Campus Cuore 2021

SGLT2i nello SC cronico: evidenze e linee guida ESC 2021

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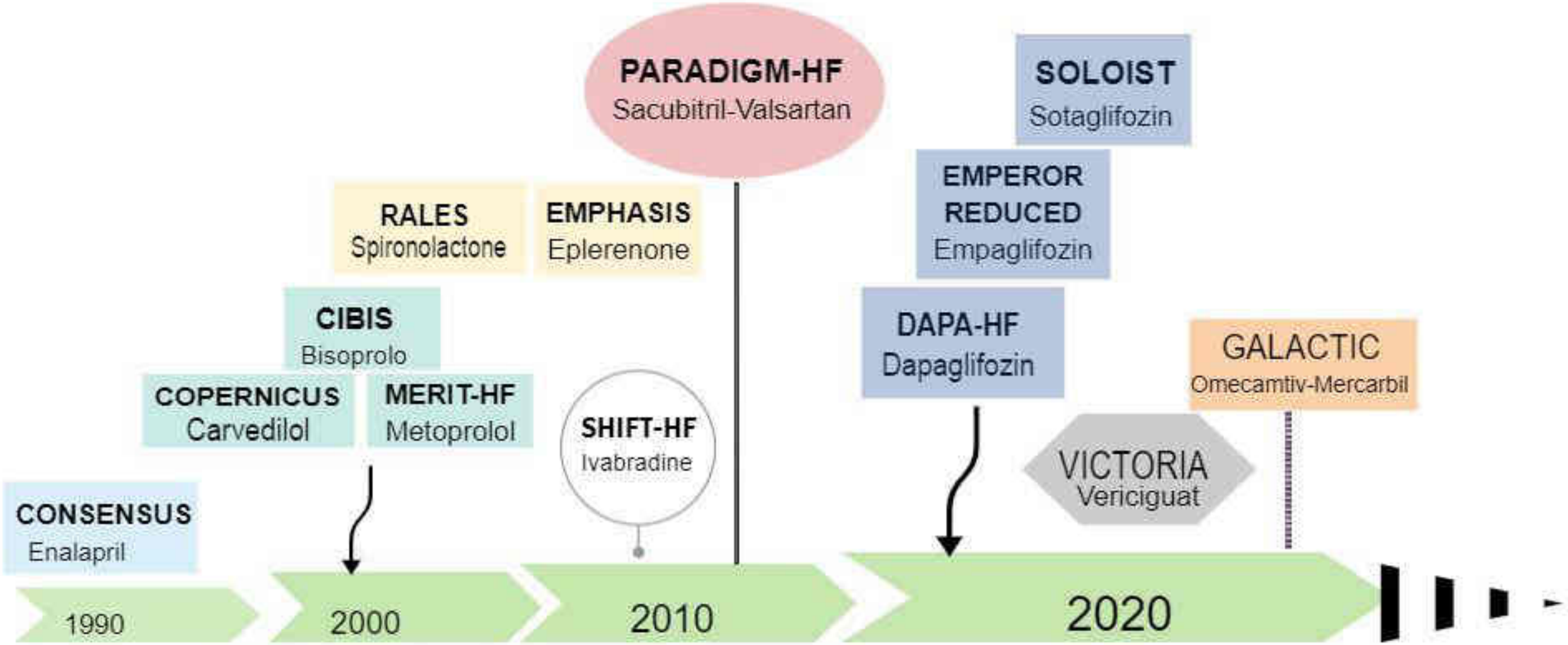
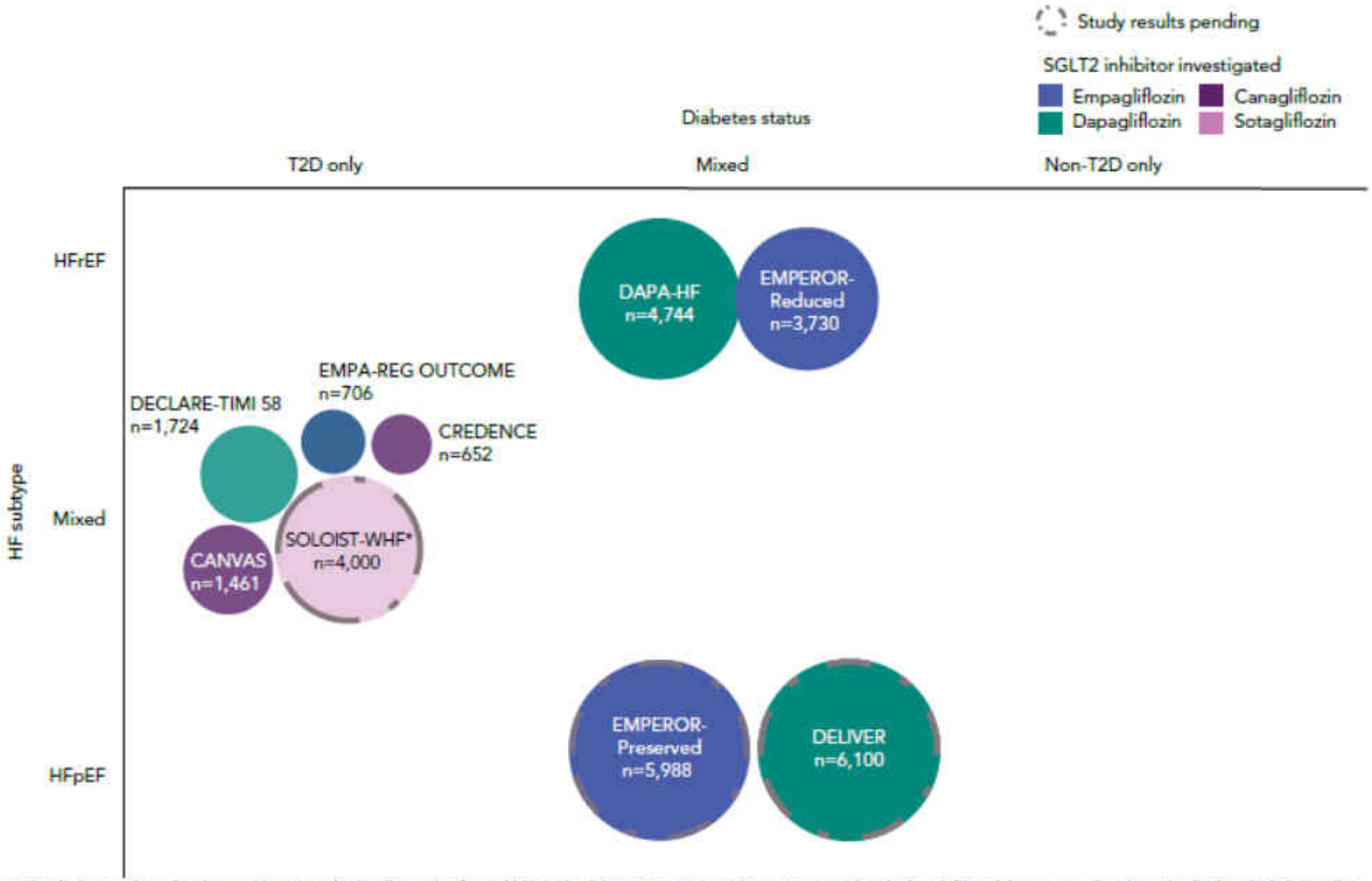

PARADIGM-HF
Sacubitril-Valsartan
SOLOIST
Sotaglifozin
EMPEROR
REDUCED
Empaglifozin
RALES
Spironolactone
EMPHASIS
Eplerenone
CIBIS
Bisoprolo
DAPA-HF
Dapaglifozin
GALACTIC
Omecamtiv-Mercarbil
COPERNICUS
Carvedilol
MERIT-HF
Metoprolol
SHIFT-HF
Ivabradine
VICTORIA
Vericiguat
CONSENSUS
Enalapril
1990
2000
2010
2020

Large-scale Randomised Controlled Trials of SGLT2 Inhibitors



*Each n is the number of patients with reported prior diagnosis of HF within each trial. *SOLOIST-WHF trial was terminated early due to financial concerns; data from the final analysis is pending. HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; SGLT2 = sodium–glucose co-transporter 2; T2D = type 2 diabetes.*

Rosano et al, Cardiac Failure Review 2020;6:e31.

Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure

ESC European Society of Cardiology

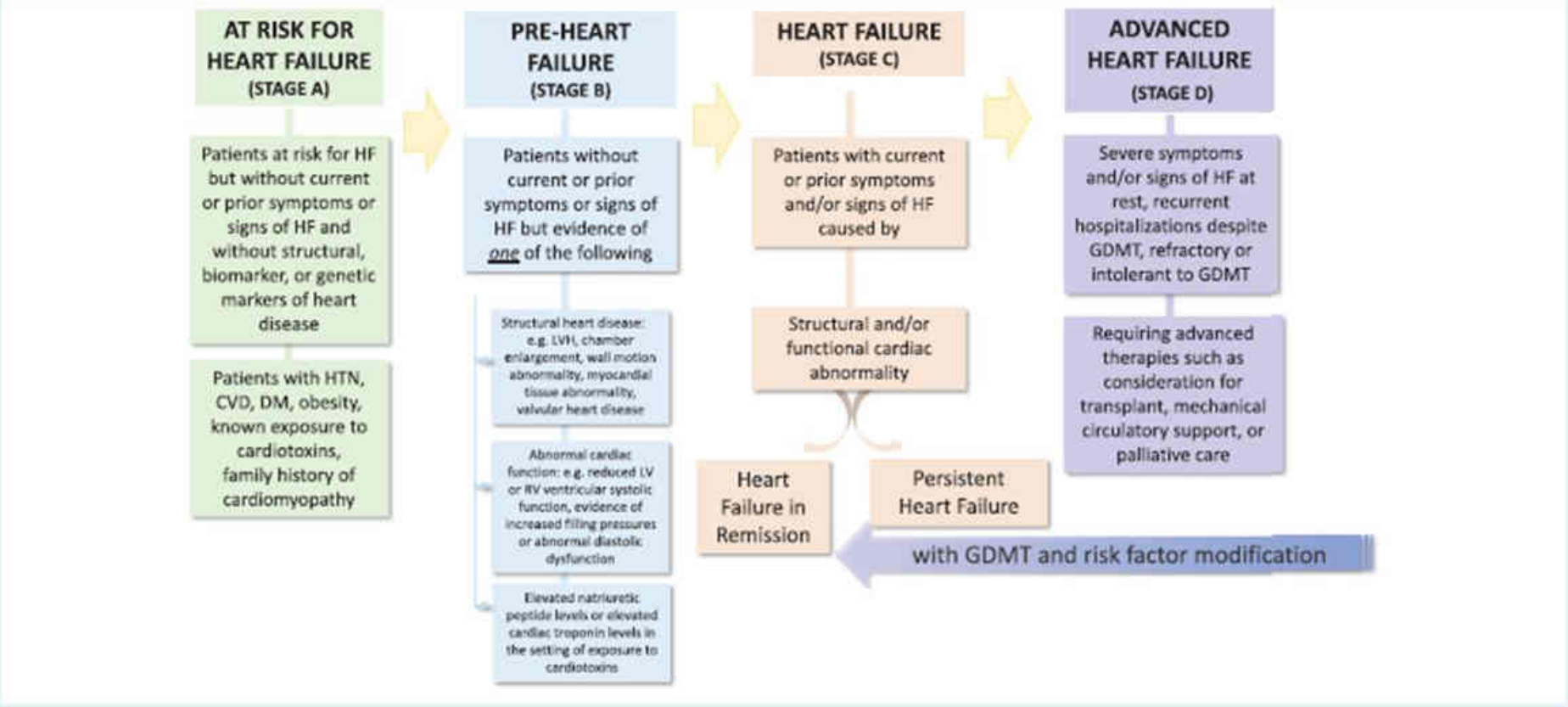


Figure 2 Stages in the development and progression of heart failure (HF). CVD, cardiovascular disease; DM, diabetes mellitus; GDMT, guideline-directed medical therapy; HTN, hypertension; LV, left ventricular; LVH, left ventricular hypertrophy; RV, right ventricular.

Bozkurt et al, European Journal of Heart Failure (2021) **23**, 352–380

JACC VOL. 77, NO. 6, 2021
FEBRUARY 16, 2021:772–810

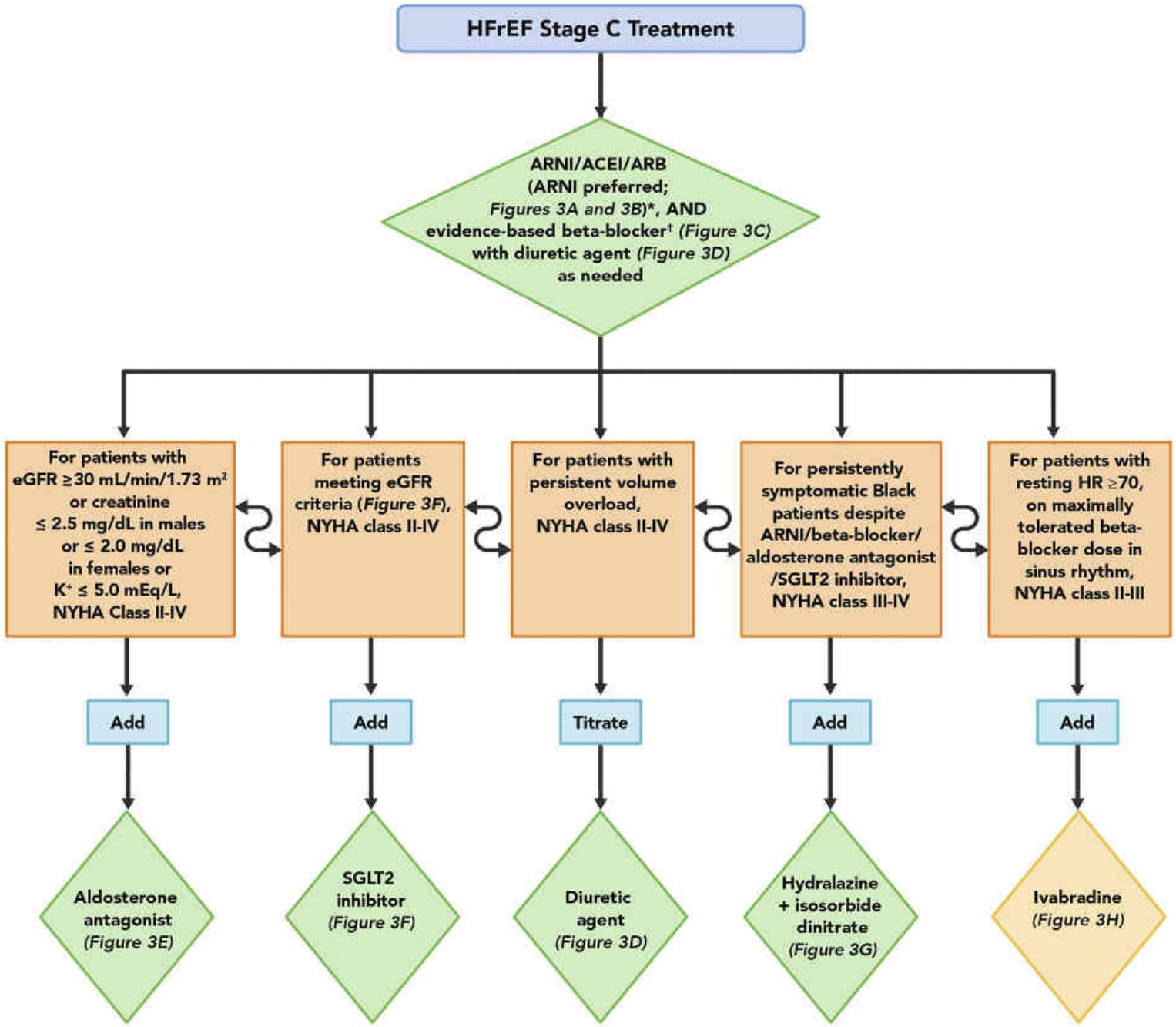
EXPERT CONSENSUS DECISION PATHWAY

2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

A Report of the American College of Cardiology Solution Set Oversight Committee

RECOMMENDATIONS FOR STARTING GDMT IN A PATIENT WITH A NEW DIAGNOSIS OF SYMPTOMATIC HFREF

- adjustment of therapies should occur every 2 weeks, **to achieve optimal GDMT ≤ 3-6 months**
- GLT2i are added in as part of the therapy for patients with chronic HFrEF who are already receiving BB, an ARNI/ACEI/ARB and MRA
  - achieving target or **maximally tolerated doses of other drugs is not necessary before adding SGLT2i**



