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)

Further Milestone of SGLT2i in Heart Failure management

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Sheraton Grand Jakarta Gandaria City, Jakarta, Indonesia

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Disclaimer

- This is a collaboration session with Astra Zeneca

Scientific speaker for:
Novartis, Otsuka, Merck, Boehringer Ingelheim (ZPT), Servier, Menarini,

Cardiovascular Outcome Trials of Glucose-Lowering Drugs(CVOT)

Rosiglitazone (Approved by the FDA in 1999)

In 2007, a meta-analysis published in NEJM (including 42 trials) raised safety concerns regarding the use of this drug

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

Significantly increased

Increased, but not significantly different

N Engl J Med 2007; 356:2457-2471

The Importance of Cardiovascular Outcome Trials (CVOT) for Glucose-Lowering Drugs

In 2008, the FDA required all new glucose-lowering drugs to pass Cardiovascular Outcome Trials (CVOT) to demonstrate that they do not increase the risk of Major Adverse Cardiovascular Events (MACE)

Outcome trial must exclude HR 1.8 (preapproval) and 1.3 (postapproval)
Patient selection should include high-risk population, including the elderly and those with advanced cardiovascular disease, and some degree of renal impairment
Duration must be at least 2 y
Required cardiovascular events: cardiovascular mortality, myocardial infarction, stroke
Optional cardiovascular events: hospitalization for acute coronary syndrome or urgent revascularization procedures
Cardiovascular events must be adjudicated in a blinded, independent process

95% Confidence Interval Upper Limit

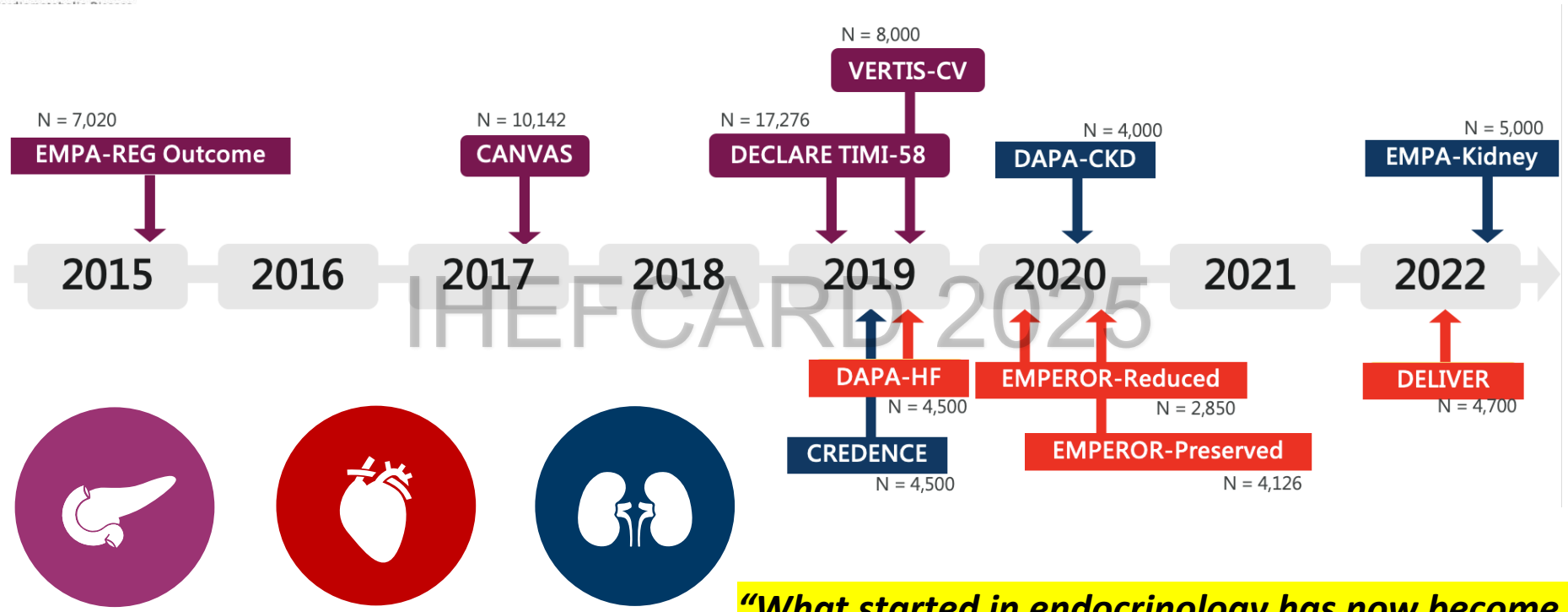
(MACE)

FDA indicates US Food and Drug Administration; and HR, hazard ratio.

Circulation. 2020 Mar 10;141(10):843-862.

CVOT: Cardiovascular outcome trial; MACE: Major adverse cardiovascular event

The Journey of SGLT2i in HF – A Recap



"What started in endocrinology has now become cardiology's newest frontier."

Circulation. 2020 Mar 10;141(10):843-862.

DECLARE TIMI-58, Three Main Features

	EMPA-REG OUTCOME (2015)	CANVAS Program (2017)	DECLARE-TIMI 58 (2019)	VERTIS-CV (2020)
Active Ingredient (Dosage)	Empagliflozin (10, 25 mg)	Canagliflozin (100, 300 mg)	**Dapagliflozin (10 mg)**	Ertugliflozin (5, 15 mg)
Number of Participants, n	7,020	10,142	**17,160**	8,246
Follow-up Duration, Years [Median]	3.1	2.4	**4.2**	3.0
Number of Female Participants, n (%)	2,004 (28.5)	3,633 (35.8)	6,422 (37.4)	2,477 (30.0)
Age, Years [Mean]	63.1	63.3	63.9	64.4
HbA1c, % [Mean]	8.1	8.2	8.3	8.2
Cardiovascular Disease, n (%)	7,020 (100)	6,656 (65.6) (MRF: 34.4)	**6,974 (40.6) (MRF: 59.4)**	8,246 (100)
History of Heart Failure, n (%)	706 (10.1)	1,461 (14.4)	1,724 (10.0)	1,958 (23.7)
Worsening Kidney Function[a], n (%)	1,819 (25.9)	2,039 (20.1)	1,265 (7.4)	1,807 (21.9)
UACR ≥300 mg/g, n (%)	769 (11.0)	760 (7.6)	1,169 (6.8)	755 (9.2)

[a]Estimated glomerular filtration rate <60 mL/min per 1.73 m2 based on the Modification of Diet in Renal Disease equation in EMPA-REG OUTCOME, the CANVAS Program, and VERTIS CV, and the Chronic Kidney Disease Epidemiology Collaboration equation in DECLARE-TIMI 58

SGLT2 Inhibitors CVOTs: Enrolled Participants

DECLARE TIMI-58	CANVAS Program	EMPA-REG	VERTIS-CV
Follow-up: 4.2 years	Follow-up: 2.4 years	Follow-up: 3.1 years	Follow-up: 3.0 years
40.6% eCVD	65.6% eCVD	99% eCVD	100% eCVD
MRF patients N = 10,186	N = 3,486		

Men≥ 55 yrs and women ≥ 60 yrs with at least one additional risk factor:

