

最新心衰竭治療指引

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Outline

- 心衰竭的成因、盛行率、預後
- 心衰竭治療指引更新-ESC
 - SGLT2i in HFrEF
 - Recently reported advances from trials in HFrEF
 - HFmrEF, HFpEF
- 總結

什麼是心衰竭？

心臟衰竭，俗稱**心臟無力**，是指心臟功能受損，心臟無法打出足夠的血液量，以滿足身體及組織代謝的所需求，而產生一連串的症狀，如**呼吸困難、喘、運動耐力變差、疲倦及全身或四肢水腫**，臨床檢查會發現有**心臟肥大**的情形。

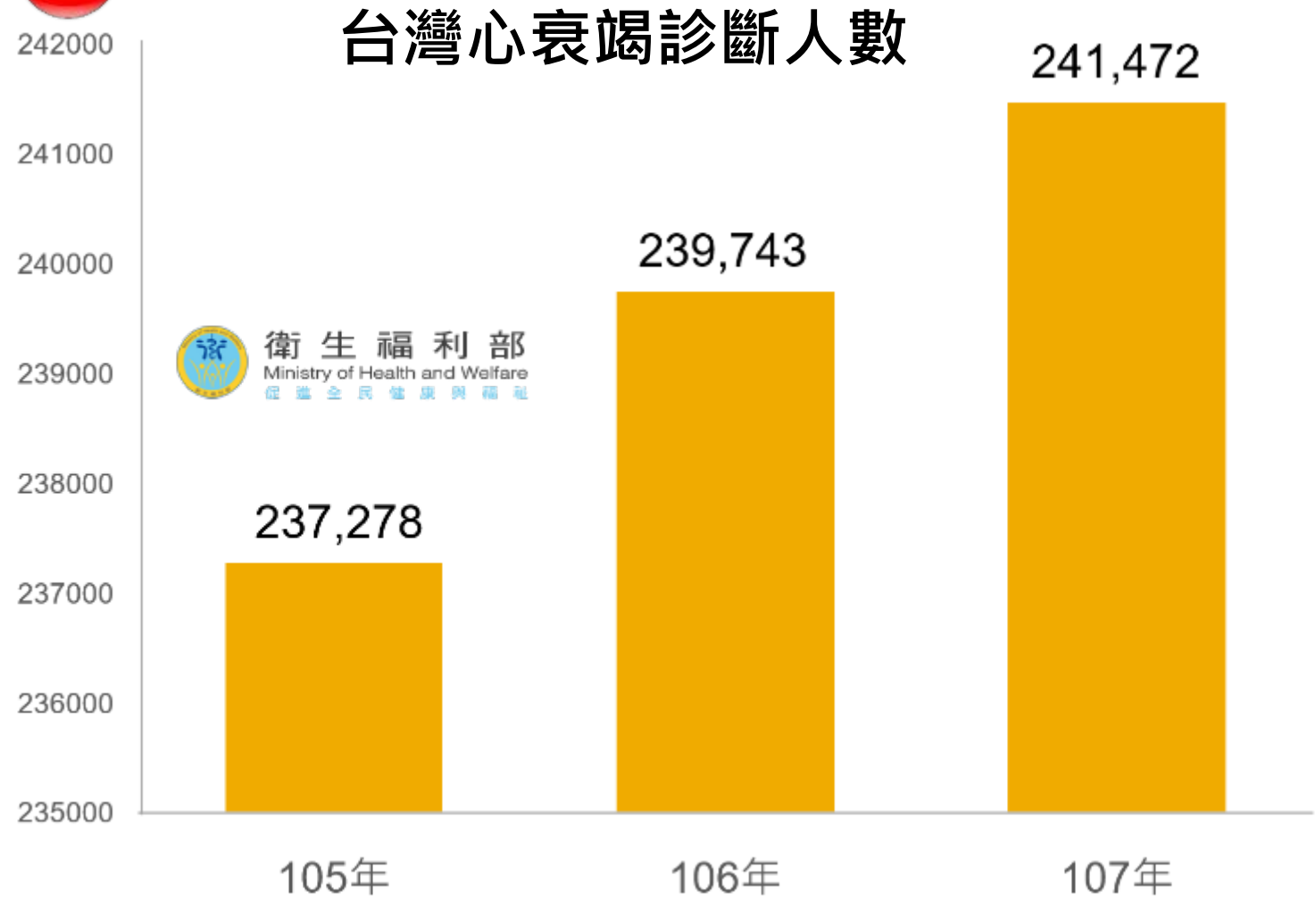


心臟如同您身體內的幫浦馬達，負責打出足夠的血液量供各器官使用，以維持身體功能。

而心臟衰竭即為心臟幫浦馬達因某些因素導致功能不如預期(常常是能力下降)，沒有能力打出足夠血液量以供應身體需求而導致身體產生不適。

根據統計，高達50%的心臟衰竭患者，於診斷後五年內死亡，心臟衰竭就如同是心臟的『癌症』！所帶來的影響巨大，患者不可輕忽！

台灣心衰竭人口約 24萬，逐年增加中，每年導致近8萬人住院



7.9萬人因心衰竭住院
每年住院1.5次
平均住院9.9天

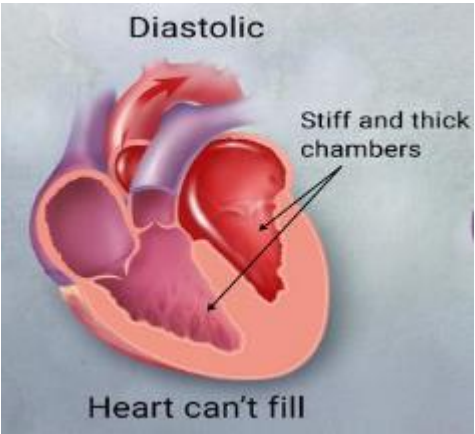
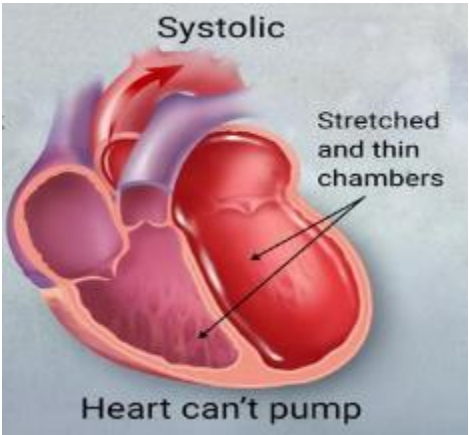


每年花費約24.7億



每年2.1萬人
心因性死亡

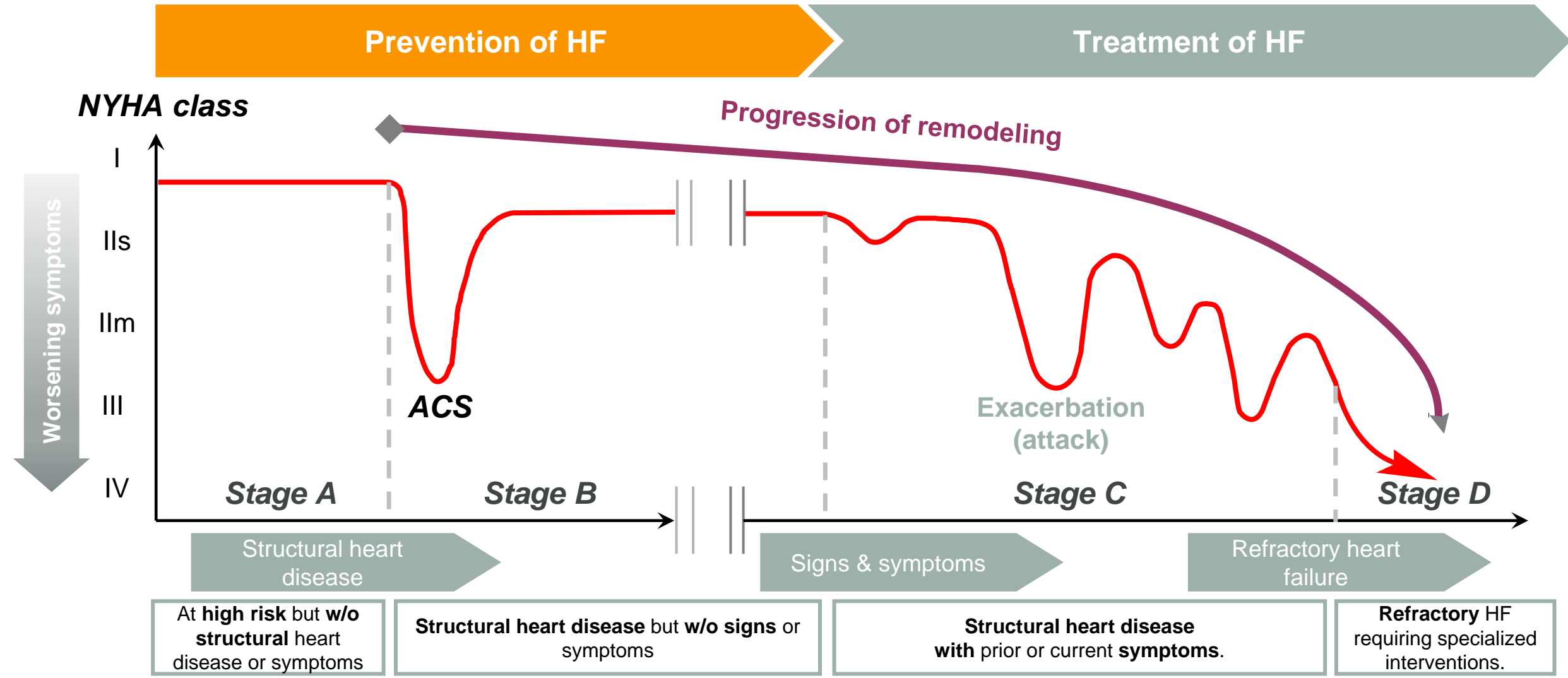
心衰竭的分類



HFrEF	HFmrEF	HFpEF
Symptoms ± signs ^a		
LVEF <40%	LVEF 40-49%	LVEF ≥50%
—	<ul style="list-style-type: none">Elevated levels of natriuretic peptidesAt least one additional criterion:<ol style="list-style-type: none">Relevant structural heart disease (LVH and/or LAE)Diastolic dysfunction	

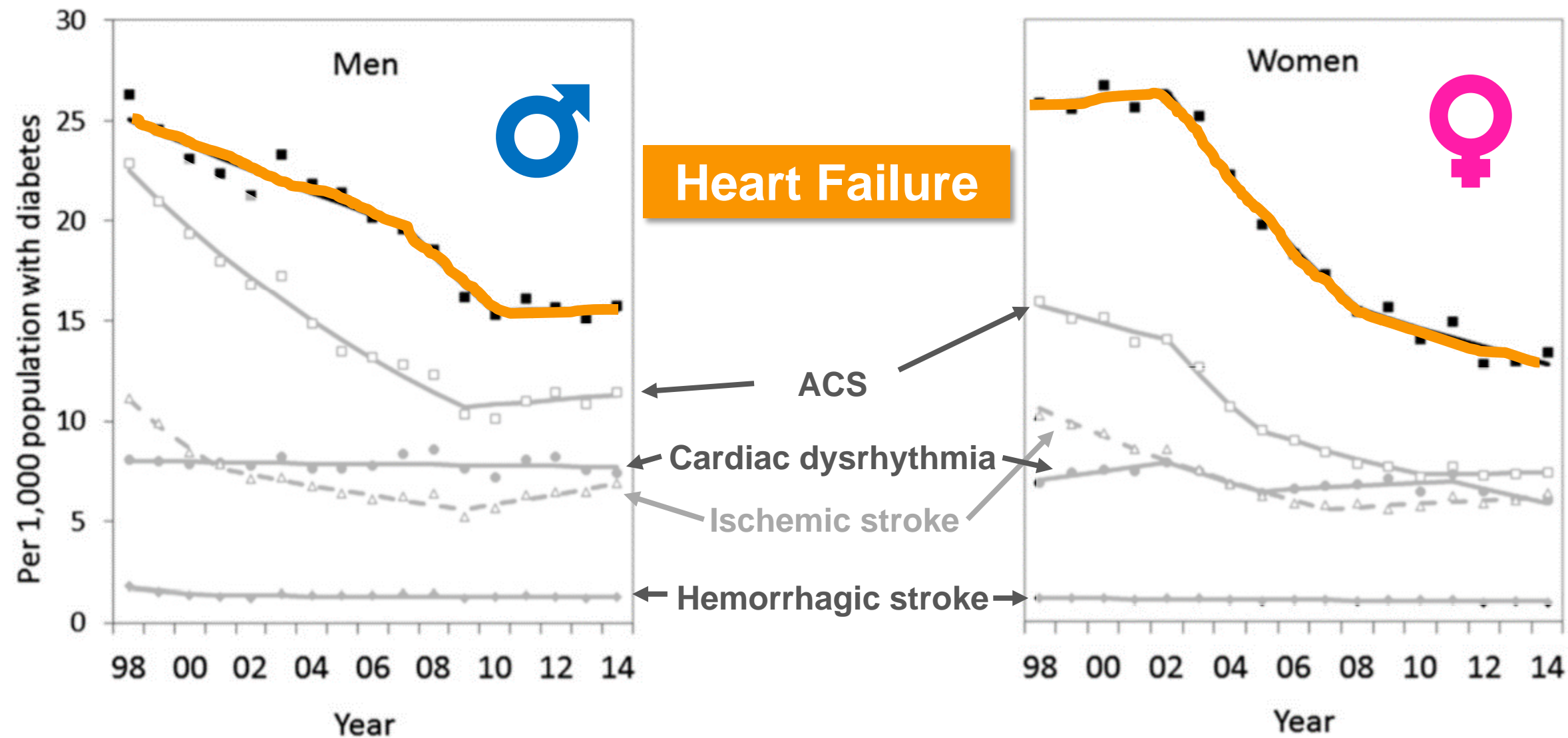
^aSigns may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics;
^bBNP >35 pg/mL and/or NT-proBNP >125 pg/mL.
HFrEF = heart failure with reduced ejection fraction; HFmrEF = heart failure with mid-range ejection fraction;
HFpEF = heart failure with preserved ejection fraction
LAE = left atrial enlargement; LVH = left ventricular hypertrophy; LVEF = left ventricular ejection fraction; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-B type natriuretic peptide.
Ponikowski P et al. Eur Heart J. 2016;37:2129-2200.

