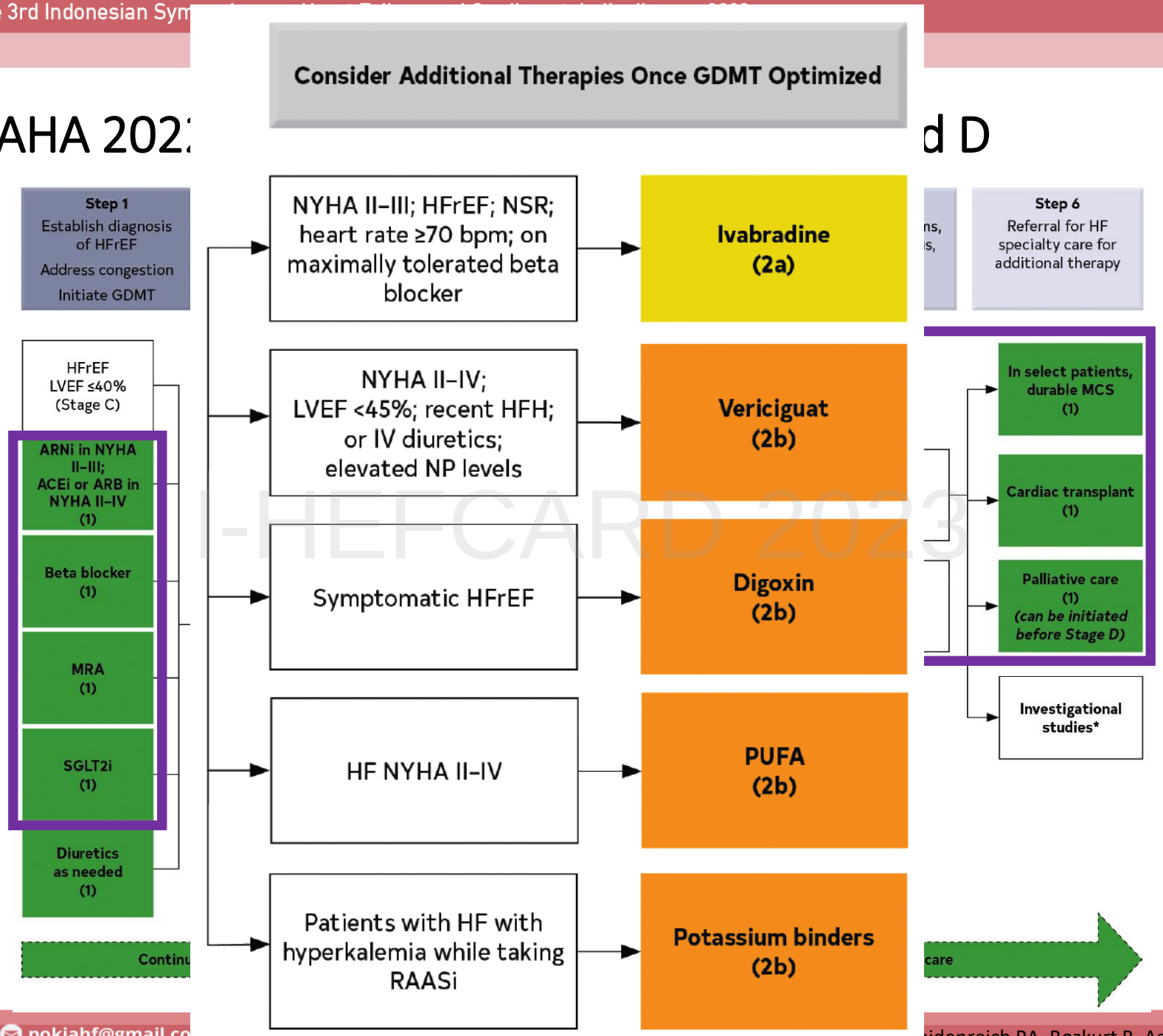
Mortality significantly increases after each HF readmission[3]

[a]Data from the Get With the Guidelines-HF registry and merged with claims from the US Centers for Medicare and Medicaid Services including a cohort of patients age ≥65 years (N=39,982) from 254 hospitals admitted for HF between 2005 and 2009; [b]Reference uses the term HFbEF (EF 41-49%) for this group.

EF = ejection fraction; HF = heart failure; HFbEF = heart failure with borderline ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; US = United States.