Canadian Journal of Cardiology
Volume 37 2021

Canadian Journal of Cardiology 37 (2021) 531–546

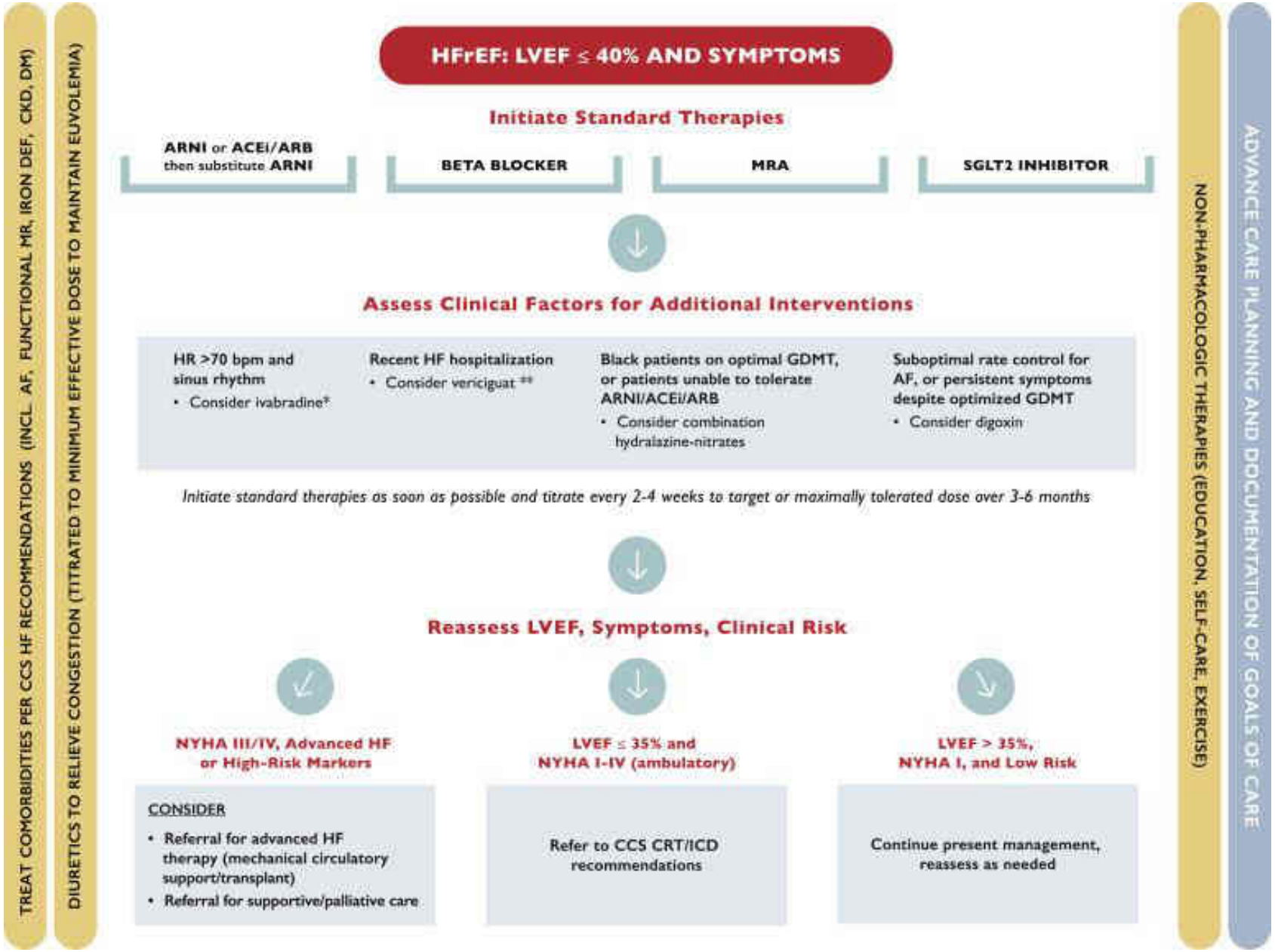
Society Guidelines

CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction

Primary Panel: Michael McDonald, MD (Co-chair),[a] Sean Virani, MD (Co-chair),[b] Michael Chan, MBBS,[c] Anique Ducharme, MD,[d] Justin A. Ezekowitz, MBBCh,[e] Nadia Giannetti, MD,[f] George A. Heckman, MD,[g] Jonathan G. Howlett, MD,[h] Sheri L. Koshman, Pharm D,[e] Serge Lepage, MD,[i] Lisa Mielniczuk, MD,[j] Gordon W. Moe, MD,[k] Eileen O'Meara, MD,[d] Elizabeth Swiggum, MD,[l] Mustafa Toma, MD,[b] Shelley Zieroth, MD,[m] **Secondary Panel:** Kim Anderson, MD,[n] Sharon A. Bray, EdD,[a] Brian Clarke, MD,[h] Alain Cohen-Solal, MD,[o] Michel D'Astous, MD,[p] Margot Davis, MD,[b] Sabe De, MD,[q] Andrew D.M. Grant, MD,[h] Adam Grzeslo, MD,[r] Jodi Heshka, MD,[s] Sabina Keen, MD,[r] Simon Kouz, MD,[t] Douglas Lee, MD, PhD,[a] Frederick A. Masoudi, MD MSPH,[u] Robert McKelvie, MD,[v] Marie-Claude Parent, MD,[d] Stephanie Poon, MD,[w] Miroslaw Rajda, MD,[n] Abhinav Sharma, MD,[f] Kyla Siatecki, MN, NP,[m] Kate Storm, NP,[n] Bruce Sussex, MBBS,[x] Harriette Van Spall, MD MPH,[r] and Amelia Ming Ching Yip, MD[y]

TREATMENT ALGORITHM FOR MANAGEMENT OF HFrEF

- titrate of all standard therapies concurrently to target doses ≤ 3-6 months
- prescribe ARNI as first-line therapy or before full titration of ACEIs/ARBs
- SGLT2i should be considered as standard or foundational therapy in patients with HFrEF
- start SGLT2i early in the disease course for eligible patients



2021 – Joint position paper of SIC/SID

SOCIETÀ ITALIANA DI CARDIOLOGIA

SID Società Italiana di Diabetologia

ELSEVIER

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

POSITION PAPER

Cardiovascular risk management in type 2 diabetes mellitus: A joint position paper of the Italian Cardiology (SIC) and Italian Diabetes (SID) Societies☆

Angelo Avogaro [a], Francesco Barillà [b], Franco Cavalot [c], Agostino Consoli [d], Massimo Federici [b], Massimo Mancone [e], Stefania Paolillo [f,l], Roberto Pedrinelli [g], Gianluca Perseghin [h], Pasquale Perrone Filardi [f,l], Roberto Scicali [i], Gianfranco Sinagra [j], Carmen Spaccarotella [k], Ciro Indolfi [k,l,**], Francesco Purrello [i,*]

2021 Cardiovascular risk management in type 2 diabetes mellitus: A joint Position paper of the Italian Cardiology (SIC) and Italian Diabetes (SID) Societies

Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology

ESC European Society of Cardiology

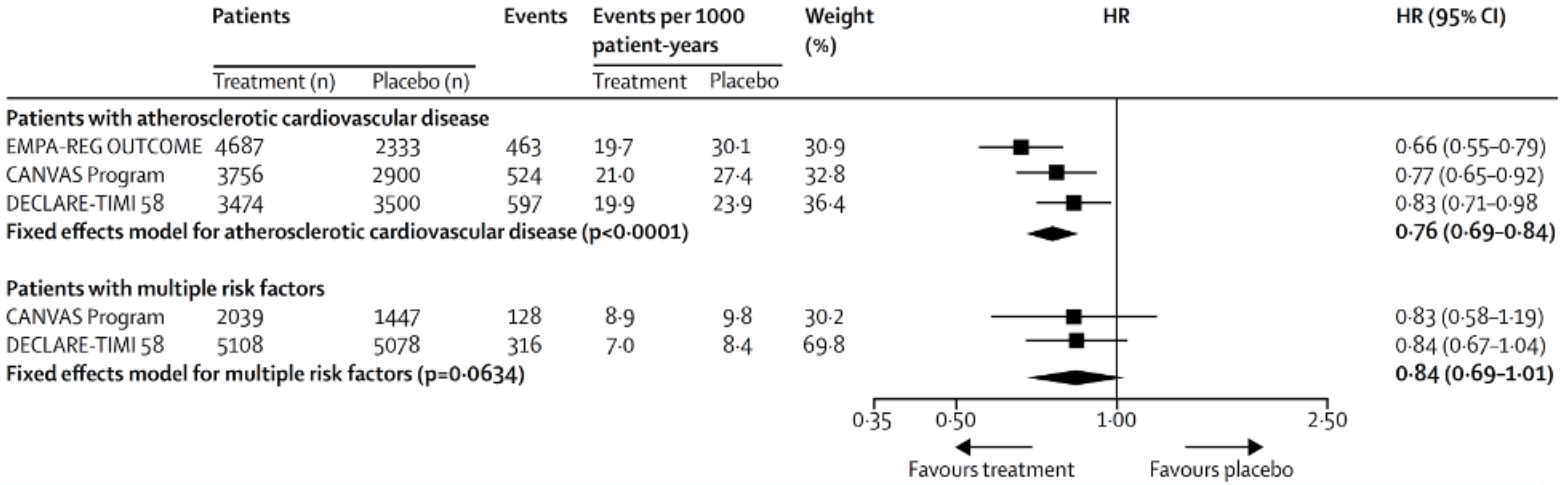
The increasing knowledge about the different HF phenotypes, based on either aetiology or disease mechanisms, or on outcomes and bio-profiling, may allow an evolution from large-scale clinical trials performed in heterogeneous LVEF-classified patients, to personalized mechanistic trials on small populations of homogeneous HF patients.

Rosano et al, European Journal of Heart Failure (2021) doi:10.1002/ejhf.2206

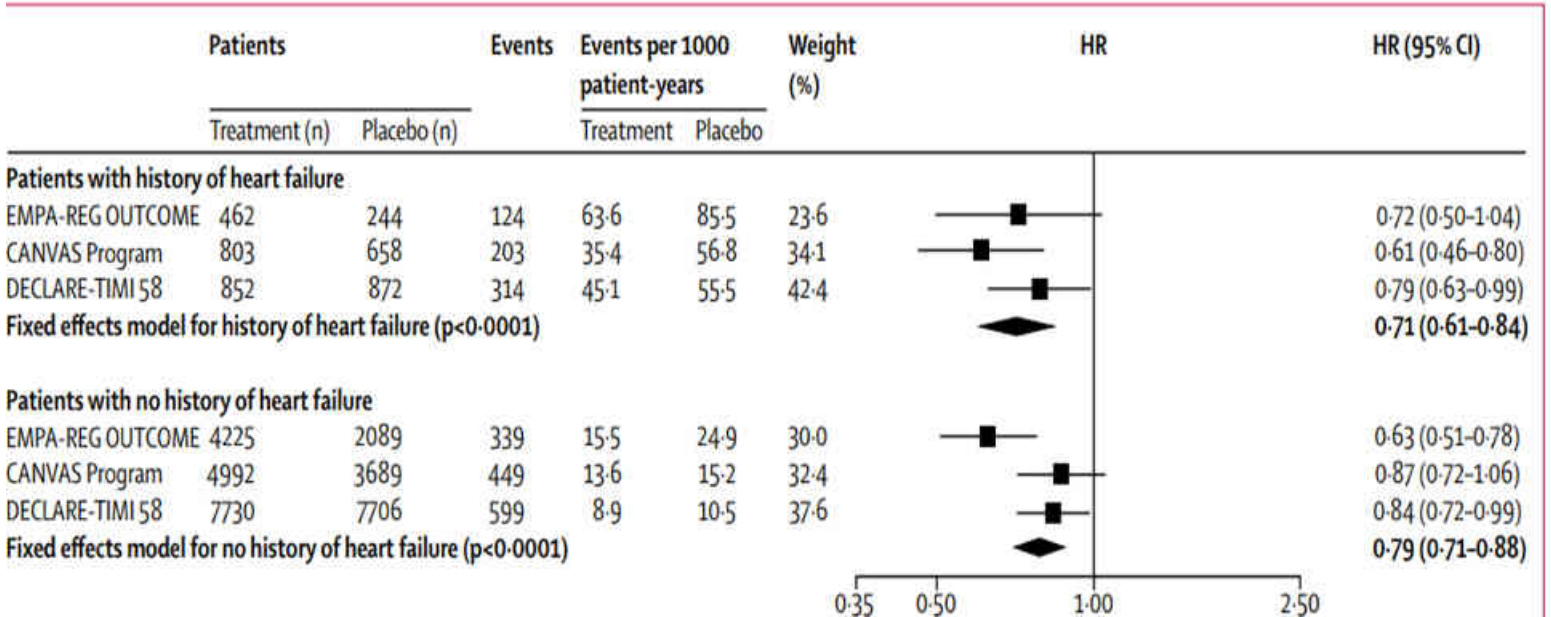
SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Doses analysed	10 mg, 25 mg (once daily)	100 mg, 300 mg (once daily)	10 mg (once daily)
Median follow-up time, years	3·1	2·4	4·2
Trial participants	7020	10 142	17 160
Age, mean	63·1	63·3	63·9
Women	2004 (28·5%)	3633 (35·8%)	6422 (37·4%)
Patients with established atherosclerotic cardiovascular disease	7020 (100%)	6656 (65·6%)	6974 (40·6%)
Patients with a history of heart failure	706 (10·1%)	1461 (14·4%)	1724 (10·0%)
Patients with eGFR <60 mL/min per 1·73 m²	1819 (25·9%)	2039 (20·1%)	1265 (7·4%)



HHf - CVd



HHf - CVd

Lancet 2019; 393: 31–39

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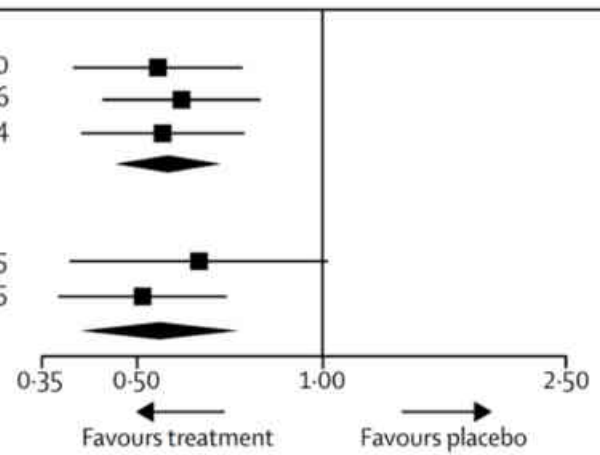
	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687	2333	772	37·4	43·9	29·4		0·86 (0·74–0·99)
CANVAS Program	3756	2900	796	34·1	41·3	32·4		0·82 (0·72–0·95)
DECLARE-TIMI 58	3474	3500	1020	36·8	41·0	38·2		0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)								**0·86 (0·80–0·93)**
Patients with multiple risk factors								
CANVAS Program	2039	1447	215	15·8	15·5	25·9		0·98 (0·74–1·30)
DECLARE-TIMI 58	5108	5078	539	13·4	13·3	74·1		1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)								**1·00 (0·87–1·16)**

MI-Stroke-CVd (MACE)

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4645	2323	152	6·3	11·5	31·0		0·54 (0·40–0·75)
CANVAS Program	3756	2900	179	6·4	10·5	35·6		0·59 (0·44–0·79)
DECLARE-TIMI 58	3474	3500	183	4·7	8·6	33·4		0·55 (0·41–0·75)
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)								**0·56 (0·47–0·67)**
Patients with multiple risk factors								
CANVAS Program	2039	1447	70	4·1	6·6	29·5		0·63 (0·39–1·02)
DECLARE-TIMI 58	5108	5078	182	3·0	5·9	70·5		0·51 (0·37–0·69)
Fixed effects model for multiple risk factors (p<0·0001)								**0·54 (0·42–0·71)**



WESRD

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

What's new?

Recommendations for treatment of chronic HF	
HFrEF	
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I

Recommendations for management of patients after HF hospitalization	
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment.	I
It is recommended that evidence-based oral medical treatment be administered before discharge.	I
An early follow-up visit is recommended at 1–2 weeks after discharge to assess signs of congestion, drug tolerance, and start and/or uptitrate evidence-based therapy.	I

Recommendations for management of patients with HF and diabetes	
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with T2DM at risk of CV events to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death.	I
SGLT2 inhibitors (dapagliflozin, empagliflozin, and sotagliflozin) are recommended in patients with T2DM and HFrEF to reduce hospitalizations for HF and CV death.	I

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–128
doi:10.1093/eurheartj/ehab368

Chronic HFrEF (EF ≤ 40%)

Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	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.[105]	I	B

The sodium-glucose co-transporter 2 (SGLT2) inhibitors dapagliflozin and empagliflozin added to therapy with ACE-I/ARNI/beta-blocker/MRA reduced the risk of CV death and worsening HF in patients with HFrEF.[108,109] Unless contraindicated or not tolerated, dapagliflozin or empagliflozin are recommended for all patients with HFrEF already treated with an ACE-I/ARNI, a beta-blocker, and an MRA, regardless of whether they have diabetes or not.

