The 4th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

The fog of war in acute heart failure: initiate, conquest, wins!

dr. Edrian Zulkarnain, Sp.JP-FIHA

KSM Kardiologi, RSUP Moh. Hoesin Palembang

Working Group on Heart Failure and Cardiometabolic

Indonesian Heart Association

Disclaimer

All information presented in these slides are intended for scientific exchange and not to solicit off-label use.
Please refer to local prescribing information for all drugs mentioned in this presentation for further details before prescribing.
In Indonesia, EMPAGLIFLOZIN is indicated:

1.Type 2 Diabetes Mellitus

Add on combination:
In adult patients with type 2 diabetes mellitus to improve glycemic control, when metformin used alone does not provide adequate glycemic control, combination with:
Metformin,
Metformin and a sulfonylurea,
Metformin and pioglitazone

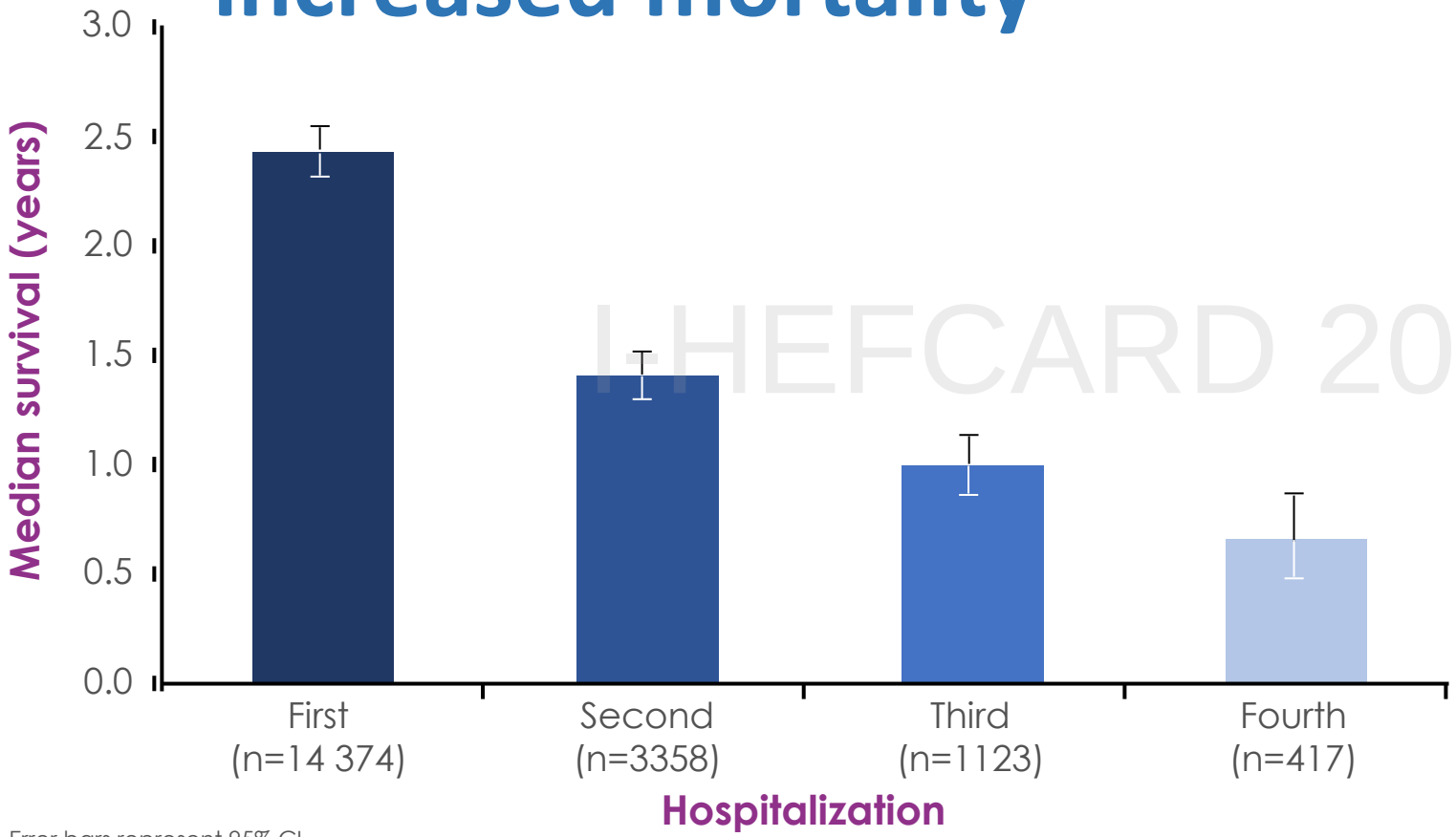
when the existing therapy, along with diet and exercise, does not provide adequate glycemic control.
For study results with respect to combination, effects on glycaemic control and cardiovascular events, and the populations studied, see sections Special warnings and precautions for use, Interaction with other medicinal products and other forms of interactions, and Pharmacodynamic properties.

2. Heart Failure

In adult patients for the treatment of symptomatic chronic heart failure

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

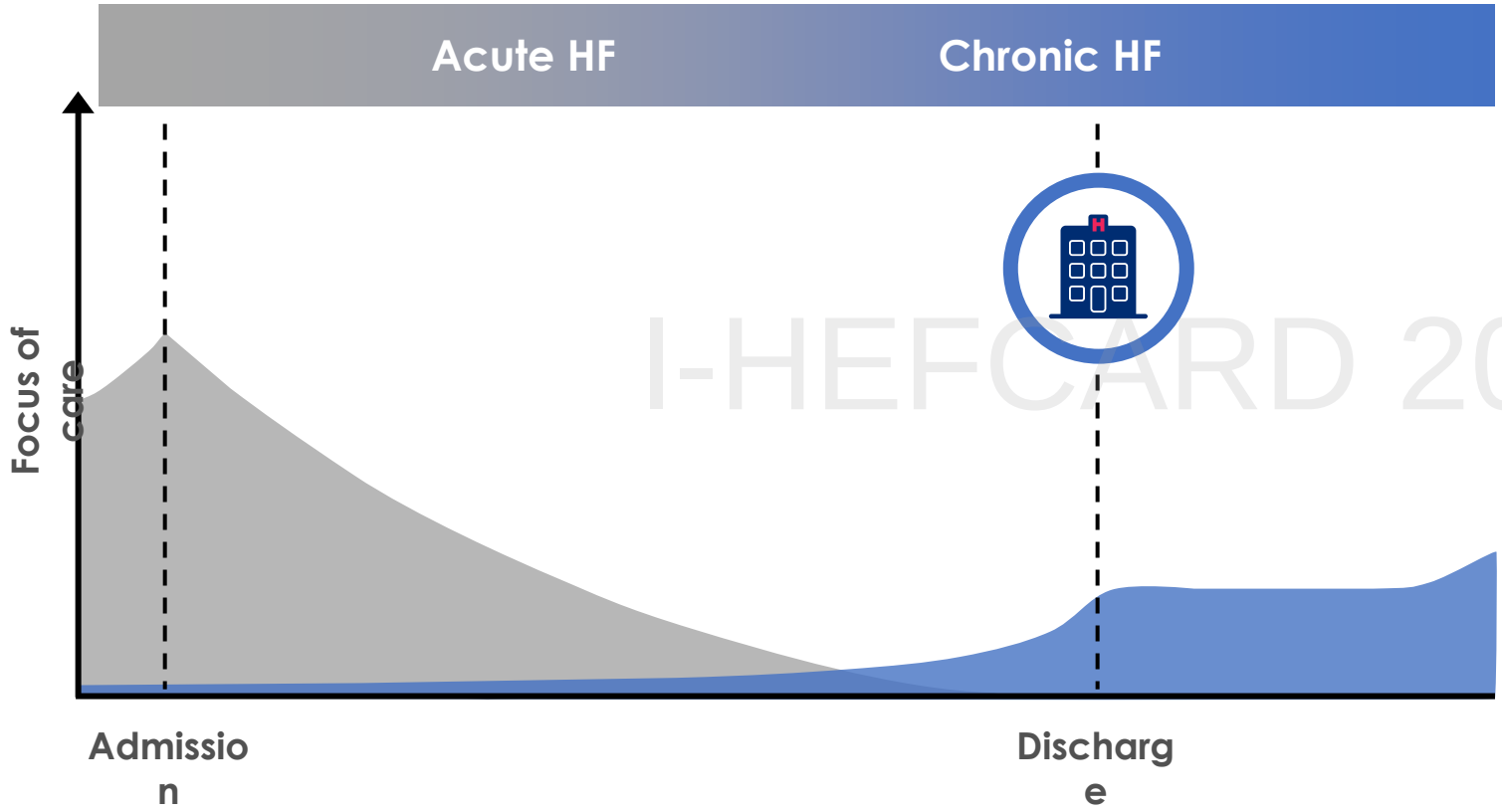
Repeat hospitalization for HF is associated with increased mortality



Survival for patients with HF deteriorates after each HHF

Error bars represent 95% CI.
CI, confidence interval; HF, heart failure; HHF, hospitalization for heart failure.
Setoguchi S *et al*. *Am Heart J.* 2007;154:260.