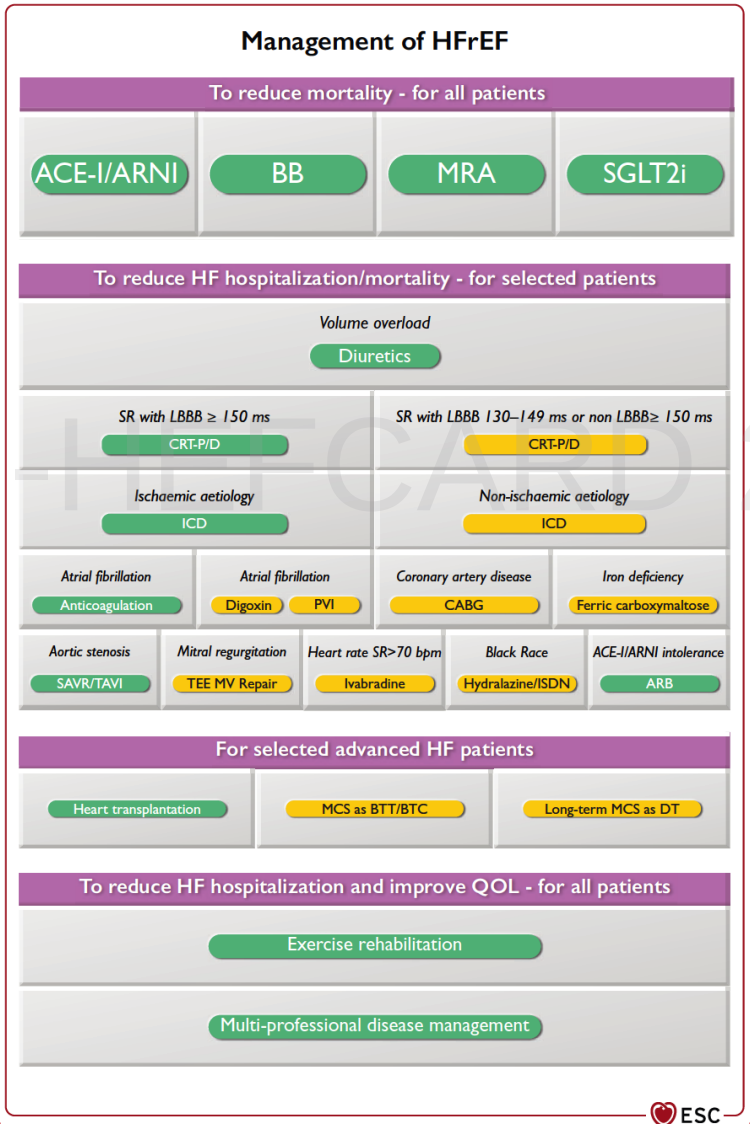
1. Shah KS et al. *J Am Coll Cardiol.* 2017;70:2476-2486; 2. Groenewegen A et al. *Eur J Heart Fail*. 2020;22:1342-1356; 3. Setoguchi S et al. *Am Heart J*. 2007;154:260-266.

ACC/AHA 202 d D



eidenreich PA, Bozkurt B, Aguilar D, et al. *Circulation*. 2022;145(18).

ESC 2021: Phenotypic Approach to the Management of HFrEF



McDonagh TA, et al. Eur Heart J. 2021

Recommendations for the treatment of patients with HFpEF

2021 ESC Guidelines

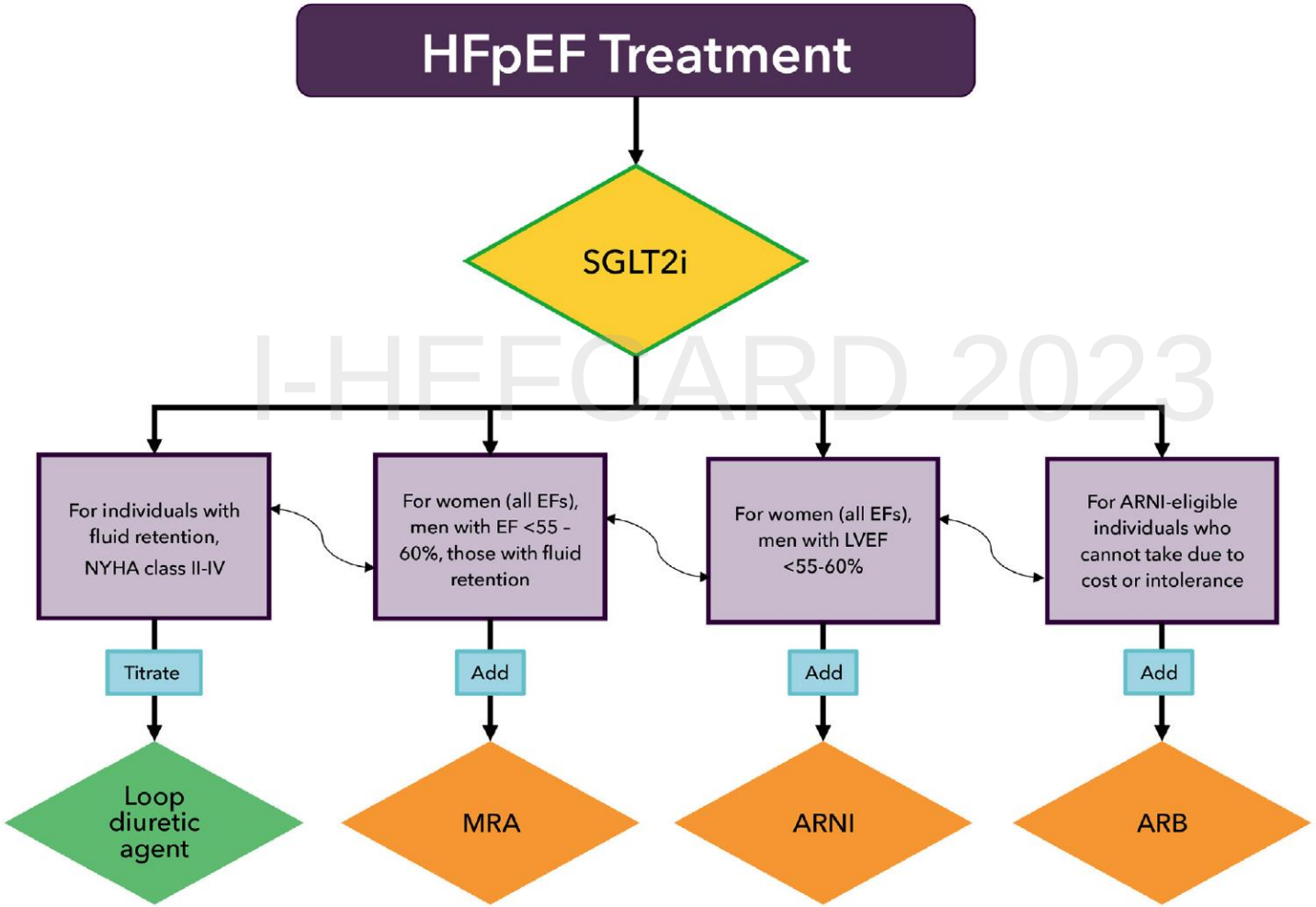
Recommendations	Class[a]	Level[b]
Screening for, and treatment of, aetiologies, and cardiovascular and non-cardiovascular comorbidities is recommended in patients with HFpEF (see relevant sections of this document).	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs.[137]	I	C