Therefore, dapagliflozin or empagliflozin are recommended, in addition to OMT with an ACE-I/ARNI, a beta-blocker and an MRA, for patients with HFrEF regardless of diabetes status. The diuretic/natriuretic properties of SGLT2 inhibitors may offer additional benefits in reducing congestion and may allow a reduction in loop diuretic requirement.[135]

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–128
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The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 NOVEMBER 21, 2019 VOL. 381 NO. 21

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

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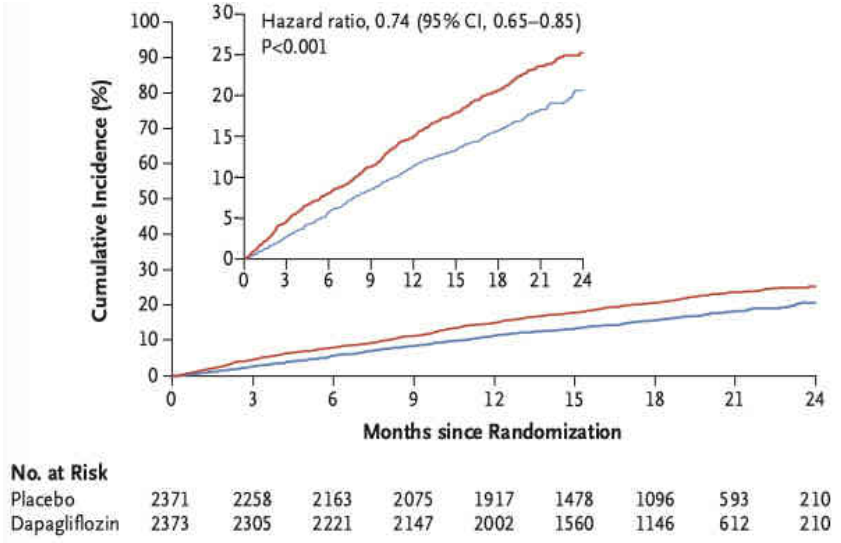
PRIMARY OUTCOME: CV death or worsening HF



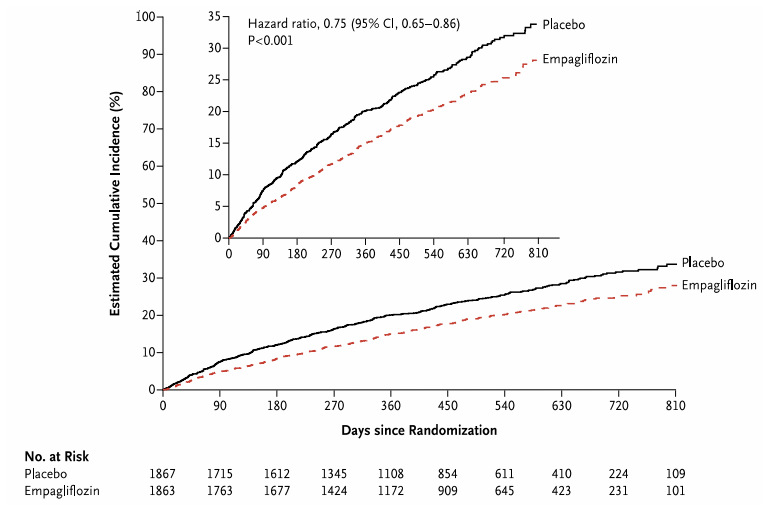
N Engl J Med 2019; 381:1995-2008

ORIGINAL ARTICLE

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

PRIMARY OUTCOME: CV death or hospitalization for HF



N Engl J Med 2020; 383:1413-1424

DAPA HF - Key Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Men and women ≥18 years of age, with or without T2D
- Documented diagnosis of symptomatic HFrEF for ≥2 months (NYHA class II-IV)
- LVEF ≤40% within the last 12 months
- Elevated NT-proBNP (≥600 pg/mL or ≥400 pg/mL if hHF within 12 months or ≥900 pg/mL if atrial fibrillation/flutter irrespective of hHF history)
- Optimal pharmacological and device therapy for HF
- Optimal and stable[a] (≥4 weeks) background standard of care for HFrEF as per local guidelines including (unless contraindicated or not tolerated): ACEI, ARB, or sacubitril/valsartan; beta-blocker; and if appropriate a MRA
- eGFR[b] ≥30 mL/min/1.73 m^2

Key Exclusion Criteria

- Treatment within 8 weeks or intolerance to SGLT2 inhibitor
- T1D
- Symptomatic hypotension or SBP <95 mmHg
- Current acute decompensated HF or hospitalization within last 4 weeks due to decompensated HF
- Coronary revascularization (PCI or CABG), valve repair/replacement, or CRT device implantation within last 12 weeks or planned after randomization
- HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic cardiomyopathy, or uncorrected primary valvular disease
- eGFR <30 mL/min/1.73 m^2 or rapidly declining renal function

[a]This does not apply to diuretics; diuretic dosing may be titrated to symptoms, signs, weight and other information and may thus vary. Each patient should, however, be treated with a diuretic regimen aimed at achieving optimal fluid/volume status for that individual; [b]CKD-EPI formula.

McMurray JJV et al. Article and supplementary appendix. *Eur J Heart Fail.* 2019;21:665-675.

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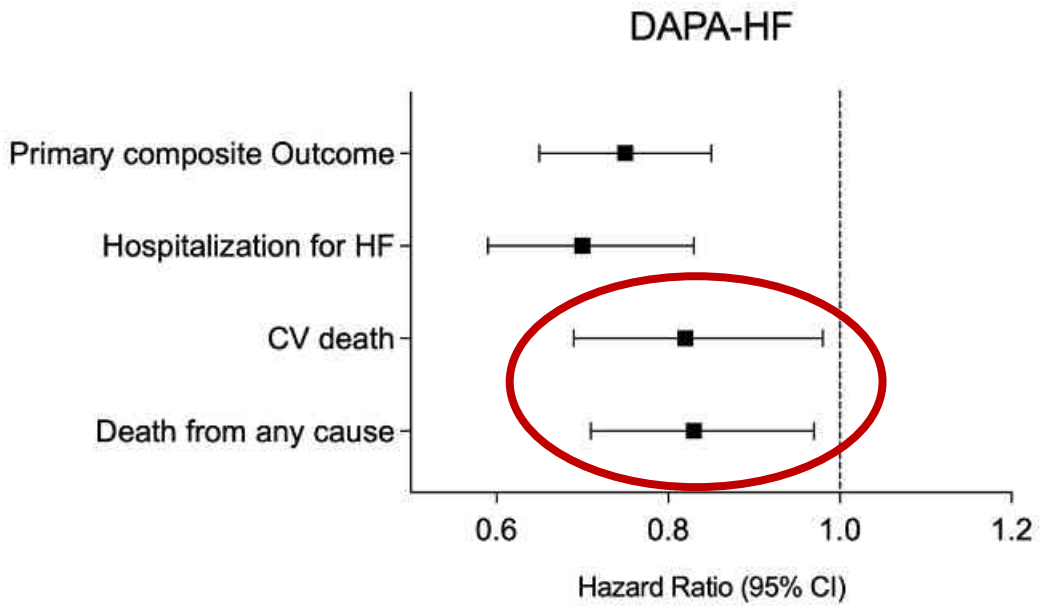

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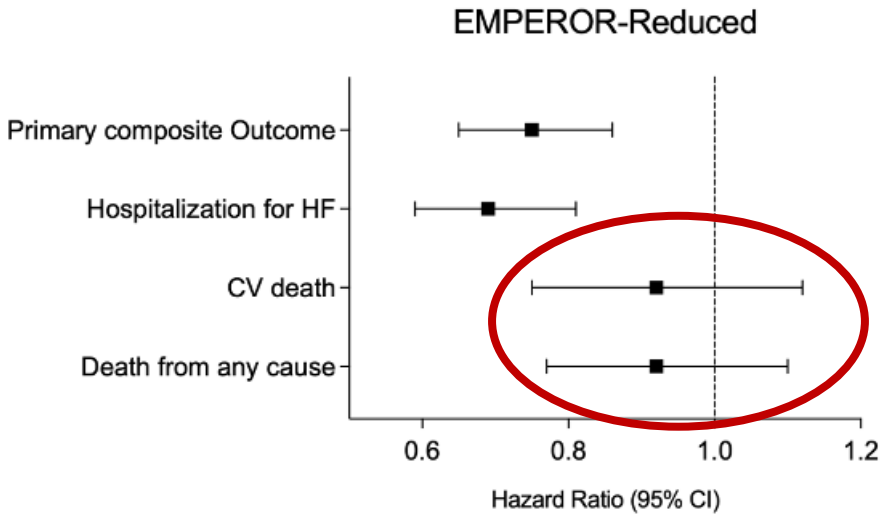


N Engl J Med 2020; 383:1413-1424

	PARADIGM-HF		DAPA-HF; FU 18.2 mo		EMPEROR-reduced; FU 16 mo	
	Sacubitril/Valsartan	Placebo	Dapaglifozin	Placebo	Empaglifozin	Placebo
Age (years)	63.8±11.5	63.8±11.3	62.2±11.0	66.5±10.8	67.2±10.8	66.5±11.2
Female (%)	21.0	22.6	23.8	23.0	23.5	24.4
Ischemic etiology (%)	59.9	60.1	55.5	57.3	52.8	50.7
NYHA class, (%)						
I	4.3	5.0				
II	71.6	69.3	67.7	67.4	75.1	75
III	23.1	24.9	31.5	31.7	24.4	24.4
IV	0.8	0.6	0.8	1.0	0.5	0.6
LVEF (%)	29.6±6.1	29.4±6.3	**31.2±6.7**	**30.6±6.9**	**27.7±6.0**	**27.2±6.1**
Median NT-proBNP	1631	1594	**1428**	**1446**	**1887**	**1926**
GFR (ml/min *1.73 m2)			66.0±19.6	65.5±19.3	61.8±21.7	62.2±21.5
Therapy (%)						
ACEi/ARBs	-	100	84.5	82.8	70.5	68.9
ARNI	100	-	10.5	10.9	18.3	20.7
MRA	54.2	57.0	71.5	70.6	70.1	72.6
Beta-blockers	93.1	92.9	96.0	96.2	94.7	94.7
Diuretics	80.3	80.1	93.4	93.5		
ICD	14.9	14.7	26.2	26.1	**31.0**	**31.8**
CRT	7.0	6.7	8.0	6.9	**11.8**	**11.9**

McMurray JJV et al. NEJM 2014

McMurray JJV et al. NEJM 2019

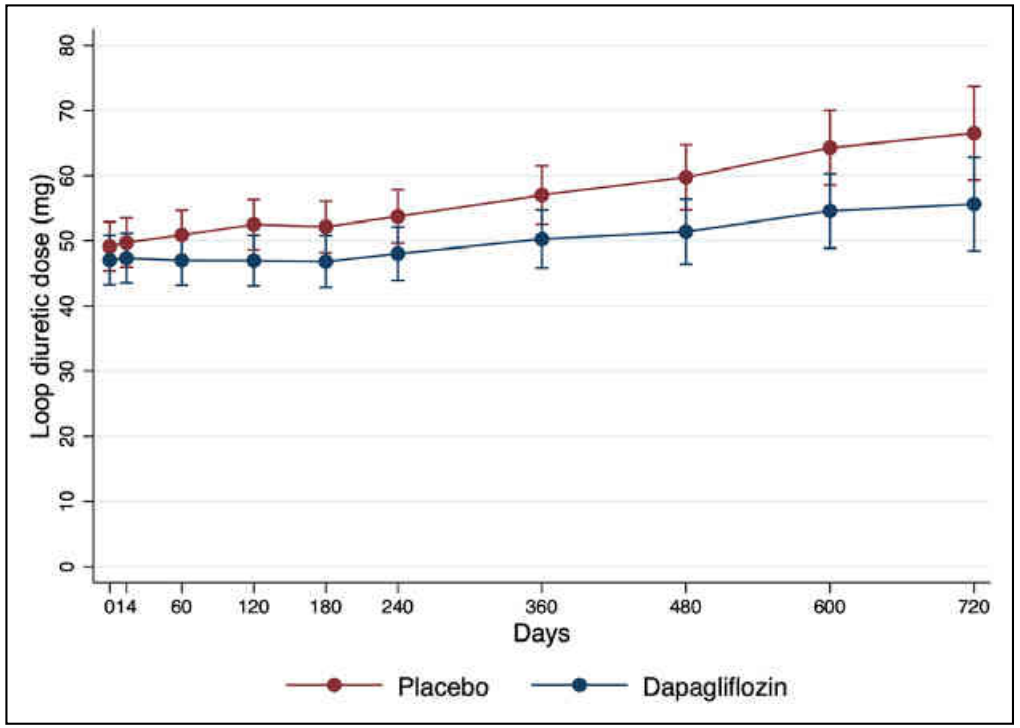
Packer M et al. NEJM 2020

Circulation

ORIGINAL RESEARCH ARTICLE

Dapagliflozin and Diuretic Use in Patients With Heart Failure and Reduced Ejection Fraction in DAPA-HF

Figure 1. Change in loop diuretic dose over time in all patients.