心衰竭是每況欲下的疾病，心臟功能會持續惡化



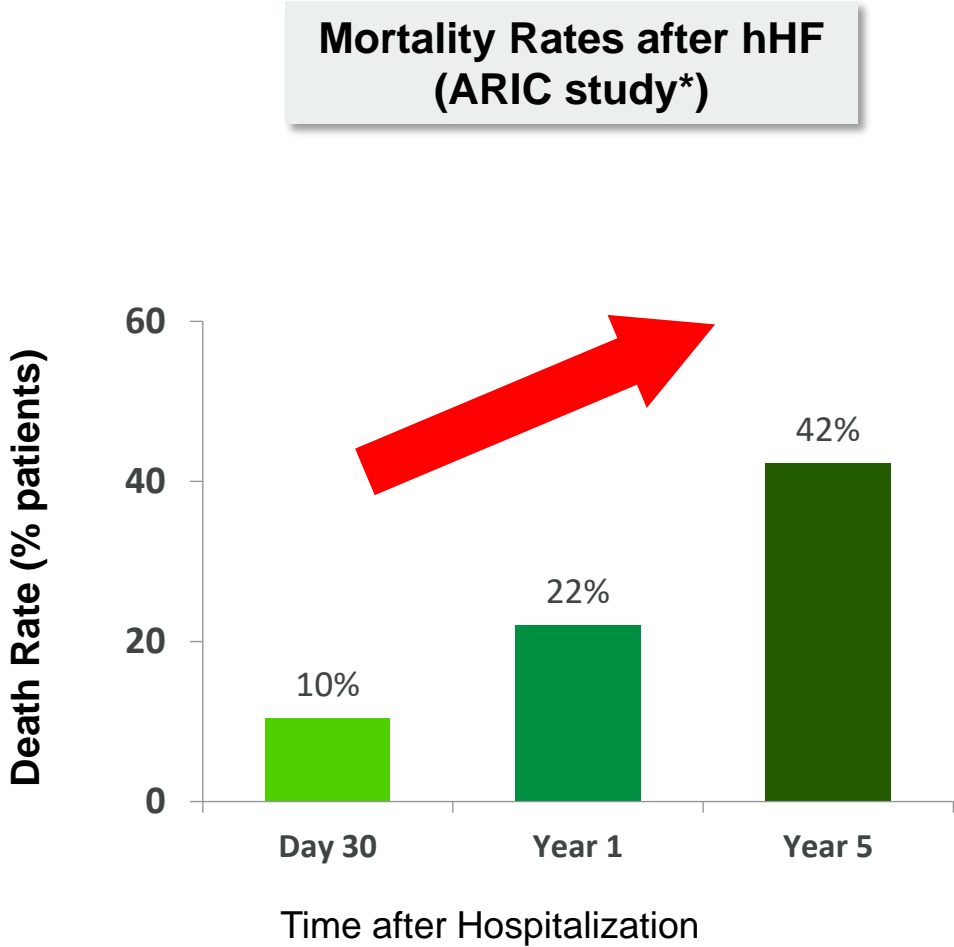
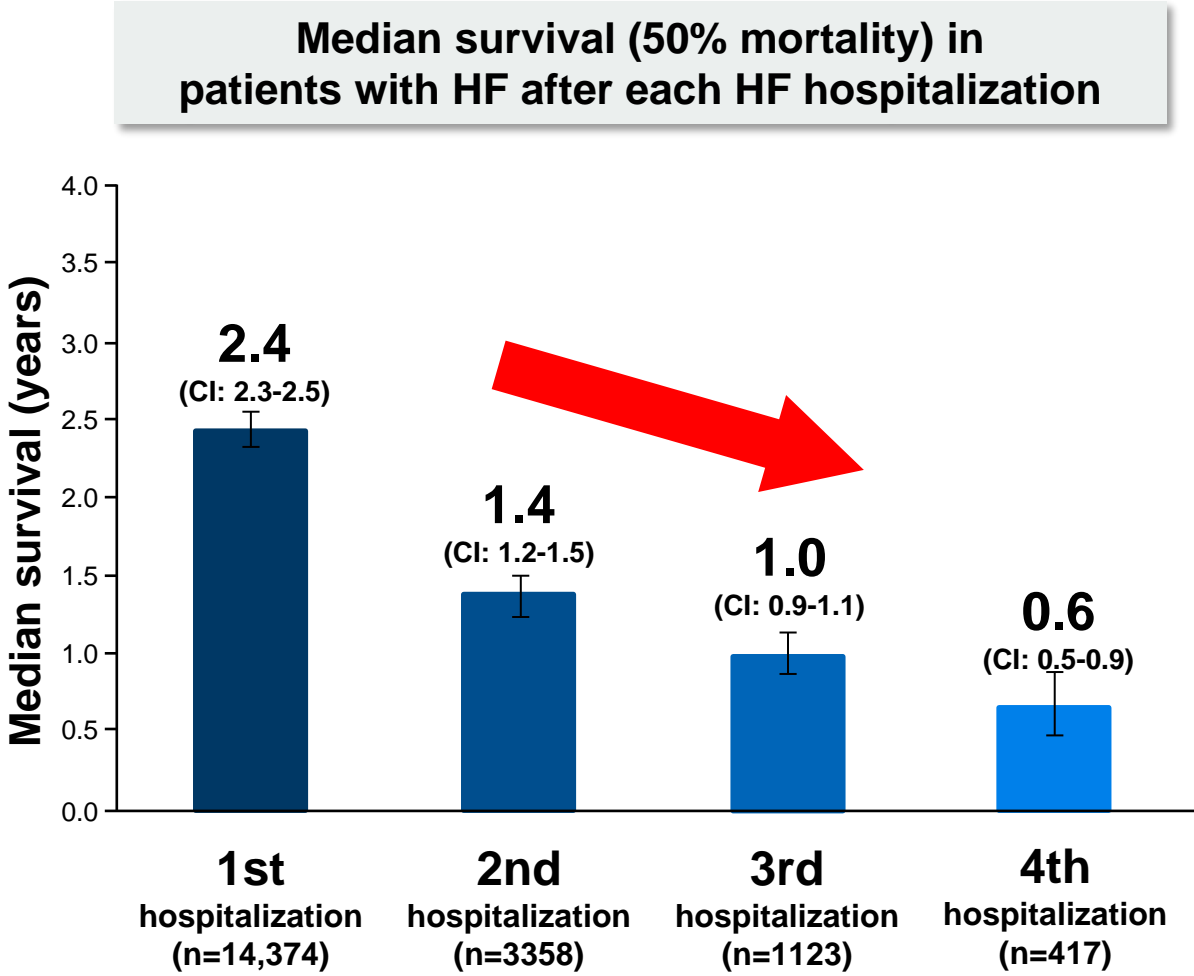
ACS = acute coronary syndrome; HF = heart failure; NYHA = New York Heart Association; w/o = without.
Kato M. The concept of heart failure: chronic diseases accompanied by an attack of acute exacerbation. In: Sato N, eds. Therapeutic Strategies for Heart Failure. Tokyo, Japan: Springer: 2018:1-15.

心衰竭為導致美國心血管疾病相關住院的主要原因



ACS, acute coronary syndrome; HHF, hospitalization for heart failure. Burrows NR et al. Diabetes Care. 2018;41(2):293-302.

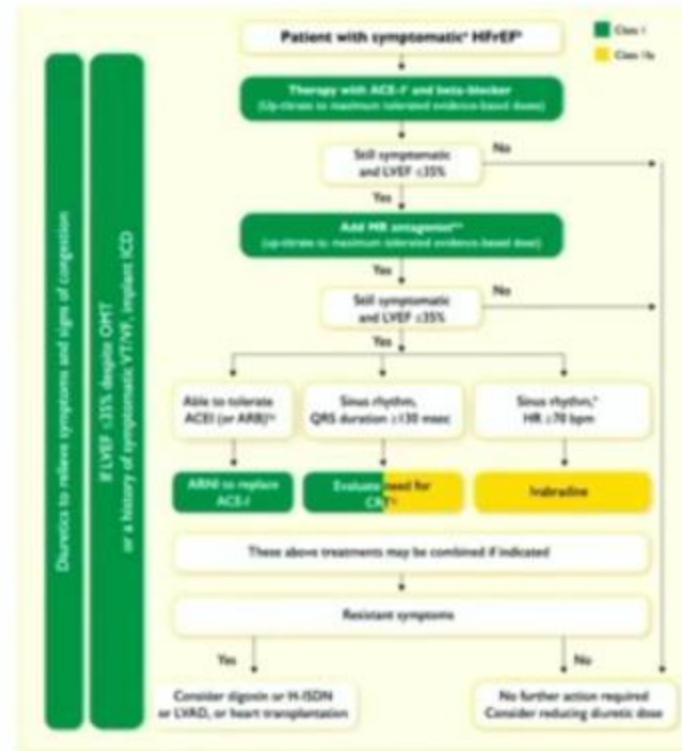
反覆的心衰竭住院會增加死亡風險，5年死亡率近50%



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Start Point-ESC HF Guideline 2016: Treatment of HFrEF



No change in evidence
ACEI/ARB/BB/MRA
Diuretics
Digoxin
Ivabradine
Hydralazine-nitrate

What's new in medical treatment in the ESC HF Guidelines 2021

- A simplified treatment algorithm for HFrEF based on the early administration of four major classes of drugs: ACEi/ARNI, BBs, MRA, SGLT2i
- Recommendations for the treatment of HFmrEF
- A classification of acute HF
- Treatment algorithms based on phenotypes
 - QRS duration and morphology
 - Aetiology (ischaemic / not ischaemic)
 - Cardiac rhythm, valvular heart disease
 - Diabetes, iron deficiency, electrolyte abnormalities (hyperkalemia)
 - Cancer
 - Amyloidosis and other cardiomyopathies

2021 ESC Guidelines for Heart Failure



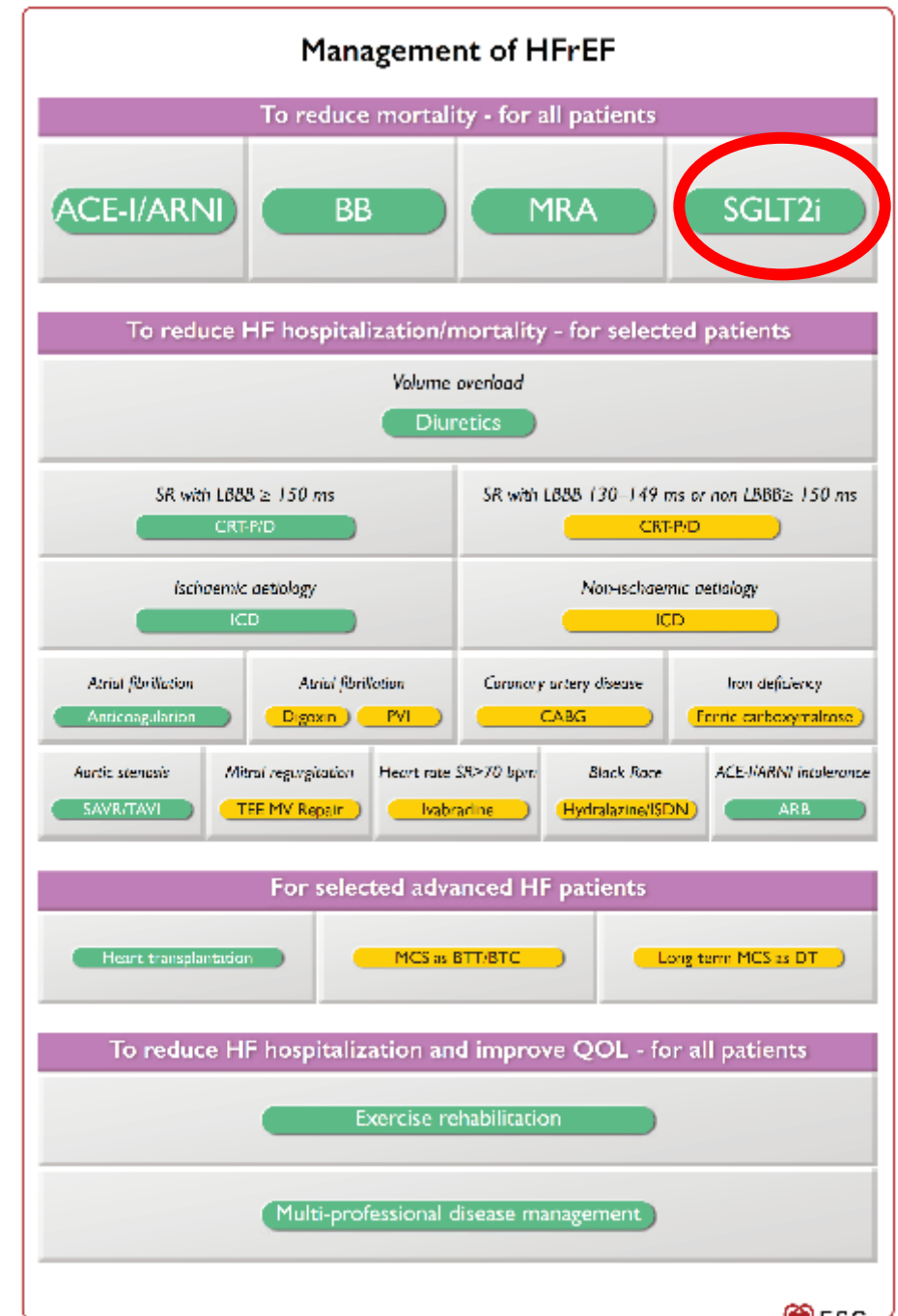
European Heart Journal (2021) 00, 1–128
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

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

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC



新增SGLT2i：‘Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death (1A)’，其餘與2016年版本相同

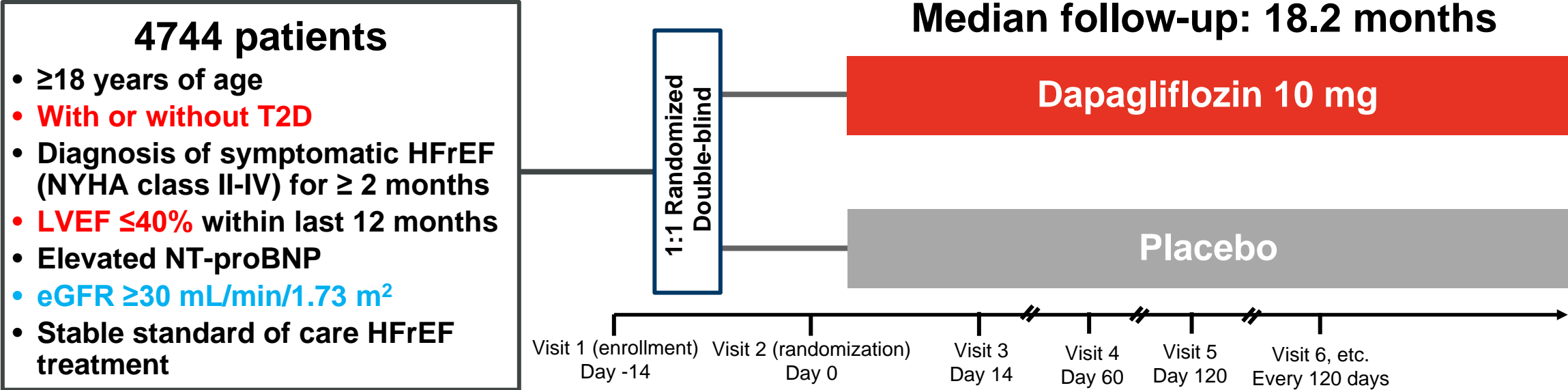
Drugs recommended in all patients with heart failure with reduced ejection fraction

Recommendations	Class ^a	Level ^b
ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	I	A
MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B



ARNI維持1B

Study Design of DAPA-HF



Primary Endpoint

- Time to first occurrence of any of the components of the composite: **CV death or hHF or an urgent HF visit**

Exclusion criteria (partial):

- SBP < 95 mmHg
- Current acute decompensated HF or hospitalization due to decompensated HF <4 weeks prior to enrolment

141 patients enrolled



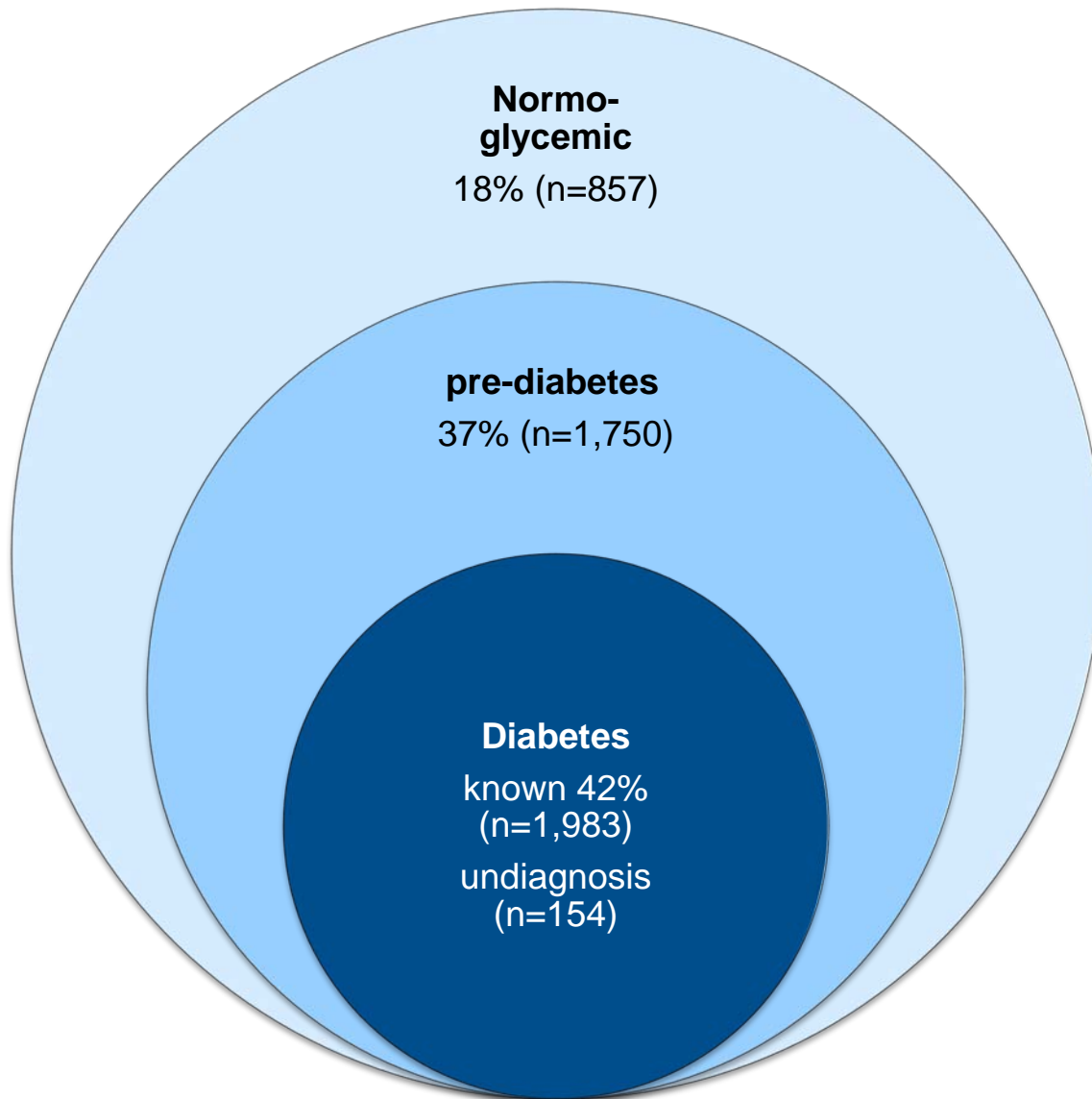
1. Eur J Heart Fail. 2019;21:665-675; 2. N Engl J Med. 2019 Nov 21;381(21):1995-2008.