Timeline of heart failure: The vulnerable period

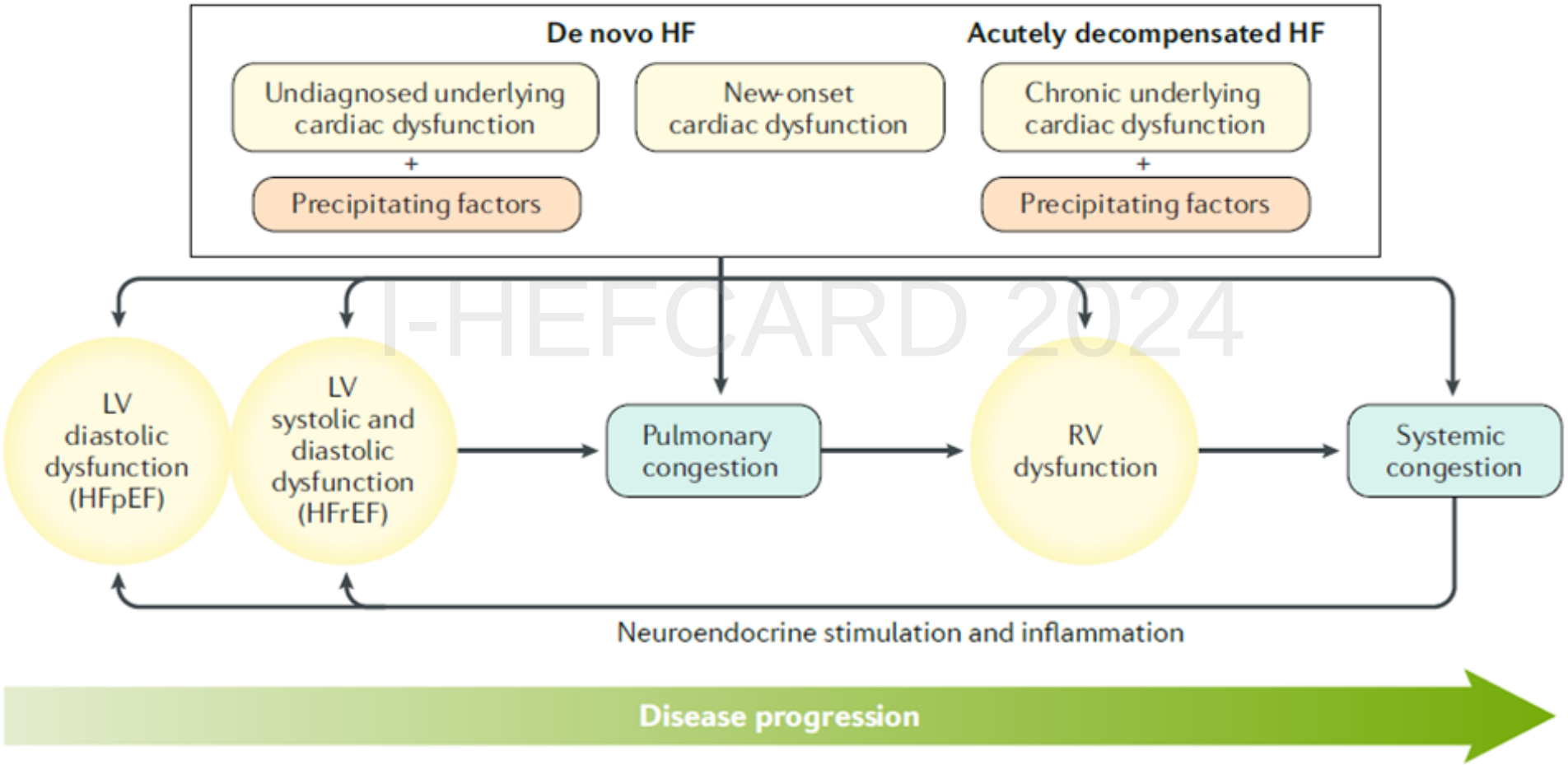


Readmission rates after HHF are as high as **30% within 60–90 days**[1]

Approximately **10% of patients die within 1 month** of HHF[2]

HF, heart failure; HHF, hospitalization for heart failure.
Figure adapted from Cox ZL *et al. Am Heart J.* 2021;232:116.
1. Fonarow GC *et al. J Am Coll Cardiol.* 2007;50:768; 2. Bueno H *et al. JAMA.* 2010;303:2141.

Schematic representation of possible pathophysiological mechanisms in AHF



Nature Reviews| Disease Primers | Article citation ID: (2020) 6:16
https://doi.org/10.1038/s41572-020-0151-7

Box 1 | The '7-P' protocol

1. The assessment of the clinical phenotype based on peripheral perfusion (whereby normal perfusion is considered 'warm' and symptoms or signs of hypoperfusion are considered 'cold') and/or systemic congestion (whereby no congestion is considered 'dry' and the presence of congestion is considered 'wet') enables the classification of patients into one of four profiles. The vast majority of patients with AHF are well perfused but congested ('warm–wet').
2. The initial treatment tackling haemodynamic disorders (for example, vasodilators and/or diuretics to reduce systemic congestion and positive inotropic drugs to improve peripheral perfusion) should be personalized according to the clinical phenotype and the leading pathophysiology (for example, fluid accumulation, fluid redistribution or peripheral hypoperfusion).
3. Identification of the precipitants of AHF is essential for providing optimal specific (medical and/or surgical) therapy and for estimating both prognosis and recovery potential.
4. Similarly, identification of the underlying cardiac pathology can contribute to tailoring the treatment.
5. The assessment of polymorbidity (for example, renal and hepatic dysfunction) or other relevant conditions (such as pregnancy, bleeding risk and allergies) should be integrated into the management plan.
6. Potential iatrogenic harms associated with diagnostic procedures and treatment should also be considered.
7. Patient preferences and ethical considerations should be integrated into the personalization of the treatment. Discussion with the patient or with relatives about resuscitation directives and treatment options are crucial and need to be evaluated early rather than late, particularly in patients with AHF who might show rapid deterioration. In the absence of long-term therapeutic options, palliation and supportive care should be offered to patients and relatives.