- Hyperlipidemia
- hypertension
- smoking

~60% MRF participants included in DECLARE TIMI-58

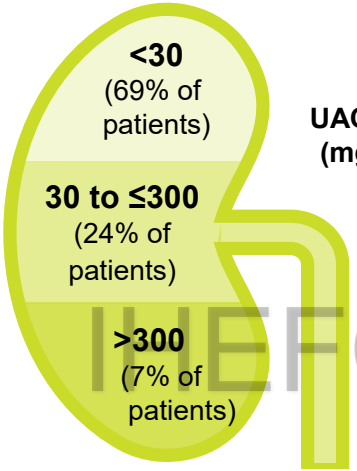
eCVD: Established CV disease; MACE: Major Cardiovascular events; MRF: Multiple risk factors

[1] *N Engl J Med* 2015;373:2117–2128; [2] *N Engl J Med* 2017;377:644–657; [3] *Diabetes Obes Metab* 2018;20:1102–1110; [4] *N Engl J Med*. 2018

Exploratory CV and renal outcomes in patients with T2D and Atherosclerotic CVD or multiple risk factors

DECLARE TIMI-58 TIMI STUDY GROUP/BWH/BRIGHAM AND WOMEN'S HOSPITAL MEDICAL ORG

N=17,160[1]



UACR[2,a] (mg/g)

Exploratory study objectives

Renal-specific composite outcome[1,b]

47% RRR

1.3% ARR

(1.5% vs 2.8%)

hHF[1,c]

27% RRR

0.8% ARR

HR: 0.73; 95% CI: 0.61, 0.88[1,a]

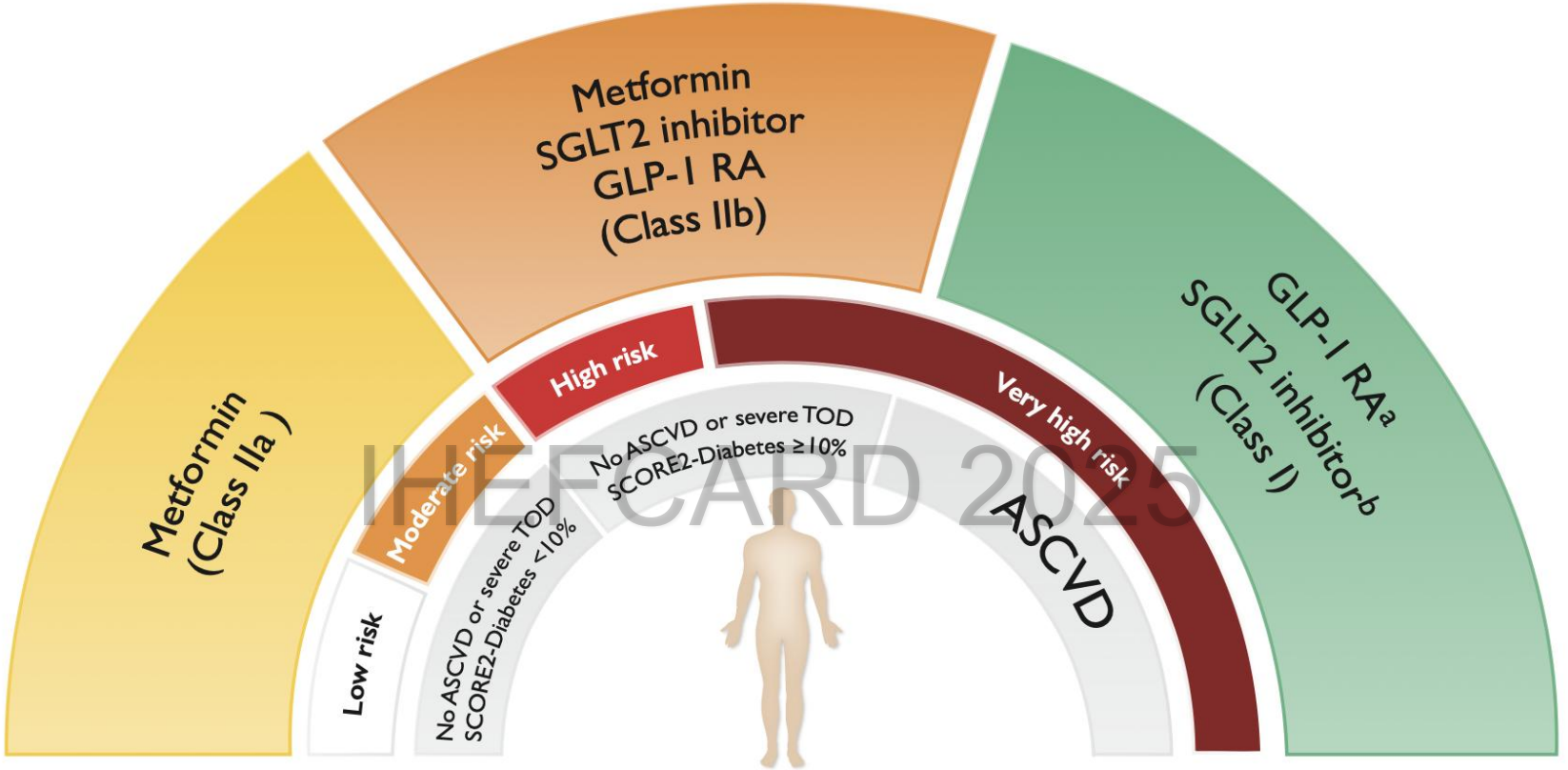
In DECLARE-TIMI 58, which included patients with established atherosclerotic CVD or multiple risk factors for this disease, Dapagliflozin demonstrated reductions in the exploratory endpoints of risk of hHF and reduced progression of nephropathy in a T2D population[1,2,d]

A diabetes trial... with a heart failure twist

[a]Baseline UACR data were missing from 318 (2%) patients[2]; [b]Nominally significant, prespecified exploratory renal composite outcome of a sustained decrease of ≥40% in eGFR to <60 mL/min/1.73 m^2, new ESKD, or death from kidney causes[1]; [c]hHF alone was a separate, nominally significant exploratory endpoint in DECLARE. The primary endpoint composite of CV death/hHF (17% RRR [0.9% ARR]) was driven by hHF[1]; [d]The co-primary efficacy endpoints of the DECLARE-TIMI 58 trial were MACE, and a composite of CV death or hHF. Dapagliflozin did not meet the criterion for non-inferiority vs placebo with respect to MACE.

aCVD, atherosclerotic cardiovascular disease; ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; hHF, hospitalization for heart failure; HR, hazard ratio; RRR, relative risk reduction; T2D, Type 2 diabetes; UACR, urine albumin:creatinine ratio