2022 ACC/AHA/HFSA Guidelines

COR	LOE	Recommendations
1	C-LD	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity.[1–3]
2a	B-R	2. In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.[4]
2a	C-EO	3. In patients with HFpEF, management of AF can be useful to improve symptoms.
2b	B-R	4. In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[5–7]
2b	B-R	5. In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[8,9]
2b	B-R	6. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[10,11]

McDonagh TA, et al. Eur Heart J. 2021
Heidenreich PA, Bozkurt B, Aguilar D, et al. Circulation. 2022;145(18).

2023 ACC Expert Consensus: Treatment Algorithm for GDMT in HFpEF



Kittleson MM, Panjrath GS, Amancherla K, Davis LL, Deswal A, Dixon DL, et al. Journal of the American College of Cardiology. 2023;81(18):1835–78.

Selected Randomized Controlled Trials in Individuals With HFpEF

	DELIVER	TOPCAT	PARAGON-HF	CHARM-PRESERVED
Size	N = 6263	N = 3445	N = 4822	N = 3023
Agent	Dapagliflozin	Spironolactone	Sacubitril/valsartan	Candesartan
EF entry criteria	>40%	≥45%	≥45%	>40%
Mean baseline LVEF	54%	56%	58%	54%
T2DM	45%	33%	43%	29%
HF medical therapy				
Diuretic agent	77%	82%	95%	75%
ACE-I or ARB	73%	84%	86%	19%
ARNi	5%	N/A	N/A	N/A
Beta-blocker	83%	N/A	80%	56%
MRA	43%	N/A	26%	12%
Primary composite outcome	Worsening HF and CV death: HR: 0.82 (0.73-0.92)	Hospitalization for HF, aborted cardiac arrest, CV death: HR: 0.89 (0.77-1.04)	Total hospitalizations for HF and CV death: Rate ratio: 0.87 (0.75-1.01)	Hospitalization for HF and CV death: HR: 0.86 (0.74-1.00)
Hospitalization for HF, HR or rate ratio (95% CI)	HR: 0.77 (0.67-0.89)	HR: 0.83 (0.69-0.99)	Rate ratio: 0.85 (0.72-1.00)	HR: 0.84 (0.70-1.00)
Urgent visit for HF, HR (95% CI)	0.76 (0.55-1.07)	NR	NR	NR
CV death, HR (95% CI)	0.88 (0.74-1.05)	0.90 (0.73-1.12)	0.95 (0.79-1.16)	0.95 (0.76-1.18)

Kittleson MM, Panjrath GS, Amancherla K, Davis LL, Deswal A, Dixon DL, et al. Journal of the American College of Cardiology. 2023;81(18):1835–78.

DELIVER: The largest trial to date in patients with LVEF >40%[1]

DELIVER[1,2]

N=6263

- LVEF >40% and evidence of structural heart disease
- Elevated NT-proBNP
- Ambulatory or hospitalized
- eGFR ≥25 mL/min/1.73 m^2

1:1 randomization

DAPA 10 mg | **Placebo**

Median follow-up: 2.3 years

Primary endpoint[2]

Composite of CV death or worsening HF (hHF or an urgent HF visit):

- Full patient population
- Patients with LVEF <60%

Secondary endpoints[2]

- Total number of hHF (first and recurrent) and CV death
- Change in KCCQ-TSS from baseline to 32 weeks
- CV death
- All-cause mortality

Baseline characteristics[1,2]

1011 pg/mL
Median NT-proBNP

54%
Average LVEF

55%
Without T2D

50%
With an eGFR <60 mL/min/1.73 m^2

10%
Hospitalized or recently discharged

~18%
With prior LVEF ≤40%

DISCLAIMER: In Indonesia, Dapagliflozin is now approved for heart failure with ejection fraction ≤40%