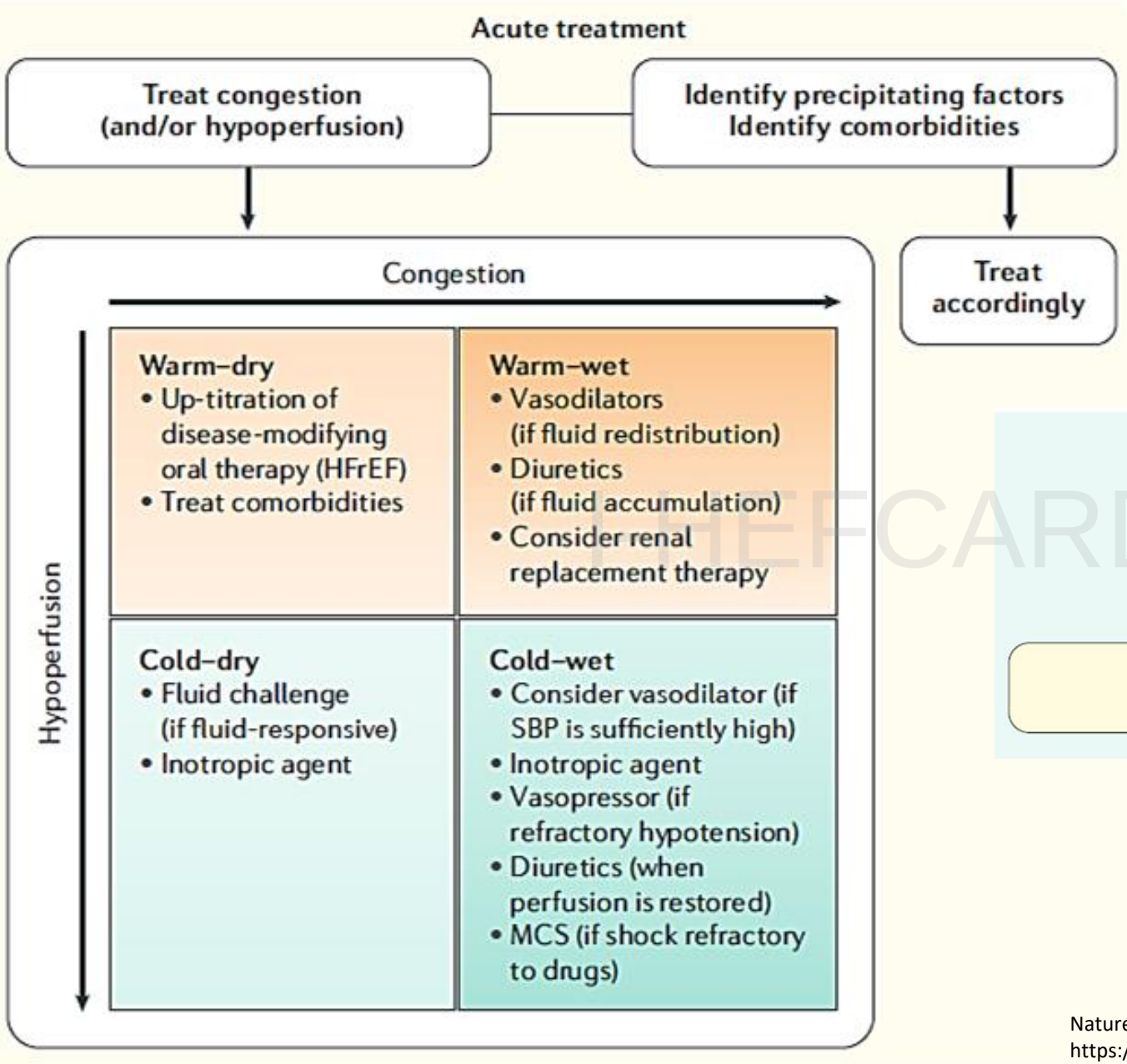
PRIMER

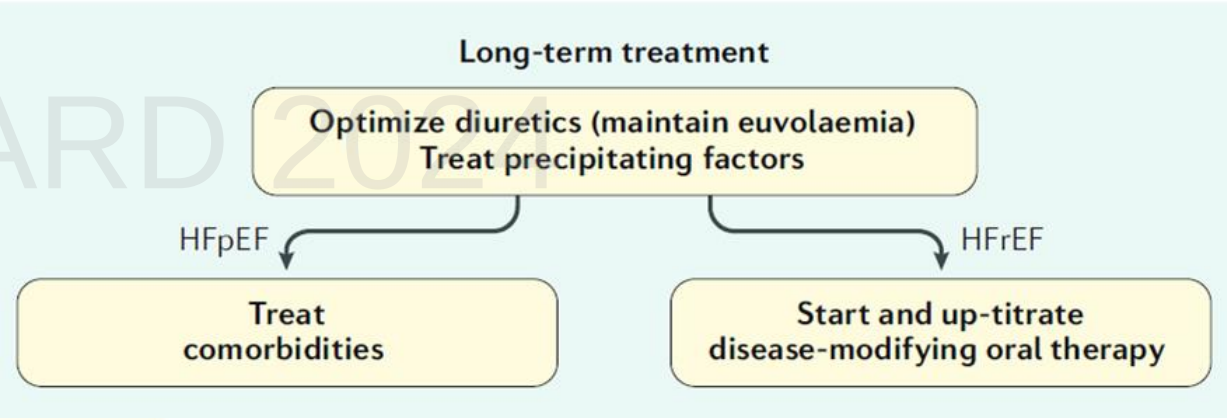
Check for updates

Acute heart failure

Mattia Arrigo[1], Mariell Jessup[2], Wilfried Mullens[3,4], Nosheen Reza[2], Ajay M. Shah[5], Karen Sliwa[6] and Alexandre Mebazaa[7,8]✉

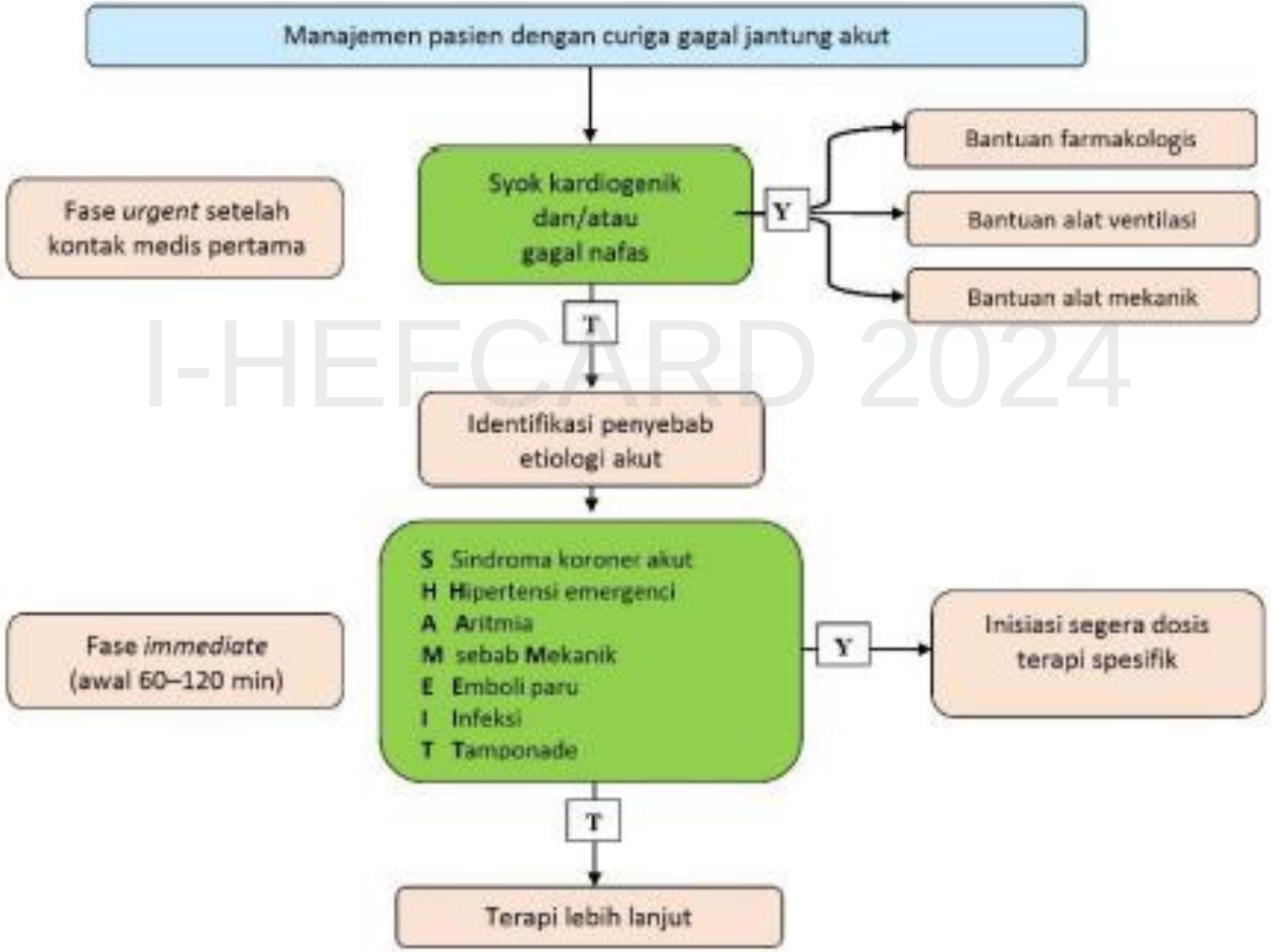
Nature Reviews| Disease Primers | Article citation ID: (2020) 6:16
https://doi.org/10.1038/s41572-020-0151-7