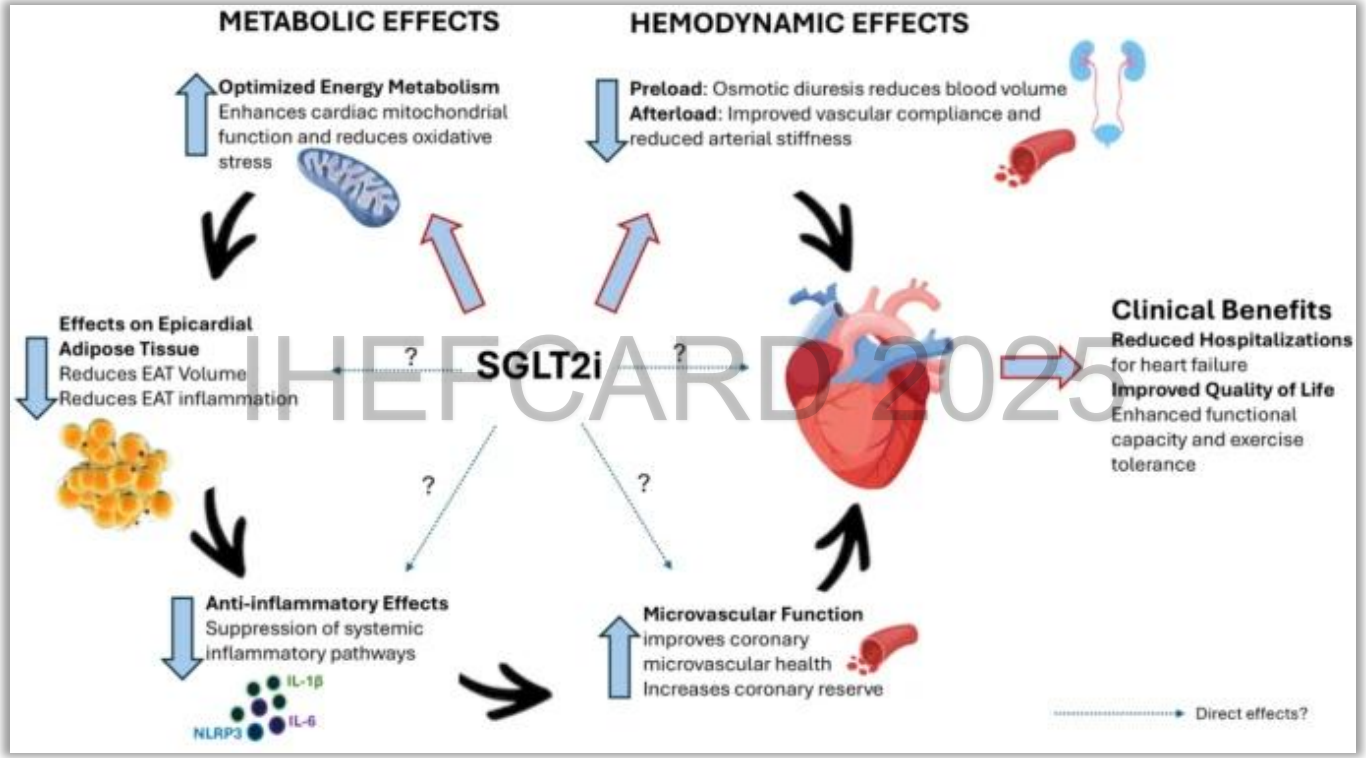
1. Wiviott SD, et al. *N Engl J Med* 2019:380;347–357; 2. Mosenzon O, et al. *Lancet Diabetes Endocrinol* 2019;7:606–617



Risk assessment for patients with type 2 diabetes based on the presence of ASCVD/severe TOD and 10-year CVD risk estimation via SCORE2-Diabetes

European Heart Journal (2023) **44**, 4043–4140

Mechanism of action revisited—beyond glycemic effects

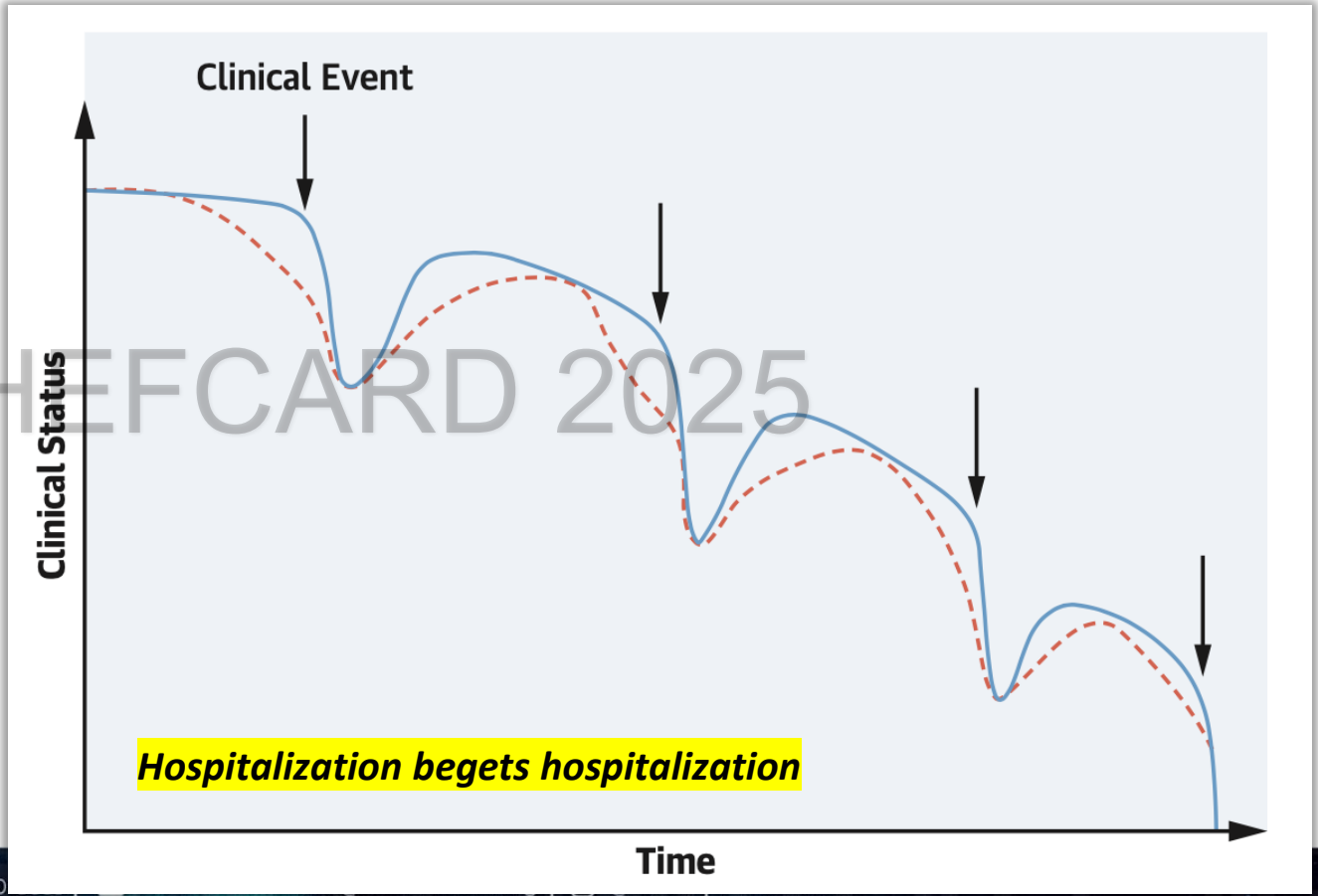


Cinti, F., et al. *Cardiovasc Diabetol* **24**, 208 (2025)

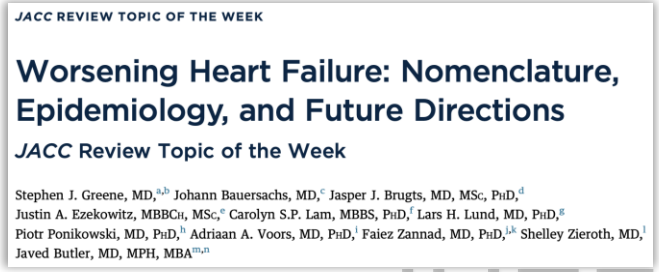
Key point: natriuresis, improved cardiac metabolism, anti-inflammatory, antifibrotic

Then, when it comes to HF, what's changing the game?

Worsening Heart Failure



Greene SJ, et al. J Am Coll Cardiol. 2023;81(4):413–424.



