SESSION 3
Treatments and Guidelines for HFrEF

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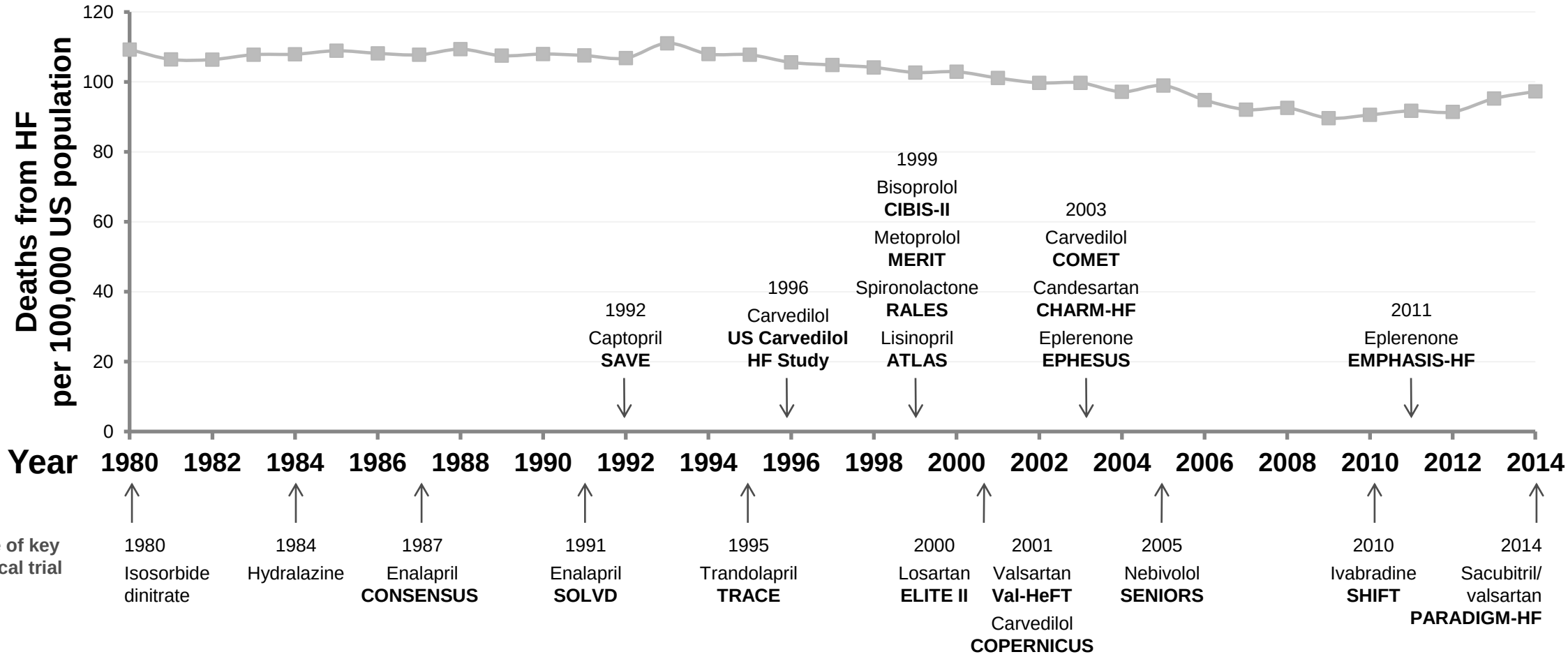
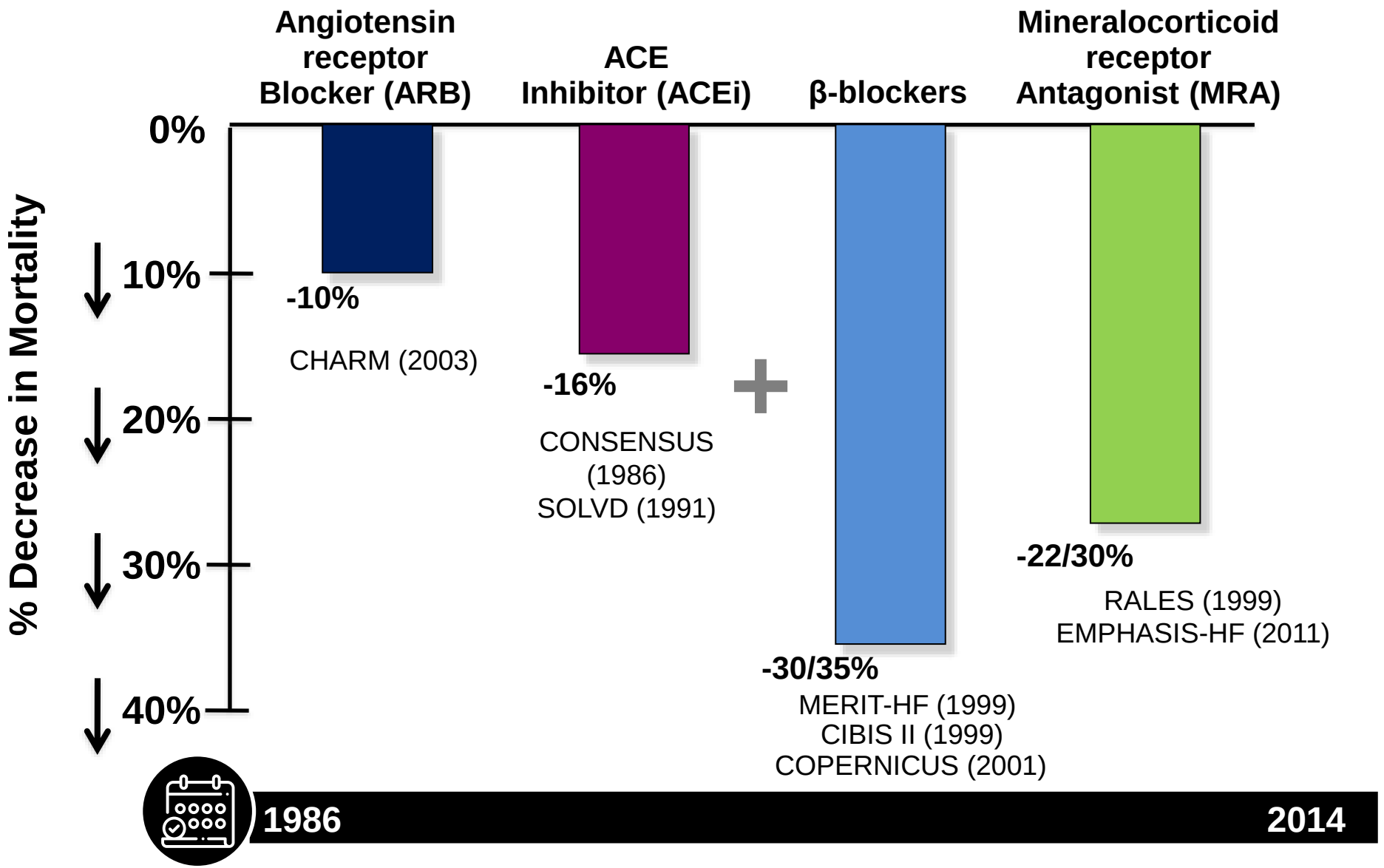
HF Mortality Has Declined Over Time but Remains High Despite an Increased Number of Available Therapies[1-5]