Circulation. 2020;142:1040–1054. DOI: 10.1161/CIRCULATIONAHA.120.047077

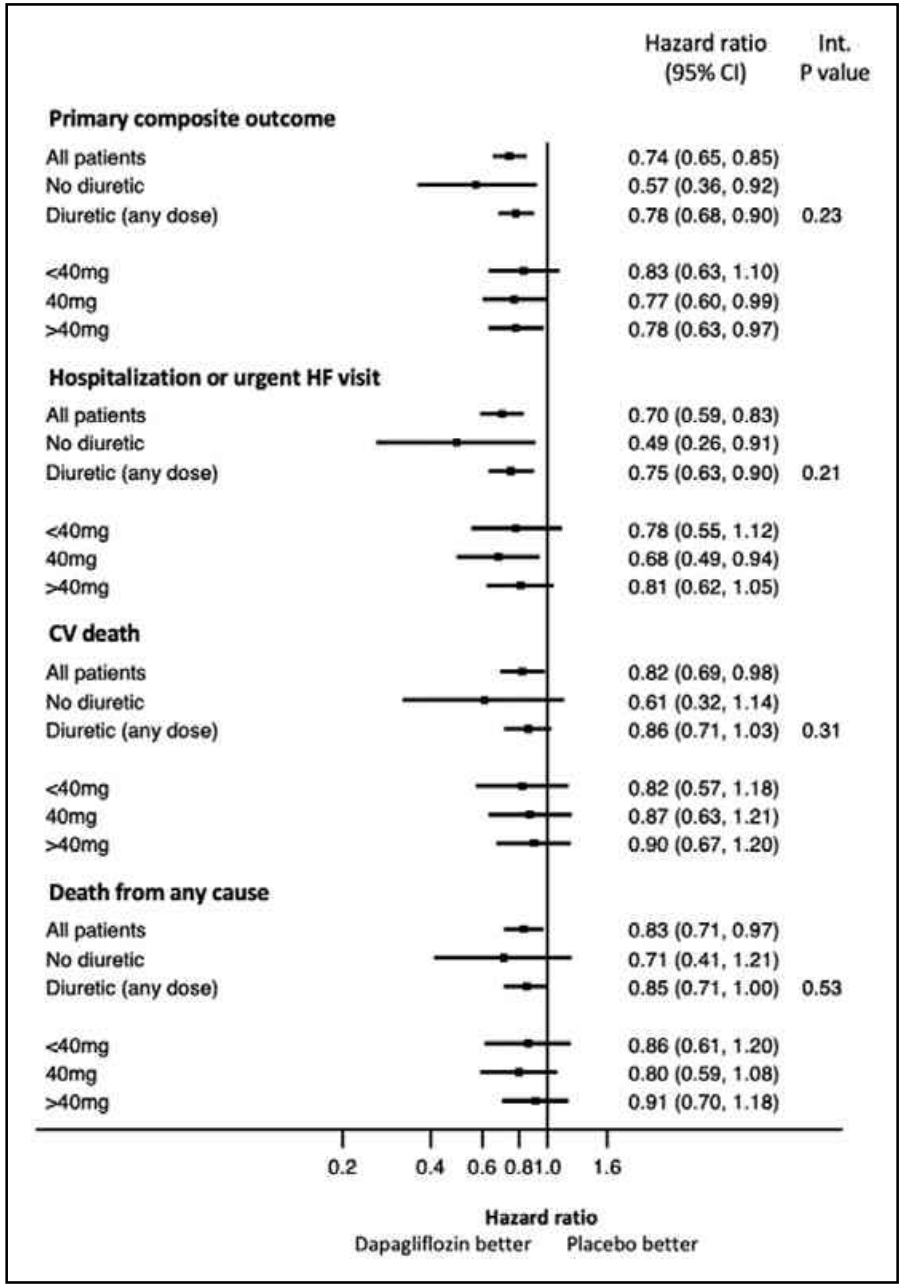


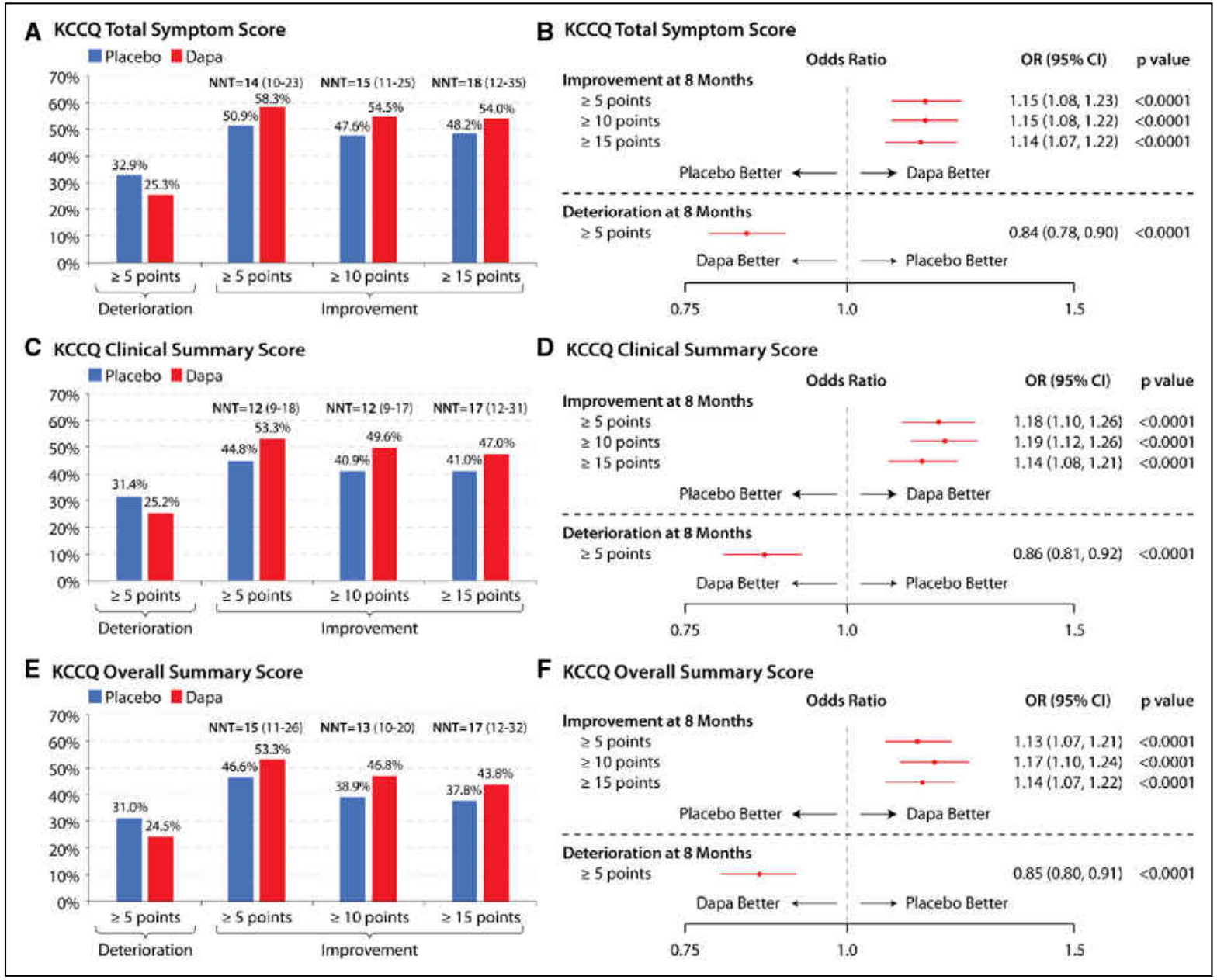
Figure 2. Forest plot of efficacy outcomes according to diuretic therapy at baseline.

Circulation

ORIGINAL RESEARCH ARTICLE

Effects of Dapagliflozin on Symptoms, Function, and Quality of Life in Patients With Heart Failure and Reduced Ejection Fraction

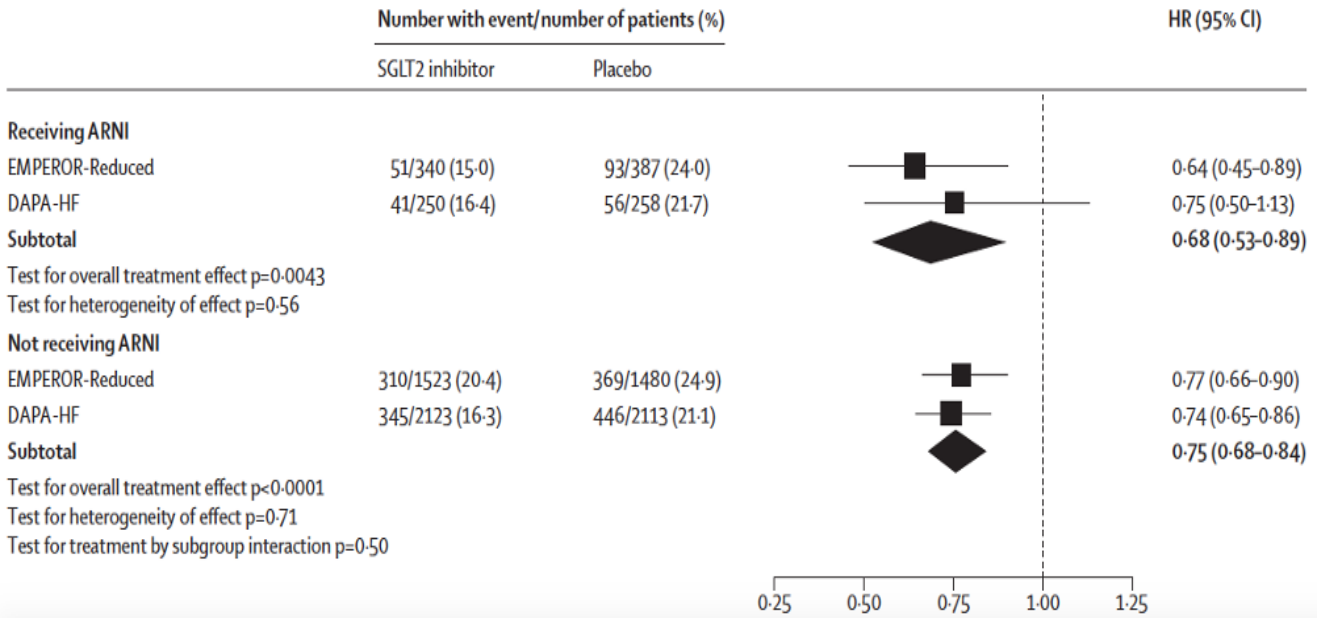
Results From the DAPA-HF Trial



Circulation. 2020;141:90–99. DOI: 10.1161/CIRCULATIONAHA.119.044138

SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials

Faiez Zannad, João Pedro Ferreira, Stuart J Pocock, Stefan D Anker, Javed Butler, Gerasimos Filippatos, Martina Brueckmann, Anne Pernille Ofstad, Egon Pfarr, Waheed Jamal, Milton Packer



	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin	Placebo	Dapagliflozin	Placebo
Number of participants	1863	1867	2373	2371
Age, years	67·2 (10·8)	66·5 (11·2)	66·2 (11·0)	66·5 (10·8)
Sex				
Men	1426 (76.5%)	1411 (75·6%)	1809 (76·2%)	1826 (77·0%)
Women	437 (23·5%)	456 (24·4%)	564 (23·8%)	545 (23·0%)
NYHA functional classification				
II	1399 (75·1%)	1401 (75·0%)	1606 (67·7%)	1597 (67·4%)
III	455 (24·4%)	455 (24·4%)	747 (31·5%)	751 (31·7%)
IV	9 (0·5%)	11 (0·6%)	20 (0·8%)	23 (1·0%)
Mean LVEF, %	27·7 (6·0)	27·2 (6·1)	31·2 (6·7)	30·9 (6·9)
NT-pro BNP, pg/mL	1887 (1077–3429)	1926 (1153–3525)	1428 (857–2655)	1446 (857–2641)
Medical history				
Hospitalisation for heart failure*	577 (31·0%)	574 (30·7%)	1124 (47·4%)	1127 (47·5%)
Diabetes†	927 (49·8%)	929 (49·8%)	1075 (45·3%)	1064 (44·9%)
eGFR, mL/min per 1·73 m²‡	61·8 (21·7)	62·2 (21·5)	66·0 (19·6)	65·5 (19·3)
Heart failure medications				
ACE inhibitor	867 (46·5%)	836 (44·8%)	1332 (56·1%)	1329 (56·1%)
ARB	451 (24·2%)	457 (24·5%)	675 (28·4%)	632 (26·7%)
Mineralocorticoid receptor antagonist	1306 (70·1%)	1355 (72·6%)	1696 (71·5%)	1674 (70·6%)
ARNI	340 (18·3%)	387 (20·7%)	250 (10·5%)	258 (10·9%)
Device therapy				
ICD or CRT-D	578 (31·0%)	593 (31·8%)	622 (26·2%)	620 (26·1%)
CRT-D or CRT-P	220 (11·8%)	222 (11·9%)	190 (8·0%)	164 (6·9%)

Lancet 2020; 396: 819–29

HF and diabetes

Based on these results, the SGLT inhibitors canagliflozin, dapagliflozin, empagliflozin, ertugliflozin or sotagliflozin are recommended to prevent HF and CV death and worsening kidney function in patients with type 2 diabetes and CV disease and/or CV risk factors, or CKD. Dapagliflozin and empagliflozin are also indicated for the treatment of patients with type 2 diabetes and HFrEF (see section 5.3.5 and section 11.2.4) and sotagliflozin was shown to reduce CV deaths and HF rehospitalizations in patients recently hospitalized for HF.[6,296,646,647,650]

Recommendations for the treatment of diabetes in heart failure

Recommendation	Class[a]	Level[b]
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with T2DM at risk of CV events to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death.[293–297]	I	A
SGLT2 inhibitors (dapagliflozin, empagliflozin, and sotagliflozin) are recommended in patients with T2DM and HFrEF to reduce hospitalizations for HF and CV death.[108,109,136]	I	A

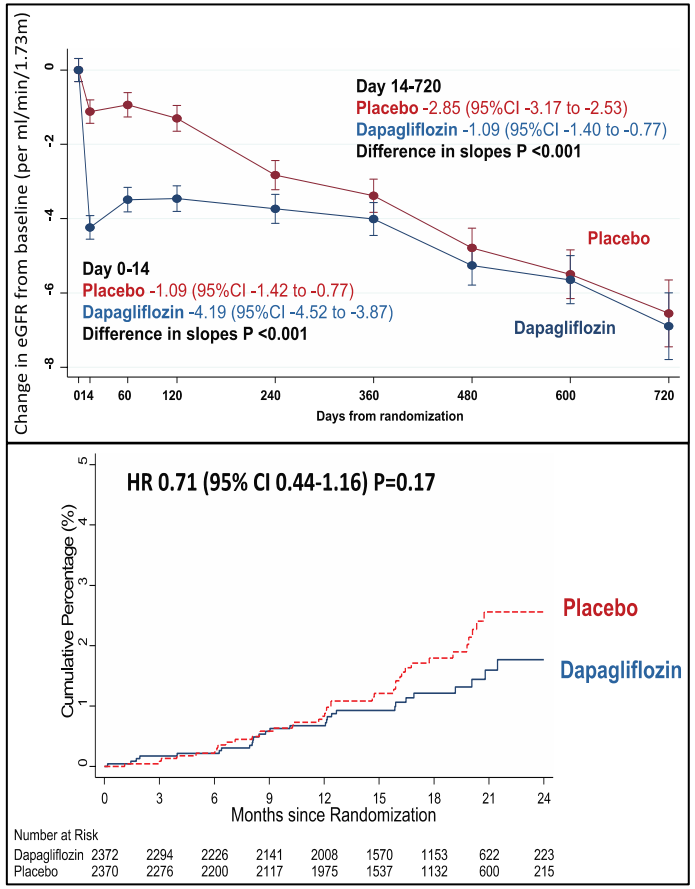
Circulation

ORIGINAL RESEARCH ARTICLE

Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction

Results of DAPA-HF

Pardeep S. Jhund, MBChB, MSc, PhD
⋮
John J.V. McMurray, MD

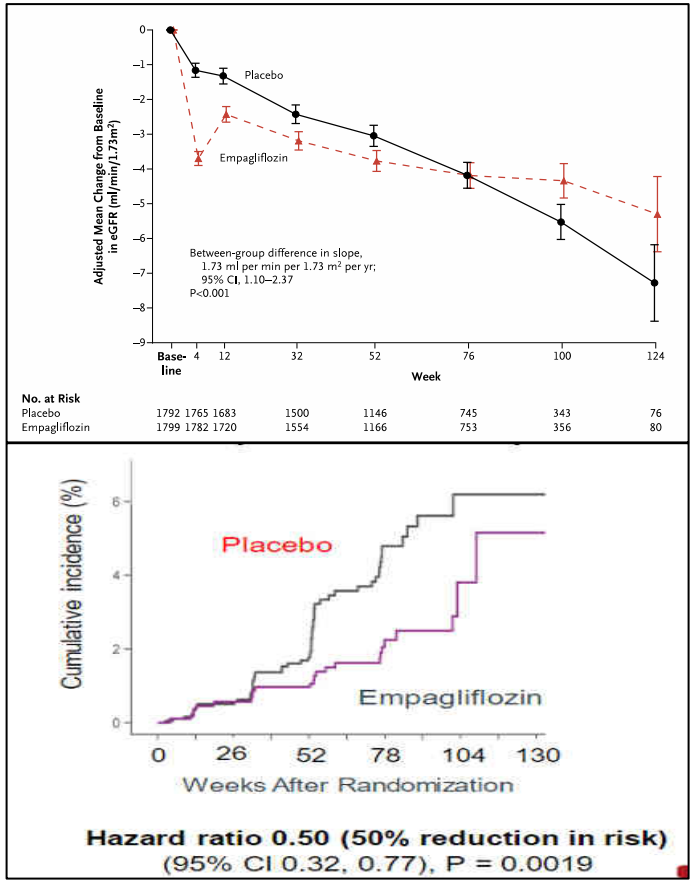


Circulation. 2021;143:298–309.