JACC REVIEW TOPIC OF THE WEEK

Worsening Heart Failure: Nomenclature, Epidemiology, and Future Directions

JACC Review Topic of the Week

Stephen J. Greene, MD,[a,b] Johann Bauersachs, MD,[c] Jasper J. Brugts, MD, MSc, PhD,[d] Justin A. Ezekowitz, MBBCh, MSc,[e] Carolyn S.P. Lam, MBBS, PhD,[f] Lars H. Lund, MD, PhD,[g] Piotr Ponikowski, MD, PhD,[h] Adriaan A. Voors, MD, PhD,[i] Faiez Zannad, MD, PhD,[j,k] Shelley Zieroth, MD,[l] Javed Butler, MD, MPH, MBA[m,n]

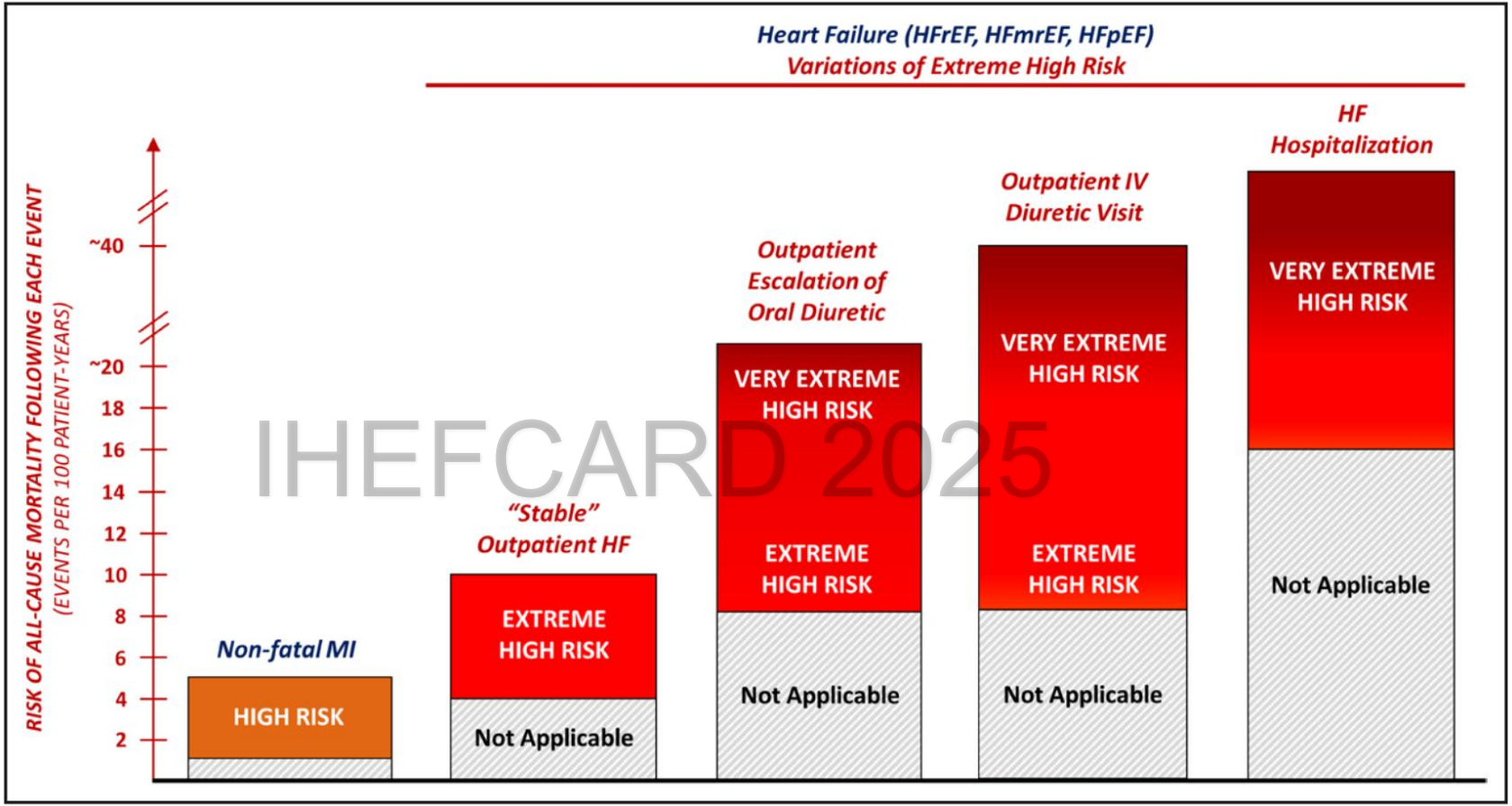
Worsening Heart Failure

Current Definition:

- Deterioration of HF signs and symptoms in a patient with chronic HF, despite previous stable background therapy
- Requires urgent escalation of therapy, including hospitalization, ED visit, or outpatient IV diuretic therapy, ± outpatient oral therapy*

Worsening HF (WHF) recognized as a distinct, urgent phenotype

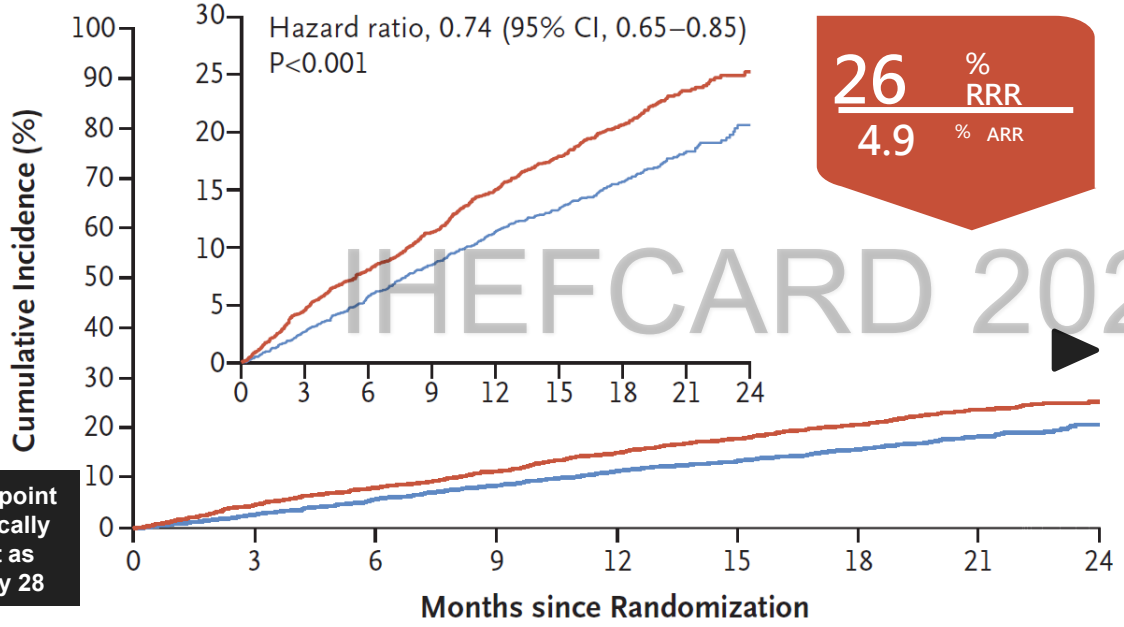
Greene SJ, et al. J Am Coll Cardiol. 2023;81(4):413–424.