Key baseline characteristics

Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Mean age (yr)	66	67
Male (%)	76	77
NYHA class II/III/IV (%)	68 / 31 / 1	67 / 32 / 1
Mean LVEF (%)	31	31
Median NT pro BNP (pg/mL)	1428	1446
Mean systolic BP (mmHg)	122	122
Ischaemic aetiology (%)	55	57
Atrial fibrillation (%)	38.6	38
Mean eGFR (mL/min/1.73m ²)	66	66
Prior diagnosis T2D (%)	42	42
Any baseline T2D (%) ^a	45	45

^a Includes 82 dapagliflozin and 74 placebo patients with previously undiagnosed diabetes i.e. two HbA1c ≥6.5% (≥48 mmol/mol).
BP = blood pressure; eGFR = estimated glomerular filtration rate; NT pro BNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; T2D = type 2 diabetes.

Glycemic status of patients



No Diabetes **55%**
(n=2,607)

67% pre-diabetes
33% normo-glycemic

Diabetes **45%**
(n=2,137)

- **previously undiagnosed diabetes:**
- HbA1c $\geq 6.5\%$ at both visit 1 and visit 2, without a history of diabetes
- **pre-diabetes:**
- HbA1c $\geq 5.7\%$ at visit 1 or visit 2, without known or undiagnosed diabetes
- **normoglycaemic (euglycaemic):**
- HbA1c $< 5.7\%$ at both visit 1 and visit 2 (*HbA1c was measured in a central laboratory*)

Baseline Treatment

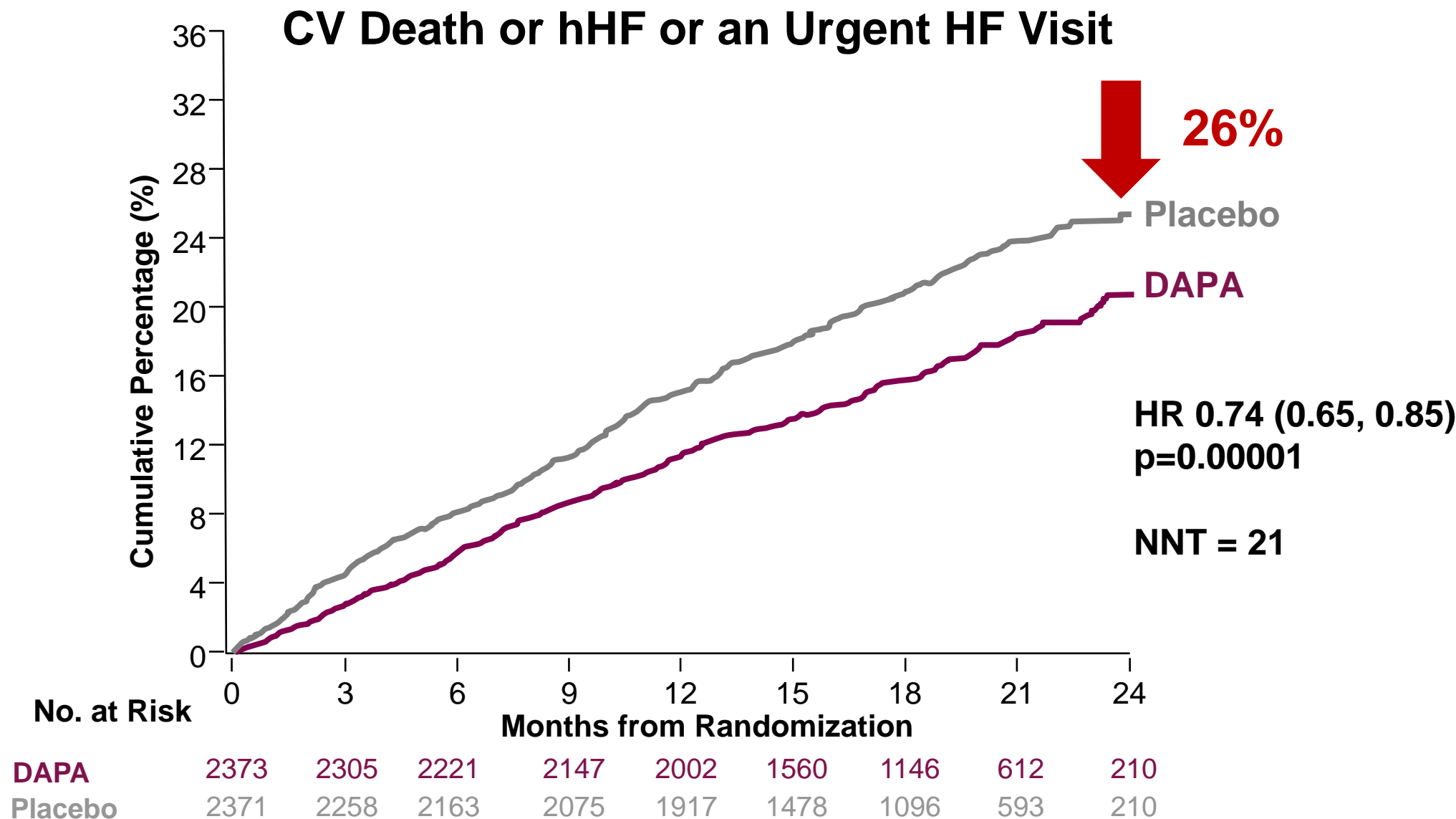
Treatment (%)	Dapagliflozin (n=2373)	Placebo (n=2371)
Diuretic	93	94
ACE-inhibitor/ARB/ARNI	94	93
ACE inhibitor	56	56
ARB	28	27
Sacubitril/valsartan	11	11
Beta-blocker	96	96
MRA	71	71
Digitalis	18.8	18.6
ICD*	26	26
CRT**	8	7

13% receiving ARNI in **CHAMP-HF registry** (included outpatients in the US with chronic HFrEF)

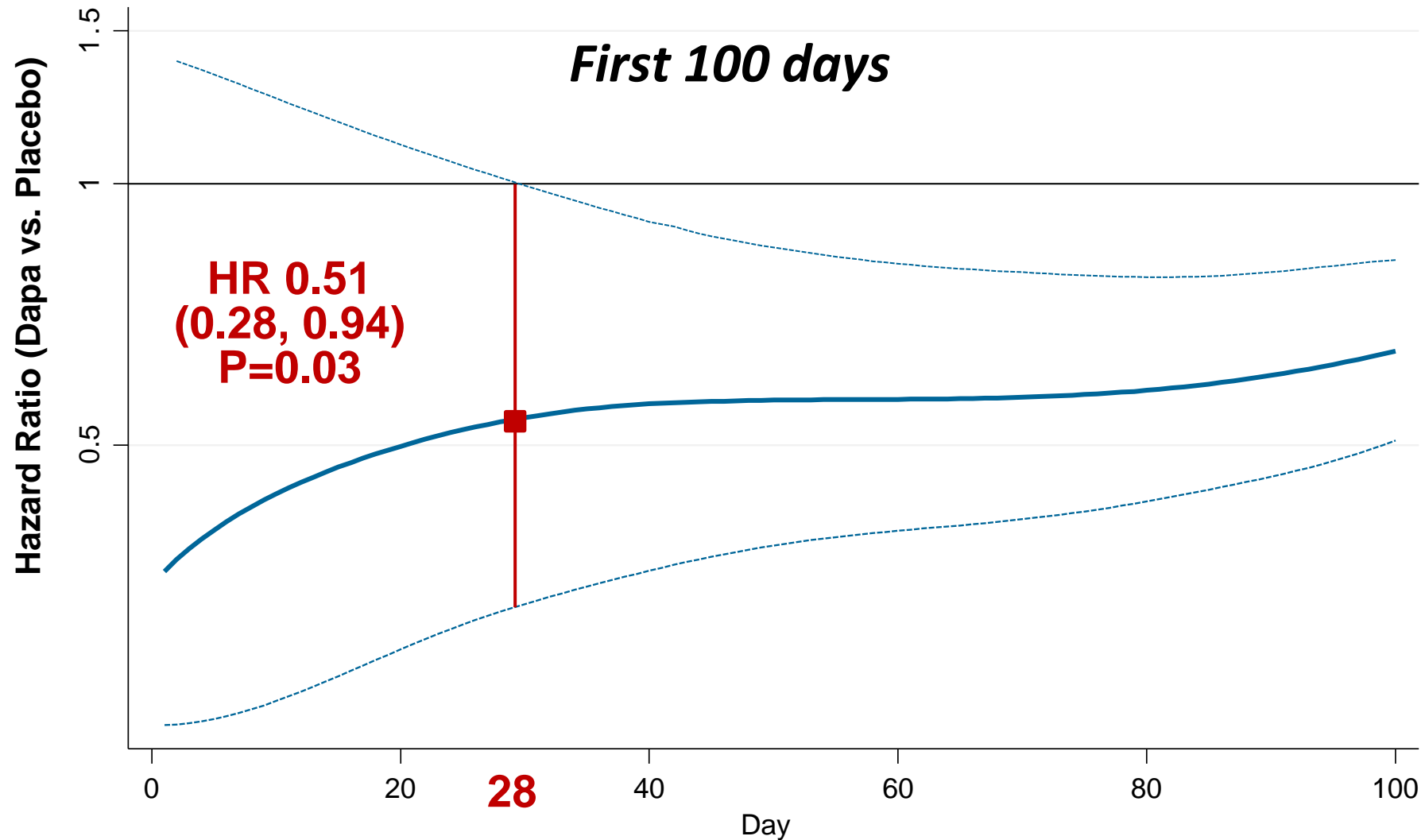
*ICD or CRT-D **CRT-P or CRT-D

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator.

DAPA-HF Primary Endpoint



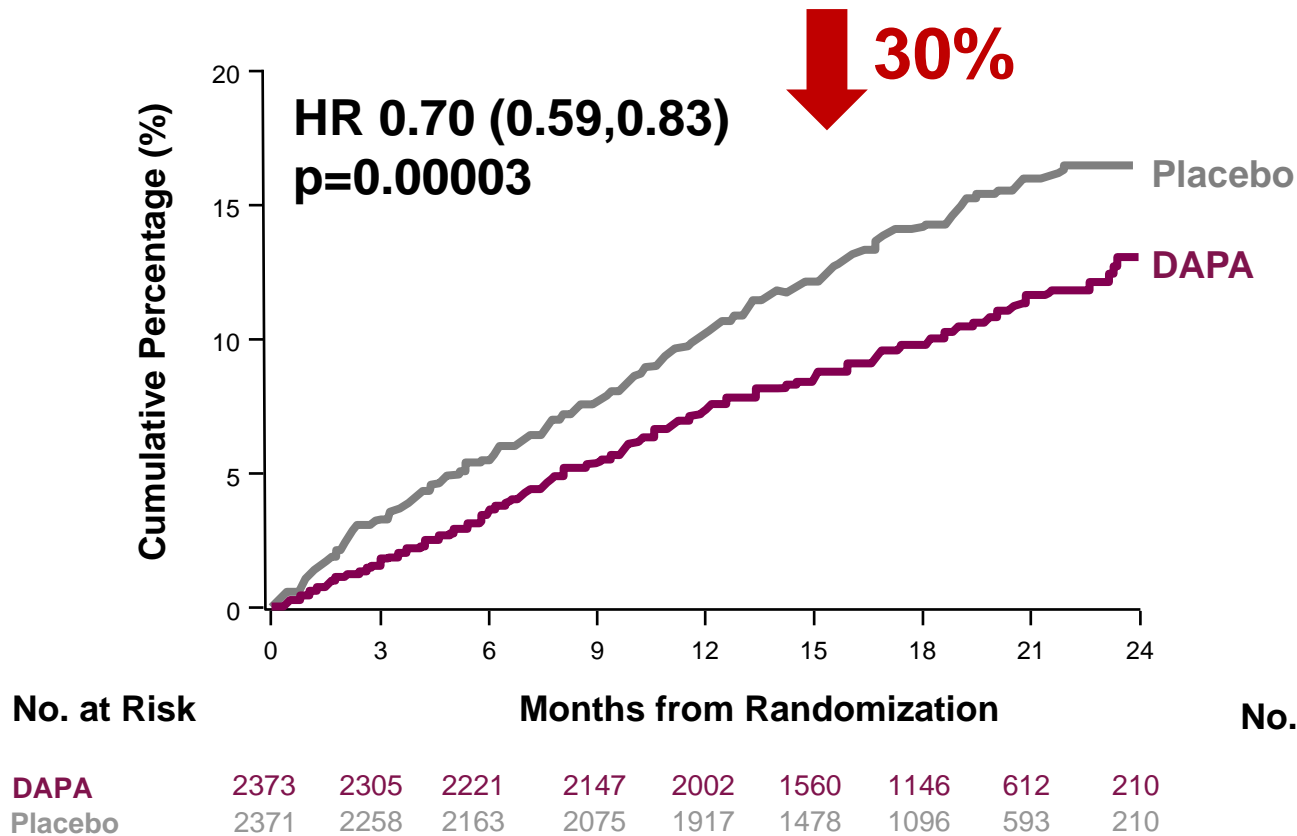
Time of onset of benefit



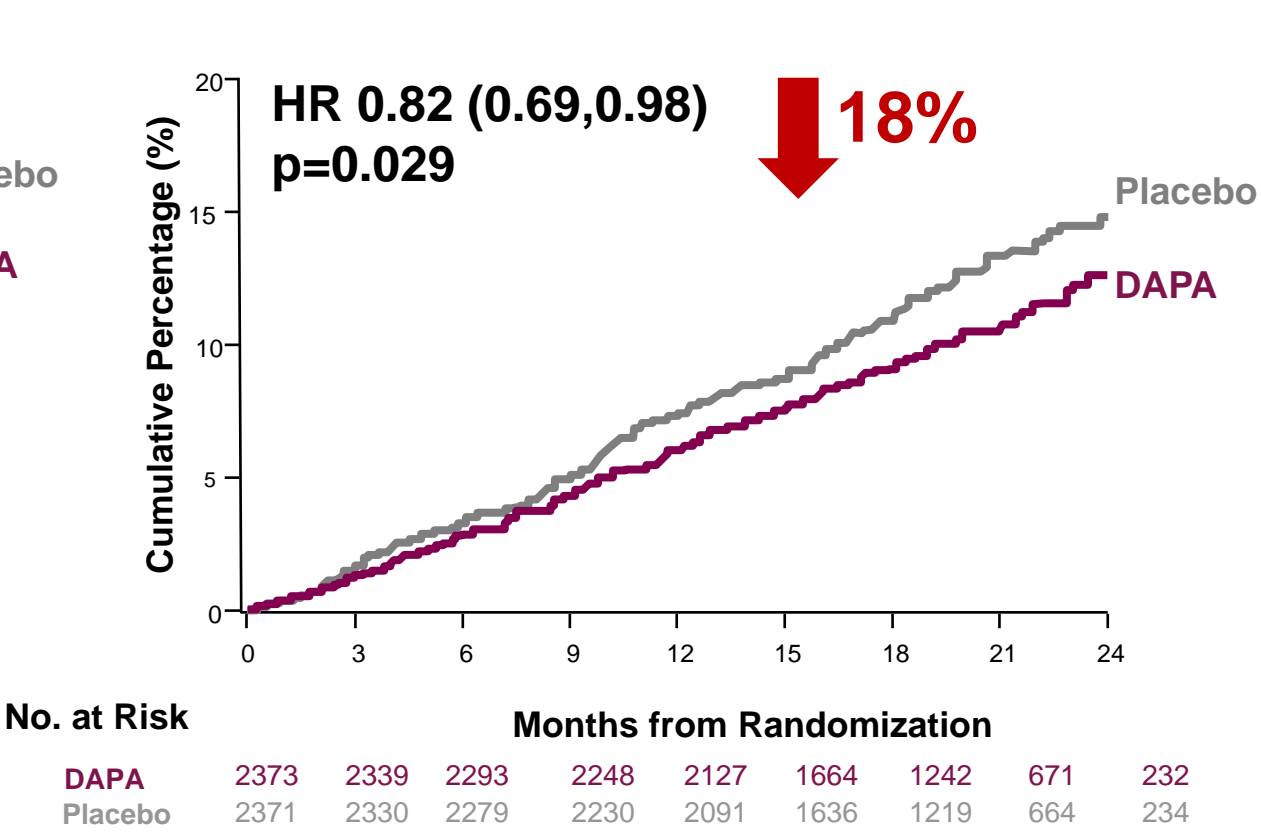
Sabatine MS et al. Presented at: AHA Scientific Sessions; November 16-18, 2019; Philadelphia, PA.