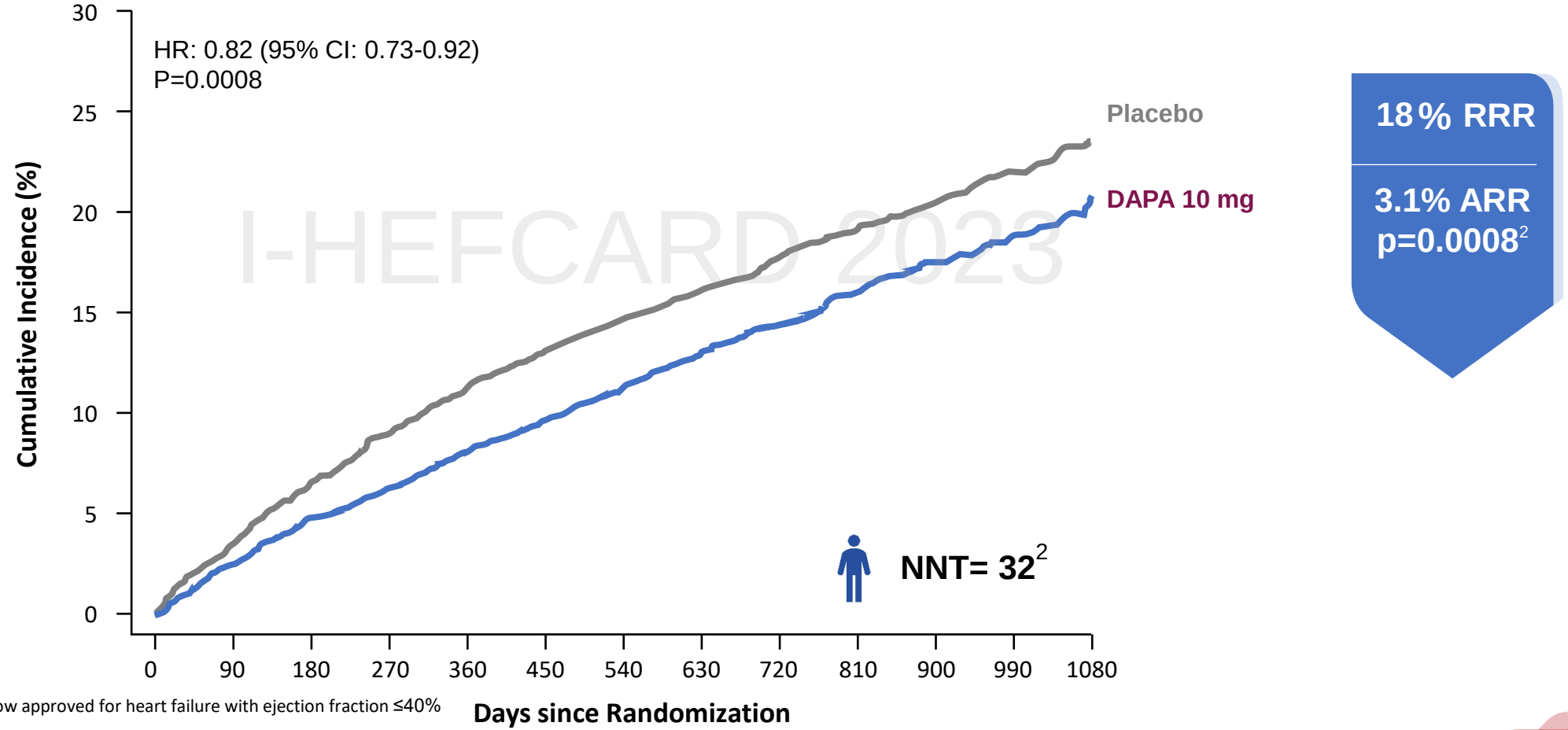
1. Solomon SD et al. *JACC Heart Fail*. 2022;10(3):184-197; 2. Solomon SD et al. Article and supplementary appendix online ahead of print. *N Engl J Med*. 2022.

Primary Endpoint: CV death or worsening HF[a] in patients with LVEF >40%[1]

DELIVER

Primary Endpoint

Composite of CV Death or Worsening HF[a]



DISCLAIMER: In Indonesia, Dapagliflozin is now approved for heart failure with ejection fraction ≤40%

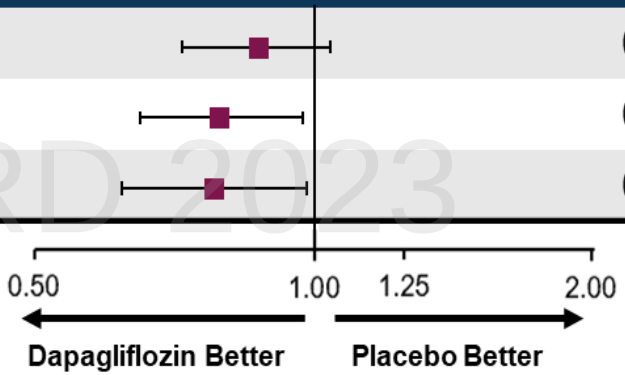
[a]hHF or an urgent HF visit.

1. Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022; 2. Solomon SD. Presented at: ESC Congress; August 26-29, 2022; Barcelona, Spain.

Primary composite endpoint across baseline LVEF subgroups[1]

DELIVER

LVEF at enrollment	DAPA 10 mg n=3131	Placebo n=3132	HR (95% CI)	HR (95% CI)	p-value
≤49%	207/1067	229/1049		0.87 (0.72-1.04)	0.72
50-59%	174/1133	211/1123		0.79 (0.65-0.97)	
≥60%	131/931	170/960		0.78 (0.62-0.98)	



No attenuation of benefit even in patients with an LVEF≥60%

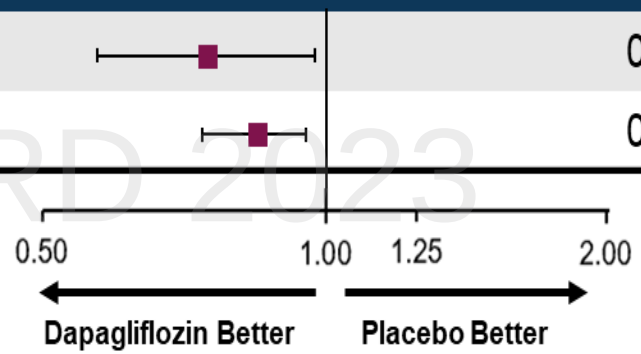
DISCLAIMER: In Indonesia, Dapagliflozin is now approved for heart failure with ejection fraction ≤40%

1. Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022; 2. Solomon SD. Presented at: ESC Congress; August 26-29, 2022; Barcelona, Spain.