Redefining Worsening Heart Failure: The Crisis Is No Longer Inpatient-Only

Greene SJ, et al. Circulation.2023

DAPA-HF: Dapagliflozin Significantly Reduce the Primary Composite Endpoint (CV death or worsening HF) in HFrEF patients



Primary endpoint was statistically significant as early as Day 28

Primary Composite Endpoint

HR: 0.74 (95% CI: 0.65-0.85)

- Type 2 DM
HR: 0.75 (95% CI: 0.63-0.90)
-Non-DM
HR: 0.73 (95% CI: 0.60-0.88)

hHF

HR: 0.70 (95% CI: 0.59-0.83)

CV Death

HR: 0.82 (95% CI: 0.69-0.98)

-Placebo
273 patients with events

-Dapagliflozin
227 patients with events

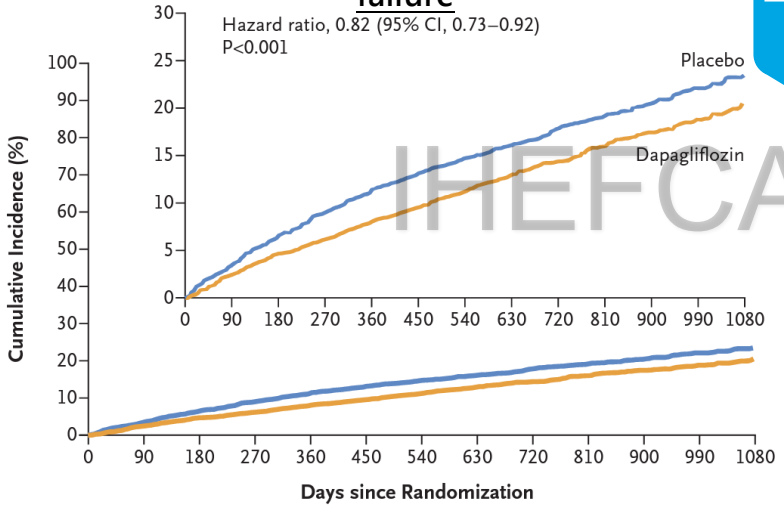
DELIVER: Dapagliflozin significantly reduce Primary composite endpoint (CV Death and Worsening of Heart Failure) in HFpEF patients

The 5th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

The population included in DELIVER includes currently/recently hospitalized patients

CV death/hospitalization for heart failure

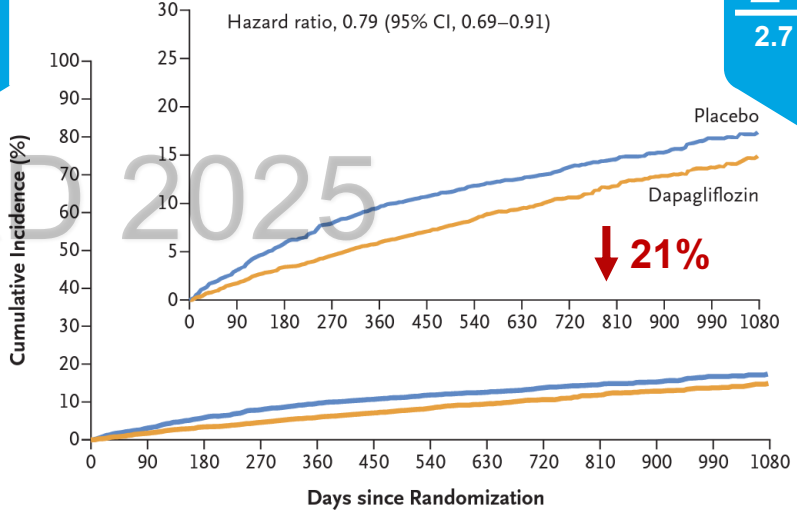
18% RRR
3.1 % ARR



No. at Risk													
Placebo	3132	3007	2896	2799	2710	2608	2318	2080	1923	1554	1140	772	383
Dapagliflozin	3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389

Worsening of heart failure

21% RRR
2.7 % ARR



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Dapagliflozin	3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389

HFpEF used to mean limited options. DELIVER proves that's no longer true

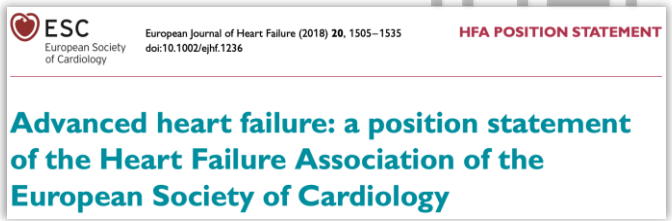
…and also, Severe Heart Failure


ORIGINAL RESEARCH

HEART FAILURE

Severe Heart Failure and Treatment With Dapagliflozin Across the Ejection Fraction Spectrum

DAPA-HF and DELIVER


ESC European Society of Cardiology

European Journal of Heart Failure (2018) 20, 1505–1535
doi:10.1002/ejhf.1236

HFA POSITION STATEMENT

Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology

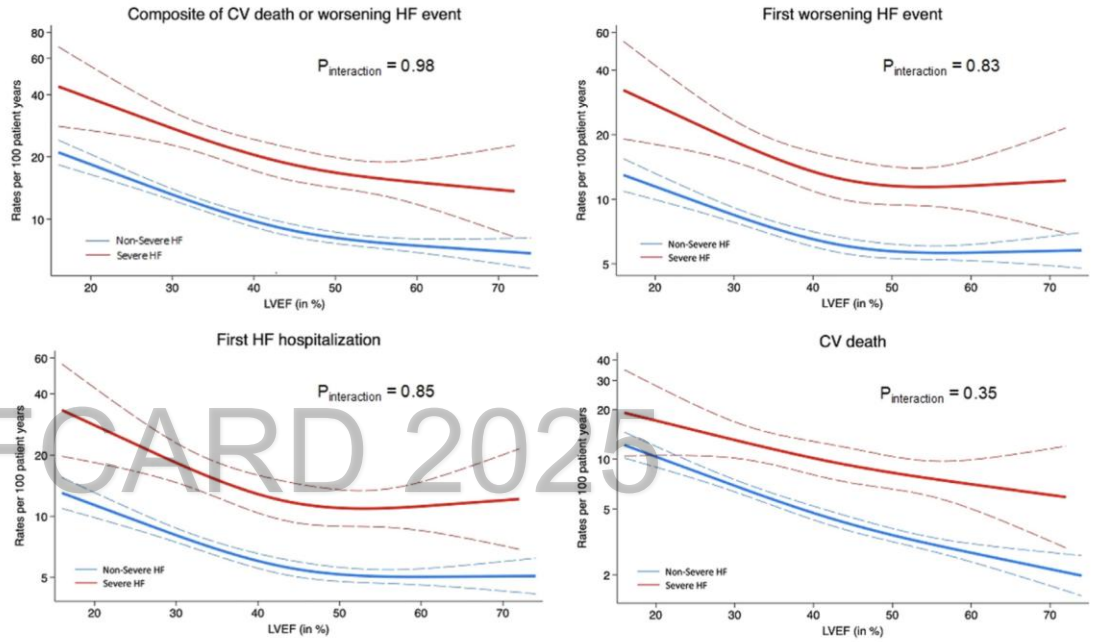
Definition (adapted from 2018 HFA Position Statement & recent trials):
A patient is considered to have **severe HF** if **all** the following are met:

1. **NYHA Class III–IV symptoms**
2. Evidence of **HFrEF, HFmrEF, or HFpEF** (per ESC definitions)
3. **Hospitalization for HF** in the **past 12 months**
4. **KCCQ-Total Symptom Score (TSS) < 75** (impaired health status)