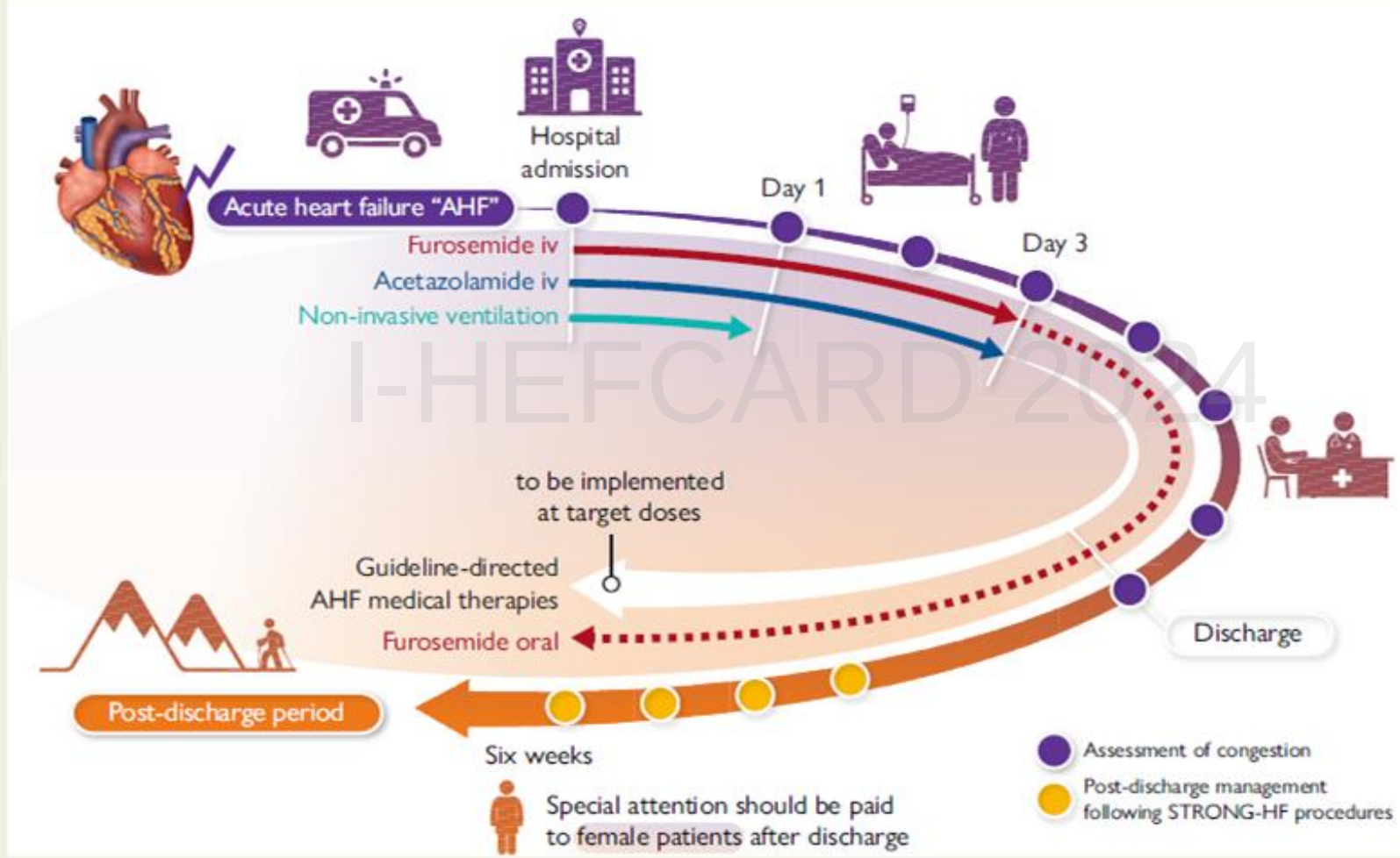
Nature Reviews| Disease Primers | Article citation ID: (2020) 6:16
https://doi.org/10.1038/s41572-020-0151-7

Management of patients with suspected acute heart failure



Hasanah, D.Y, Zulkarnain, E., Ariefianto, H., Sasmaya, H., Suciadi, I.P., Dewi, P.P., Soearso, R., Nauli, S. E., Putri, V.K.P., Aditya, W., Sarastri,Y. 2023. Pedoman tatalaksana gagal jantung. PERHIMPUNAN DOKTER SPESIALIS KARDIOVASKULAR INDONESIA. Edisi ketiga..

Schematic Representation of Management of Acute Heart Failure



Schematic representation of management of acute heart failure (AHF) patients from hospital admission to post-discharge period. Assessment of congestion includes clinical signs and symptoms (fatigue, dyspnoea, orthopnoea, oedema, and body weight), ultrasound assessment (lung, pleura, inferior vena cava, and ascites), and biology (natriuretic peptides and haematocrit). i.v., intravenous.

European Heart Journal (2023) **44**, 4634–4649 https://doi.org/10.1093/eurheartj/ehad617

ESC Guideline recommendations for pre-discharge and early post-discharge follow-up of patients hospitalised for acute heart failure

Recommendation Table 3 — Recommendation for pre-discharge and early post-discharge follow-up of patients hospitalized for acute heart failure

Recommendation	Class[a]	Level[b]
An intensive strategy of initiation and rapid up-titration of evidence-based treatment before discharge and during frequent and careful follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce the risk of HF rehospitalization or death.[c,d,e] [16]	I	B

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ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; 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; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Recommendation Table 4 — Recommendations for the prevention of heart failure in patients with type 2 diabetes mellitus and chronic kidney disease

Recommendations	Class[a]	Level[b]
In patients with T2DM and CKD,[c] SGLT2 inhibitors (dapagliflozin or empagliflozin) are recommended to reduce the risk of HF hospitalization or CV death.[5,7,35]	I	A
In patients with T2DM and CKD,[c] finerenone is recommended to reduce the risk of HF hospitalization.[10,11,34,40]	I	A

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[a]Class of recommendation
[b]Level of evidence
[c]In STRONG-HF, the use of ACE-I/ARB/ARNI, beta-blockers, and MRA was evaluated in patients with HFrEF, HFmrEF, and HFpEF
[d]This recommendation is based on the reduction of the primary endpoint used in the STRONG-HF trial. However, it should be noted that there was a significant reduction only in HF hospitalization and no reduction in CV death or all-cause death alone and that these results were obtained in a specific patient population, not already on full doses of evidence-based HF therapies, who were haemodynamically stable, with elevated NT-proBNP concentrations at screening (>2500 pg/mL), and a >10% decrease in concentration between screening and randomization, according to the enrolment criteria
[e]Although STRONG-HF was based only on triple therapy with neurohormonal modulators, this recommendation also includes **empagliflozin** or dapagliflozin based on recent evidence

ESC, European Society of Cardiology; STRONG-HF, Titration of Optimal Therapy for Patients Hospitalized With Acute Heart Failure
McDonagh TA *et al. Eur Heart J* 2021;42:3599

ESC European Society of Cardiology
European Heart Journal (2023) **44**, 4634–4649
https://doi.org/10.1093/eurheartj/ehad617

Table 2 Trials showing benefits of heart failure medications at and after discharge of acute heart failure