Primary composite endpoint depending on presence or absence of improved EF to >40%

DELIVER

Prior LVEF ≤40%	DAPA 10 mg n=3131	Placebo n=3132	HR (95% CI)	HR (95% CI)	p-value
Yes	92/572	119/579		0.74 (0.56-0.97)	NS
No	420/2559	491/2553		0.84 (0.73-0.95)	



Consistent benefit in patients with heart failure with improved ejection

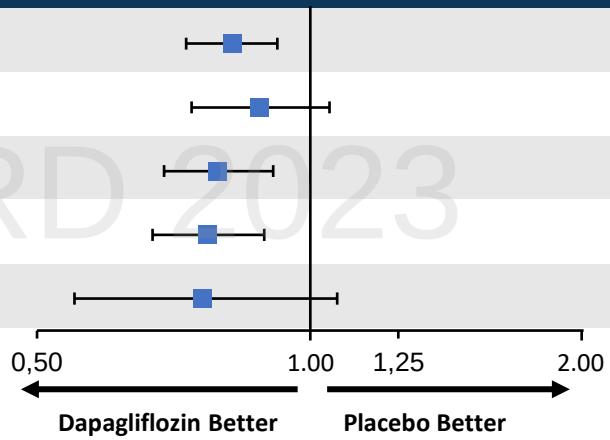
DISCLAIMER: In Indonesia, Dapagliflozin is now approved for heart failure with ejection fraction ≤40%
[a]hHF or an urgent HF visit; [b]Also a prespecified secondary endpoint.

1. Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022; 2. Solomon SD. Presented at: ESC Congress; August 26-29, 2022; Barcelona, Spain.

Components of the primary composite endpoint[1]

DELIVER

Outcome, n (%)	DAPA 10 mg n=3131	Placebo n=3132	HR (95% CI)	p-value
CV death or worsening HF[a]	512 (16.4)	610 (19.5)	0.82 (0.73, 0.92)	0.0008[2]
CV death[b]	231 (7.4)	261 (8.3)	0.88 (0.74, 1.05)	
Worsening HF[a]	368 (11.8)	455 (14.5)	0.79 (0.69, 0.91)	
hHF	329 (10.5)	418 (13.3)	0.77 (0.67, 0.89)	
Urgent HF visit	60 (1.9)	78 (2.5)	0.76 (0.55, 1.07)	



DISCLAIMER: In Indonesia, Dapagliflozin is now approved for heart failure with ejection fraction ≤40%

[a]hHF or an urgent HF visit; [b]Also a prespecified secondary endpoint.

1. Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022; 2. Solomon SD. Presented at: ESC Congress; August 26-29, 2022; Barcelona, Spain.

Safety Outcomes across Dapagliflozin Heart Failure Trials[1,2]

Event, n (%)	DAPA-HF[1]		DELIVER[2]	
	Dapagliflozin n=2368[a]	Placebo n=2368[a]	Dapagliflozin n=3126[a]	Placebo n=3127[a]
Volume depletion[b]	178 (7.5)	162 (6.8)	42 (1.3)	32 (1.0)
Renal AE[b]	153 (6.5)	170 (7.2)	73 (2.3)	79 (2.5)
Fracture	49 (2.1)	50 (2.1)	NR	NR
Amputation	13 (0.5)	12 (0.5)	19 (0.6)	25 (0.8)
Major hypoglycemia	4 (0.2)	4 (0.2)	6 (0.2)	7 (0.2)
DKA[c]	3 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Fournier's gangrene	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)

Volume depletion was similar in patients taking dapagliflozin and placebo[1,2]