ORIGINAL ARTICLE

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

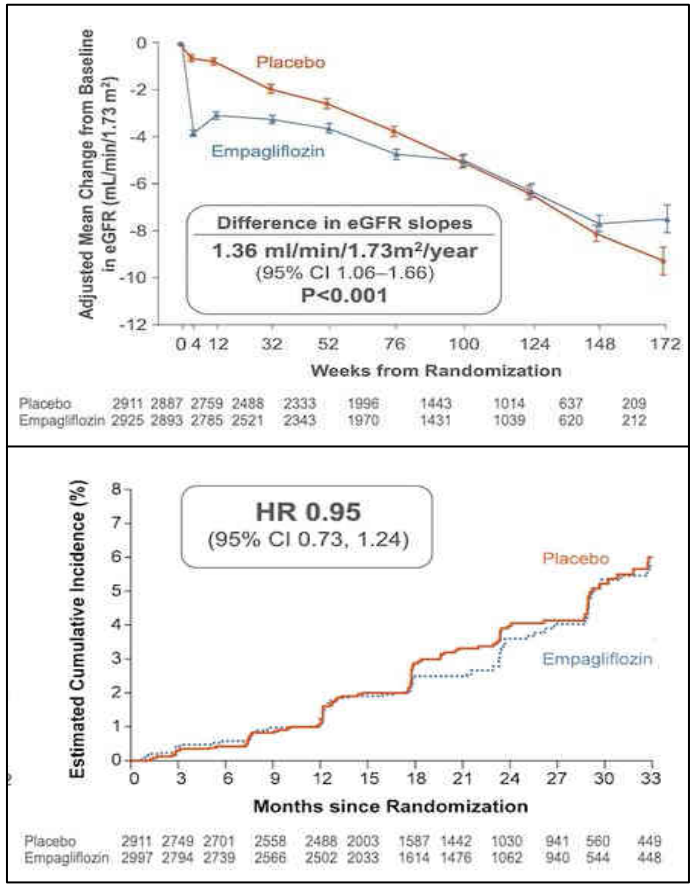


N Engl J Med 2020; 383:1413-1424

ORIGINAL ARTICLE

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Stefan D. Anker, Javed Butler, Gerasimos Filippatos, João P. Ferreira, Edimar Bocchi, Michael Böhm, Hans-Peter Brunner–La Rocca, Dong-Ju Choi, Vijay Chopra, Eduardo Chuquiure-Valenzuela, Nadia Giannetti, Juan Esteban Gomez-Mesa, et al., for the EMPEROR-Preserved Trial Investigators



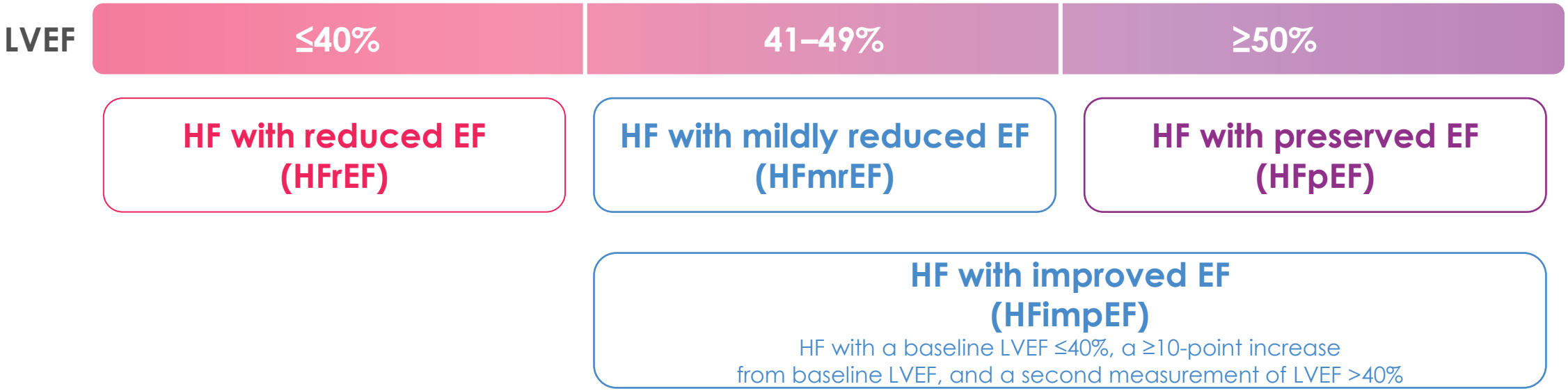
N Engl J Med 2021 Aug 27; [e-pub].

HF and CKD

CKD is a major independent determinant of increased mortality and morbidity in HF.[471,734–736] However, there are settings in which changes in serum creatinine are not associated with worse outcomes. When RAAS inhibitors, ARNI or SGLT2 inhibitors are started, the initial decrease in the glomerular filtration pressure may decrease GFR and increase serum creatinine. However, these changes are generally transient and occur despite improvement in patient outcomes and slower worsening of renal function in the long term. For instance, in EMPEROR-Reduced, the placebo-corrected eGFR dip induced by empagliflozin at week 4 was of 2.4 mL/min/1.73 m^2 for patients with CKD and 2.7 mL/min/1.73 m^2 for those without CKD, corresponding to a decrease from baseline of 5.2% and 3.8%, respectively. This was followed by a slower slope of eGFR decline and by a reduced rate of the composite kidney outcome with empagliflozin vs. placebo, with no difference between patients with or without CKD at baseline.[109,737]

impairment (eGFR <30 mL/min/1.73 m^2).[743] Sacubitril/valsartan, compared with enalapril, led to a slower decline in renal function, despite a slight increase in the urinary albumin/creatinine ratio, and improved CV outcomes to a similar extent in patients with CKD vs. the others in PARADIGM-HF.[127] SGLT2 inhibitors lead to a slower decline in renal function, compared with placebo, both in patients with HFrEF and in those with CKD.[108,109,737,738,744] The improve-

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



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

ORIGINAL ARTICLE FREE PREVIEW

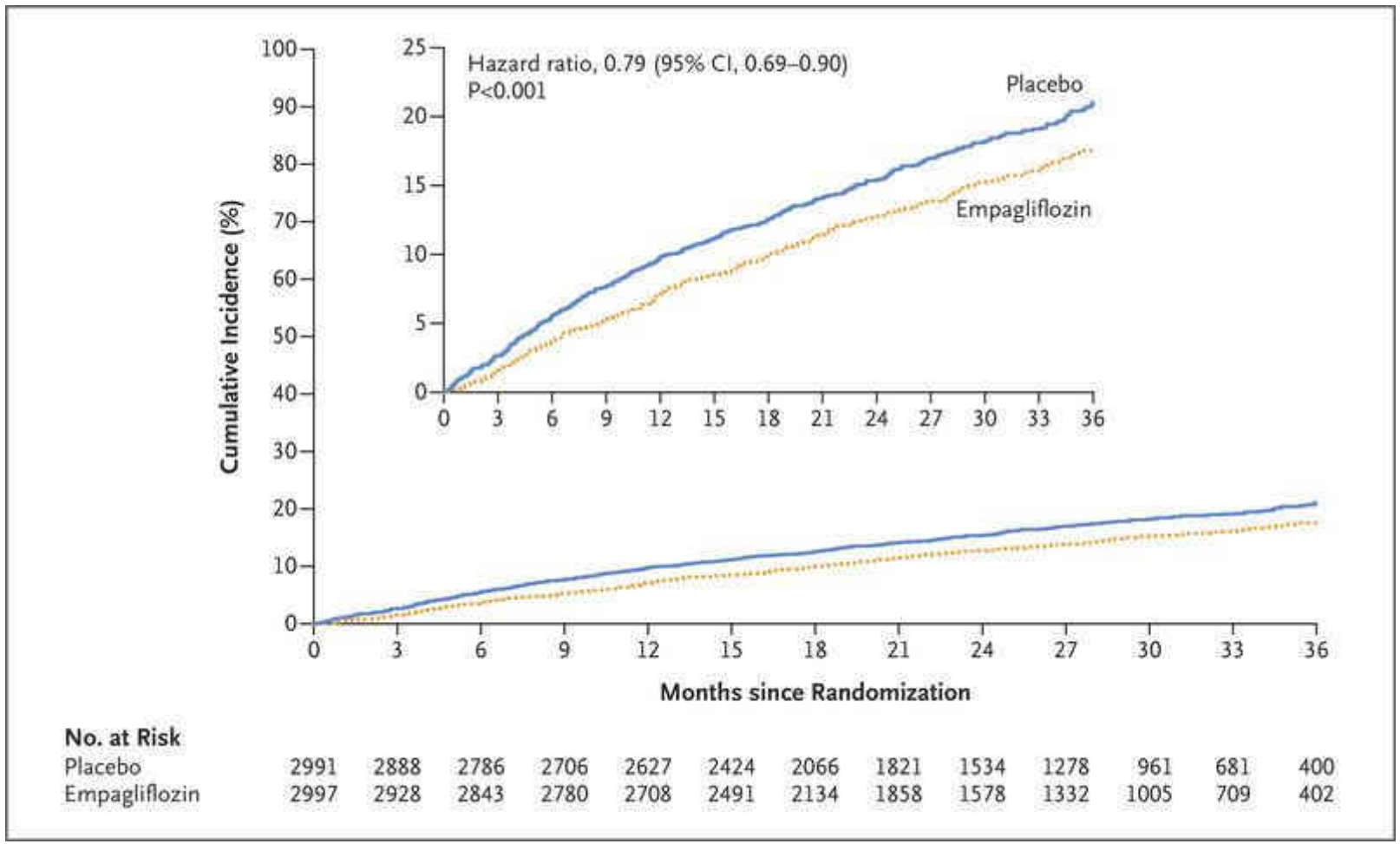
Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Stefan D. Anker, M.D., Ph.D., Javed Butler, M.D., Gerasimos Filippatos, M.D., Ph.D., João P. Ferreira, M.D., Edimar Bocchi, M.D., Michael Böhm, M.D., Ph.D., Hans-Peter Brunner–La Rocca, M.D., Dong-Ju Choi, M.D., Vijay Chopra, M.D., Eduardo Chuquiure-Valenzuela, M.D., Nadia Giannetti, M.D., Juan Esteban Gomez-Mesa, M.D., et al., for the EMPEROR-Preserved Trial Investigators*

METHODS In this double-blind trial, we randomly assigned 5988 patients with class II–IV heart failure and an ejection fraction of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.

RESULTS Over a median of 26.2 months, a primary outcome event occurred in 415 of 2997 patients (13.8%) in the empagliflozin group and in 511 of 2991 patients (17.1%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001). This effect was mainly related to a lower risk of hospitalization for heart failure in the empagliflozin group. The effects of empagliflozin appeared consistent in patients with or without diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001). Uncomplicated genital and urinary tract infections and hypotension were reported more frequently with empagliflozin.

CONCLUSIONS Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Preserved ClinicalTrials.gov number, NCT03057951).



August 27, 2021 DOI: 10.1056/NEJMoa2107038

ORIGINAL ARTICLE FREE PREVIEW

Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Stefan D. Anker, M.D., Ph.D., Javed Butler, M.D., Gerasimos Filippatos, M.D., Ph.D., João P. Ferreira, M.D., Edimar Bocchi, M.D., Michael Böhm, M.D., Ph.D., Hans-Peter Brunner–La Rocca, M.D., Dong-Ju Choi, M.D., Vijay Chopra, M.D., Eduardo Chuquiure-Valenzuela, M.D., Nadia Giannetti, M.D., Juan Esteban Gomez-Mesa, M.D., et al., for the EMPEROR-Preserved Trial Investigators*

Phase III trial* in patients with HFpEF

Aim: To investigate the safety and efficacy of empagliflozin versus placebo in patients with HF with **preserved ejection fraction**

Population: T2D and non-T2D, aged ≥18 years, chronic HF (NYHA class II–IV)

EMPEROR-Preserved
LVEF >40%

5988 patients

- Empagliflozin 10 mg OD
- Placebo

Median follow-up 26.2 months

COMPOSITE PRIMARY ENDPOINT

- **Time to first event of adjudicated CV death or adjudicated HHF**

CONFIRMATORY KEY SECONDARY ENDPOINTS

- **First and recurrent adjudicated HHF**
- **Slope of change in eGFR (CKD-EPI) from baseline**

*Randomized, double-blind, placebo-controlled trial.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OD, once daily; T2D, type 2 diabetes.
Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038

August 27, 2021 DOI: 10.1056/NEJMoa2107038

EMPEROR-Preserved: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria

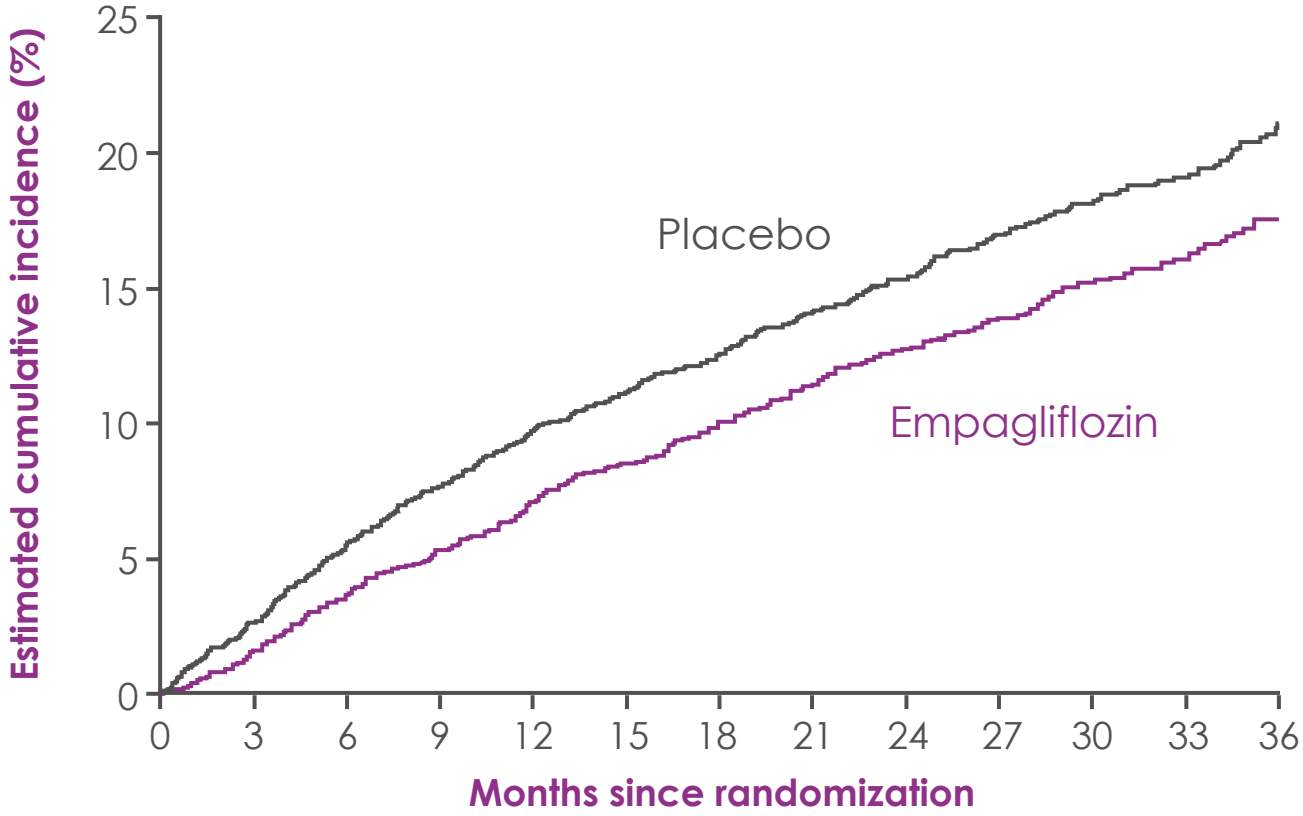
• Age ≥18 years
• Chronic HF NYHA class II–IV
• **LVEF >40%**
• **NT-proBNP:**
  • **>300 pg/mL** in patients without AF
  • **>900 pg/mL** in patients with AF
• **Structural changes in the heart** (increases in left atrial size or left ventricular mass) **or HHF within 12 months of screening**
	• MI, coronary artery bypass graft surgery or other major CV surgery, stroke or TIA ≤90 days before visit
	• Heart transplant recipient, or listed for heart transplant
	• Acute decompensated HF
	• SBP ≥180 mmHg at randomization
	• **Symptomatic hypotension and/or SBP <100 mmHg**
	• **eGFR <20 mL/min/1.73 m^2 or requiring dialysis**

Further criteria apply

AF, atrial fibrillation; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TIA, transient ischaemic attack.

Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038

Empagliflozin demonstrated a clinically meaningful 21% RRR in the composite primary endpoint of CV death or HHF



Patients at risk

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

RRR 21%

ARR 3.3%

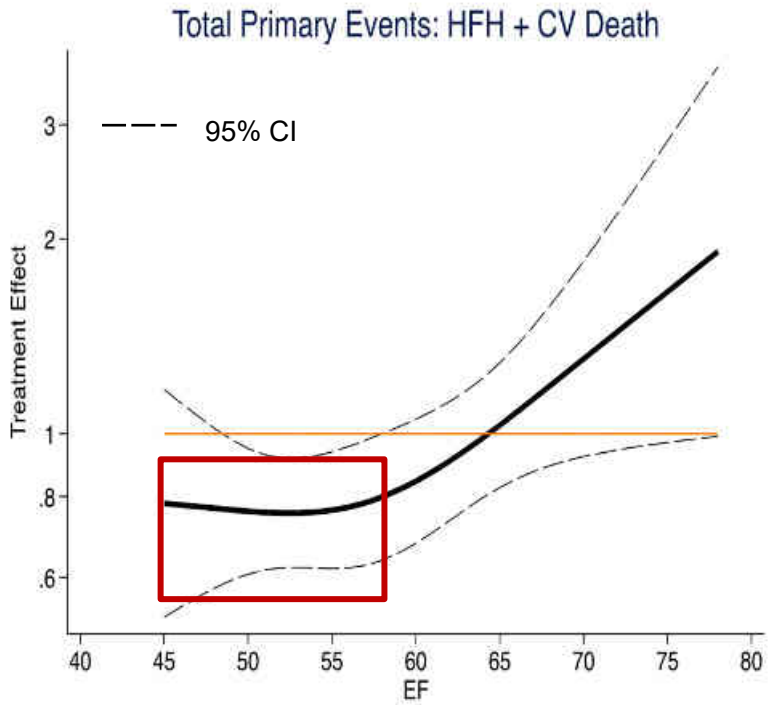
NNT*=31

HR: 0.79
(95% CI: 0.69, 0.90)
p<0.001

Empagliflozin:
415 (13.8%) patients with event
Rate: 6.9/100 patient-years
Placebo:
511 (17.1%) patients with event
Rate: 8.7/100 patient-years

*During a median trial period of 26 months. ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; NNT, number needed to treat; RRR, relative risk reduction. Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038.