TABLE 1 Patient Characteristics According to Severe HF Status

	Nonsevere HF (n = 10,218)	Severe HF (n = 730)	*P* Value
Age, y	69.3 ± 10.5	69.6 ± 10.8	0.55
Female	3,536 (34.6)	287 (39.3)	0.010
BMI, kg/m^2	29.0 ± 6.1	30.3 ± 6.5	<0.001
Race			<0.001
Asian	2,281 (22.3)	88 (12.1)	
Black	362 (3.5)	22 (3.0)	
Other	450 (4.4)	8 (1.1)	
White	7,125 (69.7)	612 (83.8)	
Region			<0.001
Europe and Saudi Arabia	4,626 (45.3)	503 (68.9)	
Asia/Pacific	2,214 (21.7)	88 (12.1)	
Latin America	1,937 (19.0)	57 (7.8)	
North America	1,441 (14.1)	82 (11.2)	
NYHA functional class			<0.001
I/II	7,917 (77.5)	0 (0.0)	
III	2,262 (22.1)	710 (97.3)	
IV	39 (0.4)	20 (2.7)	
Clinical history			
Heart rate, beats/min	71.3 ± 11.7	73.4 ± 11.8	<0.001
Systolic blood pressure, mm Hg	125.5 ± 16.2	124.9 ± 14.7	0.32
Diastolic blood pressure, mm Hg	73.7 ± 10.4	75.1 ± 10.0	<0.001
LVEF, %	44.3 ± 14.0	43.6 ± 12.6	0.24
Type 2 diabetes mellitus	4,526 (44.3)	385 (52.7)	<0.001
Atrial fibrillation	4,900 (48.0)	441 (60.4)	<0.001
eGFR, mL/min/1.73 m^2	63.3 ± 19.4	59.9 ± 19.6	<0.001
KCCQ-TSS	77.1 (59.4-91.7)	51.0 (37.5-62.5)	<0.001
KCCQ-OSS	71.7 (55.4-85.0)	47.4 (36.2-58.3)	<0.001
KCCQ-CSS	74.1 (57.6-87.5)	50.7 (38.9-61.1)	<0.001
NT-proBNP, pg/mL	1,152 (693-2,045)	1,790 (869-3,356)	<0.001
Baseline treatment			
Dapafliglozin	5,126 (50.2)	351 (48.1)	0.28
Diuretic	9,787 (95.8)	711 (97.4)	0.034
ACEI	4,585 (44.9)	346 (47.4)	0.19
ARB	3,353 (32.8)	208 (28.5)	0.016
ARNI	758 (7.4)	46 (6.3)	0.26
Beta-blocker	9,020 (88.3)	662 (90.7)	0.049
MRA	5,546 (54.3)	447 (61.2)	<0.001
Digitalis	1,071 (10.5)	99 (13.6)	0.009
CRT-P or CRD-D	419 (4.1)	32 (4.4)	0.71
ICD or CRD-D	1,336 (13.1)	68 (9.3)	0.003

FIGURE 1 Rates of Events According to Severe HF Status, Across the Spectrum of LVEF

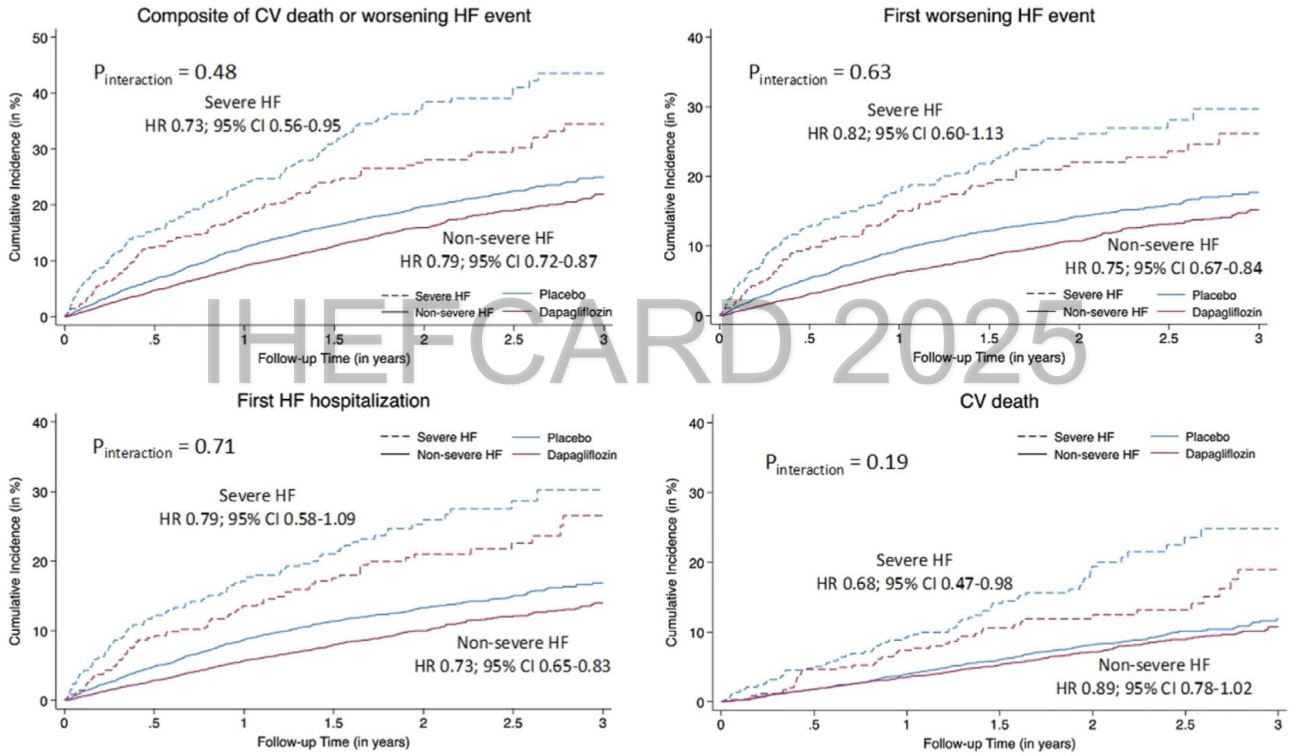


CV = cardiovascular; HF = heart failure; LVEF = left ventricular ejection fraction.

"Severe heart failure isn't just a label—it's a warning. These patients face twice the risk."

Dapagliflozin Works — Even in Severe HF

FIGURE 2 Treatment Effect of Dapagliflozin vs Placebo, by Severe HF Status



Abbreviations as in Figure 1.