Study name	Type	Intervention	Primary outcome	Duration of intervention and follow-up	Number of patients	Main results	Impact on mortality
EMPagliflozin in patients hospitalized with acUte heart failure who have been StabilisEd **EMPULSE study**[98,99] NCT04157751	Randomized clinical trial	Patients admitted for acute *de novo* or decompensated chronic HF 2 groups – Empagliflozin 10 mg once daily – Placebo	Clinical benefit, defined as a hierarchical composite of death from any cause, number of HF events and time to first HF event, or a 5 point or greater difference in change from baseline in the Kansas City Cardiomyopathy Questionnaire total symptom score at 90 days	90 days	530 patients	Better clinical benefit in empagliflozin group (stratified win ratio, 1.36; 95% CI 1.09–1.68; $P = .0054$)	Yes (4.2% in empagliflozin group vs. 8.3% in placebo group)
Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode **PIONEER-HF study**[101] NCT02554890	Randomized clinical trial	HFrEF patients admitted for acute decompensated HF 2 groups – Sacubitril (97 mg) + valsartan (103 mg) twice daily – Enalapril 10 mg twice daily	Time-averaged proportional change in the NT-proBNP concentration from baseline through weeks 4 and 8	60 days	881 patients	Reduced time-averaged in the NT-proBNP concentration in the sacubitril/valsartan group: (i) reduced geometric mean of values at weeks 4 and 8 to the baseline (0.53 in the sacubitril/valsartan group vs. 75 in the enalapril group (per cent change, −46.7% vs. −25.3%; ratio of change with sacubitril/valsartan vs. enalapril, 0.71; 95% CI 0.63–0.81; $P < .001$). (ii) Greater reduction in the NT-proBNP concentration with sacubitril/valsartan at 1 week (ratio of change, 0.76; 95% CI 0.69–0.85). No difference of worsening renal function, hyperkalaemia, symptomatic hypotension, and angioedema between groups.	No (2.3% in sacubitril–valsartan group vs. 3.4% in enalapril group, HR 0.66 (0.30–1.48))

There is an urgent unmet need to improve care for patients hospitalized with acute heart failure

Heart failure is the number one reason for hospitalization in patients aged >65 years, with 24% of patients rehospitalized within 30 days of discharge[1,2]

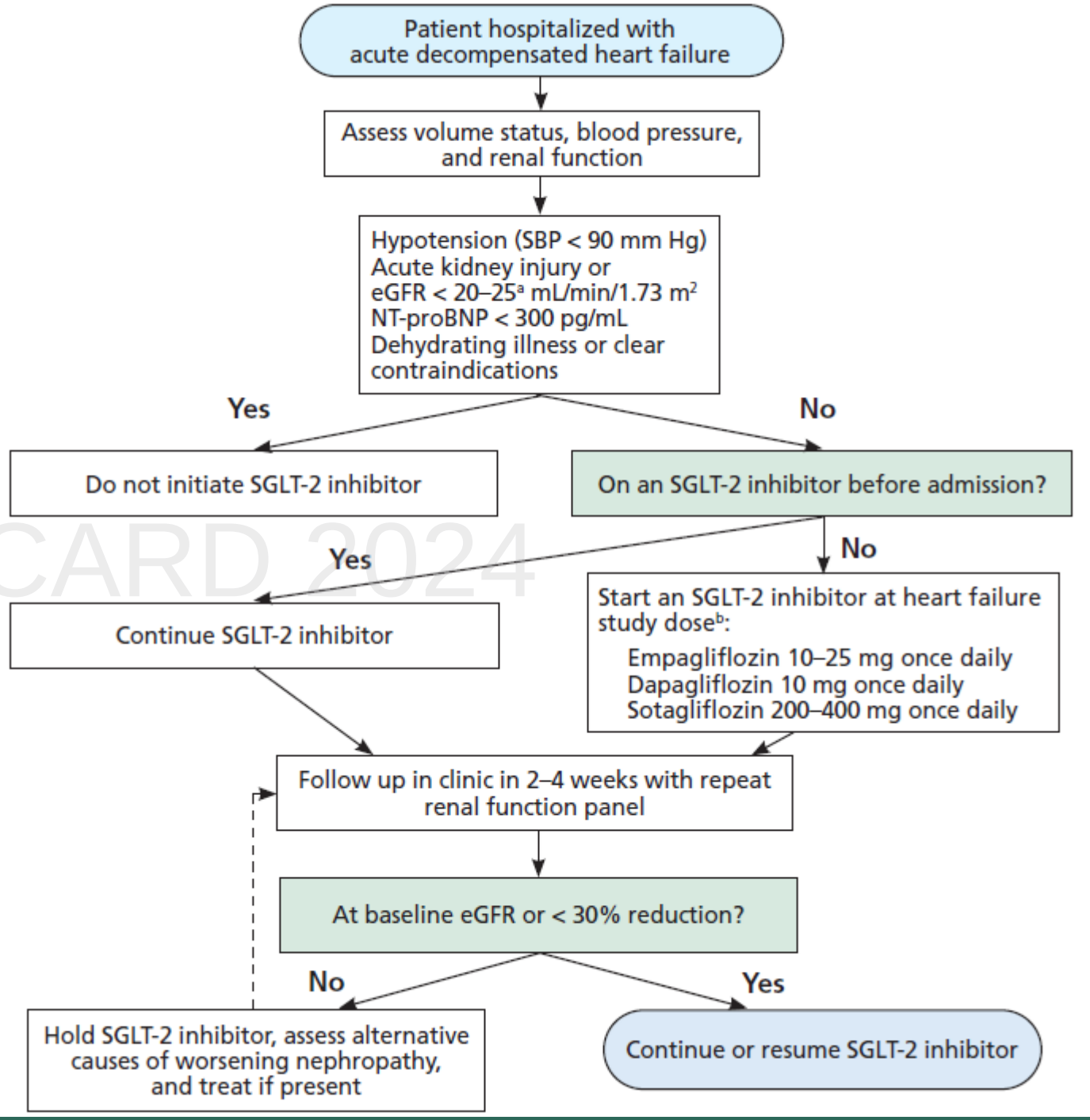
In-hospital initiation of therapies is one of the best predictors of long-term adherence to medications[3,4]

In EMPEROR-Reduced and EMPEROR-Preserved, there was an early benefit in reducing CV death or HHF for patients with chronic HFrEF and HFpEF treated with empagliflozin, respectively[5–8]

EMPULSE was specifically designed to prospectively address **in-hospital initiation of empagliflozin** in patients hospitalized for **acute heart failure,** regardless of LVEF or de novo or decompensated chronic presentation[9]

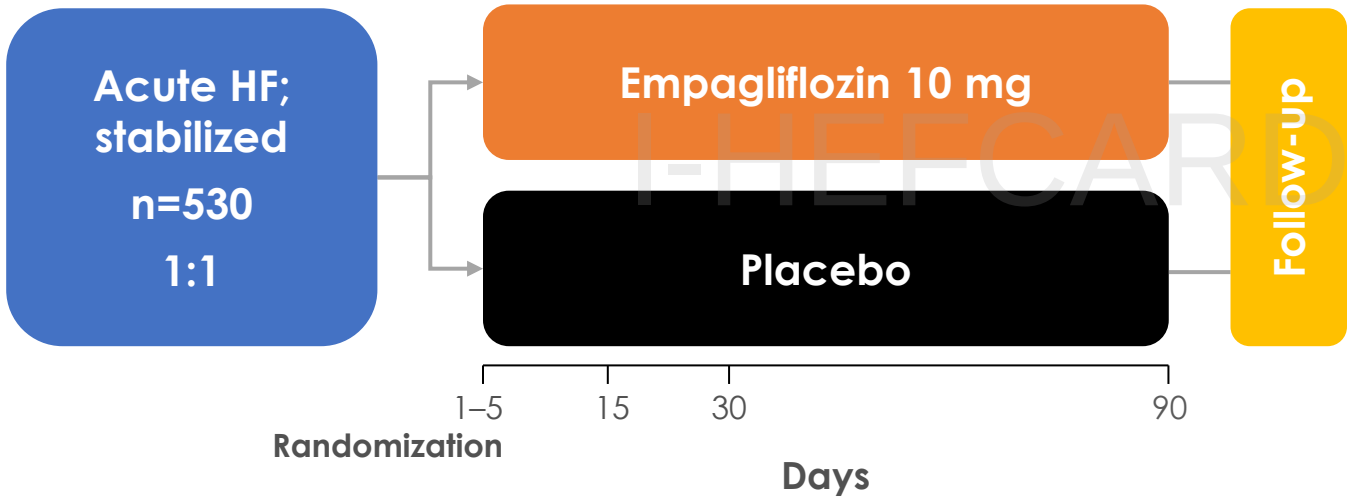
1. Azad N *et al. J Geriatr Cardiol.* 2014;11:329; 2. Krumholz HM *et al. Circ Cardiovasc Qual Outcomes.* 2009;2:407; 3. Curtis LH *et al. Am Heart J* 2013;165:979; 4. Butler J *et al. J Am Coll Cardiol.* 2004;43:2036; 5. Packer M *et al. N Engl J Med.* 2020;383:1413; 6. Anker SD *et al. N Engl J Med.* 2021;385:1451; 7. Packer M *et al. Circulation.* 2021;143:326; 8. Butler J *et al. Eur J Heart Fail.* 2022;doi:10.1002/ejhf.2420; 9. Tromp J *et al. Eur J Heart Fail.* 2021;23:826.