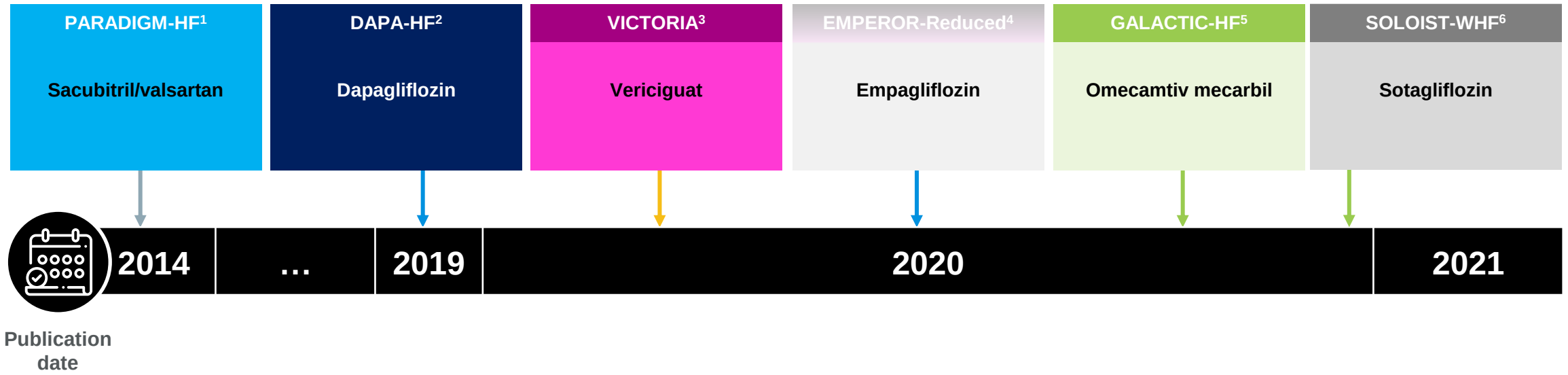
HF=heart failure; HFrEF=heart failure with reduced ejection fraction.