Greater Absolute Benefit in Severe HF

NNT (Number Needed to Treat) to prevent one primary event:

- Severe HF: **14**
- Non-severe HF: **45**

✅ Same relative risk reduction

📉 **Greater absolute risk** in severe HF → **greater absolute benefit**

"Treat 14 to save 1. In severe HF, the sicker they are, the more they gain"

The ESC recommends an SGLT2 inhibitor as first-line therapy for patients across all EFs to reduce the risk of hHF or CV death[a]

ESC European Society of Cardiology

ESC 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[1,2]

HFrEF[1,b]	Class/level
Dapagliflozin/empagliflozin	1A
ACEi/ARNI[c]	1A
Beta blocker	1A
MRA	1A
Loop diuretic for fluid retention	1

HFpEF[2,b]	Class/level
Dapagliflozin/empagliflozin	1A
Diuretics for fluid retention	1
Treatment for etiology, CV and non-CV comorbidities	1

HFmrEF[2,b]	Class/level
Dapagliflozin/empagliflozin	1A
Diuretics for fluid retention	1
ACEi/ARNi/ARB	2B
MRA	2B
Beta blockers	2B

Consult guidelines for full information and context

[a]This recommendation is based on the reduction of the primary composite endpoint used in the EMPEROR-Preserved and DELIVER trials and in a meta-analysis. However, it should be noted that there was a significant reduction only in HF hospitalizations and no reduction in CV death; [b]Number indicates class of recommendation, letter indicates level of evidence; [c]ARNi used as a replacement for ACEi

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; EF, ejection fraction; 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;

The ACC recognizes SGLT2 inhibitors as a core therapy for HFrEF; treatment should be initiated rapidly as a pillar of comprehensive GDMT

2024 ACC Expert Consensus Decision Pathway

SGLT2 inhibitor + ARNI + MRA + evidence-based beta blocker

For patients with persistent volume overload, NHYA class II–IV	For persistently symptomatic African American patients despite ARNI/beta blocker/SGLT2, NHYA class III–IV	For patients with resting heart rate of ≥70, on maximally tolerated beta-blocker dose in sinus rhythm, NYHA class II–III	For high-risk patients already on optimal GDMT with worsening HF as evidenced by a hHF or requirement for IV diuretics
Titrate	Add	Add	Add
Loop diuretic agent	Hydralazine + isosorbide dinitrate	Ivabradine	Vericiguat

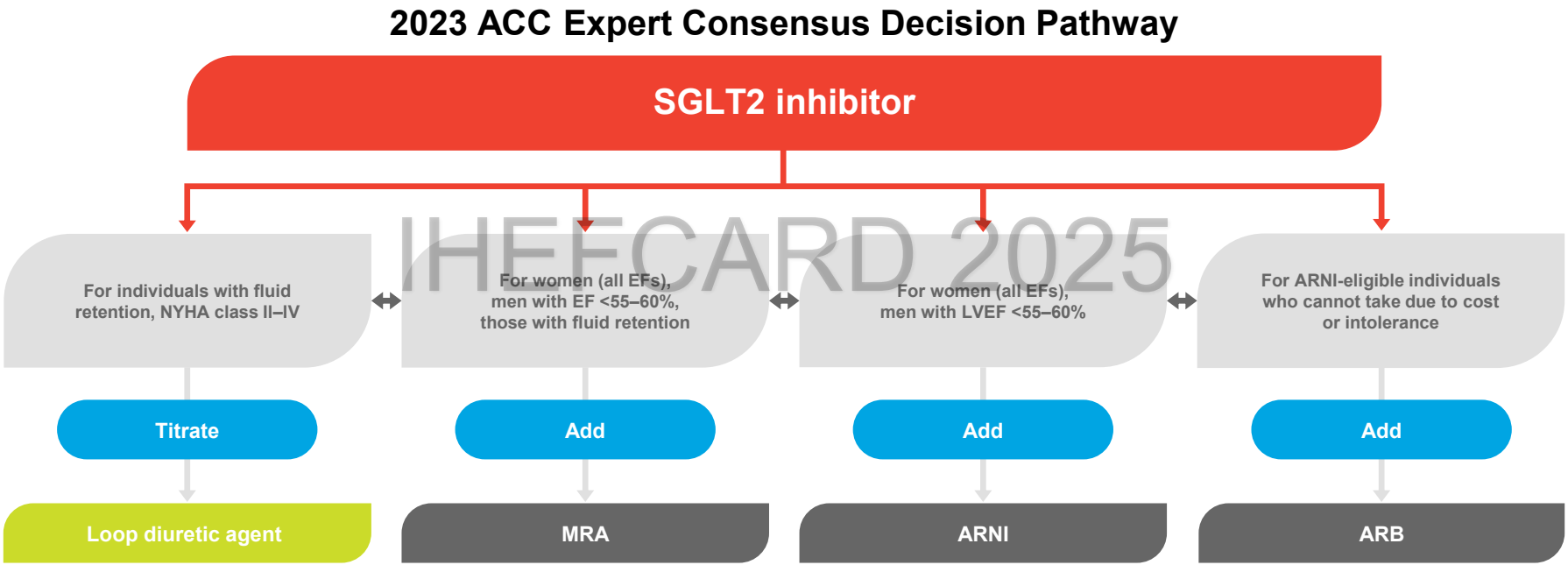
Consult guideline for full information and context and consult the prescribing information of any drug for a full list of indications, posology and adverse events before prescribing

Green color identifies a Class 1 therapy from clinical practice guidelines, red color indicates a Class 2a therapy, and gray color denotes a Class 2b therapy

ACC, American College of Cardiology; ARNI, angiotensin receptor–neprilysin inhibitor; GDMT, guideline-directed medical therapy; HF, heart failure; hHF, hospitalization for heart failure;

… again, Start Strong, Start Early!

The ACC recommends initiation of SGLT2 inhibitors as first-line therapy in patients with HFpEF to reduce CV death/hHF and improve health status



Consult guideline for full information and context

Green color identifies a Class 1 therapy from clinical practice guidelines, red color indicates a Class 2a therapy, and grey color denotes a Class 2b therapy. ACC, American College of Cardiology; AHA, American Heart Association; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; EF, ejection fraction; hHF, hospitalization for heart failure; HFpEF, heart failure with preserved ejection fraction; HFSA, Heart Failure Society of America; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid antagonist; NYHA, New York Heart Association;

2023 Indonesian Guidelines for Heart Failure Treatment

Indonesian Working Group on Heart Failure & Cardiometabolic Disease

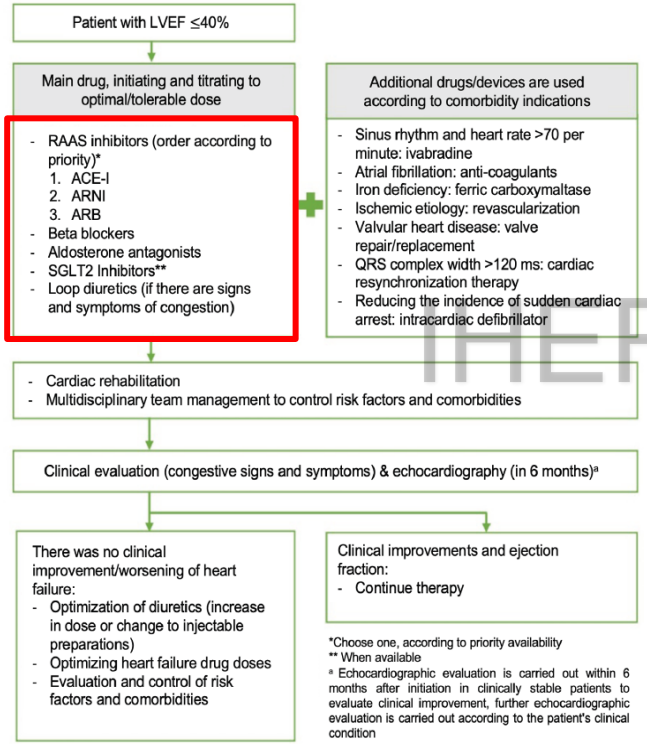


Figure 4.1 HFrEF management algorithm

Table 5.2 Recommendations for management of HFpEF.