Components of Primary Endpoint

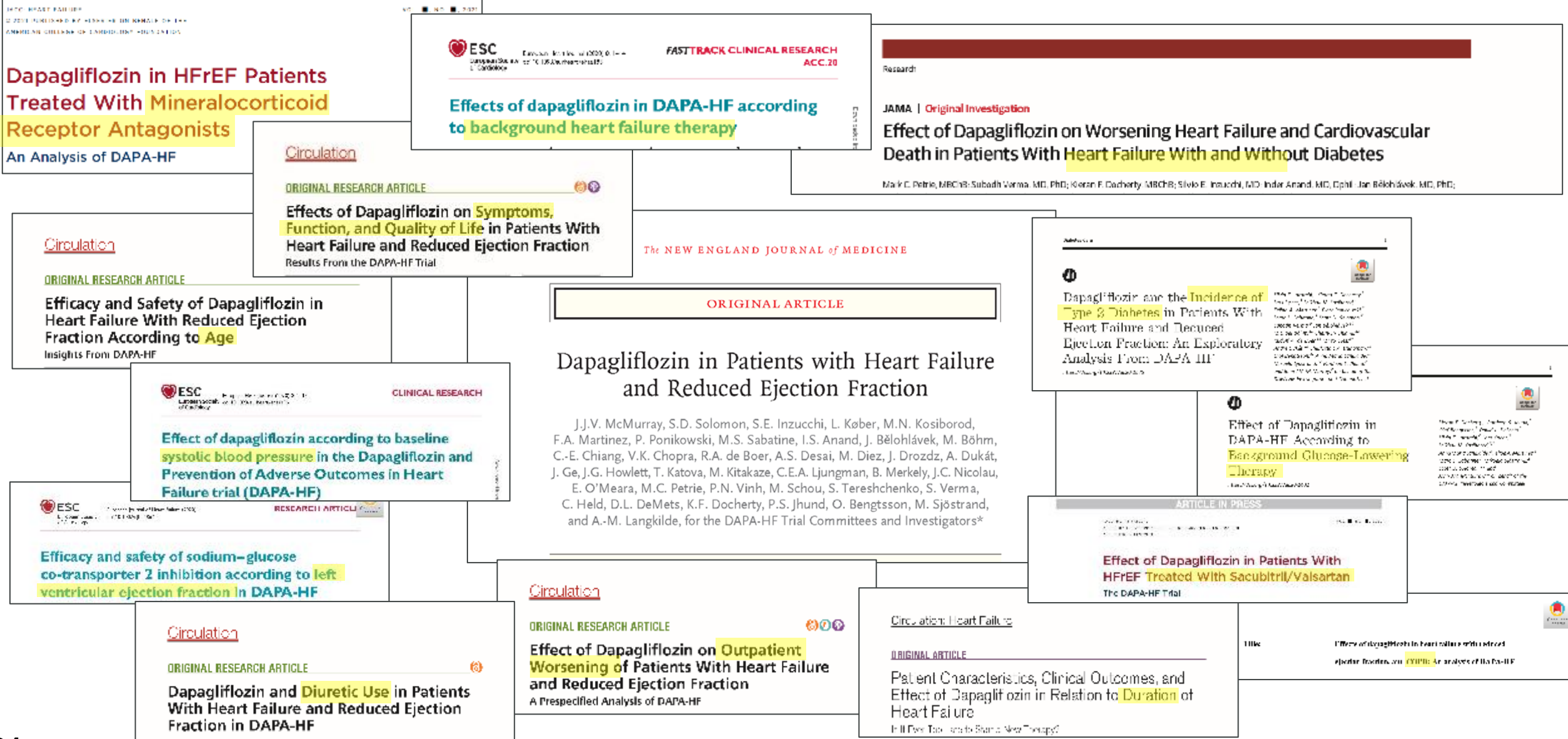
Worsening HF Event



Cardiovascular Death

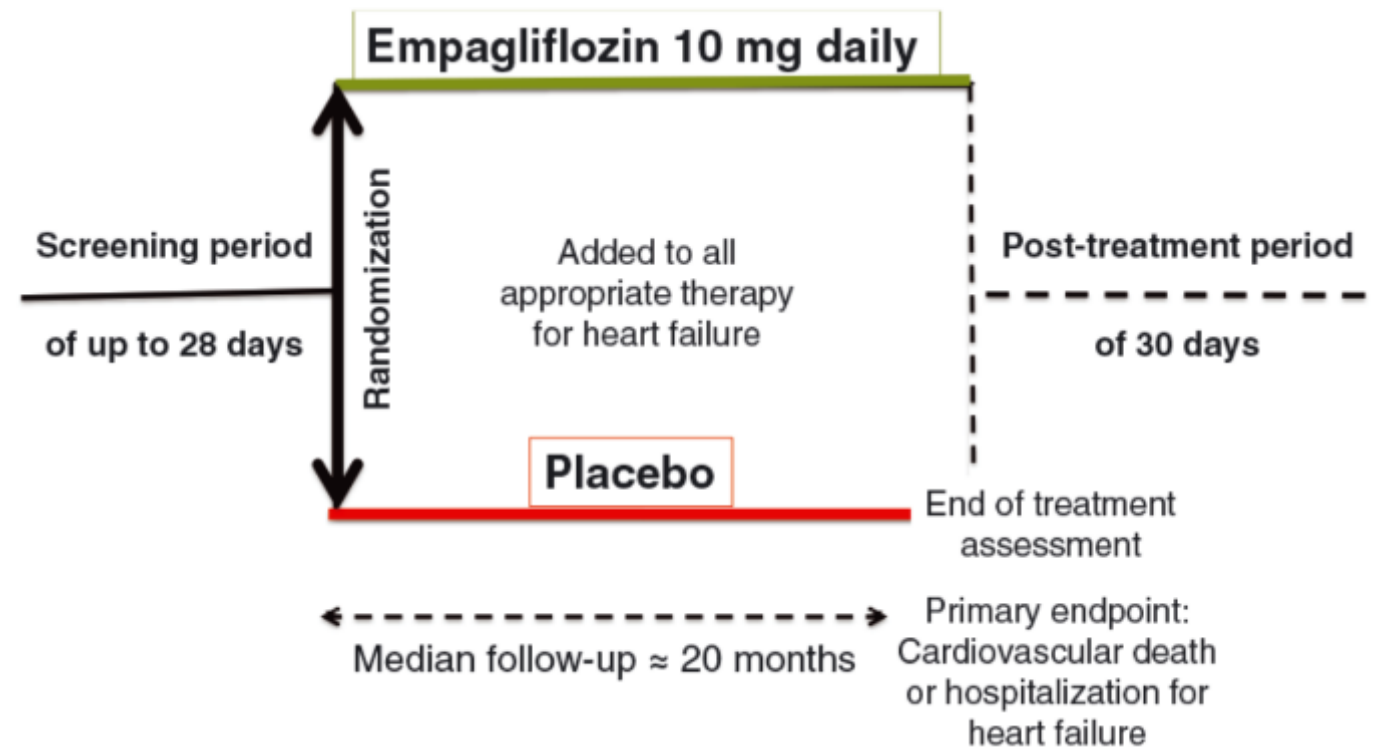
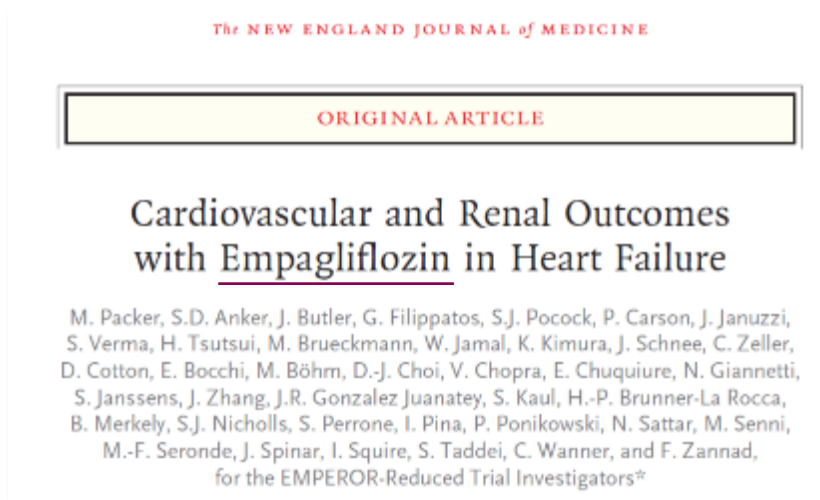


DAPA-HF publications



The second heart failure trial of SGLT2i

EMPEROR-Reduced Trial Schematic



Key inclusion criteria

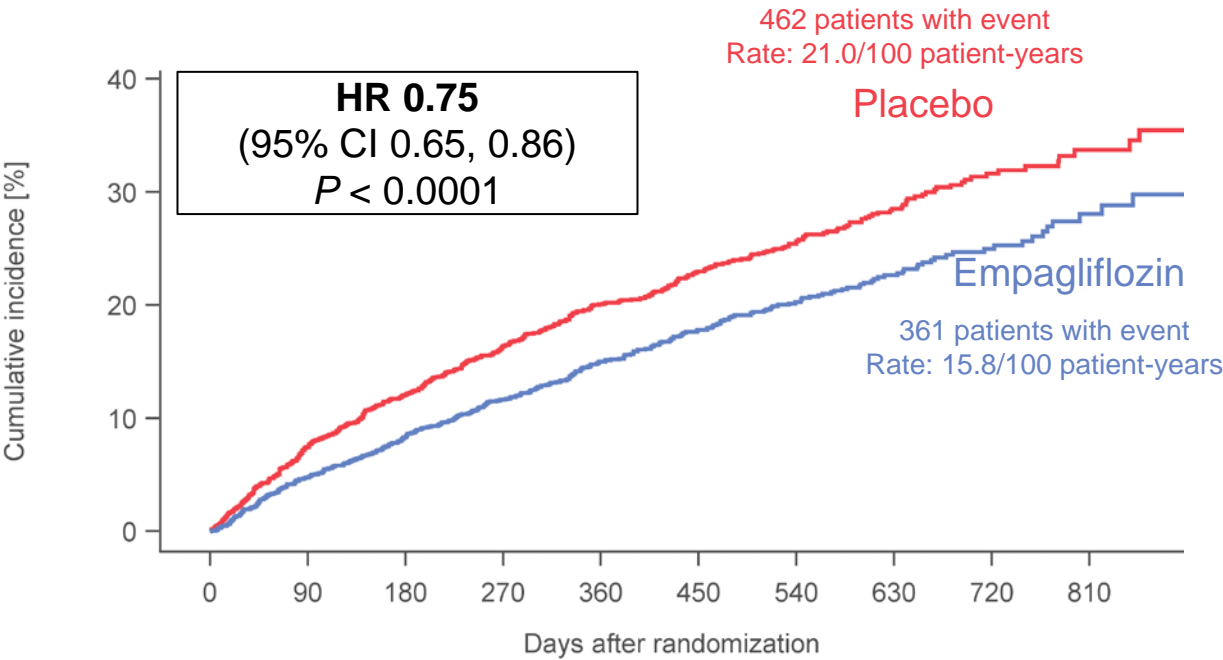
	EMPEROR-reduced	DAPA-HF
NYHA class	NYHA class II-IV	NYHA class II-IV
LVEF	LVEF ≤40%	LVEF ≤40%
eGFR	eGFR ≥20 mL/min/1.73 m ²	eGFR ≥30 ml/min/1.73 m ²
NT-proBNP	Elevated NT-proBNP LVEF ≤30%: ≥600 pg/mL (≥1200 pg/mL if concomitant AF) LVEF ≥31% to ≤35%: ≥1000 pg/mL (≥2000 pg/mL if concomitant AF) LVEF ≥36% to ≤40%: ≥2500 pg/mL (≥5000 pg/mL if concomitant AF) hHF ≤12 months: ≥600 pg/mL (≥1200 pg/mL if concomitant AF)	NT-proBNP≥600pg/ml (if hospitalized for HF within last 12 months ≥400 pg/mL; if atrial fibrillation/flutter ≥900 pg/mL)
Sample size	3730	4744
Median duration	16 months	18.2 months

Baseline Characteristics of EMPEROR-reduced

	EMPEROR-Reduced		DAPA-HF
	Empagliflozin (n=1863)	Placebo (n=1867)	Dapagliflozin (n=2373)
Age (yr)	67.2 ± 10.8	66.5 ± 11.2	66.2 ± 11.0
Women (%)	437 (23.5)	456 (24.4)	564 (23.8)
Diabetes mellitus (%)	927 (49.8)	929 (49.8)	993 (41.8)
Ischemic cardiomyopathy (%)	983 (52.8)	946 (50.7)	1316 (55.5%)
NYHA functional class II (%)	1399 (75.1)	1401 (75.0)	1606 (67.7%)
LV ejection fraction (%)	27.7 ± 6.0 (72% ≤30%)	27.2 ± 6.1 (75% ≤30%)	31.2±6.7
NT-proBNP (median, IQR), pg/mL	1887 (1077, 3429) (79% ≥1000)	1926 (1153, 3525) (80% ≥1000)	1428 (857-2655)
Hospitalization for heart failure within 12 months	577 (31.0)	574 (30.7)	1124 (47.4)
Atrial fibrillation	664 (35.6)	705 (37.8)	916 (38.6)
Glomerular filtration rate (ml/min/1.73 m²)	61.8 ± 21.7	62.2 ± 21.5	66.0 ± 19.6
Treatment for heart failure			
RAS inhibitor without neprilysin inhibitor	1314 (70.5)	1286 (68.9)	2007 (84.6)
RAS inhibitor with neprilysin inhibitor	340 (18.3)	387 (20.7)	250 (10.5)
Mineralocorticoid receptor antagonist	1306 (70.1)	1355 (72.6)	1696 (71.5)
Beta blocker	1765 (94.7)	1768 (94.7)	2278 (96.0)
Implantable cardioverter-defibrillator	578 (31.0)	593 (31.8)	622 (26.2%)
Cardiac resynchronization therapy	220 (11.8)	222 (11.9)	190 (8.0%)