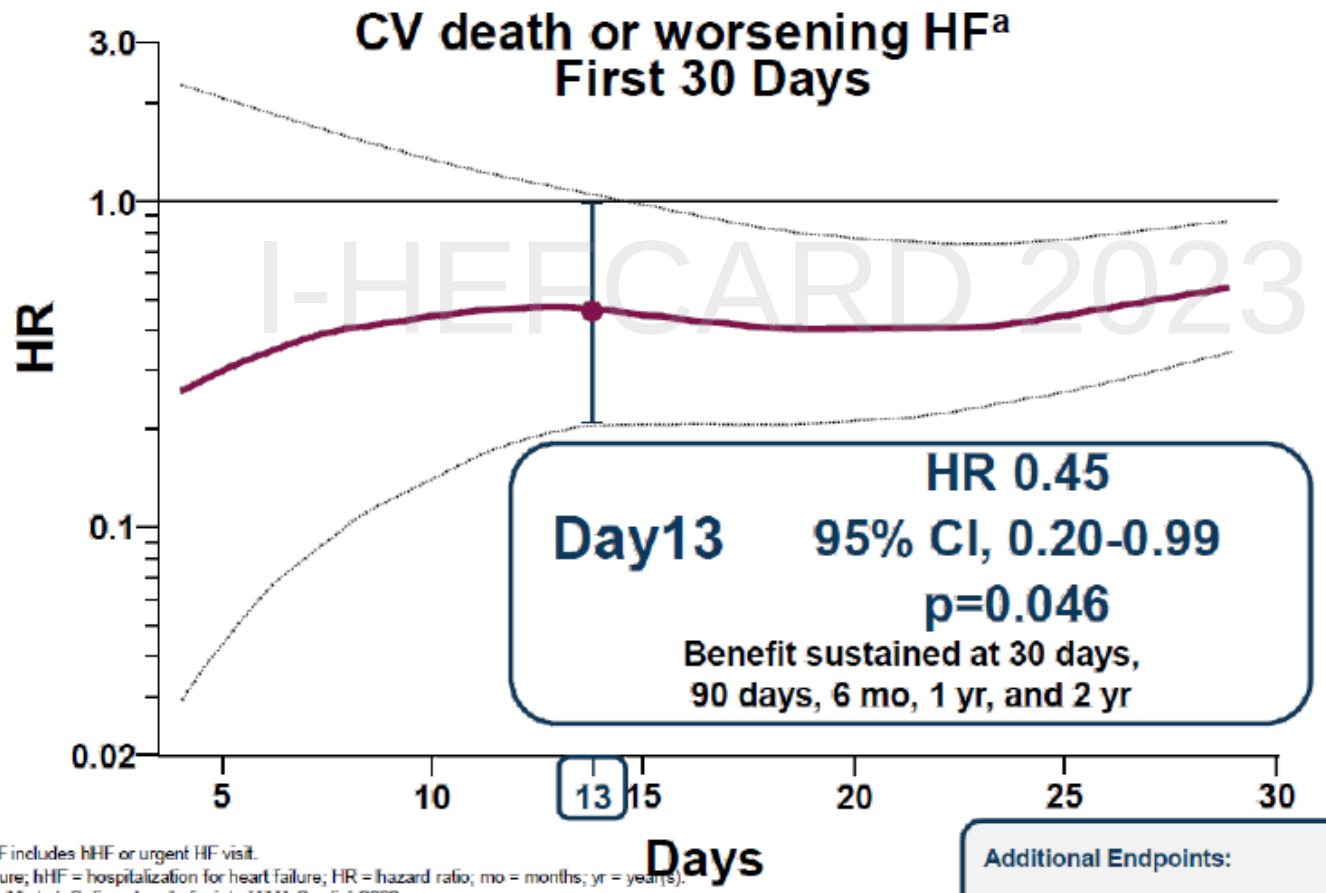
DISCLAIMER: In Indonesia, Dapagliflozin is now approved for heart failure with ejection fraction ≤40%

[a]The safety population included patients who received at least 1 dose of the trial medication; [b]Defined as any serious AE or treatment discontinuation AE in the DELIVER trial; [c]Definite or probable.

1. McMurray JJV et al. Article and supplementary appendix. *N Engl J Med*. 2019;381(21):1995-2008; 2. Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022.

DELIVER: Time to Effect

Benefit of Dapagliflozin on the Primary Composite Endpoint Occurred Within 2 Weeks



[a]Worsening HF includes hHF or urgent HF visit.
HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; mo = months; yr = year(s).
Vaduganathan M et al. Online ahead of print. *JAMA Cardiol*. 2022.

Additional Endpoints:

Worsening HF- Day 16 hHF- Day 16

 Disclaimer: In Indonesia, Dapagliflozin is currently indicated for HF with ejection fraction ≤ 40%. Dapagliflozin is not approved for HFpEF in Indonesia.

DELIVER adds to the evidence of dapagliflozin across the range of LVEF

DAPA-HF[1]

EF ≤40%

- Significant reduction in the composite of CV death or worsening HF[a] as well as each individual component
- Reduction in all-cause mortality
- HF symptom benefit
- Consistent benefit across subgroups

DELIVER[2,3]