Primary endpoint:
Treatment effect by ejection fraction



CI, confidence interval; CV, cardiovascular; EF, ejection fraction; HFH, hospitalization for heart failure; HFpEF, heart failure and preserved ejection fraction; LV, left ventricular

1. Data on file

EMPEROR-Preserved: Characteristics of patients at baseline (2 of 4)

	Empagliflozin (n=2997)	Placebo (n=2991)
NYHA functional class, n (%)		
Class I	3 (0.1)	1 (<0.1)
Class II	2432 (81.1)	2451 (81.9)
Class III	552 (18.4)	531 (17.8)
Class IV	10 (0.3)	8 (0.3)
BMI, kg/m^2	29.77±5.8	29.90±5.9
Heart rate, bpm	70.4±12.0	70.3±11.8
Systolic BP, mmHg	131.8±15.6	131.9±15.7
LVEF, %	54.3±8.8	54.3±8.8
>40 to <50%, n (%)	995 (33.2)	988 (33.0)
≥50 to <60%, n (%)	1028 (34.3)	1030 (34.4)
≥60%, n (%)	974 (32.5)	973 (32.5)

Values are mean ± standard deviation unless stated otherwise.
BMI, body mass index; BP, blood pressure; bpm, beats per minute; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038;

EMPEROR-Preserved: Characteristics of patients at baseline (3 of 4)

	Empagliflozin (n=2997)	Placebo (n=2991)
NT-proBNP, median (IQR), pg/mL	994 (501, 1740)	946 (498, 1725)
Aetiology of HF, n (%)		
Ischaemic	1079 (36.0)	1038 (34.7)
Non-ischaemic	1917 (64.0)	1953 (65.3)
CV history, n (%)		
HHF <12 months	699 (23.3)	670 (22.4)
Atrial fibrillation	1543 (51.5)	1514 (50.6)
Diabetes mellitus	1466 (48.9)	1472 (49.2)
Hypertension	2721 (90.8)	2703 (90.4)

CV, cardiovascular; HF, heart failure; HHF, hospitalization for heart failure; IQR, interquartile range; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.
Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038

EMPEROR-Preserved: Characteristics of patients at baseline (4 of 4)

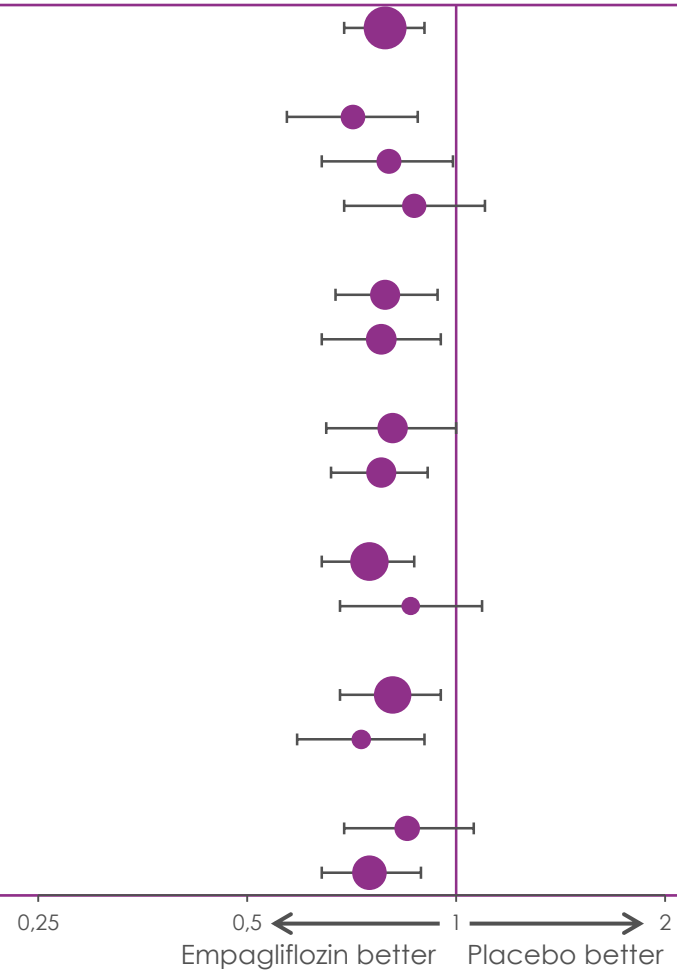
	Empagliflozin (n=2997)[1]	Placebo (n=2991)[1]
eGFR, mL/min/1.73 m^2, mean [SD]	60.6±19.8	60.6±19.9
<60 mL/min/1.73 m^2, n (%)	1504/2997 (50.2)	1484/2989 (49.6)
CV medications, n (%)		
RAASi ± neprilysin inhibitor*	2428 (81.0)	2404 (80.4)
MRA	1119 (37.3)	1125 (37.6)
Beta blocker	2598 (86.7)	2569 (85.9)
Digitalis glycosides	293 (9.8)	263 (8.8)
Aspirin	1240 (41.4)	1272 (42.5)
Statins	2042 (68.1)	2089 (69.8)

*2% of patients in EMPEROR-Preserved were receiving ARNI at baseline.[2]
ARNI, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor; SD, standard deviation

1. Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038; 2. Anker S *et al. Eur J Heart Fail*. 2020;22:2383.

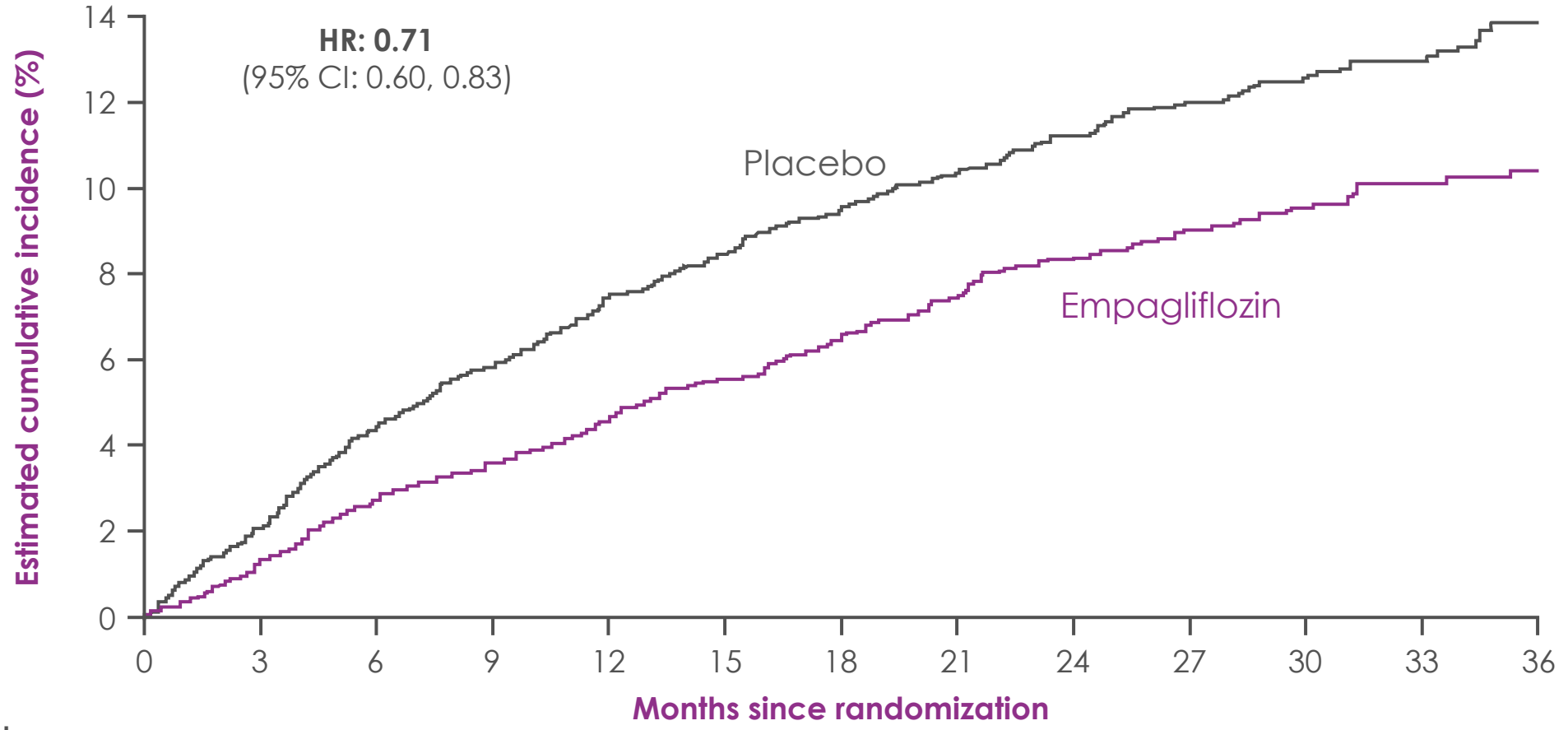
EMPEROR-Preserved: Primary endpoint
Subgroup analysis (2 of 3)

	Empagliflozin	Placebo	HR (95% CI)
	n with event/N analysed		
Overall	415/2997	511/2991	0.79 (0.69, 0.90)
Baseline LVEF			
<50%	145/995	193/988	0.71 (0.57, 0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64, 0.99)
≥60%	132/974	145/973	0.87 (0.69, 1.10)
Baseline diabetes status			
Diabetes	239/1466	291/1472	0.79 (0.67, 0.94)
No diabetes	176/1531	220/1519	0.78 (0.64, 0.95)
Baseline eGFR (CKD-EPI)			
≥60 mL/min/1.73 m²	152/1493	189/1505	0.81 (0.65, 1.00)
<60 mL/min/1.73 m²	263/1504	321/1484	0.78 (0.66, 0.91)
Baseline NYHA class			
II	275/2435	361/2452	0.75 (0.64, 0.87)
III/IV	140/562	150/539	0.86 (0.68, 1.09)
HF hospitalization in ≤12 months			
No	258/2298	319/2321	0.81 (0.68, 0.95)
Yes	157/699	192/670	0.73 (0.59, 0.90)
Cause of HF			
Ischaemic	157/1079	177/1038	0.85 (0.69, 1.06)
Non-ischaemic	258/1917	334/1953	0.75 (0.64, 0.89)



See slide notes for abbreviations. Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038.

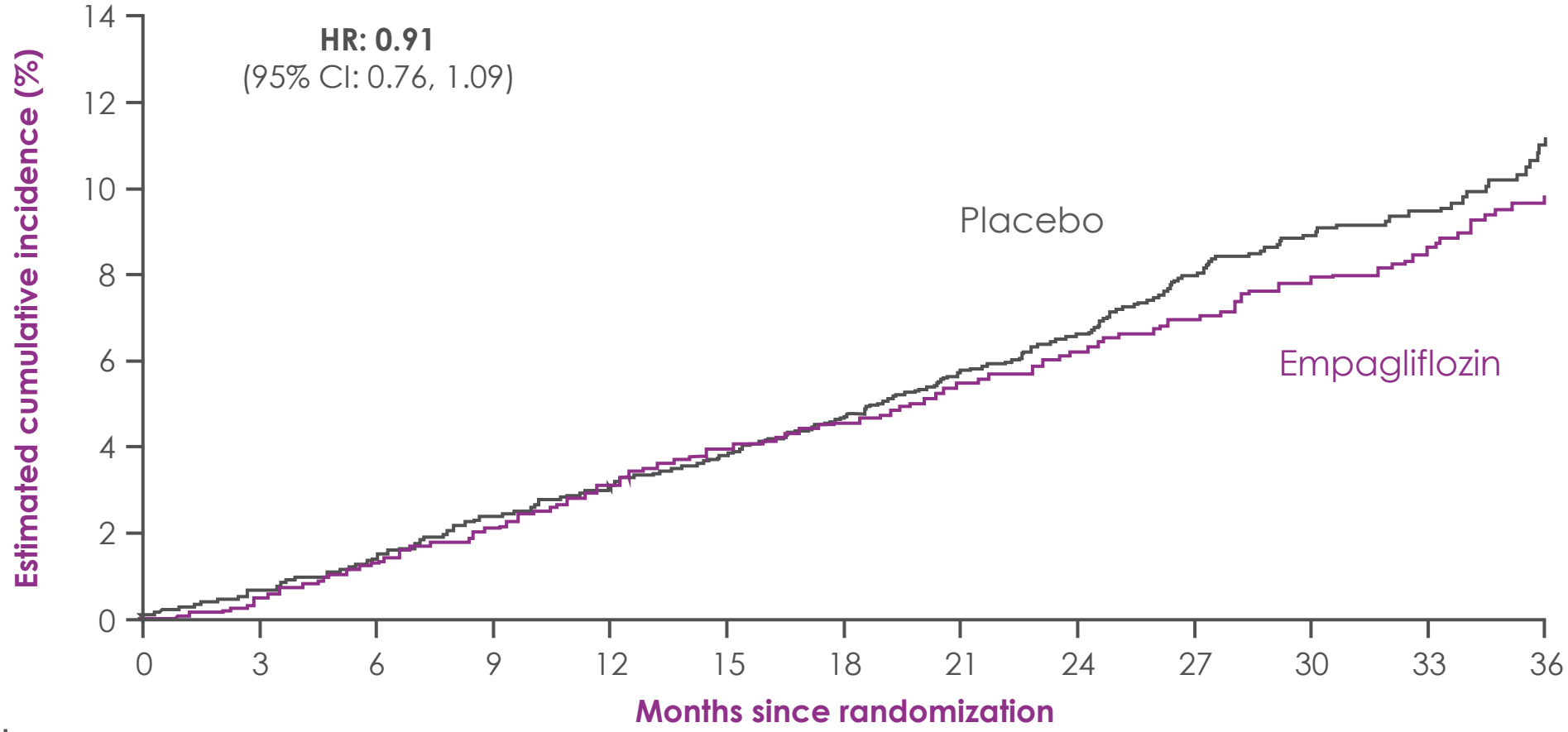
EMPEROR-Preserved: First hospitalizations for HF



Patients at risk													
Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

CI, confidence interval; HF, heart failure; HR, hazard ratio.
Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038.