When should we consider SGLT2-i in patients with acute decompensated heart failure?



Cleve Clin J Med 2024;91(1):47–51.
doi:10.3949/ccjm.91a.23034

EMPULSE studied the effect of empagliflozin in patients hospitalized for acute heart failure[1,2]



Median time from hospital admission to randomization was **3 days**

Primary endpoint

- **Clinical benefit evaluated with a win ratio based on a composite of:**
  - Death
  - Number of HFEs (including HHFs, urgent HF visits and unplanned outpatient visits)
  - Time to first HFE
  - ≥5 point difference in the KCCQ-TSS change from baseline after 90 days of treatment

EMPULSE: Selected inclusion and exclusion criteria

INCLUSION

- Currently hospitalized for the primary diagnosis of AHF (de novo or decompensated chronic HF), regardless of EF
- Meets stabilization criteria
- Randomization ≥24 hours and no later than 5 days after admission, as early as possible after stabilization and while still in hospital
- Elevated NT-proBNP or BNP:
  Without AF: NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL
  With AF: NT-proBNP ≥2400 pg/mL or BNP ≥600 pg/mL
- Treatment with minimum dose of 40 mg of IV furosemide (or equivalent of other IV loop diuretic)

EXCLUSION

- Cardiogenic shock
- HHF triggered by secondary cause (e.g. acute MI, pulmonary embolism)
- Planned or previous (within 30 days) cardiovascular revascularization or major cardiac surgery/intervention/ device implantation
- Prior ACS, MI, stroke or TIA within 90 days
- eGFR <20 mL/min/1.73 m^2
- Type 1 diabetes mellitus

Further criteria apply

EMPULSE: Primary diagnosis of acute heart failure

Patients hospitalized due to HF must have HF symptoms at the time of hospital admission

MANDATORY

Persistent dyspnoea at rest or with minimal exertion

+

MANDATORY

Signs of decompensation

At least **two** of the following must apply

- Congestion on chest X-ray
- Rales on chest auscultation
- Clinically relevant oedema (e.g. ≥1+ on a 0–3+ scale), indicating indentation of skin with mild digital pressure that requires 10 or more seconds to resolve in any dependent area
- Elevated jugular venous pressure

EMPULSE: Stabilization criteria

All of the following criteria must apply for inclusion

1. Systolic BP ≥100 mmHg and no symptoms of hypotension in the preceding **6 hours**
2. No increase in IV diuretic dose for **6 hours** prior to randomization
3. No IV vasodilators including nitrates within the last **6 hours** prior to randomization
4. No IV inotropic drugs for **24 hours** prior to randomization

EMPULSE: Study endpoints

Primary endpoint	**Clinical benefit** Composite of death, number of HFEs (including HHFs, urgent HF visits and unplanned outpatient visits), time to first HFE and ≥5 point difference in the KCCQ-TSS change from baseline after 90 days of treatment
Selected secondary endpoints	Improvement of KCCQ-TSS of ≥10 points after 90 days of treatment
	Days alive and out of hospital until 90 days after randomization
	Days alive and out of hospital until 30 days after initial hospital discharge
	Change in log-transformed NT-proBNP level after 30 days of treatment
	Time to first occurrence of CV death or HFE until end of trial visit
	Occurrence of HHF until 30 days post-discharge
	Occurrence of chronic dialysis or renal transplant or sustained reduction of eGFR*

Primary endpoint analysis assessed by a stratified win ratio

1 Death
- Death is worse than no death
- Earlier death is worse

If there is no winner based on death

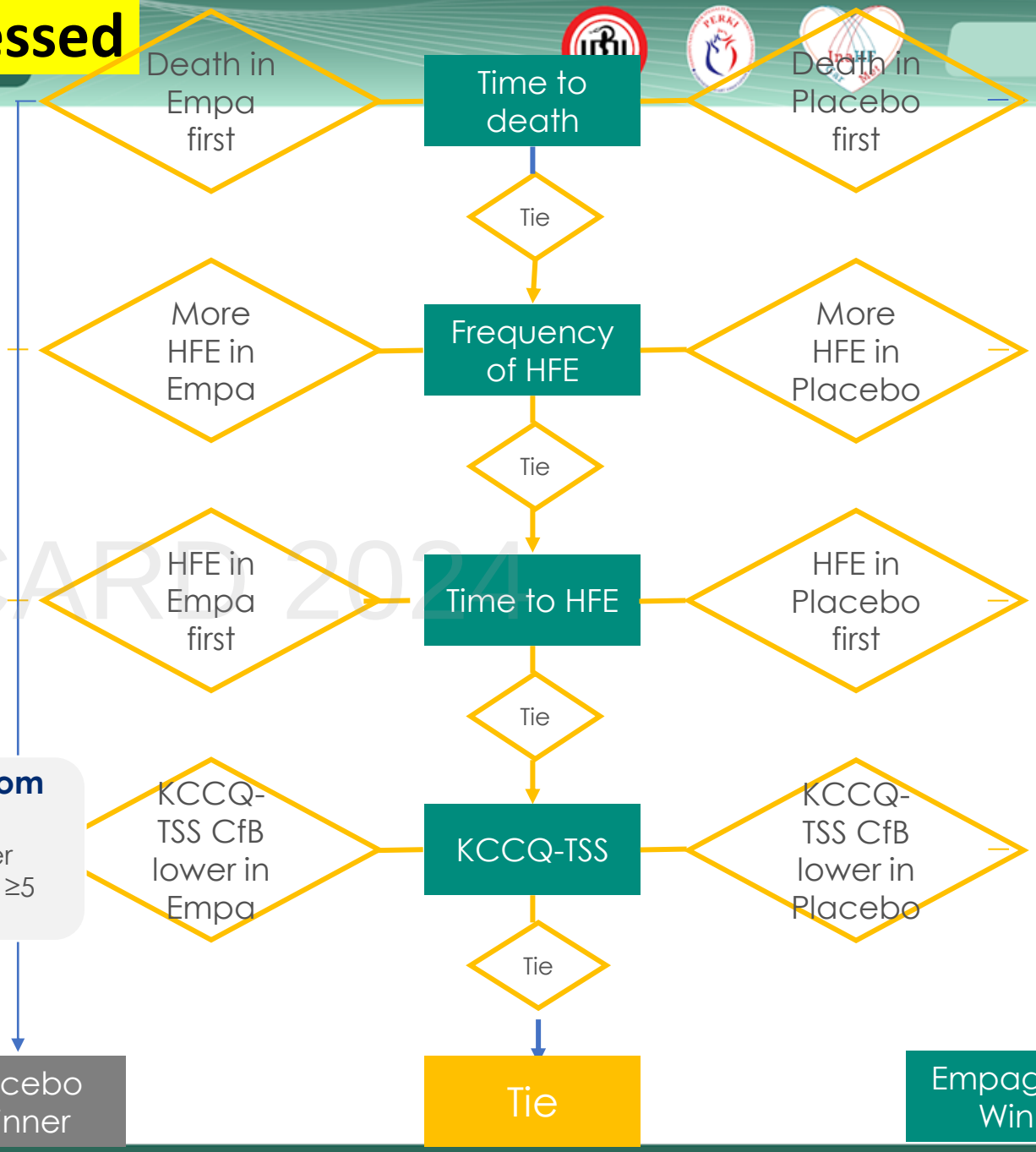
2 Number of HFEs†
- More HFEs is worse

If there is no winner based on death or number of HFEs

3 Time to first HFE†
- Earlier HFE is worse

If there is no winner based on 1–3

4 KCCQ-TSS mean change from baseline after 90 days
- More positive change is better
- Threshold for the difference is ≥5 for a win



*HFE includes hospitalizations for heart failure, urgent heart failure visits, and unplanned outpatient visits. CfB, change from baseline; Empa, empagliflozin; HFE, hospitalization for heart failure; KCCQ-TSS Kansas City Cardiomyopathy Questionnaire Clinical Summary Score.