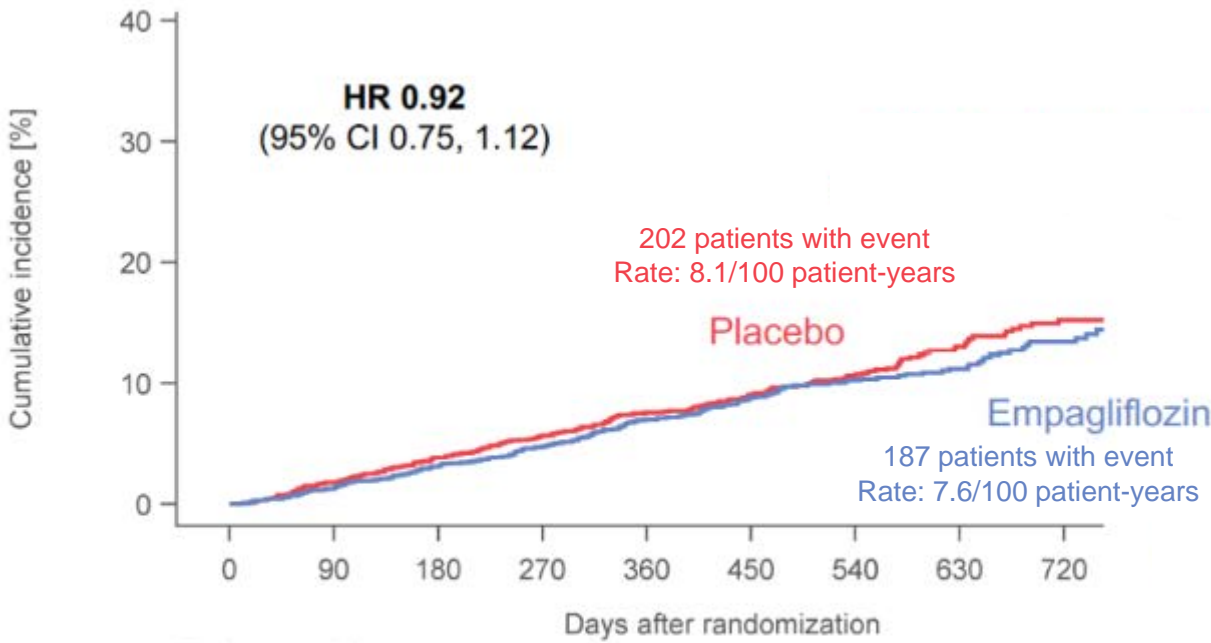
EMPEROR-Reduced: Primary endpoint

CV death or Hospitalization for Heart Failure



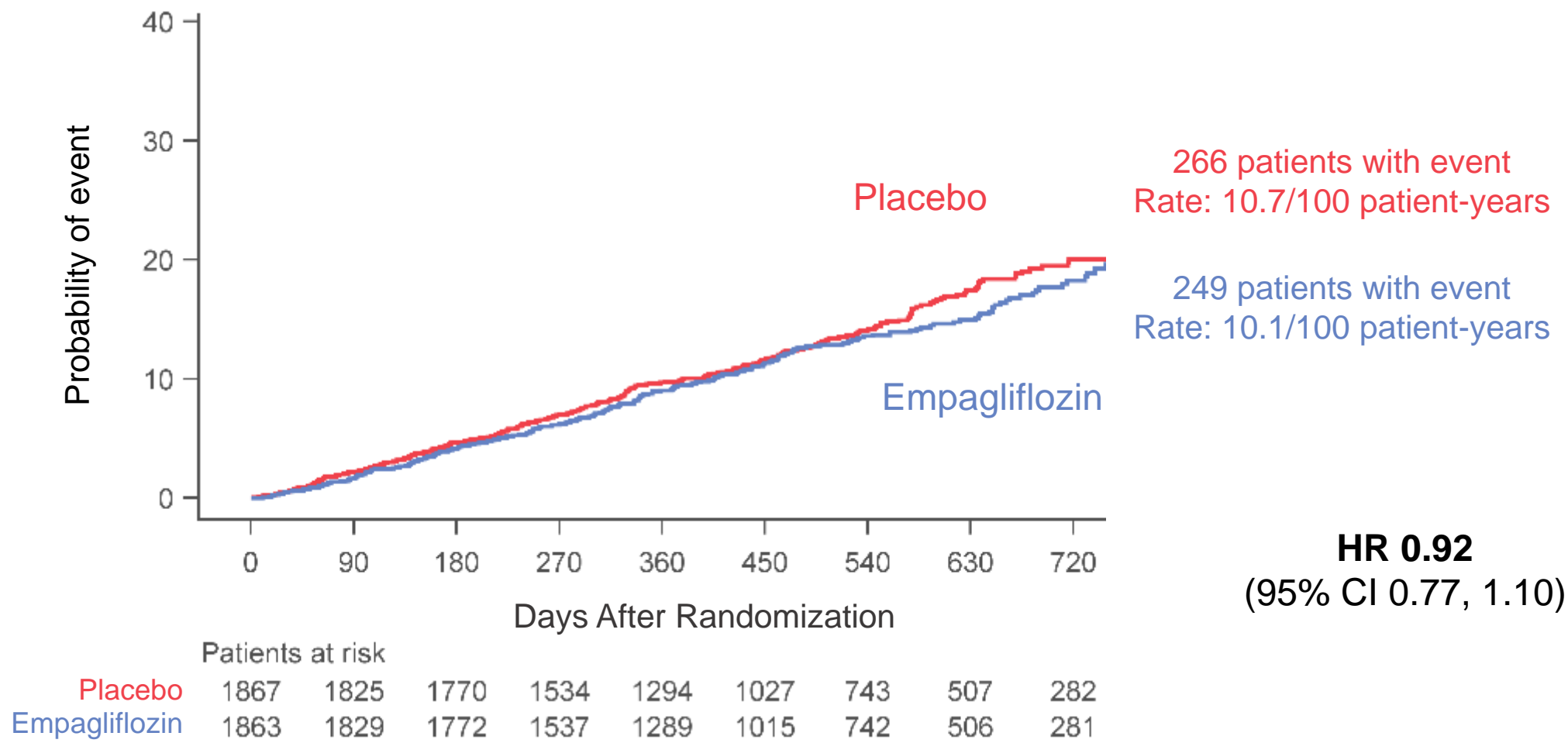
	Patients at risk									
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empa 10mg	1863	1763	1677	1424	1172	909	645	423	231	101

CV Death



	Patients at risk									
Placebo	1867	1825	1770	1534	1294	1027	743	507	282	
Empagliflozin	1863	1829	1772	1537	1289	1015	742	506	281	

EMPEROR-Reduced: All-Cause Mortality



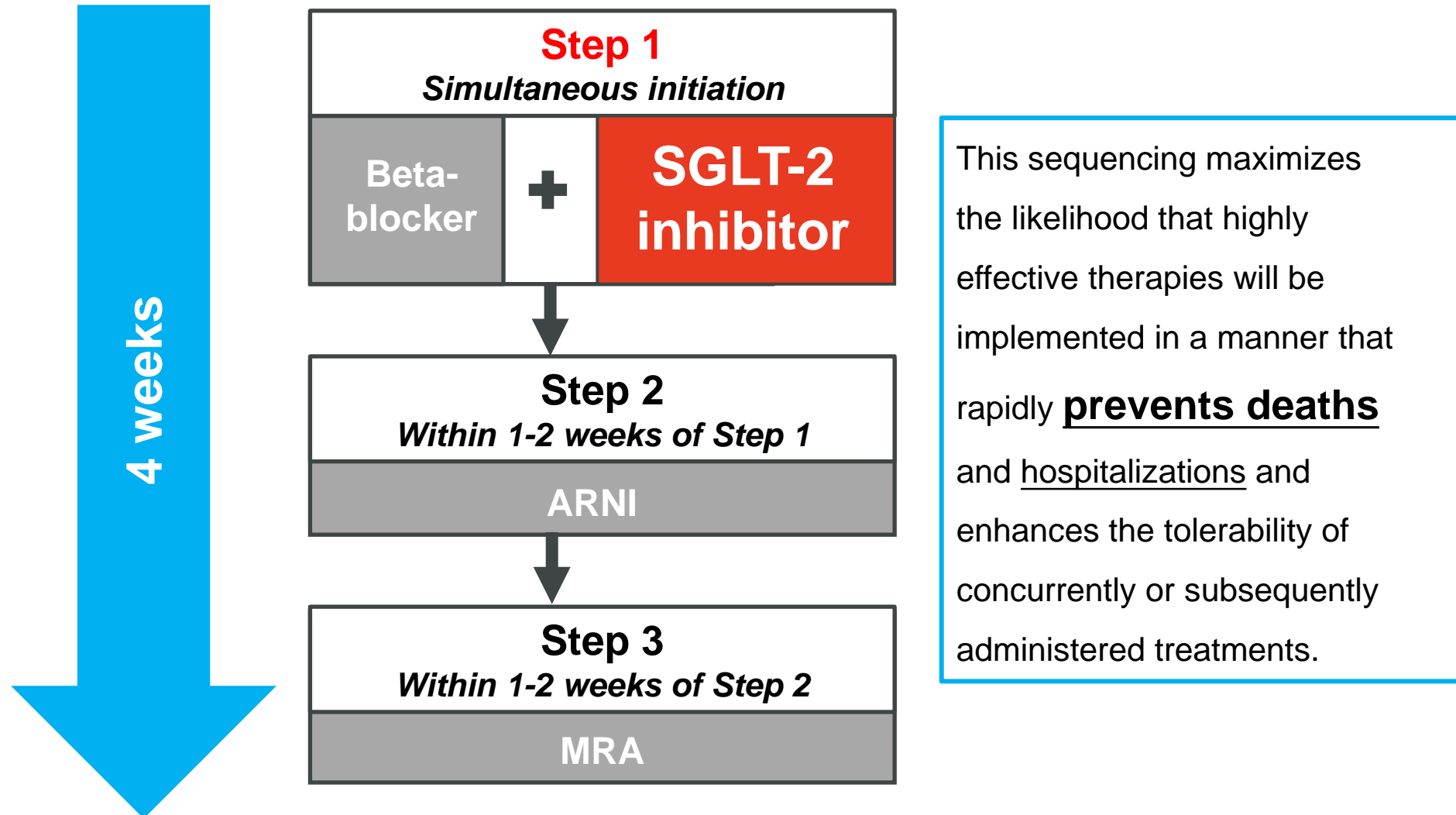
SGLT2i發表的心衰竭試驗結果 (HFrEF patient)

Trial (N; median follow-up month)	Drug	Background Rx.	CV death/HHF HR (95%CI)	HHF HR (95%CI)	CV death HR (95%CI)	All-cause mortality HR (95%CI)
DAPA-HF (N=4744;18.2 months)	Dapagliflozin 10 mg QD vs placebo	ACEI/ARB/ARNI 94% BB 96% MRA 71%	0.75 (0.65–0.85)	0.70 (0.59–0.83)	0.82 (0.69–0.98)	0.83 (0.71–0.97)
EMPEROR-reduced (N=3730;16 months)	Empagliflozin 10 mg QD vs placebo	ACEI/ARB/ARNI 89% BB 95% MRA 71%	0.75 (0.65–0.86)	0.69 (0.59–0.81)	0.92 (0.75–1.12)	0.92 (0.77–1.10)

As head-to-head studies were not conducted between these products, it is inappropriate to draw any comparisons and/or make any conclusions as the study design, demographics and other criteria may be different.

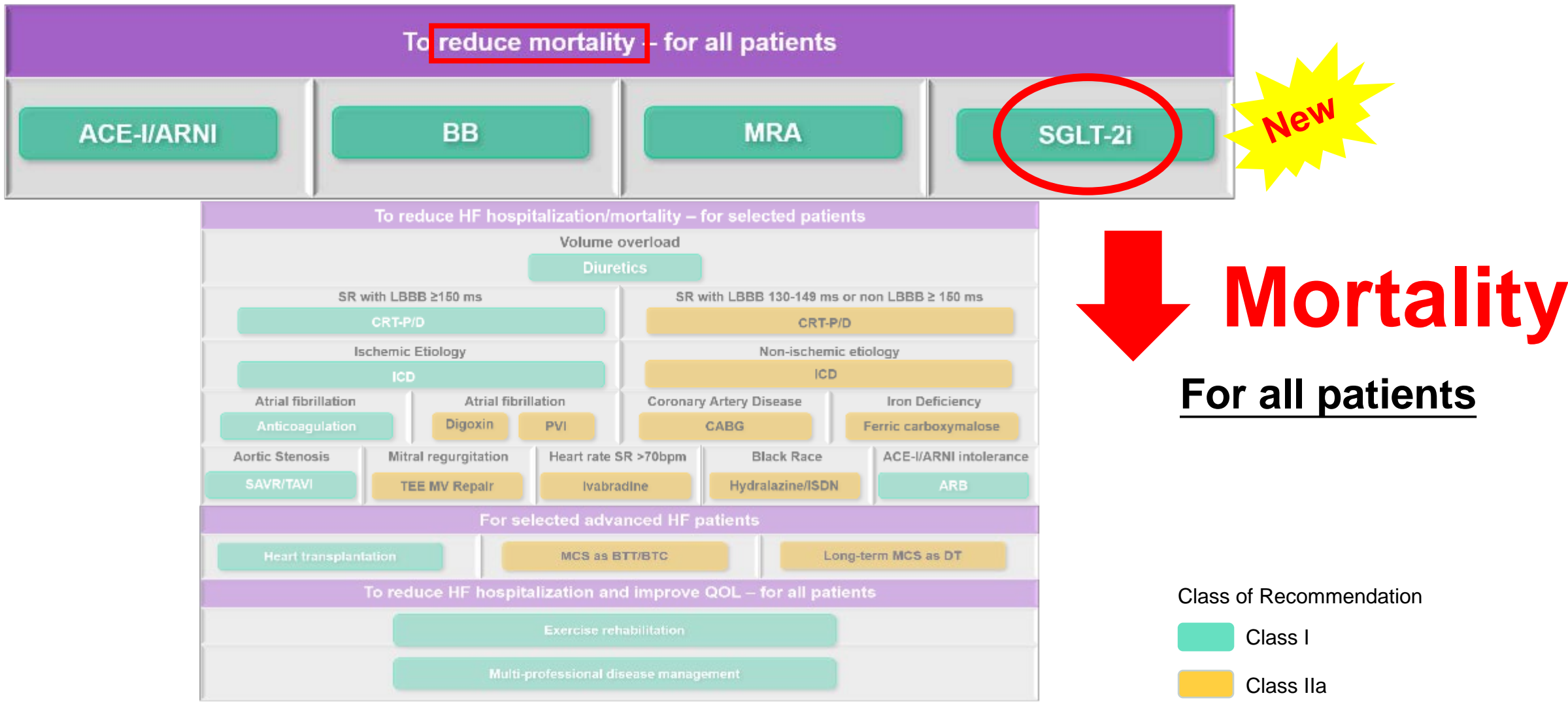
27 n/a: not applicable 1. N Engl J Med. 2011 Jan 6;364(1):11-21. 2. Lancet. 2010 Sep 11;376(9744):875-85. 3. N Engl J Med. 2014 Sep 11;371(11):993-1004. 4. N Engl J Med. 2019 Nov 21;381(21):1995-2008. 5. N Engl J Med. 2020 Oct 8;383(15):1413-1424. 6. N Engl J Med. 2020 May 14;382(20):1883-1893. 7. N Engl J Med 2021; 384:105-116.

國際心衰竭專家提出治療新序列：四週內加上能減少死亡的藥物



SGLT-2: Sodium-Glucose Cotransporter 2, ARNI: angiotensin-receptor neprilysin inhibitor, MRA: mineralocorticoid receptor antagonist
The proposed algorithm represents one possibility of many and can be individualized to specific circumstances.
John J.V. McMurray, Milton Packer. Circulation . 2021 Mar 2;143(9):875-877.

2021 ESC HF治療指引 class IA建議：
SGLT-2i為一線用藥，為HFrEF患者降低死亡



2021 ESC HFA consensus: SGLT-2i適用HFrEF全部11種情境

Total 11 Scenarios

SGLT-2i: 11

RAASi: 6

BB: 6

MRA: 9

Diuretics: 7



ESC: European Society of Cardiology

HFA: Heart Failure Association

Eur J Heart Fail. 2021 Jun;23(6):872-881.

Outline

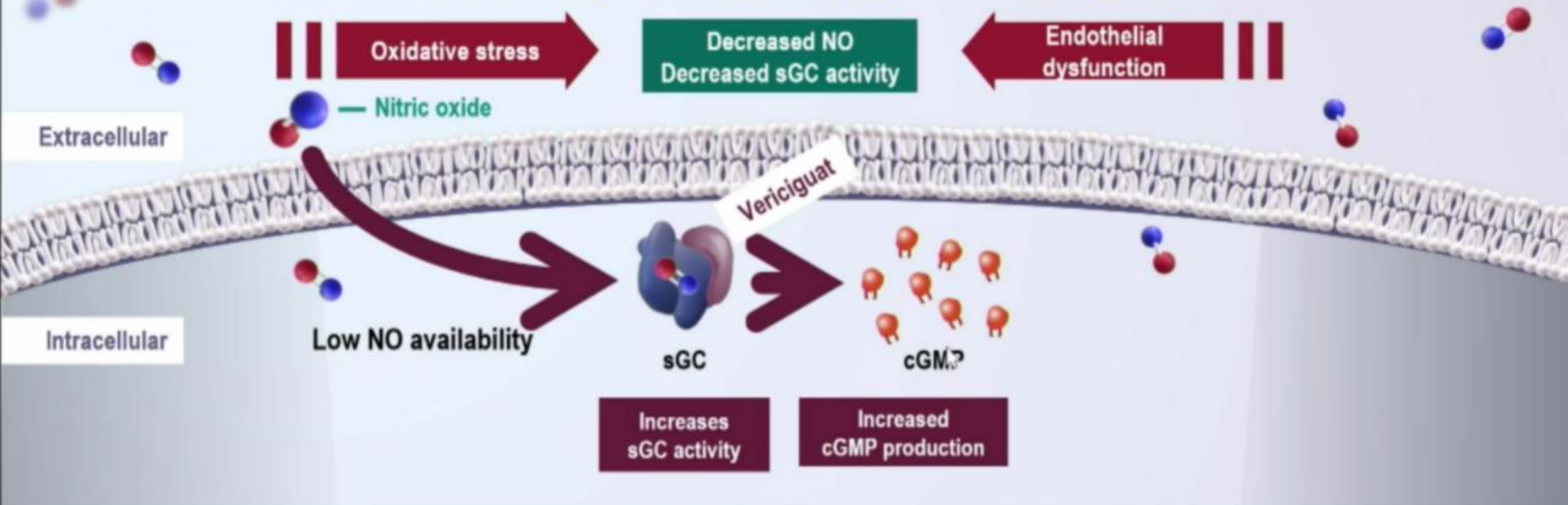
- 心衰竭的成因、盛行率、預後
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新增Soluble Guanylate Cyclase Receptor Stimulation
Ivabradine與2016年版本相同

Other drugs to be considered in selected patients with heart failure with reduced ejection fraction

Recommendations	Class ^a	Level ^b
I_f-channel inhibitor		
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I/(or ARNI) and an MRA, to reduce the risk of HF hospitalization and CV death. ¹³⁹	Ila	B
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in SR and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a beta-blocker to reduce the risk of HF hospitalization and CV death. Patients should also receive an ACE-I (or ARNI) and an MRA. ¹⁴⁰	Ila	C
Soluble Guanylate Cyclase Receptor Stimulator		
Vericiguat may be considered in patients in NYHA Class II–IV who have had worsening HF despite treatment with an ACE-I (or ARNI), a beta-blocker and an MRA to reduce the risk of CV mortality or HF hospitalization. ¹⁴¹	Ilb	B

VERICIGUAT INCREASES sGC ACTIVITY TO IMPROVE MYOCARDIAL AND VASCULAR FUNCTION



Heart

- ↓ Progressive myocardial stiffening
- ↓ Myocardial thickening
- ↓ Ventricular remodeling
- ↓ Fibrosis



Vasculature

- ↓ Arterial constriction
- ↓ Vascular stiffness

cGMP=cyclic guanosine monophosphate; HF=heart failure; NO=nitric oxide; sGC=soluble guanylate cyclase.