EMPEROR-Preserved: Cardiovascular death



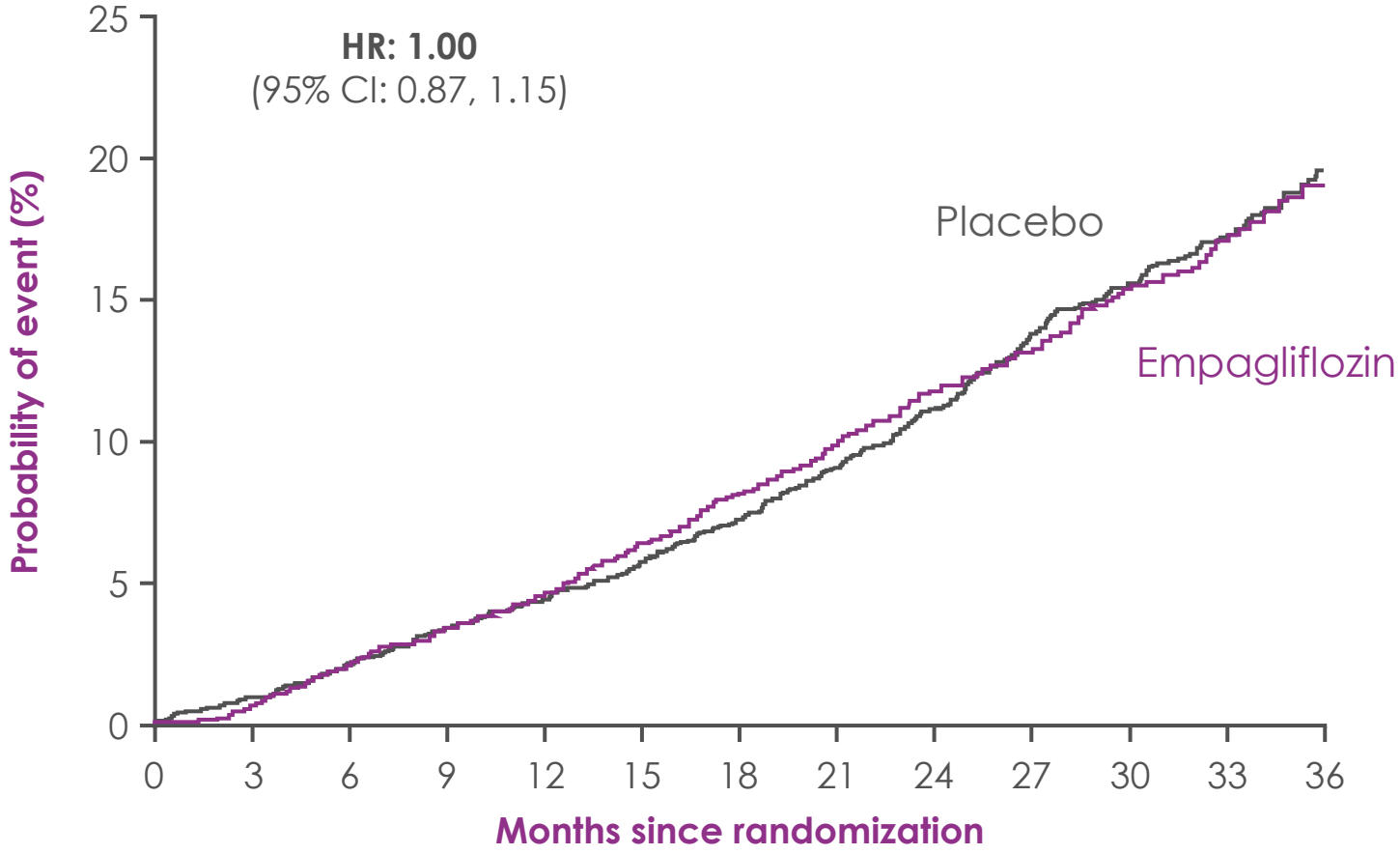
Patients at risk

Placebo	2991	2960	2923	2883	2849	2656	2302	2046	1738	1459	1107	781	471
Empagliflozin	2997	2974	2930	2891	2847	2641	2287	2022	1725	1469	1118	794	462

CI, confidence interval; HR, hazard ratio.

Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038.

EMPEROR-Preserved: All-cause mortality

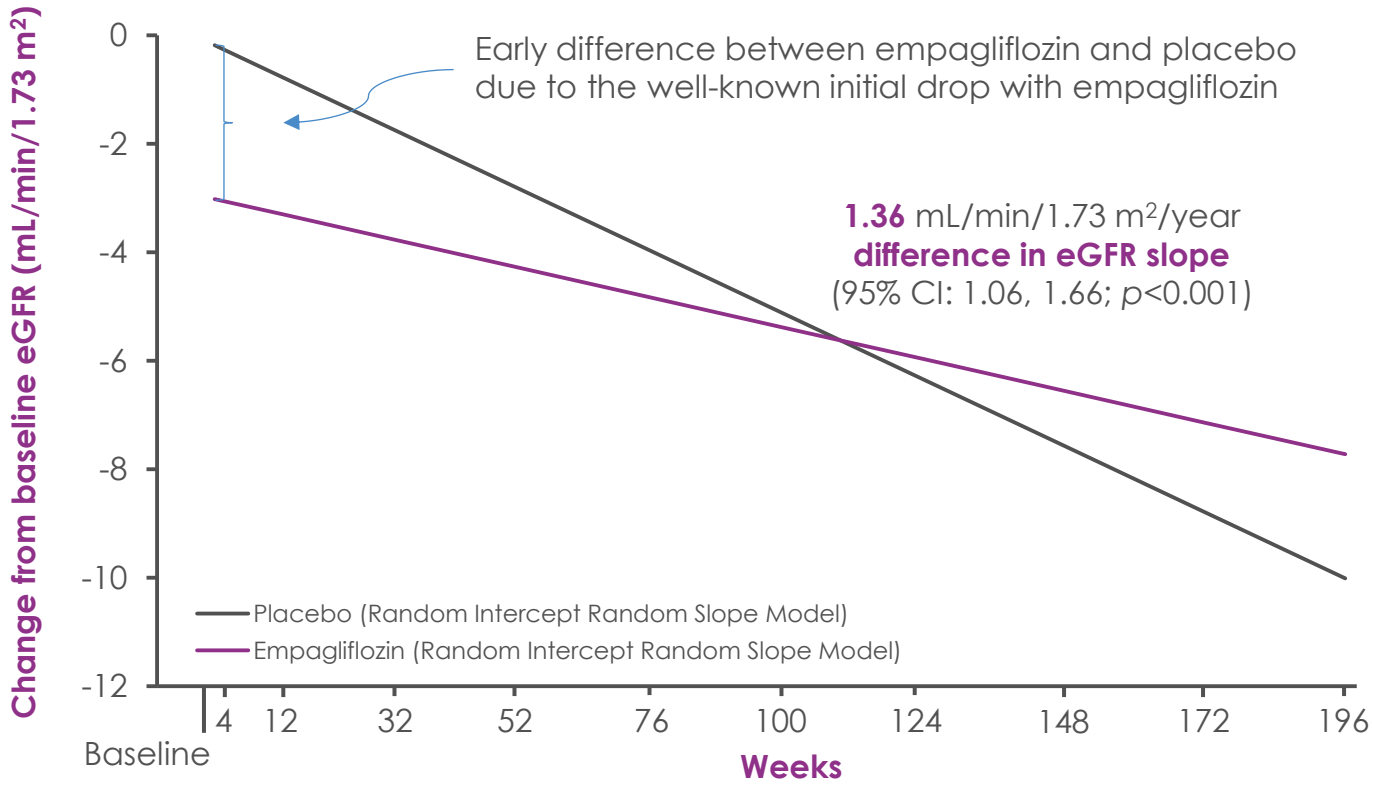


Patients at risk													
Placebo	2991	2960	2923	2883	2849	2656	2302	2046	1738	1459	1107	781	471
Empagliflozin	2997	2974	2930	2891	2847	2641	2287	2022	1725	1469	1118	794	462

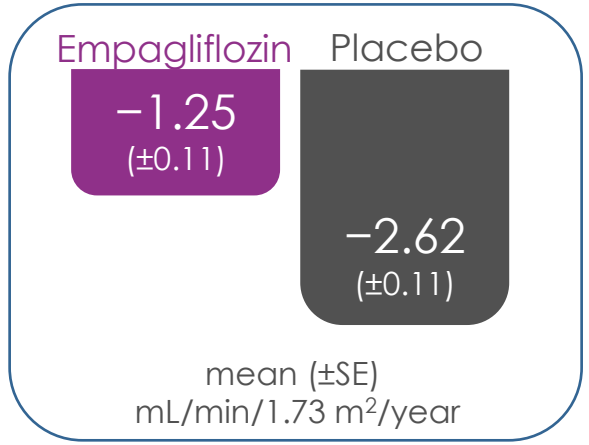
CI, confidence interval; HR, hazard ratio.

Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038.

Empagliflozin protected the kidney by significantly slowing the decline in kidney function

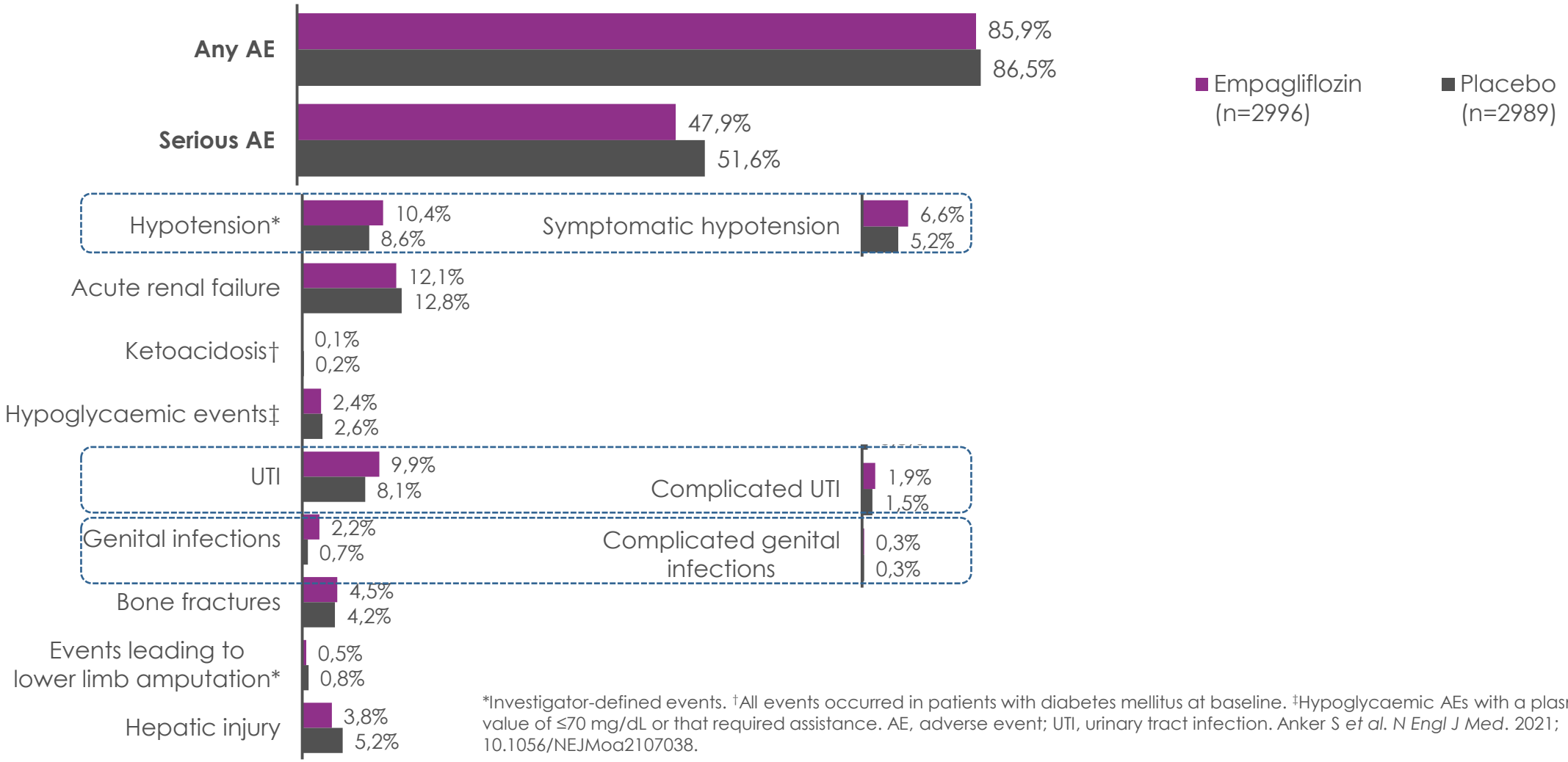


The rate of eGFR decline in patients treated with empagliflozin was half that of patients treated with placebo



eGFR slope = rate of decline (and is a measure for long-term renal function). eGFR slope is analysed based on on-treatment data using a random coefficient model including age, baseline eGFR and baseline LVEF as linear covariates and sex, region, baseline diabetes status, and baseline by time and treatment by time interactions as fixed effects; the model allows for randomly varying slope and intercept between patients.
eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; SE, standard error.
Developed from data reported in Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038.

EMPEROR-Preserved: Selected adverse events of interest



*Investigator-defined events. †All events occurred in patients with diabetes mellitus at baseline. ‡Hypoglycaemic AEs with a plasma glucose value of ≤70 mg/dL or that required assistance. AE, adverse event; UTI, urinary tract infection. Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038.

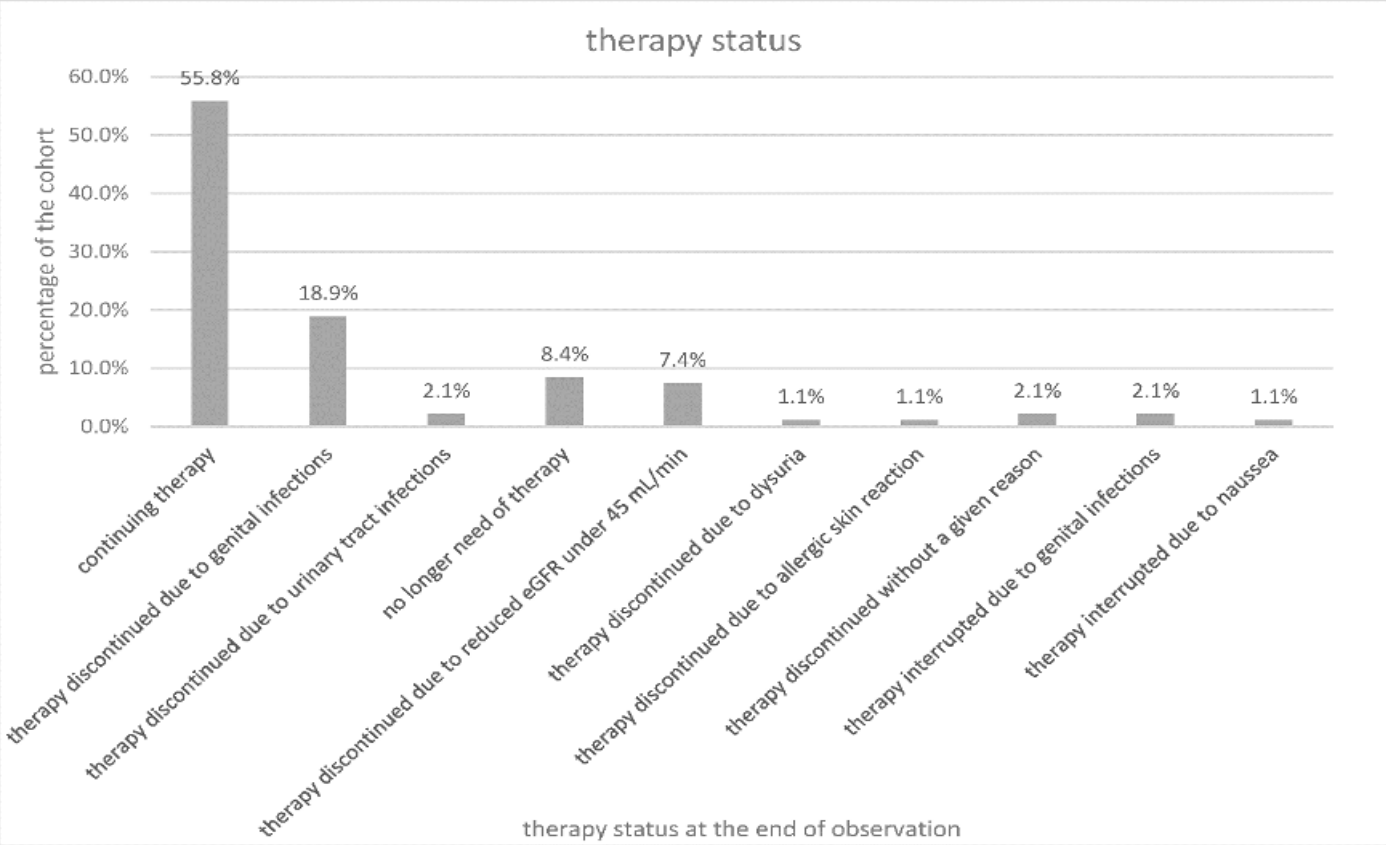
Journal of Clinical Medicine

MDPI

Article

Effectiveness and Safety of SGLT2 Inhibitors in Clinical Routine Treatment of Patients with Diabetes Mellitus Type 2