Tromp J et al. Eur J Heart Fail. 2021;23:852.

EMPULSE: Advantages of the win ratio

Advantages

Incorporates all key events[1,2]
Recognises all events, not just the first one (unlike time-to-first-event analyses) e.g. a death after a non-fatal event is included and prioritized

Clinical priorities recognized[1,2]
Hierarchical analysis prioritises outcomes based on relative clinical importance – e.g. death is prioritized over a previous non-fatal event (unlike time-to-first-event analyses)

Recurrent events easily incorporated[1]
Can account for multiple events (e.g. hospitalizations) without statistical complexity

Non-event outcomes can be included[1]
Can include continous, visit-related items (e.g. QoL scores)

Conceptually straightforward[1]
Counting "winners" across pairwise comparisons relies on the intuitive concept of judging whether a patient is doing better or worse than another patient (unlike explaining a HR)

Challenges

Lack of familarity[1,2]
Relatively new method so not as well understood as a time-to-event analysis – limited experience with the interpretation of effect size and the subcomponents

Determining sample size[1]
Power calculations rely on assumptions of effect sizes, variability and interdependence of the components

More methodological research needed
Not possible to obtain treatment effect measures (NNT) and not possible to adjust for continous covariates

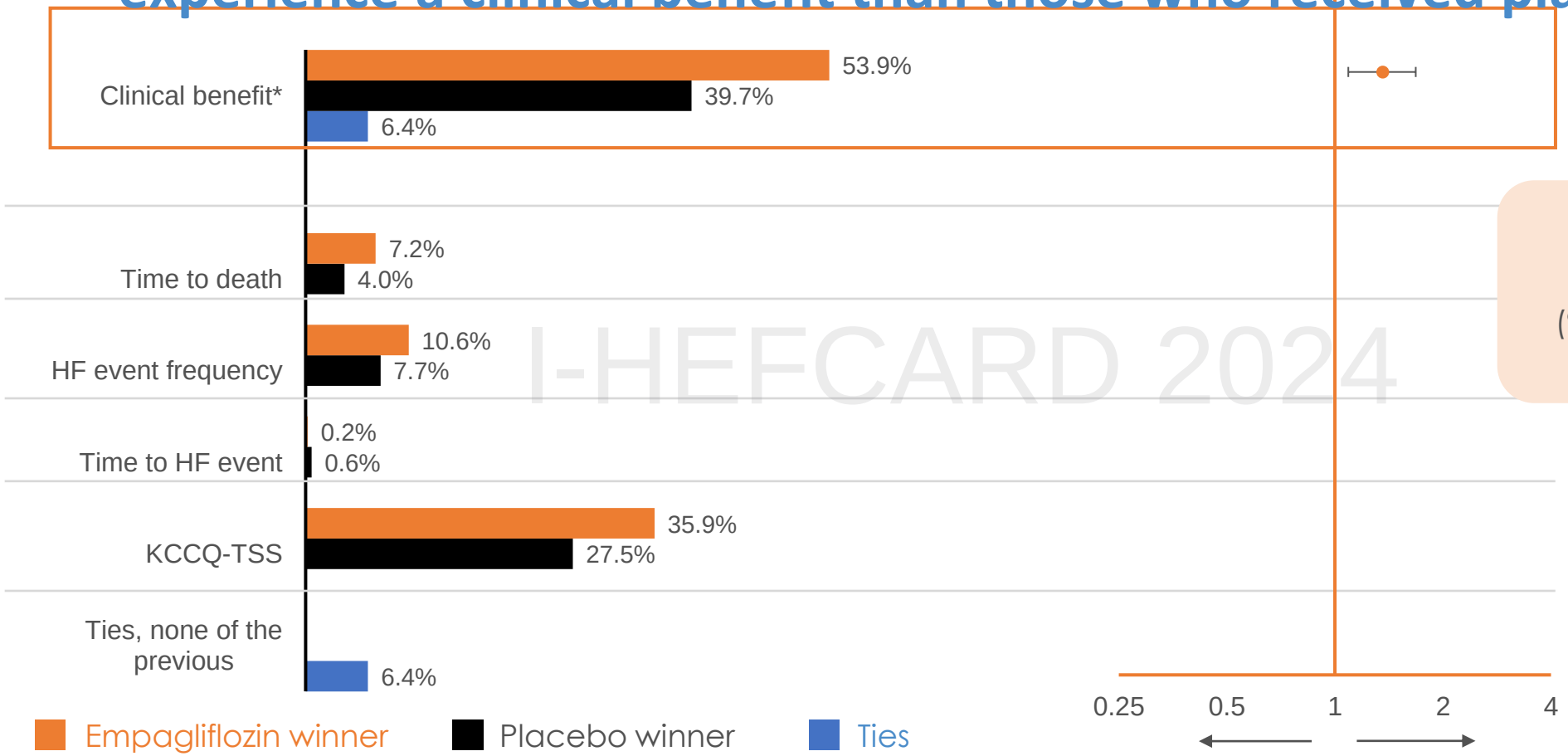
Experience

Pivotal studies where a win ratio was utilised

	Drug	*Therapy area*	*Endpoint*	
ATTR-ACT[3]	Tafimidis	Transthyretin amyloid cardiomyopathy	Primary	FDA approval based on this[6]
DAPA-HF[4]	Dapagliflozin	HFrEF	Secondary (KCCQ)	
SUMMIT[5] – *ongoing*	Tirzepatide	HFpEF	Primary	

1. Redfors B *et al. Eur Heart J.* 2020;41(46):4399; 2. Ferreira JP *et al. JACC Heart Fail.* 2020;8(6):450. 3. Maurer MS *et al. N Engl J Med.* 2018;379(11):1016; 4. McMurray *et al. N Engl J Med.* 2019;381(21):2008; 5. ClinicalTrials.gov. NCT04847557. Available at: https://clinicaltrials.gov/ct2/show/NCT04847557; 6. Pfizer Inc. Vyndaqel® (tafamidis) prescribing information. 2021.

EMPULSE: Patients treated with empagliflozin were 36% more likely to experience a clinical benefit than those who received placebo



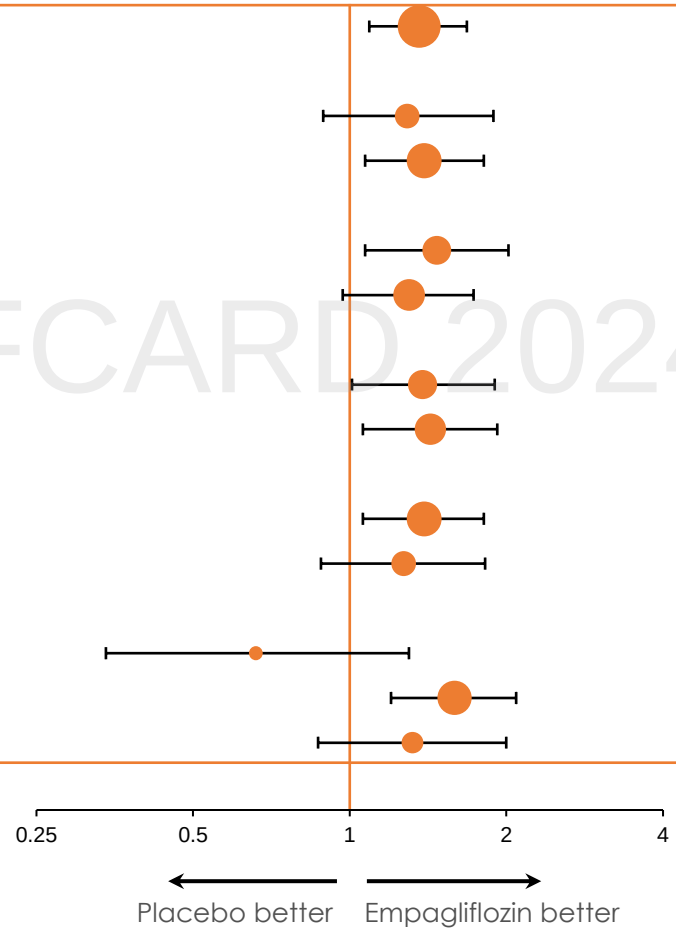
Stratified win ratio: 1.36
(95% CI: 1.09, 1.68)
p=0.0054