VICTORIA Phase III: Study Design

Primary objective: To evaluate the efficacy of vericiguat in comparison with placebo against a background of contemporary HF therapies in increasing the time to **first occurrence of the composite of CV death or HFH**

N=5050

Symptomatic chronic HFrEF after a worsening event

- EF <45%
- Chronic HF with NYHA class II–IV
- Receiving HF SOC
- Prior HFH within 6 months or outpatient IV diuretic for HF within 3 months
- Elevated natriuretic peptides**
- SBP ≥ 100 mmHg
- eGFR ≥ 15 ml/min/1.73 m²

1:1

Randomised,
double-blind

2.5 mg od 5 mg od 10 mg od

Vericiguat

Up-titration at 2-week intervals

Placebo

Event-driven study duration
Median follow-up: 10.8 months

Primary endpoint: Time to first occurrence of composite of CV death or HFH

BNP ≥ 300 or NT-proBNP ≥ 1000 pg/ml (NSR)
BNP ≥ 500 or NT-proBNP ≥ 1600 pg/ml in (AF)

The FDA requested that the primary endpoint be evaluated with respect to baseline NT-proBNP concentration by quartile





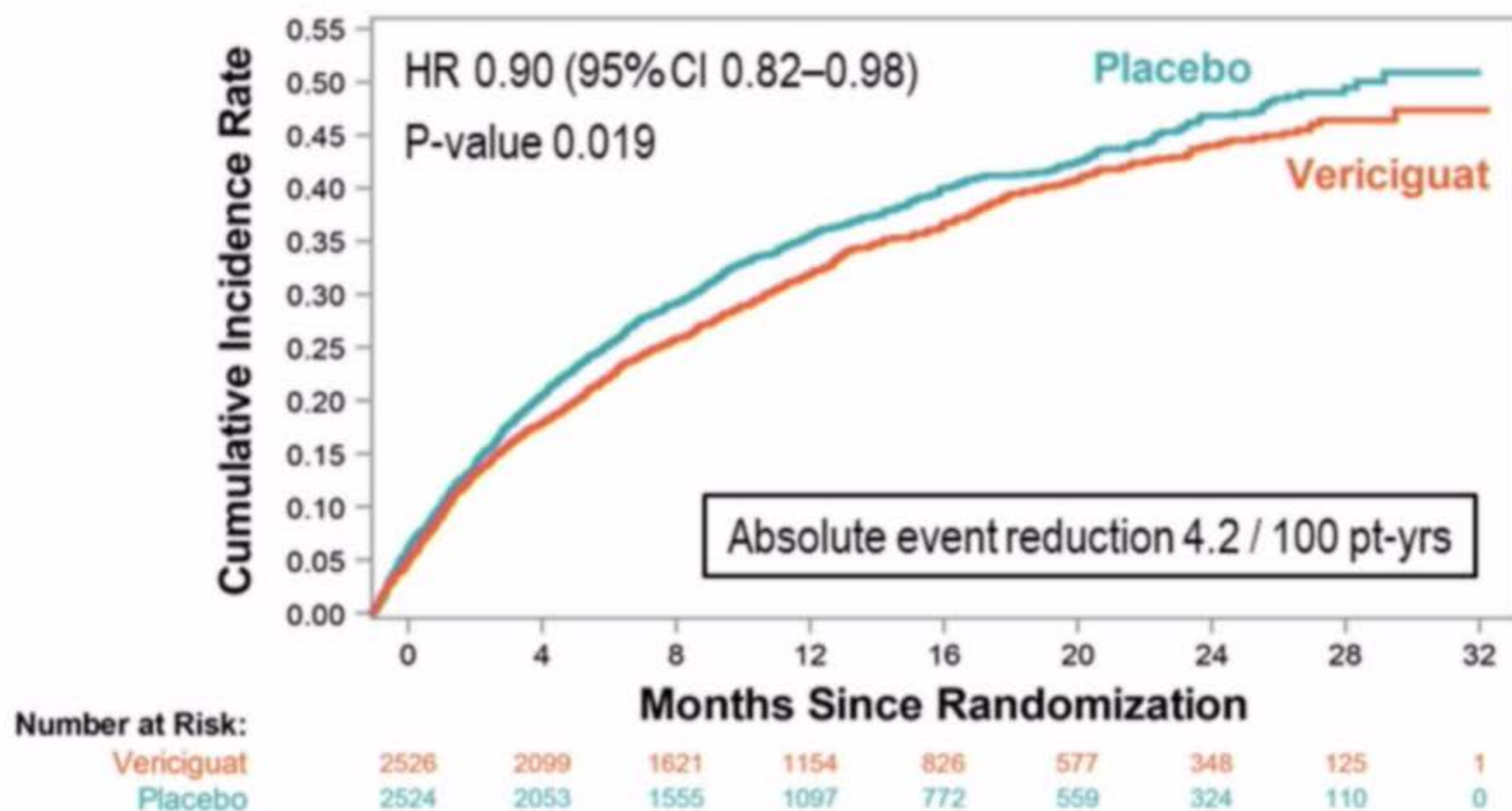
Baseline Characteristics

	Vericiguat (N=2526)	Placebo (N=2524)
Age mean (SD)	67.5 (12.2)	67.2 (12.2)
Female sex	605 (24.0%)	603 (23.9%)
Index event at Randomization		
HF hospitalization < 3 mos	1673 (66.2%)	1705 (67.6%)
HF hospitalization 3 to 6 mos	454 (18.0%)	417 (16.5%)
IV diuretic for HF < 3 mos (no hospitalization)	399 (15.8%)	402 (15.9%)
EF % (SD)	29.0 (8.3)	28.8 (8.3)
NYHA class III–IV baseline,	1045 (41.4%)	1024 (40.6%)
NT-proBNP Median (25 th – 75 th) pg/mL	2804 (1572- 5380)	2821(1548 – 5206)
Triple guide-based therapy *	1480 (58.7%)	1529 (60.7%)
ICD, BV pacemaker (or both) *	813 (32.2%)	802 (31.8%)

* For vericiguat / placebo %'s are of n's 2521 & 2519

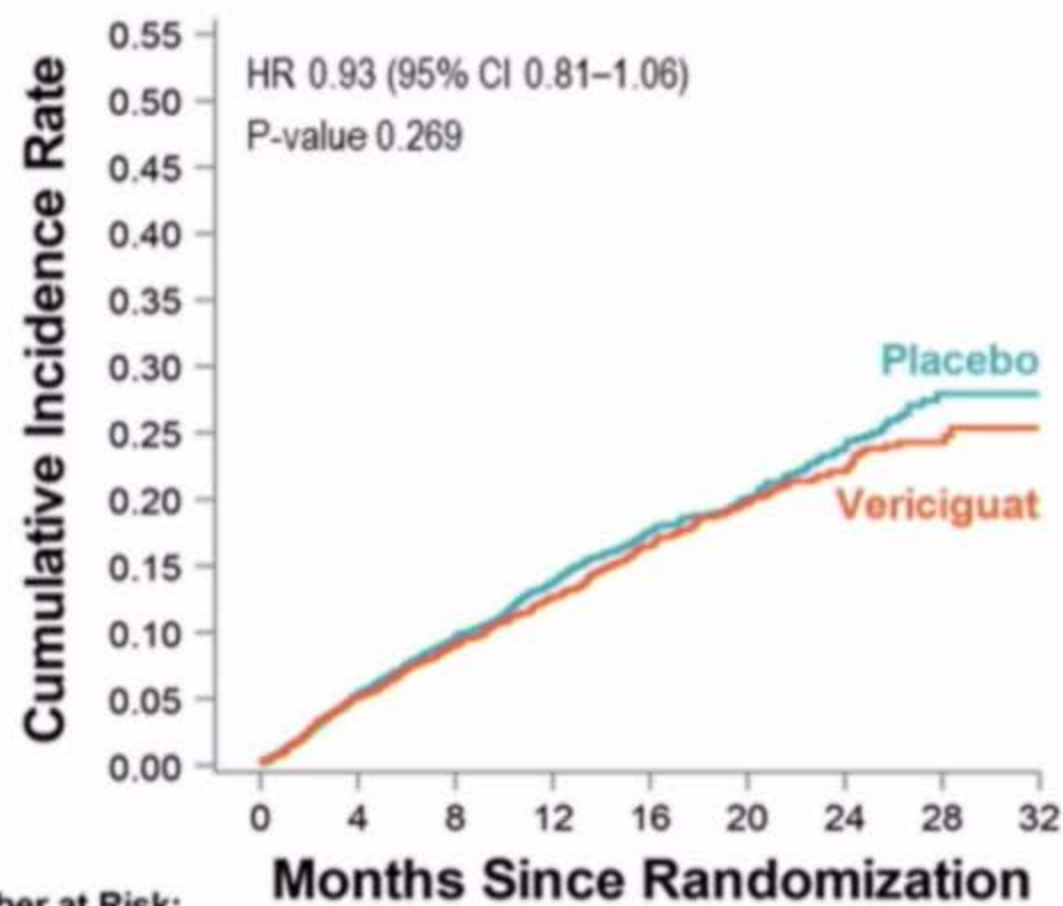


Primary Composite Endpoint: CV Death or First HF Hospitalization



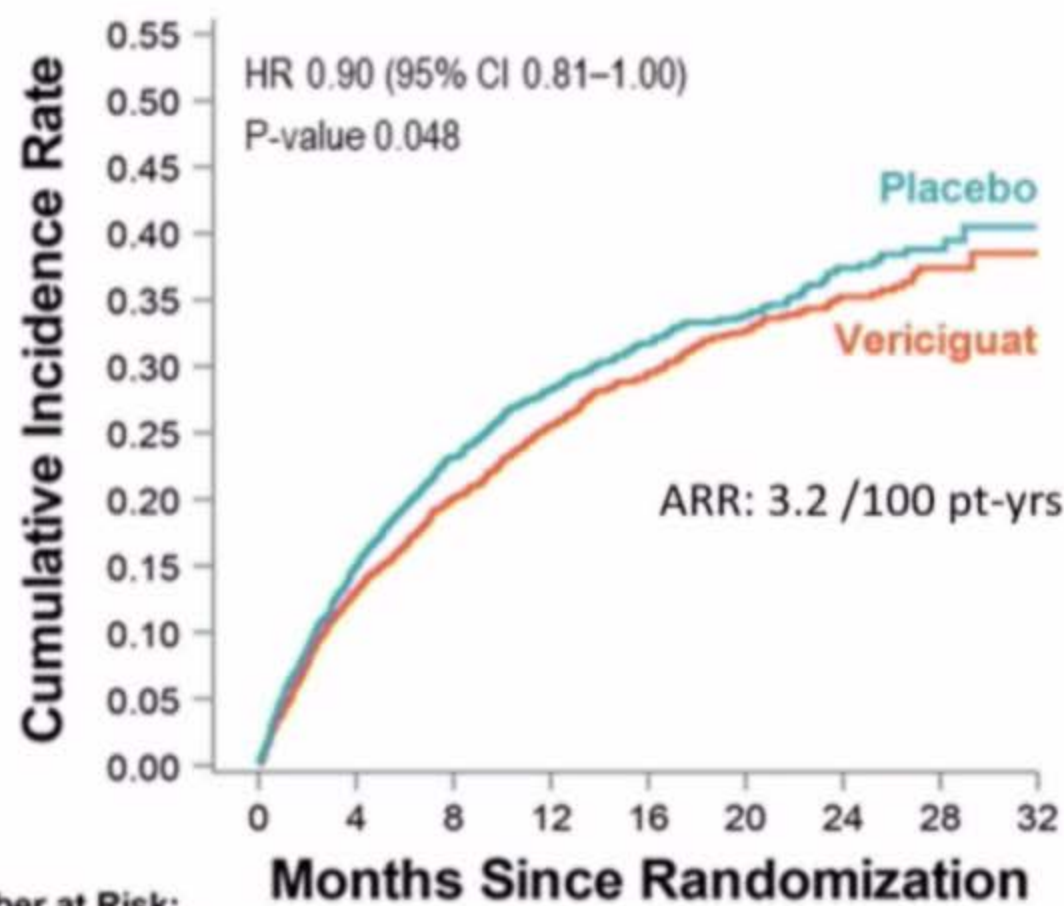
Cardiovascular Death

First HF Hospitalization



Number at Risk:

Vericiguat	2526	2376	1968	1468	1070	779	487	185	1
Placebo	2524	2370	1951	1439	1045	768	471	157	0

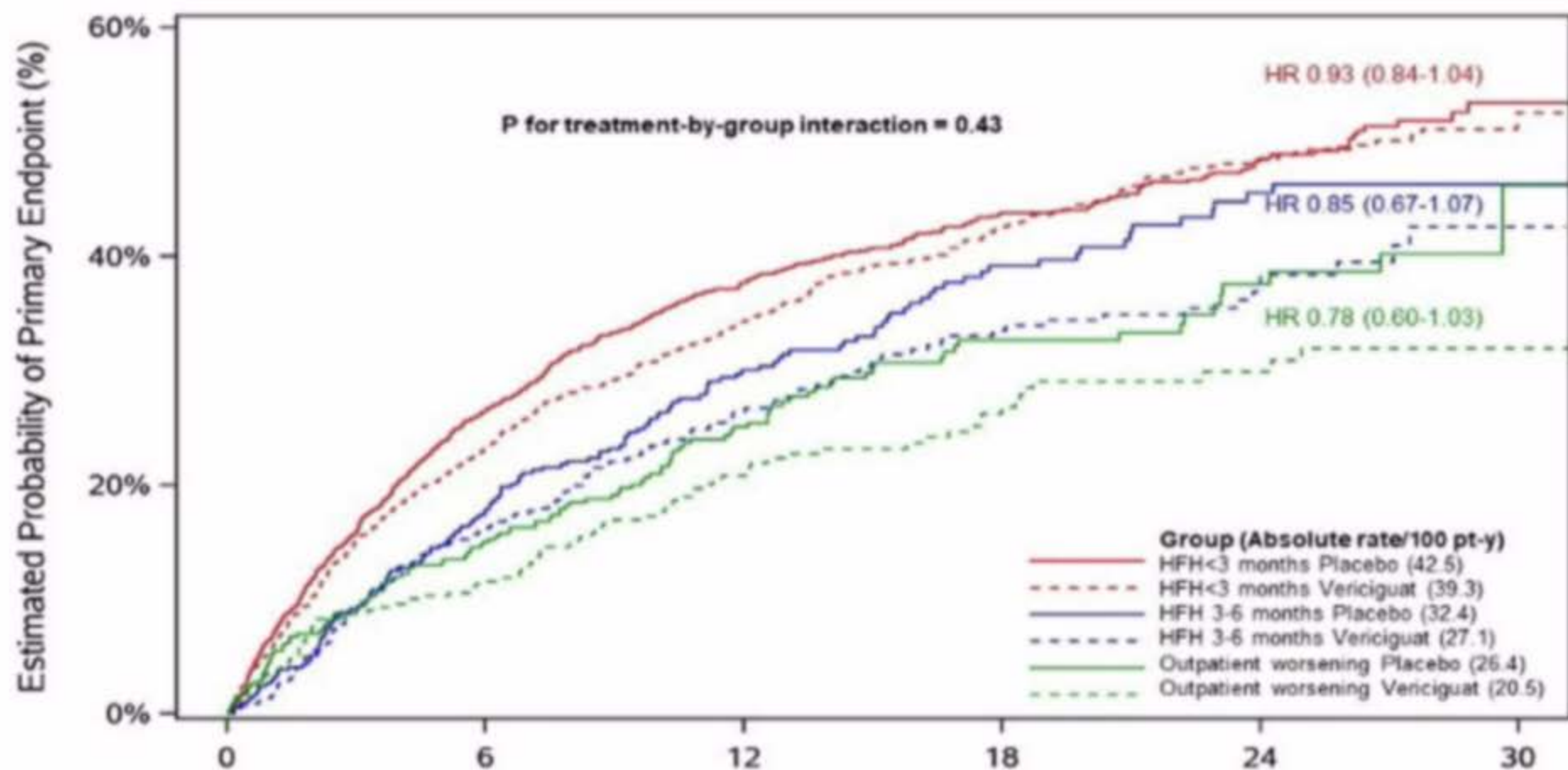


Number at Risk:

Vericiguat	2526	2098	1620	1153	825	577	348	125	1
Placebo	2524	2052	1554	1096	771	558	323	110	0



Index Event HF Event: Outcomes & Treatment Effect



FDA approves vericiguat (VERQUVO) January 19 2021



-----INDICATIONS AND USAGE -----

VERQUVO is a soluble guanylate cyclase (sGC) stimulator, indicated to reduce the risk of cardiovascular death and heart failure (HF)

hospitalization ***following a hospitalization for heart failure or need for outpatient IV diuretics***, in adults with symptomatic chronic HF and ejection fraction less than 45%.