1. National Heart, Lung, and Blood Institute. Fact Book: Fiscal Year 2012. https://www.nhlbi.nih.gov/files/docs/factbook/FactBook2012.pdf. Accessed April 8, 2019. 2. US population by year. Multpl website. http://www.multpl.com/united-states-population/table. Accessed April 8, 2019. 3. Lewis KS et al. *Handb Exp Pharmacol*. 2017;243:1-14. 4. Franciosa JA et al. *Am J Cardiol*. 1980;45(3):648-654. 5. Conradson TB et al. *Am Heart J*. 1984;108(4, Pt 1):1001-1006.

RCTs in HFrEF: in 30 yrs Progressive Benefit Increased, Mainly when ACEi/ARB were Added to β-blockers & MRA



…but Huge Improvements were Achieved in the Last 6 yrs by Means Seminal RCTs!



ARNi, angiotensin receptor–neprilysin inhibitor; CV, cardiovascular; EU, European Union; HF, heart failure; HFH, heart failure hospitalisation; HFrEF, heart failure reduced ejection fraction; IV, intravenous; LVEF, left ventricular ejection fraction; sGC, soluble guanylate cyclase; SGLT1/2i, sodium–glucose cotransporter 1/2 inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor

1. McMurray JJV et al. *N Engl J Med.* 2014;371:993–1004; 2. McMurray JJV, et al. *N Engl J Med.* 2019;381:1995–2008; 3. Armstrong PW et al. *N Engl J Med.* 2020;382:1883–1893; 4. Packer M et al. *N Engl J Med*. 2020;383:1413–1424; 5. Teerlink JR et al. *Eur J Heart Fail.* 2020. doi:10.1002/ejhf.2015; 6. Bhatt DL, *et al*. *N Engl J Med* 2020; doi: 10.1056/NEJMoa2030183 [Epub ahead of print]; 7. FDA news release. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-type-heart-failure; 8. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/forxiga-1 [accessed November 2020]; 9. Seferović PM et al. *Eur J Heart Fail*. 2020;22:1984–1986; 10. https://www.astrazeneca.com/media-centre/press-releases/2020/forxiga-approved-in-the-eu-for-heart-failure.html [accessed 5 Nov 2020]