EF >40%

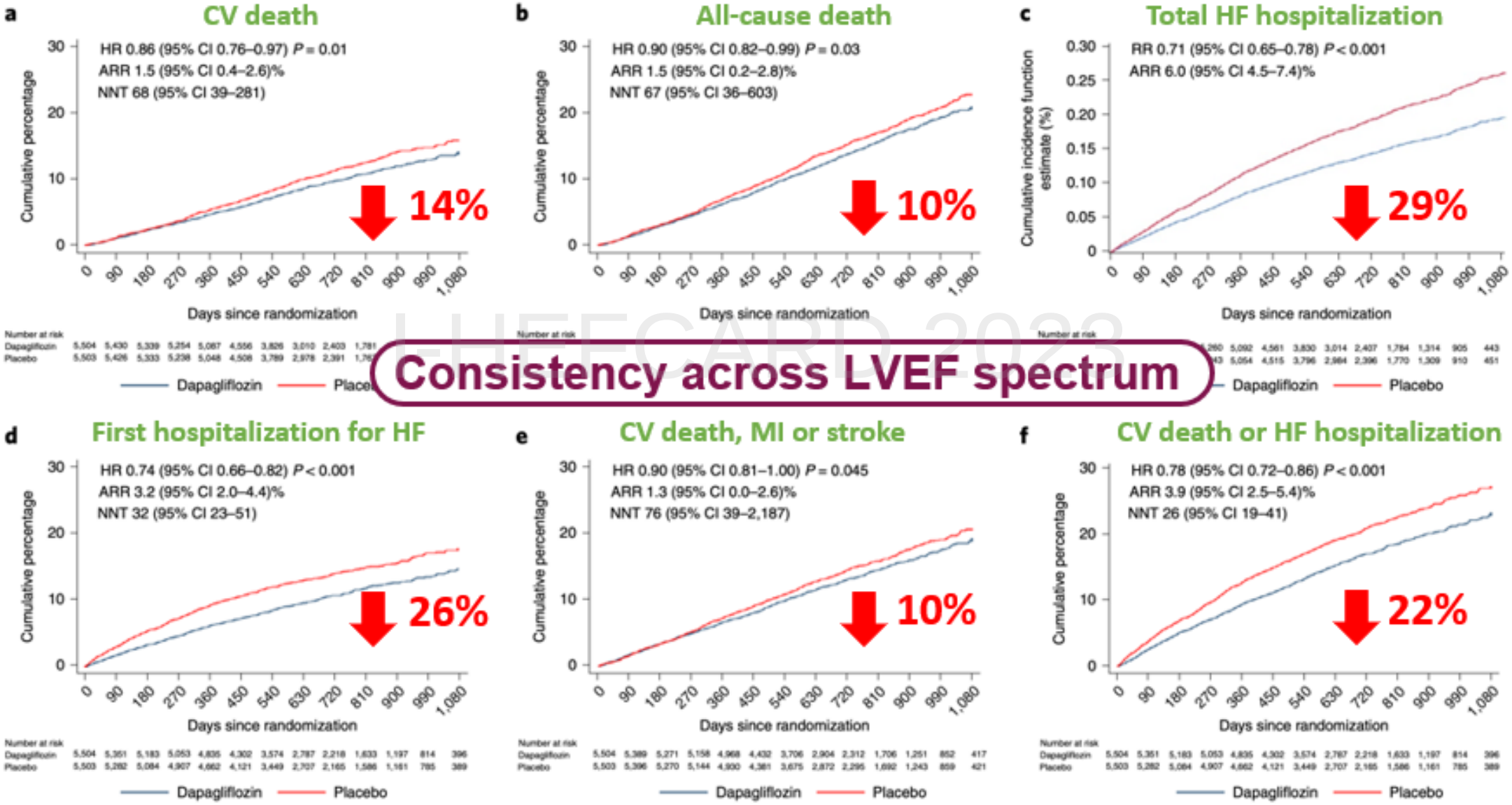
- Largest trial to date in patients with EF >40%
- Significant reduction in the composite of CV death or worsening Hf[a]
- HF symptom benefit
- Consistent benefit across all prespecified subgroups including EF≥60% and patients with prior LVEF≤40% (improved)

DISCLAIMER: In Indonesia, Dapagliflozin is now approved for heart failure with ejection fraction ≤40%

[a]hHF or an urgent HF visit.

1. McMurray JJV et al. *N Engl J Med*. 2019;381(21):1995-2008; 2. Solomon SD et al. *JACC Heart Fail*. 2022;10(3):184-197; 3. Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022.

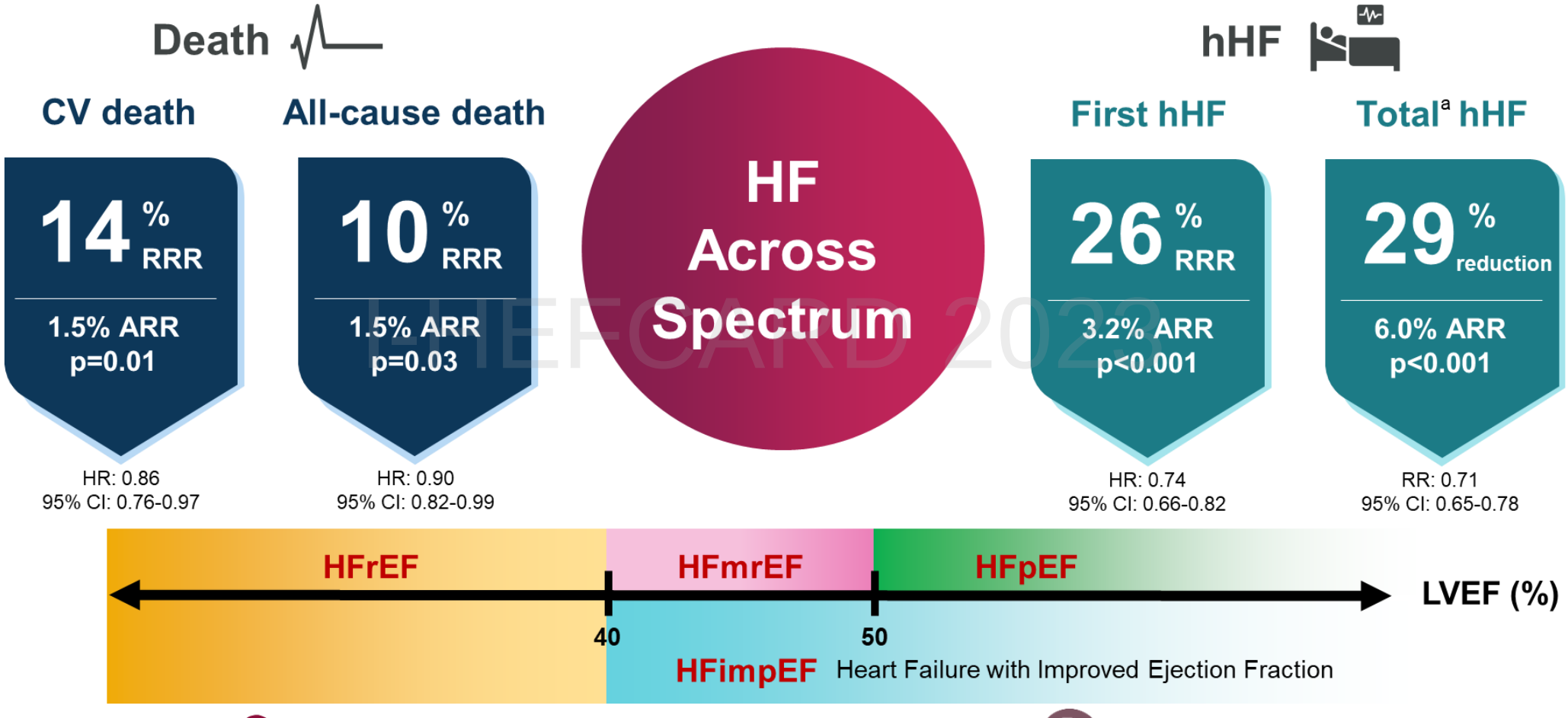
Dapagliflozin Significantly Reduced the Risk of Each Endpoint Across the Range of LVEF



Jhund PS et al. Online ahead of print. *Nat Med*. 2022.