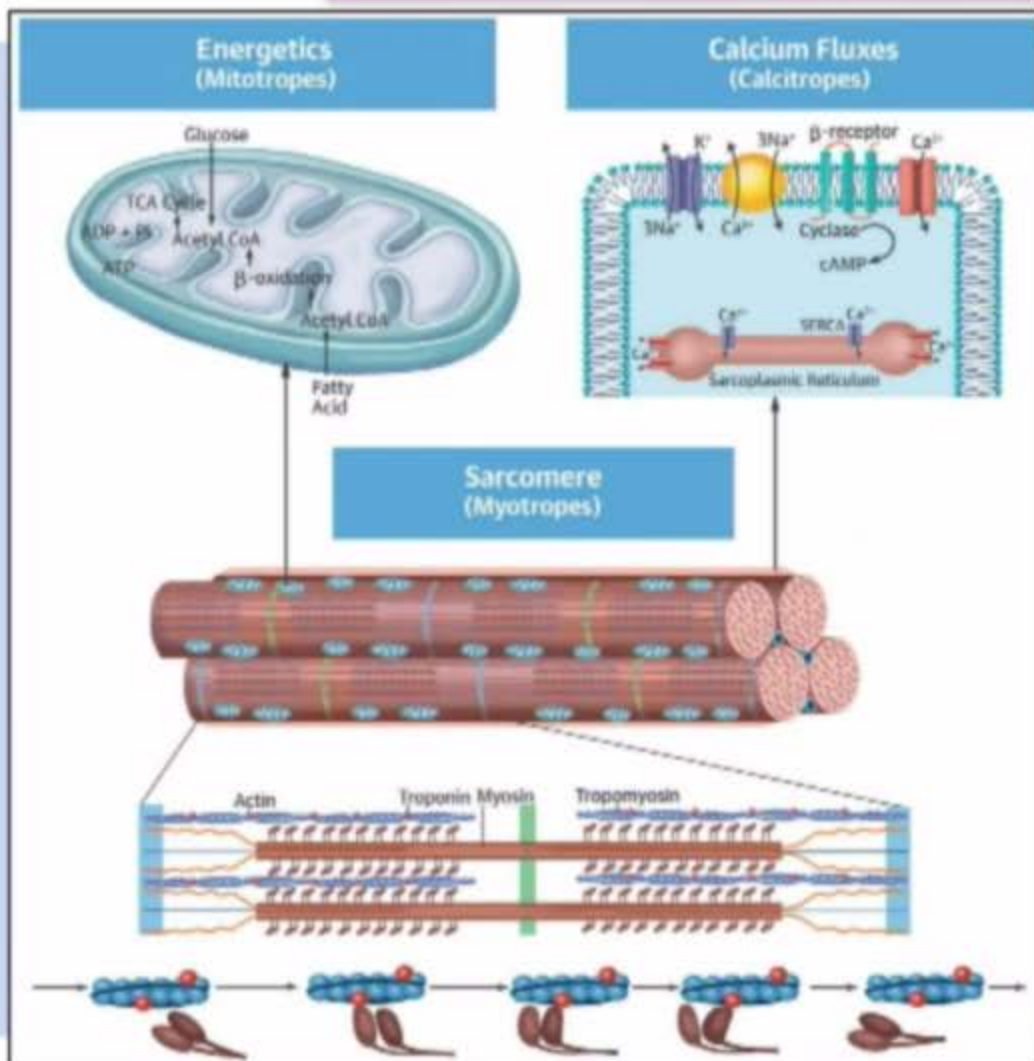


LIVE

00:00



Improving Cardiac Performance: Calcitropes, Mitotropes, and Myotropes

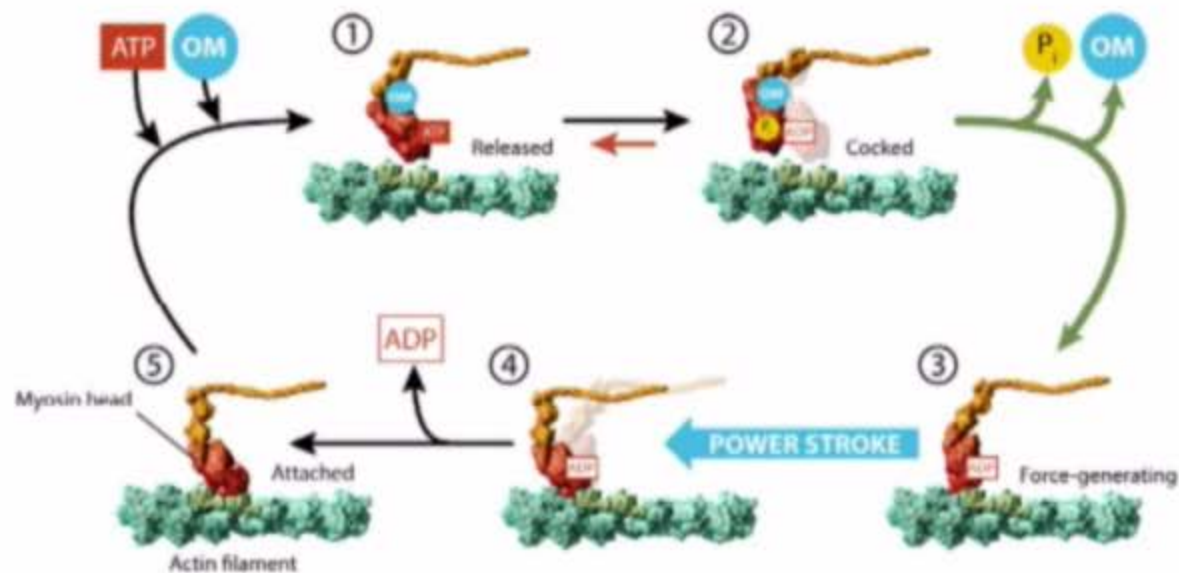


Classifying therapies by MOA:

- **Cardiac calcitropes** – alter intracellular calcium (Catecholamines, Phosphodiesterase inhibitors, etc.)
- **Mitotropes** – influence energetics (Perhexiline, trimetazidine, ranolazine, ?SGLT2i, etc.)
- **Myotropes** – affect the molecular motor and scaffolding ?

Omecamtiv Mecarbil (OM): A Novel Selective Cardiac Myosin Activator

Omecamtiv mecarbil stabilizes myosin in the Pre-Powerstroke State, increasing the entry rate of myosin into the tightly-bound, force-producing state with actin



Without omecamtiv mecarbil



With omecamtiv mecarbil

- More "hands" (myosin heads) to grasp the "rope" (actin filament) to produce more force

Malik FI, et al. *Science* 2011; 331:1439-43; Shen YT, et al. *Circ Heart Fail* 2010;3:522-7; Planelles-Herrero VJ, et al. *Nat Commun* 2017;8:190; Teerlink JR, et al. *J Am Coll Cardiol HF* 2020;8:329-340.

Cardiac Myosin Activator: Omecamtiv Mecarbil



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiac Myosin Activation with Omecamtiv Mecarbil in Systolic Heart Failure

J.R. Teerlink, R. Diaz, G.M. Felker, J.J.V. McMurray, M. Metra, S.D. Solomon, K.F. Adams, I. Anand, A. Arias-Mendoza, T. Biering-Sørensen, M. Böhm, D. Bonderman, J.G.F. Cleland, R. Corbalan, M.G. Crespo-Leiro, U. Dahlström, L.E. Echeverria, J.C. Fang, G. Filippatos, C. Fonseca, E. Goncalvesova, A.R. Goudev, J.G. Howlett, D.E. Lanfear, J. Li, M. Lund, P. Macdonald, V. Mareev, S. Momomura, E. O'Meara, A. Parkhomenko, P. Ponikowski, F.J.A. Ramires, P. Serpytis, K. Sliwa, J. Spinar, T.M. Suter, J. Tomcsanyi, H. Vandekerckhove, D. Vinereanu, A.A. Voors, M.B. Yilmaz, F. Zannad, L. Sharpsten, J.C. Legg, C. Varin, N. Honarpour, S.A. Abbasi, F.I. Malik, and C.E. Kurtz, for the GALACTIC-HF Investigators*

N Engl J Med 2021;384:105-116.

8256 Patients:

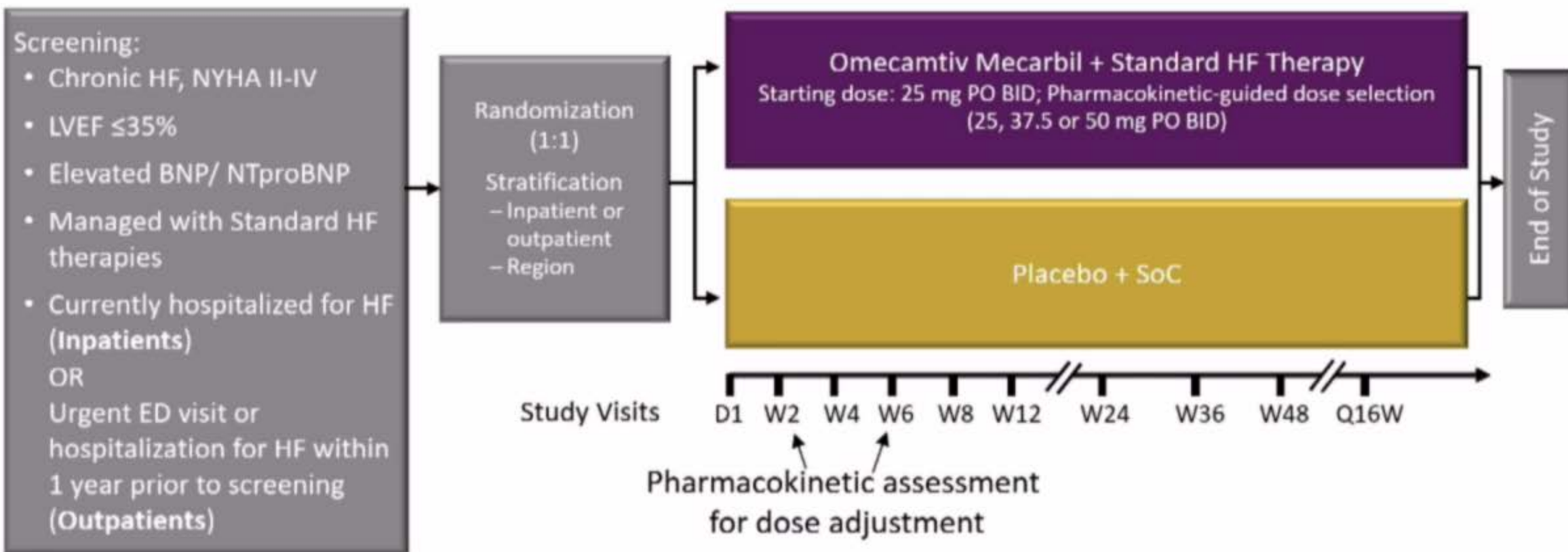
- Chronic HF, NYHA II-IV
- LVEF $\leq 35\%$
- Elevated BNP/ NTproBNP
- Hospitalized for HF (**Inpatients**)
OR Urgent ED visit or hospitalization for HF within 1 year prior to screening (**Outpatients**)

Randomized 1:1 to:

- Omecamtiv mecarbil (pharmacokinetically-guided)
- Placebo

GALACTIC-HF Trial Design

Hypothesis: Selectively improving cardiac function with the cardiac myosin activator, omecamtiv mecarbil, will improve clinical outcomes in patients with HFrEF



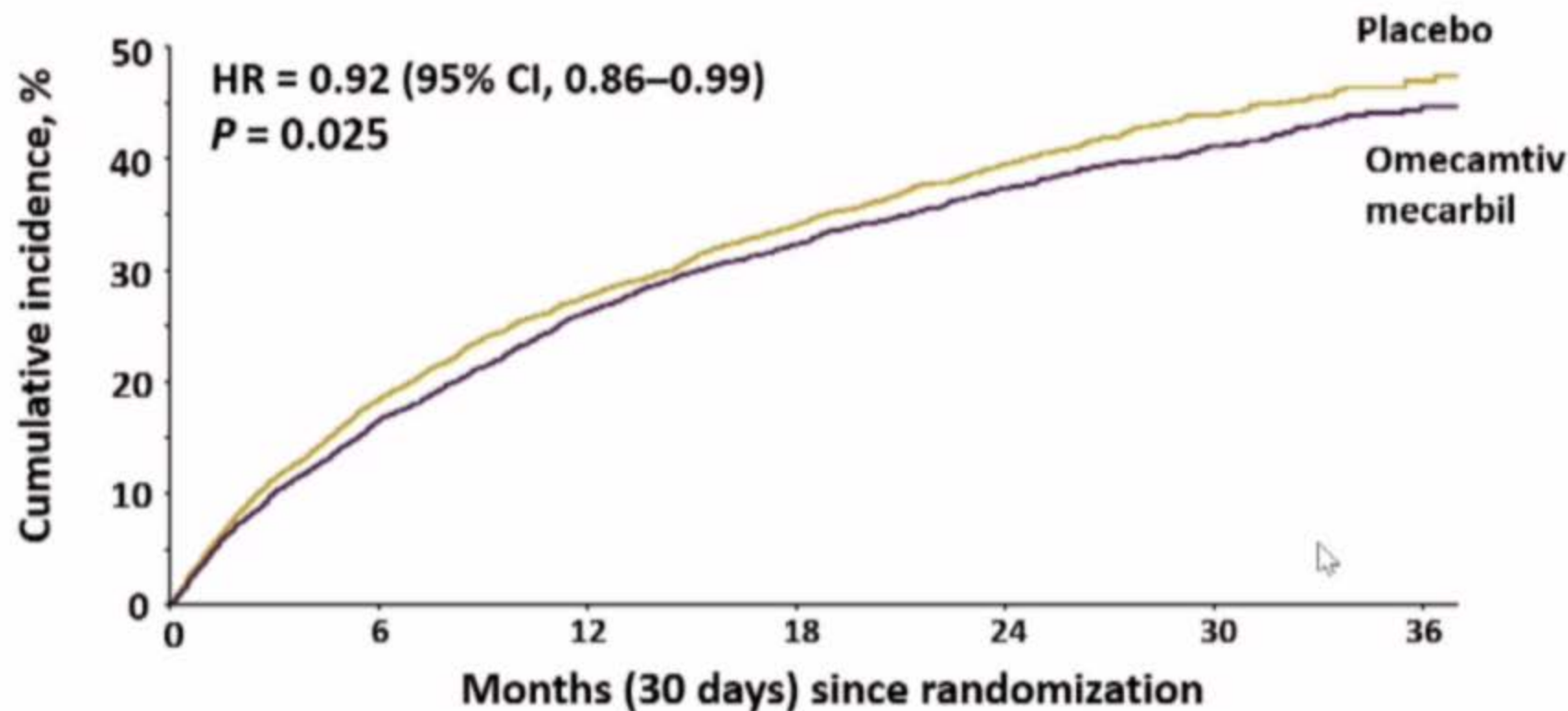
Multicenter, international, randomized, double-blind, placebo-controlled, event-driven Phase 3 study
 Teerlink JR, et al. *JACC Heart Fail* 2020;8:329–40.

Cardiac Myosin Activator: Omecamtiv Mecarbil



Teerlink JR, et al. *N Engl J Med* 2021;384:105-116.