Recommendations	COR	LOE
HFpEF patients with hypertension must receive treatment according to blood pressure targets to prevent progression of heart failure	I	A
In HFpEF, SGLT2 inhibitors reduce cardiovascular death and heart failure hospitalization	I	A
In HFpEF, cardiac rehabilitation including aerobic exercise is recommended to improve functional capacity, in addition to pharmacological treatment	I	A
In HFpEF with obesity, weight loss with calorie restriction and aerobic exercise is recommended to improve the functional status and structure of the heart	I	A
In HFpEF, AF management can improve complaints	IIa	B
In HFpEF, spironolactone may be considered to reduce hospitalization in populations with a low risk of developing hyperkalaemia and creatinine values <2.5 mg/dl	IIb	B
In HFpEF, ARB or ARNI can be considered to reduce hospitalization at the lower end of the LVEF spectrum	IIb	B
In HFpEF, routine use of Nitrates or phosphodiesterase-5 inhibitors has not been shown to be effective in improving outcome	III	A

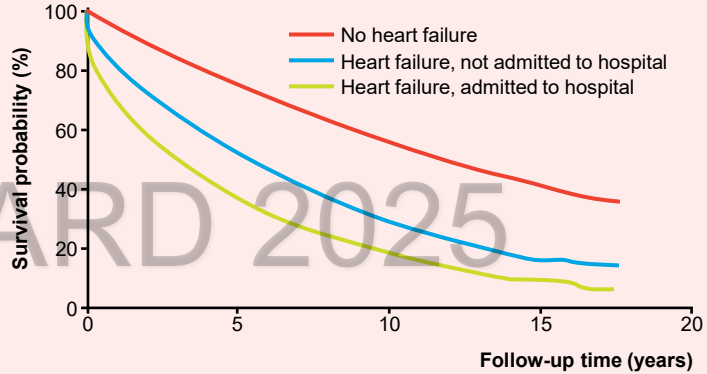
2023 Indonesian Guidelines for Heart Failure Treatment: Working Group on Heart Failure and Cardiometabolic Diseases, Indonesian Heart Association. Indonesian J Cardiol 2024:45:68-103

Survival after a diagnosis of HF has improved only modestly in the 21st century and is lower than other serious conditions

1-year survival rates increased by 6.6% (from 74.2% in 2000 to 80.8% in 2016)

New strategies to achieve timely diagnosis and treatment initiation should be a priority

Kaplan–Meier curve of survival for people with a new diagnosis of HF who were admitted to hospital or not admitted to hospital at time of diagnosis and for comparators matched by age, sex, and practice



No at risk (number censored)

No heart failure			
278 679 (0)	105 331 (120 343)	31 494 (175 326)	3130 (199 292)
Heart failure, not admitted to hospital			
31 834 (0)	9641 (9298)	2457 (13 301)	185 (14 920)
Heart failure, admitted to hospital			
24 125 (0)	4170 (7505)	729 (9457)	40 (9923)

Despite tremendous uptake, suboptimal use of GDMT remains a concern

Optimal GDMT is estimated to reduce mortality by >70%, in addition to improving QoL[3]

However, GDMT remains underused[3]

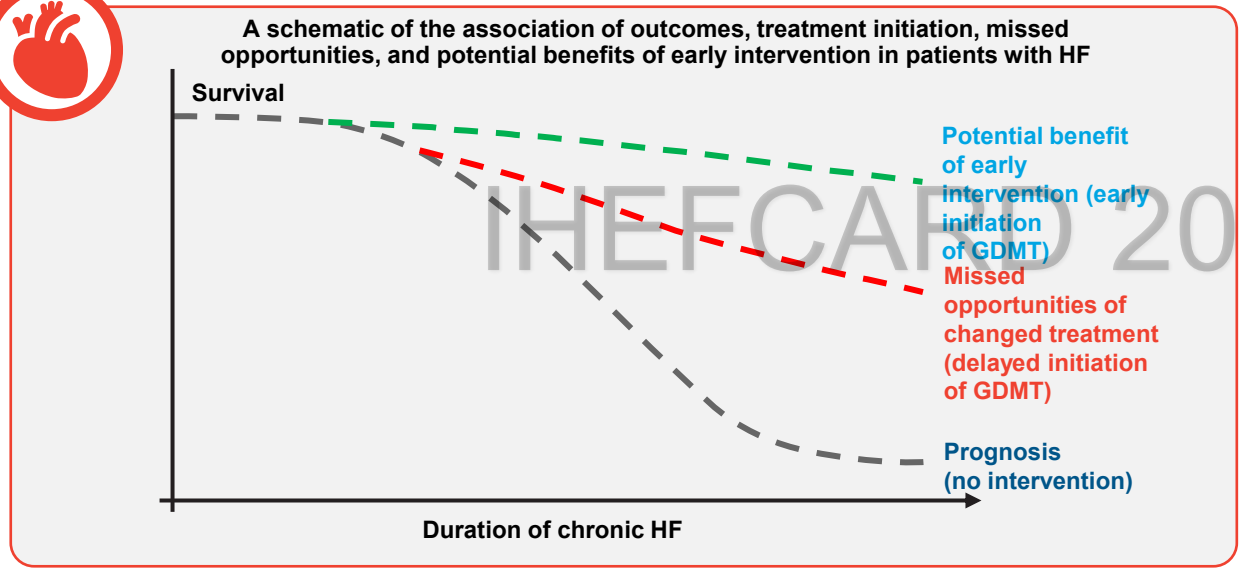
There is a critical need to identify strategies to improve GDMT implementation for patients with HF[3]

GDMT, guideline-directed medical therapy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; QoL, quality of life; SoC, standard of care

1. Vaduganathan M, et al. *J Card Fail* 2022;28:555–563; 2. Savarese G, et al. *JACC Heart Fail* 2023;11:1–14; 3. Azizi Z, et al. *J Am Heart Assoc* 2024;13:e030952

Comprehensive and rapid HF management is an important modifiable risk factor throughout the entire patient journey – Time to act now!

Time is heart. In heart failure, every delay costs survival



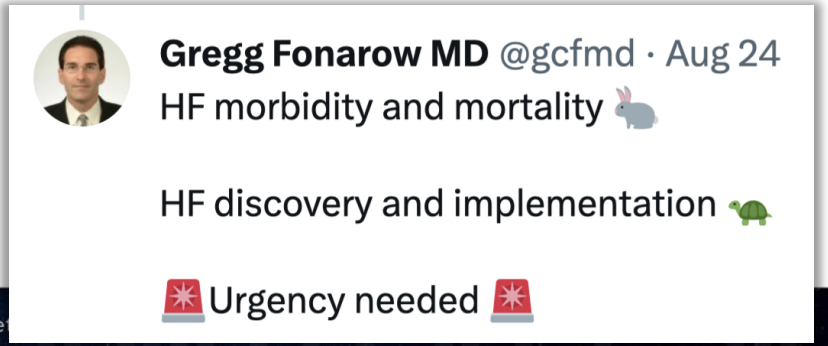
- Acute HF has poor prognosis
- **Timely diagnosis** and **immediate treatment** improves prognosis
- The immediate post-worsening HF period "**vulnerable phase**" plays an important role in clinical outcomes
- In the **stable outpatient with chronic HF**, treatments are often delayed or not initiated when symptoms are stable

Let's not wait for worsening. **Act early, act fast — because the vulnerable phase is now.**

Figure adapted from Abdin A, et al. 2021

Key Takeaways

- SGLT2i began as glucose-lowering agents, now key in heart failure care.
- Dapagliflozin showed benefits across the HF spectrum—including severe and worsening HF.
- Despite tremendous uptake, suboptimal use of GDMT in HF remains a concern, and it costs life
- ***No time to waste, Heart Failure just won't wait***



THANK YOU!