DISCLAIMER: In Indonesia, Dapagliflozin is approved for heart failure reduced ejection fraction with LVEF <40%.

DAPA-HF and DELIVER Pooled Analysis



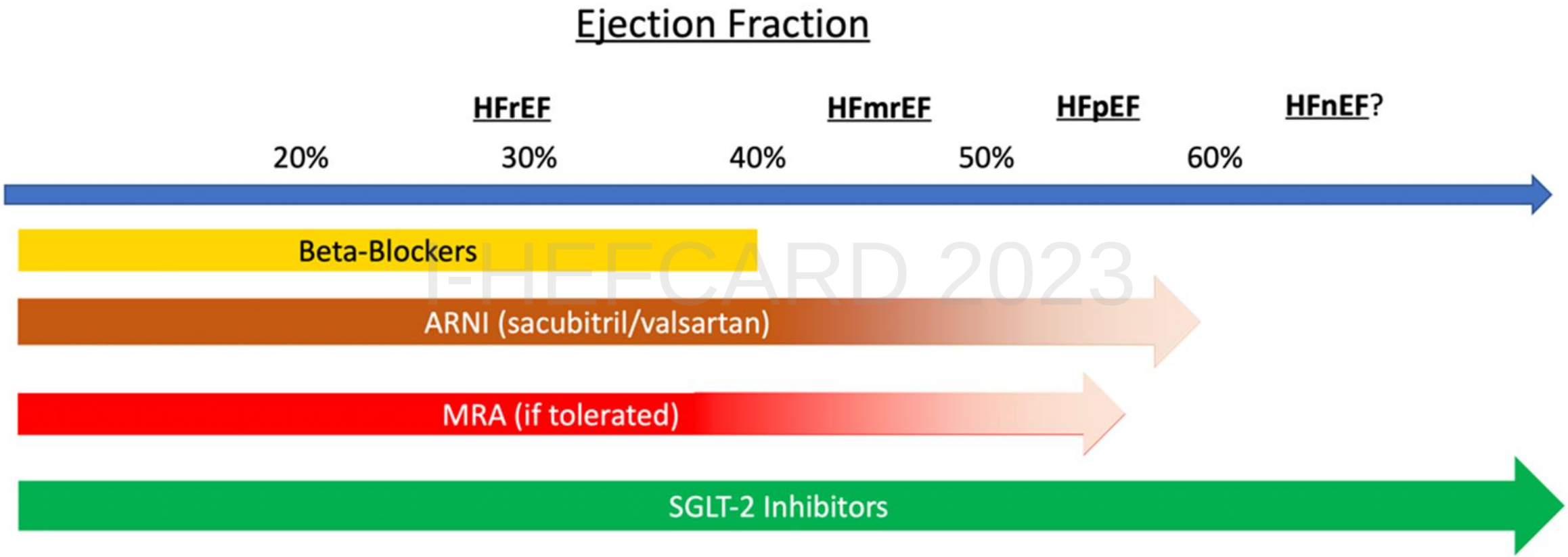
DAPA-HF

DELIVER

[a]First and repeat.

Jhund PS et al. Online ahead of print. *Nat Med*. 2022.

Pharmacologic Treatment of Heart Failure



Presented at: ESC Congress 2022; August 26-29, 2022.; Barcelona, Spain.

- **Significant reduction** in the composite of CV death or worsening HF[2]
- **No attenuation of benefit** in patients with **LVEF ≥60%**
- First trial to show benefit in patients with **HF with improved EF**[2]

- DELIVER and DAPA-HF demonstrated **significant benefits of dapagliflozin across the range of LVEF**[1,2,3]
- Pooled analysis demonstrated **consistent effects across LVEF** with a **significant 14% RRR** in **CV death**[3]

- Clinically meaningful **improvement in symptoms** and **physical limitations**[3-5]
- No new safety concerns, safety profile **consistent** with DAPA-HF[1-2]

1. McMurray JJV et al. *N Engl J Med*. 2019;381(21):1995-2008; 2. Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022; 3. Jhund PS et al. Online ahead of print. *Nat Med*. 2022; 4. Butler J et al. *Eur Heart J*. 2022;43(5):416-426; 5. Bhatt DL et al. *N Engl J Med*. 2021;384(2):117-128.

TAKE-HOME MESSAGE

- Although effective treatments exist for HFrEF, there is a paucity of treatments with proven benefits for HFmrEF and HFpEF
- Latest studies support the use of SGLT2-i as a promising treatment option in patients with HFpEF, with class 2a recommendation for use in the 2022 AHA/ACC/HFSA HF guidelines
- DELIVER trial results show that use of SGLT2-i in HFpEF led to reduction of the combined risk of worsening HF or CV death → combined with previous trial findings show benefit across the range of EF