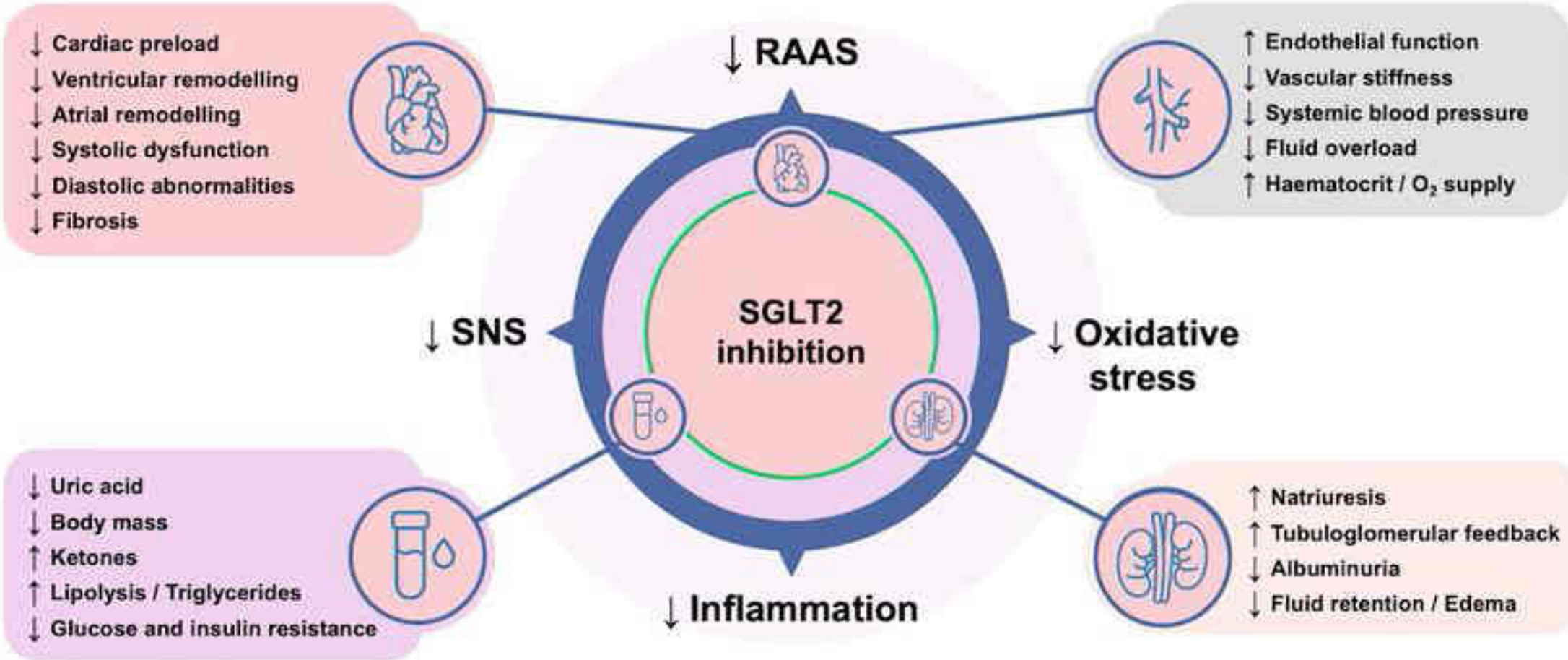
Maximilian Hopf [1], Christof Kloos [1], Gunter Wolf [1], Ulrich Alfons Müller [2] and Nicolle Müller [1,*]



95 patients
Mean follow-up: 1.2 years

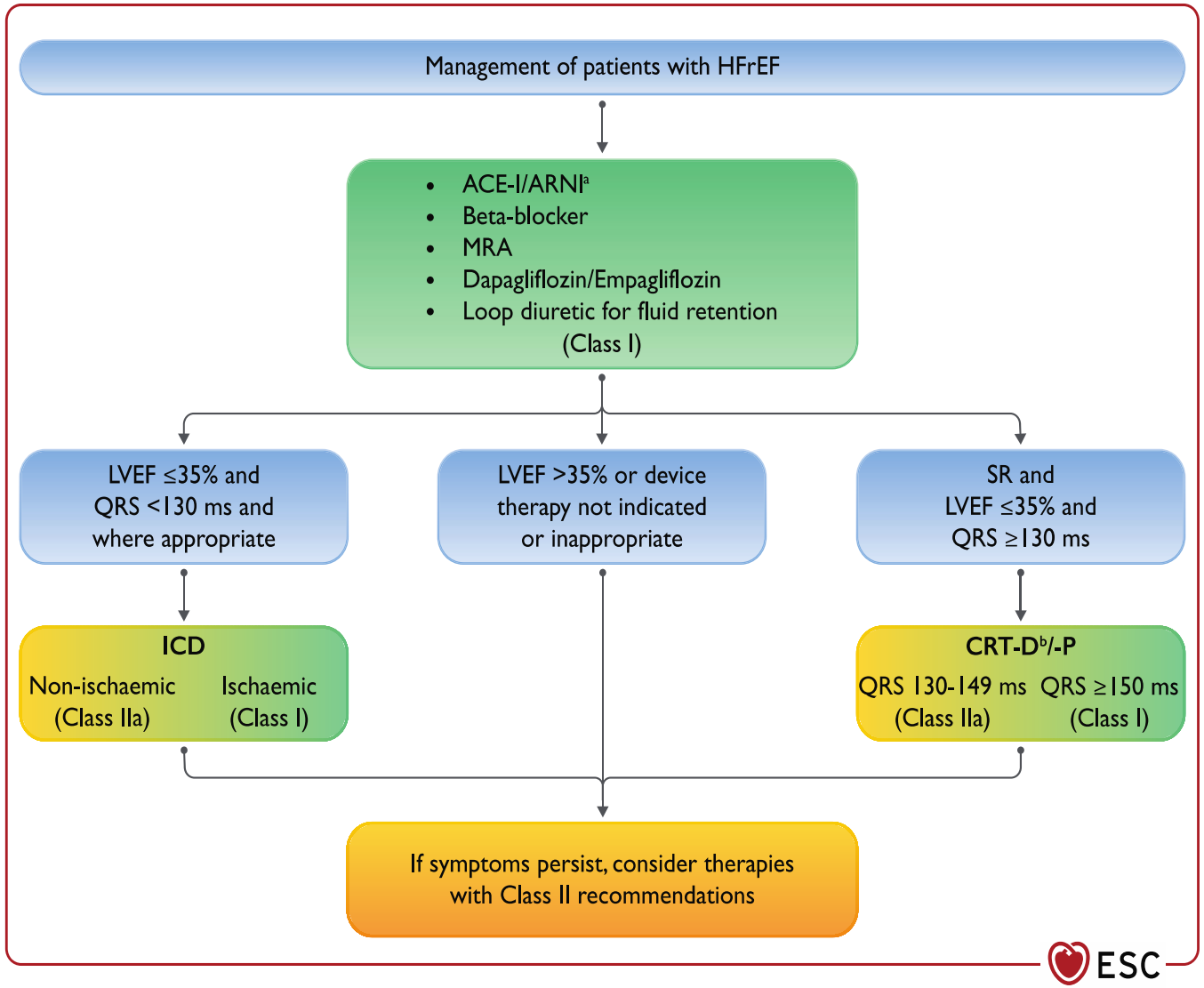
DOI: 10.3390/jcm10040571

Direct and indirect actions of SGLT2 inhibitors are likely to produce CRM benefits[1–5]



ATP, adenosine triphosphate; CRM, cardiovascular, renal and metabolic; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

1. Givens RC, Schulze PC. Molecular changes in heart failure. In: Eisen H, ed. Heart Failure: A Comprehensive Guide to Pathophysiology and Clinical Care. London: Springer Verlag; 2017:1–26. 2. Ronco C et al. J Am Coll Cardiol. 2008;52:1527. 3. Santos-Ferreira D et al. Cardiology. 2020;145:311–20. 4. Cowie M, Fisher M. Nat Rev Cardiol. 2020;17:761–72. 5. Scheen AJ. Nat Rev Endocrinol. 2020;16:556–77.



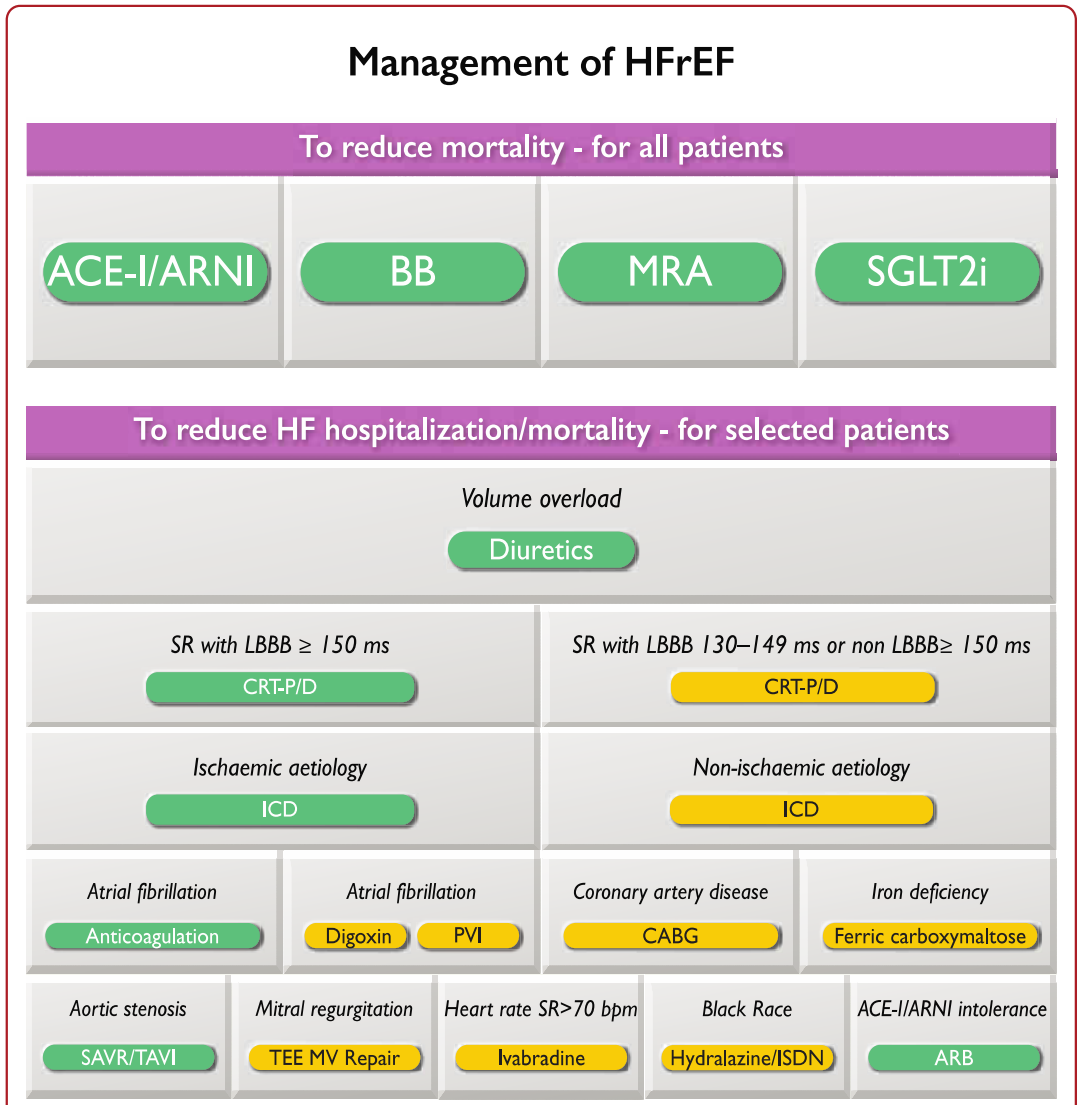
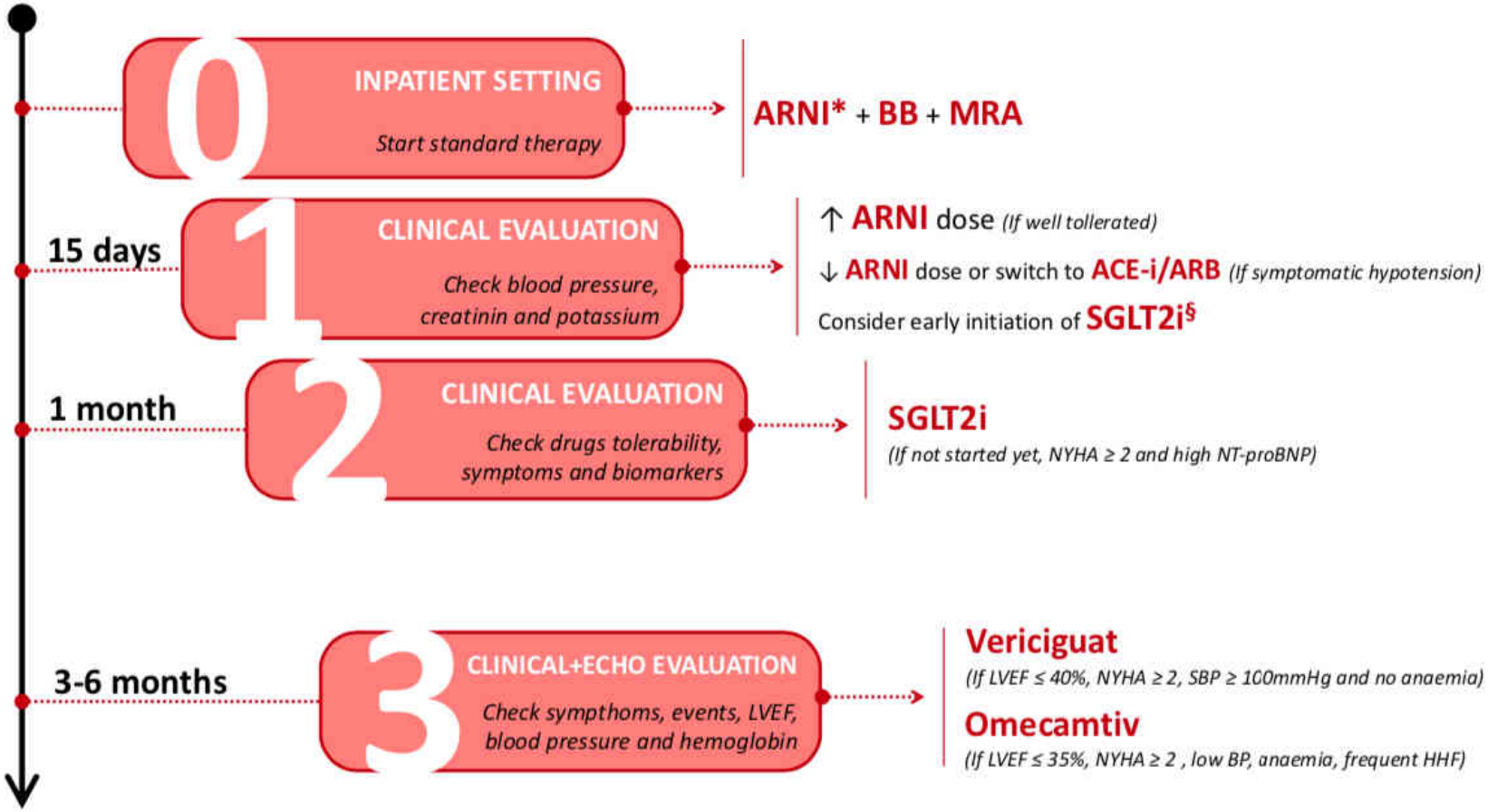


Figure 2 Therapeutic algorithm of Class I Therapy Indications for a patient with heart failure with reduced ejection fraction. ACE-I = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; ICD = implantable cardioverter-defibrillator; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; QRS = Q, R, and S waves (on a 12-lead electrocardiogram); SR = sinus rhythm. [a]As a replacement for ACE-I. [b]Where appropriate. Class I = green. Class IIa = Yellow.

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–128
doi:10.1093/eurheartj/ehab368

European Journal of Internal Medicine

COMBINING NEW CLASSES OF DRUGS FOR HFrEF: FROM TRIALS TO CLINICAL PRACTICE



*ARNI should be withheld in favour of ACEi/ARBs in case of persisting low blood pressure with hypotension events during the hospitalization.
§SGLT2i may be considered preferentially in patients not tolerating ARNi.

Sinagra et al. Eur J Int Med, 2021

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–3
doi:10.1093/eurheartj/ehab187

CARDIOPULSE

The impossible interviews—Sherlock Holmes interviews David Sackett: 'how much can we trust the guidelines?'

Claudio Rapezzi[1,2]*, Gianfranco Sinagra[3], Marco Merlo[3], and Roberto Ferrari [1,2]

Table 1 Pros and cons of the clinical guidelines

Six good reasons why we should not follow guidelines

1. They focus on the disease rather than on the patient.
2. Their recommendations are based more often on expert opinions than on solid EBM.
3. They usually refer to studies conducted on relatively young patients with a low comorbidity burden.
4. They deter individual reasoning and suppress the deductive element of diagnostic decision-making in the individual patient.
5. They attenuate scientific curiosity and the motivation for further research by shifting attention from what we (still) don't know to what we know (consolidated evidence).
6. They are the product of a 'lobby' of authors, often with strong links with pharmaceutical or biomedical companies.

Six good reasons why we should use the guidelines

1. They are an exceptional tool summarizing the latest published research.
2. They provide a useful 'checklist' of possible treatments to consider in the individual patient.
3. They explain the general rationale behind each diagnosis.
4. They outline the principles and steps for making diagnostic and therapeutic decisions.
5. They promote a more rational use of economic resources.
6. They provide a convenient line of defense in the event of malpractice charges.