Time to first Heart Failure event or Cardiovascular death



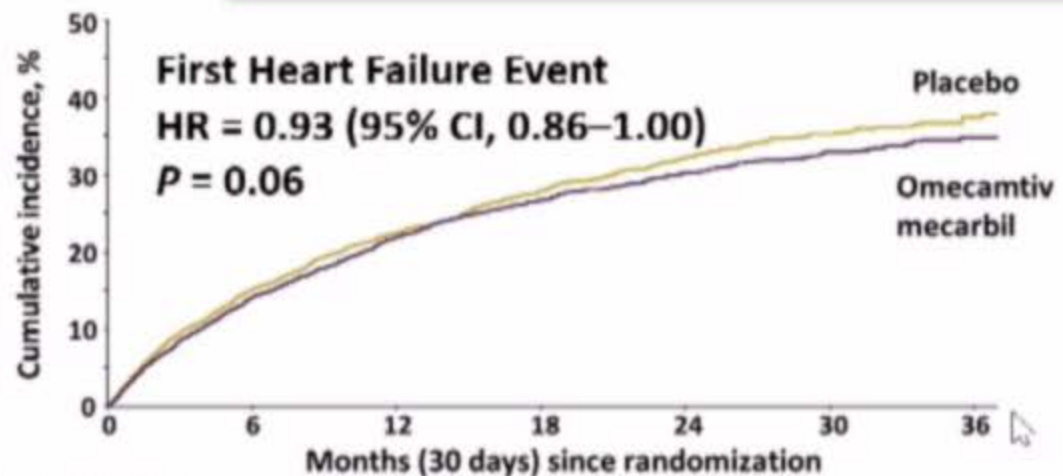
Patients at risk, n

Placebo	4112	3310	2889	2102	1349	647	141
Omecamtiv mecarbil	4120	3391	2953	2158	1430	700	164

Cardiac Myosin Activator: Omecamtiv Mecarbil

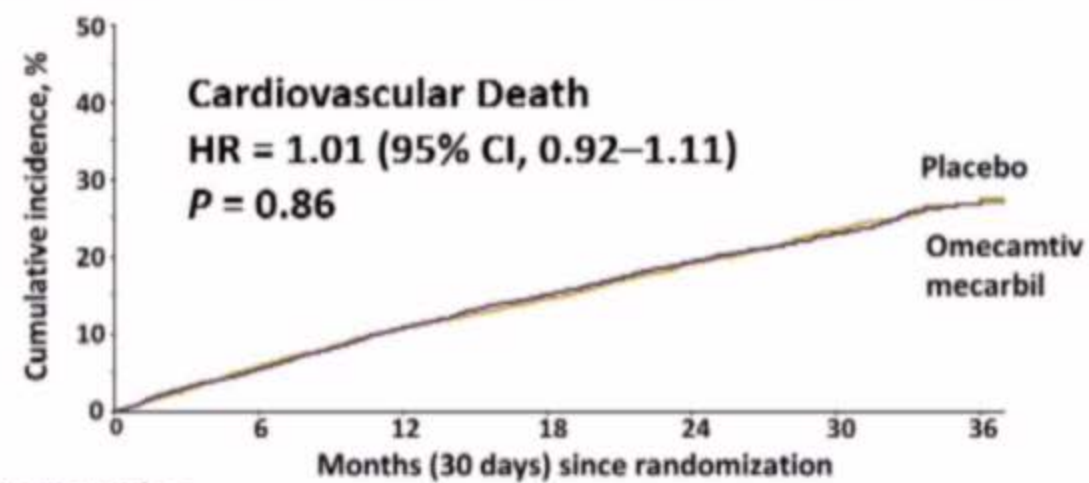


Teerlink JR, et al. *N Engl J Med*
2021;384:105-116.



Patients at risk, n

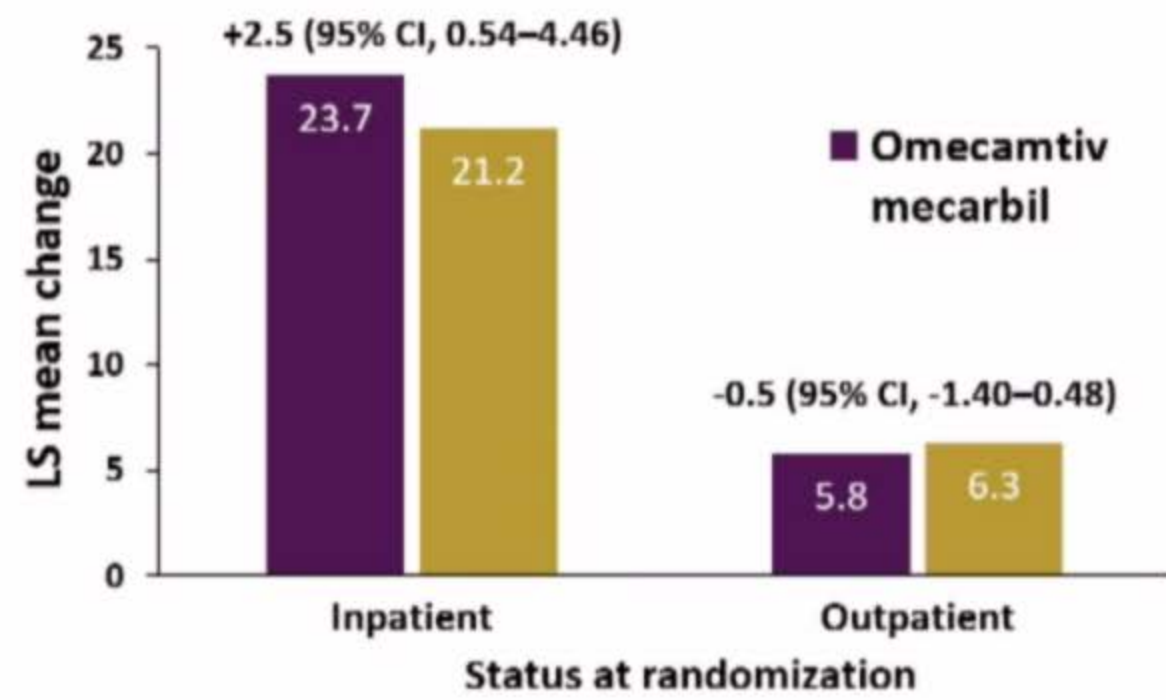
Placebo	4112	3309	2889	2102	1348	647	141
OM	4120	3391	2953	2156	1430	699	164



Patients at risk, n

Placebo	4112	3821	3560	2722	1788	885	201
OM	4120	3838	3556	2710	1838	903	224

**Change in Kansas City Cardiomyopathy Questionnaire
Total Symptom Score from Baseline to Week 24**
Joint test P = 0.028



Outline

- 心衰竭的成因、盛行率、預後
- 心衰竭治療指引更新-ESC
 - SGLT2i in HFrEF
 - Recently reported advances from trials in HFrEF
 - **HFmrEF, HFpEF**
- 總結

Only diuretics are recommended for HFpEF and HFmrEF (1B) in 2016 version

Recommendations for treatment of patients with heart failure with preserved ejection fraction and heart failure with mid-range ejection fraction

Recommendations	Class ^a	Level ^b	Ref ^c
it is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.	I	C	
<u>Diuretics</u> are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.	I	B	178, 179

新增ACEi/ARB/beta-blocker/MRA/ARNI for HFmrEF (IIb, C)

Pharmacological treatments in patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction

Recommendations	Class ^a	Level ^b
Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.	I	C
An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C
An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C
A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C
A MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death.	IIb	C

HFpEF無新增治療

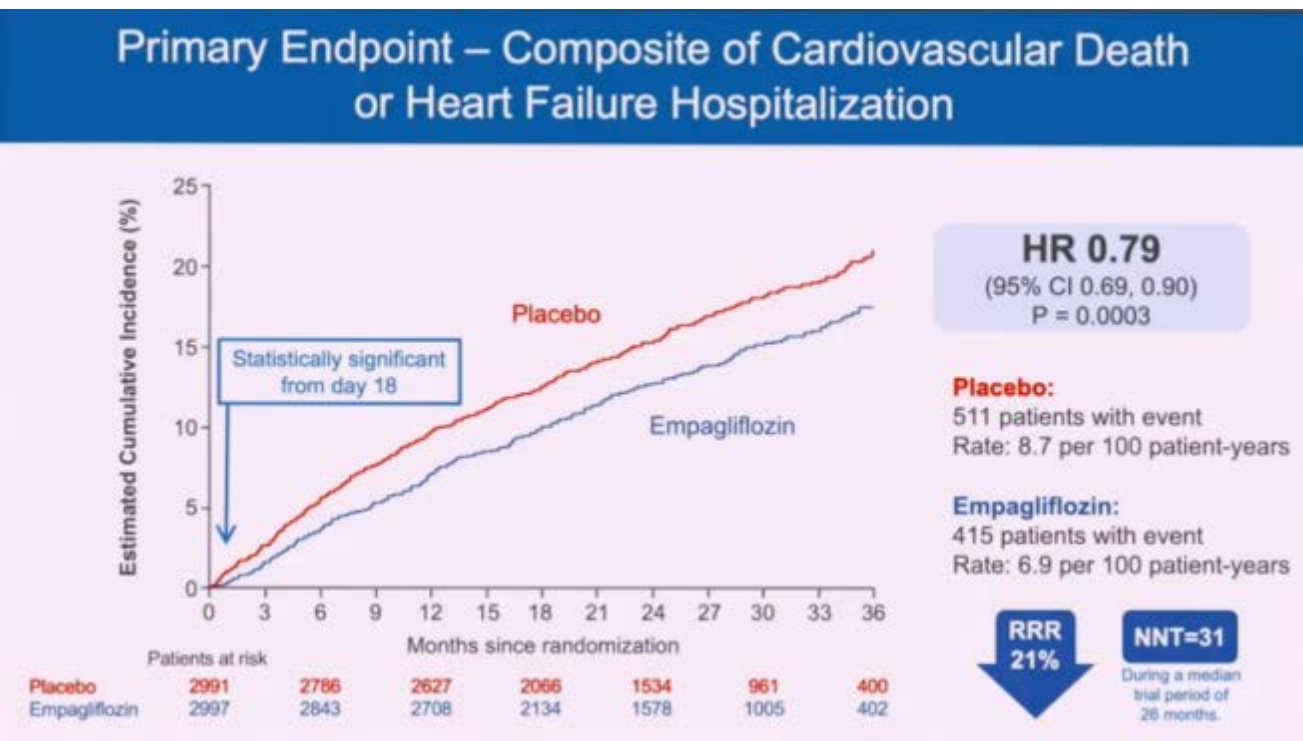
Recommendations for treatment of patients with heart failure with preserved ejection fraction

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.	I	C

Study design of HFpEF outcome trials

	DELIVER	EMPEROR-Preserved	PARAGON-HF
Number of patients	6263	5989	4822
Intervention	DAPA 10 mg vs PBO	EMPA 10 mg vs PBO	Sacubitril/valsartan vs valsartan
Key inclusion criteria	<ul style="list-style-type: none"> • NYHA class II-IV ≥6 wk with intermittent diuretics • LVEF >40% • Structural heart disease documented within last 12 mo • Elevated NT-proBNP • Ambulatory or hospitalized; if hospitalized for HF, must be off IV HF therapy for ≥24 hours • eGFR^b ≥25 mL/min/1.73 m² 	<ul style="list-style-type: none"> • NYHA class II-IV • LVEF >40% • Structural heart disease within 6 mo or hHF within 12 mo • Elevated NT-proBNP • eGFR^b ≥20 mL/min/1.73 m² 	<ul style="list-style-type: none"> • NYHA class II-IV • LVEF ≥45% • HF symptoms requiring diuretics ≥30 days • Elevated NT-proBNP • Structural heart disease • eGFR^d ≥30 mL/min/1.73 m²
Key exclusion criteria	<ul style="list-style-type: none"> • T1D • MI, UA, stroke, TIA, or CV procedure/surgery within last 12 wk • SBP ≥160^c or <95 mm Hg 	<ul style="list-style-type: none"> • MI, CABG, other major CV surgery, stroke, or TIA within 90 days • SBP ≥180 or <100 mm Hg or symptomatic hypotension • Acute decompensated HF 	<ul style="list-style-type: none"> • Prior LVEF <40% • SBP ≥180 or <110 mm Hg
Primary endpoint	<ul style="list-style-type: none"> • CV death, hHF, or urgent HF visit (in the full study population and subpopulation with LVEF <60%) 	<ul style="list-style-type: none"> • CV death or hHF 	<ul style="list-style-type: none"> • CV death or total hHF
Estimated completion	Jan 2022	April 2021 Readout in ESC 2021	Completed Readout in ESC 2020

EMPEROR-Preserved: Primary endpoint



SGLT2i發表的心衰竭試驗結果

Trial (N; median follow-up month)	Drug	Background Rx.	CV death/HHF HR (95%CI)	HHF HR (95%CI)	CV death HR (95%CI)	All-cause mortality HR (95%CI)
DAPA-HF (N=4744;18.2 months)	Dapagliflozin 10 mg QD vs placebo	ACEI/ARB/ARNI 94% BB 96% MRA 71%	0.75 (0.65–0.85)	0.70 (0.59–0.83)	0.82 (0.69–0.98)	0.83 (0.71–0.97)
EMPEROR-reduced (N=3730;16 months)	Empagliflozin 10 mg QD vs placebo	ACEI/ARB/ARNI 89% BB 95% MRA 71%	0.75 (0.65–0.86)	0.69 (0.59–0.81)	0.92 (0.75–1.12)	0.92 (0.77–1.10)
EMPEROR-Preserved (N=5988; 26.2 months)	Empagliflozin 10 mg QD vs placebo	ACEI/ARB/ARNI 81% BB 87% MRA 37%	0.70 (0.69–0.90)	0.71 (0.60–0.83)	0.91 (0.76–1.09)	1.00 (0.87–1.15)

As head-to-head studies were not conducted between these products, it is inappropriate to draw any comparisons and/or make any conclusions as the study design, demographics and other criteria may be different.

n/a: not applicable 1. N Engl J Med. 2011 Jan 6;364(1):11-21. 2. Lancet. 2010 Sep 11;376(9744):875-85. 3. N Engl J Med. 2014 Sep 11;371(11):993-1004. 4. N Engl J Med. 2019 Nov 21;381(21):1995-2008. 5. N Engl J Med. 2020 Oct 8;383(15):1413-1424. 6. N Engl J Med. 2020 May 14;382(20):1883-1893. 7. N Engl J Med 2021; 384:105-116.

Recently Published Heart Failure Outcome Trials

Trial (N; median follow-up month)	Drug	Background Rx.	CV death/HHF HR (95%CI)	HHF HR (95%CI)	CV death HR (95%CI)	All-cause mortality HR (95%CI)
EMPHASIS-HF (N=2737; 21 months)	Eplerenone vs placebo	ACEI/ARB 94% BB 87% MRA 0%	0.66 (0.56–0.78)	0.61 (0.50–0.75)	0.77 (0.62–0.96)	0.78 (0.64–0.95)
SHIFT (N=6558; 22.9 months)	Ivabradine vs placebo	ACEI/ARB 93% BB 90% MRA 60%	0.82 (0.75–0.90)	0.74 (0.66–0.83)	0.91 (0.80–1.03)	0.90 (0.80–1.02)
PARADIGM-HF (N=8399; 27 months)	Sacubitril/ valsartan vs Enalapril	ACEI/ARB 100% BB 93% MRA 56%	0.80 (0.73–0.87)	0.79 (0.71–0.89)	0.80 (0.71–0.89)	0.84 (0.76–0.93)
DAPA-HF (N=4744; 18.2 months)	Dapagliflozin vs placebo	ACEI/ARB/ARNI 94% BB 96% MRA 71%	0.75 (0.65–0.85)	0.70 (0.59–0.83)	0.82 (0.69–0.98)	0.83 (0.71–0.97)
EMPEROR-reduced (N=3730; 16 months)	Empagliflozin vs placebo	ACEI/ARB/ARNI 89% BB 95% MRA 71%	0.75 (0.65–0.86)	0.69 (0.59–0.81)	0.92 (0.75–1.12)	0.92 (0.77–1.10)
EMPEROR-Preserved (N=5988; 26.2 months)	Empagliflozin vs placebo	ACEI/ARB/ARNI 81% BB 87% MRA 37%	0.70 (0.69–0.90)	0.71 (0.60–0.83)	0.91 (0.76–1.09)	1.00 (0.87–1.15)
VICTORIA (N=5050; 10.8 months)	Vericiguat vs placebo	ACEI/ARB/ARNI 88% BB 93% MRA 70%	0.90 (0.82–0.98)	0.90 (0.81–1.00)	0.93 (0.81–1.06)	0.95 (0.84–1.07)
GALACTIC-HF (N=8256; 21.8 months)	Omecamtiv Mecarbil vs placebo	ACEI/ARB/ARNI 87% BB 94% MRA 78%	0.92 (0.86-0.99)	0.95 (0.87-1.03)	1.01 (0.92-1.11)	1.00 (0.92-1.09)

1. N Engl J Med. 2011 Jan 6;364(1):11-21. 2. Lancet. 2010 Sep 11;376(9744):875-85. 3. N Engl J Med. 2014 Sep 11;371(11):993-1004. 4. N Engl J Med. 2019 Nov 21;381(21):1995-2008. 5. N Engl J Med. 2020 Oct 8;383(15):1413-1424. 6. N Engl J Med. 2020 May 14;382(20):1883-1893. 6. N Engl J Med . 2020 May 14;382(20):1883-1893. 7. N Engl J Med . 2020 Nov 13. doi: 10.1056/NEJMoa2025797. Online ahead of print.

Conclusion

- A new simplified treatment algorithm for HFrEF, to reduce mortality in HFrEF :
ACEI/ARNI, BB, MRA, SGLT2i
- SGLT2i are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.
 - DAPA-HF : reduce risk of HHF, CV death, All-cause mortality
 - EMPEROR-REDUCE : reduce risk of HHF
- Consensus of the HFA, ESC : HR, BP, AF, CKD should be taken into account to achieve a better and more comprehensive therapy. SGLT2i are recommended for all 11 patient profiles.



**Thanks for your
attention**