Death:
Empagliflozin: 4.2%
Placebo: 8.3%

HF event:
Empagliflozin: 10.6%
Placebo: 14.7%

EMPULSE: Primary endpoint subgroup analysis (1 of 2)

	Empagliflozin	Placebo	Win ratio (95% CI)	Interaction *p*-value
	Number of patients			
All patients	265	265	1.36 (1.09, 1.68)	
HF status				0.7590
De novo	88	87	1.29 (0.89, 1.89)	
Decompensated chronic	177	178	1.39 (1.07, 1.81)	
Baseline diabetes status				0.5683
Diabetic	124	116	1.47 (1.07, 2.02)	
Non-diabetic	141	149	1.30 (0.97, 1.73)	
Age				0.8889
<70 years	116	129	1.38 (1.01, 1.90)	
≥70 years	149	136	1.43 (1.06, 1.92)	
Sex				0.6923
Male	179	172	1.39 (1.06, 1.81)	
Female	86	93	1.27 (0.88. 1.83)	
Region				0.0602
Asia	31	25	0.66 (0.34, 1.30)	
Europe	168	171	1.59 (1.20, 2.09)	
North America	66	69	1.32 (0.87, 2.00)	



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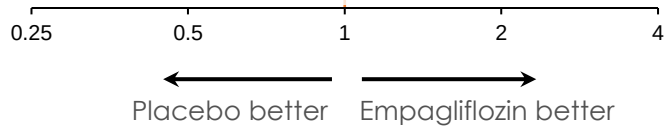
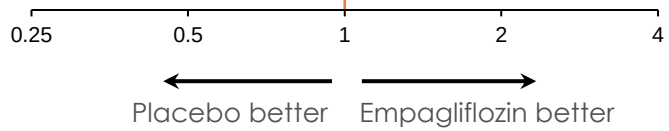


The clinical benefits were consistent, regardless of whether patients presented with de novo or decompensated chronic HF

EMPULSE: Primary endpoint subgroup analysis (2 of 2)

	Empagliflozin	Placebo	Win ratio (95% CI)	Interaction *p*-value
	Number of patients			
All patients	265	265	1.36 (1.09, 1.68)	
NT-proBNP at baseline, pg/mL				0.7904
<Median	125	130	1.36 (0.99, 1.85)	
≥Median	130	126	1.44 (1.06, 1.96)	
eGFR (CKD-EPI) at baseline, mL/min/1.73 m^2				0.7562
<60	161	145	1.38 (1.04, 1.83)	
≥60	88	106	1.48 (1.04, 2.13)	
Atrial fibrillation/flutter at baseline				0.1129
No	123	133	1.68 (1.22, 2.32)	
Yes	142	132	1.18 (0.88, 1.59)	
Baseline LVEF, %				0.9008
≤40	182	172	1.35 (1.04, 1.75)	
>40	76	93	1.39 (0.95, 2.03)	



EMPULSE: Primary endpoint subgroup analysis (2 of 2)

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eGFR (CKD-EPI) at baseline, mL/min/				0.7562
<60			4, 1.83)	
≥60			4, 2.13)	
Atrial fibrillation/flutter at baseline				0.1129
No			22, 2.32)	
Yes	142	132	1.18 (0.88, 1.59)	
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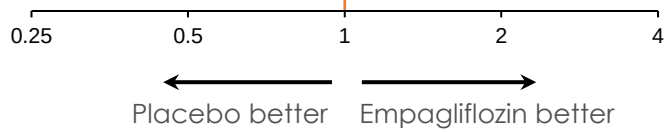
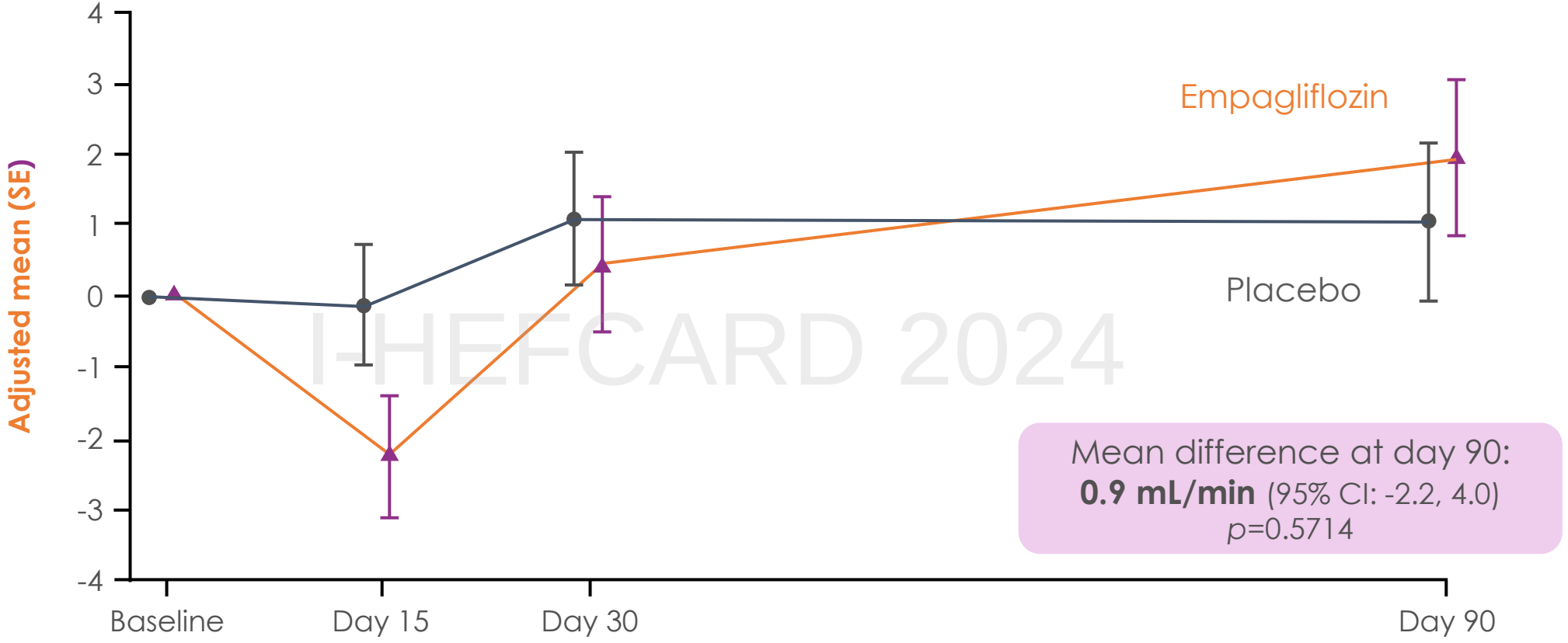
≤40	182	172	1.35 (1.04, 1.75)	
>40	76	93	1.39 (0.95, 2.03)	

The clinical benefits were independent of LVEF (including patients with HFrEF or HFpEF)



EMPULSE: eGFR change from baseline (mL/min)



Mean difference at day 90:
0.9 mL/min (95% CI: -2.2, 4.0)
p=0.5714

No. with data at visit				
Placebo	225	213	200	167
Empagliflozin	220	204	202	182

EMPULSE: Conclusions

Patients hospitalized for acute HF treated with empagliflozin were **36% more likely to experience a clinical benefit*** versus patients on placebo

The clinical benefits were **consistent in patients with HFrEF or HFpEF**, and **in patients with de novo or decompensated chronic heart failure**

Empagliflozin was **well tolerated**, with overall safety data consistent with previous studies

*Evaluated with a win ratio based on a composite of death, number of HFEs (including HHFs, urgent HF visits and unplanned outpatient visits), time to first HFE and change from baseline in KCCQ-TSS after 90 days of treatment. HF, heart failure; HFE, heart failure event; HHF, hospitalization for heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score.
Boehringer Ingelheim. Data on file.

Take home message

- Repeated hospitalization for HF is associated with increased mortality
- There is an urgent unmet need to improve care for patients hospitalized with acute or acute decompensated heart failure
- From the EMPULSE trial, the clinical benefits of Empagliflozin were consistent, regardless the LVEF, whether patients presented with de novo or decompensated chronic HF

TERIMA KASIH