Emerging Therapies and Targets in HFrEF

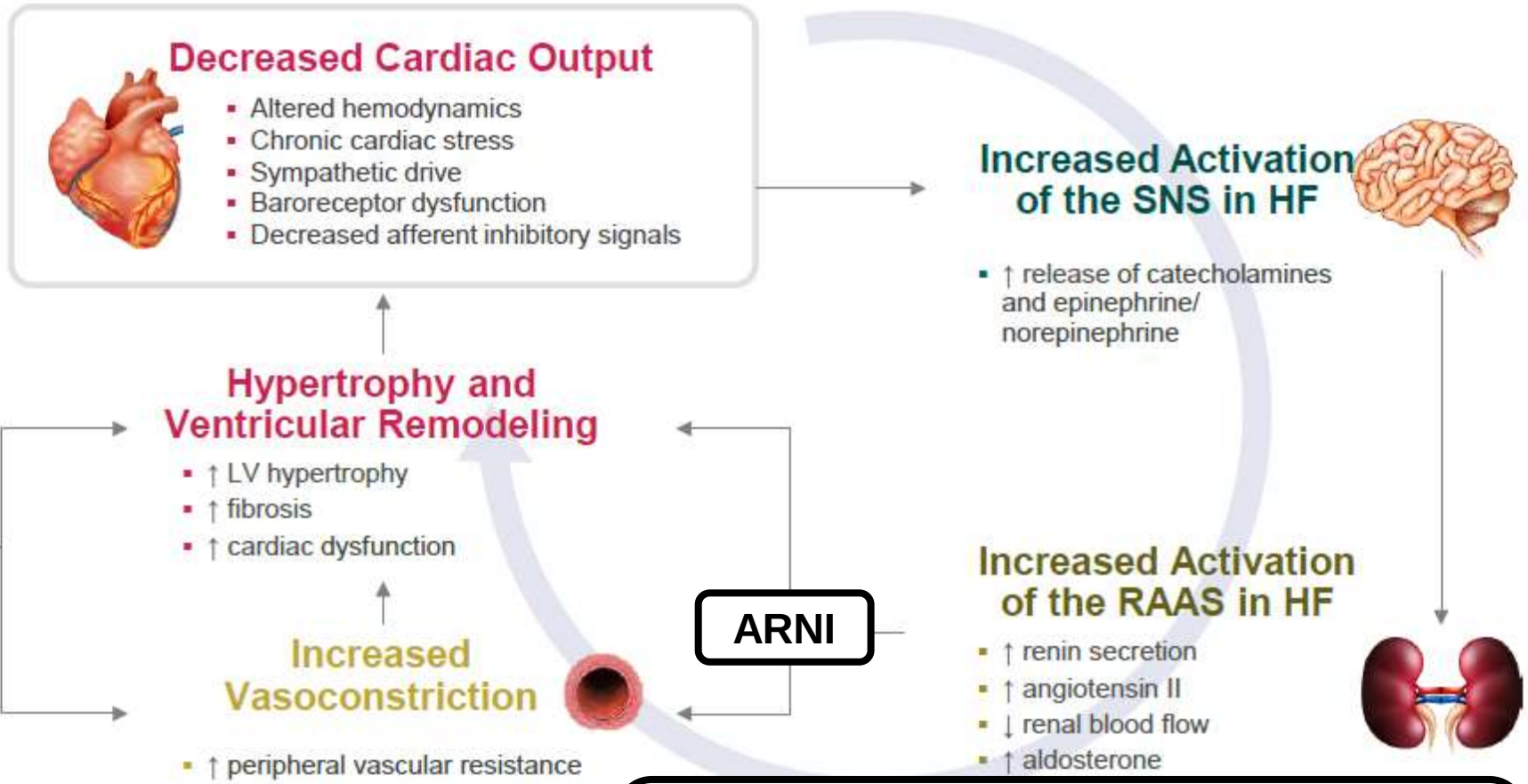
ARNI
sacubitril/valsartan:
PARADIGM-HF[1] (2014)

Endothelial Dysfunction

Impaired Signaling of the NO-sGC-cGMP Pathway

Increased oxidative stress leads to
- ↓ NO bioavailability
- ↓ sGC sensitivity and stimulation
- ↓ cGMP

sGC stimulator
vericiguat:
VICTORIA[3] (2020)



SGLT2i
dapaglifozin: DAPA-HF[2] (2019)
empaglifozin: EMPEROR-Reduced[4] (2020)
sotaglifozin: SOLOIST- WHF[6] (2020)

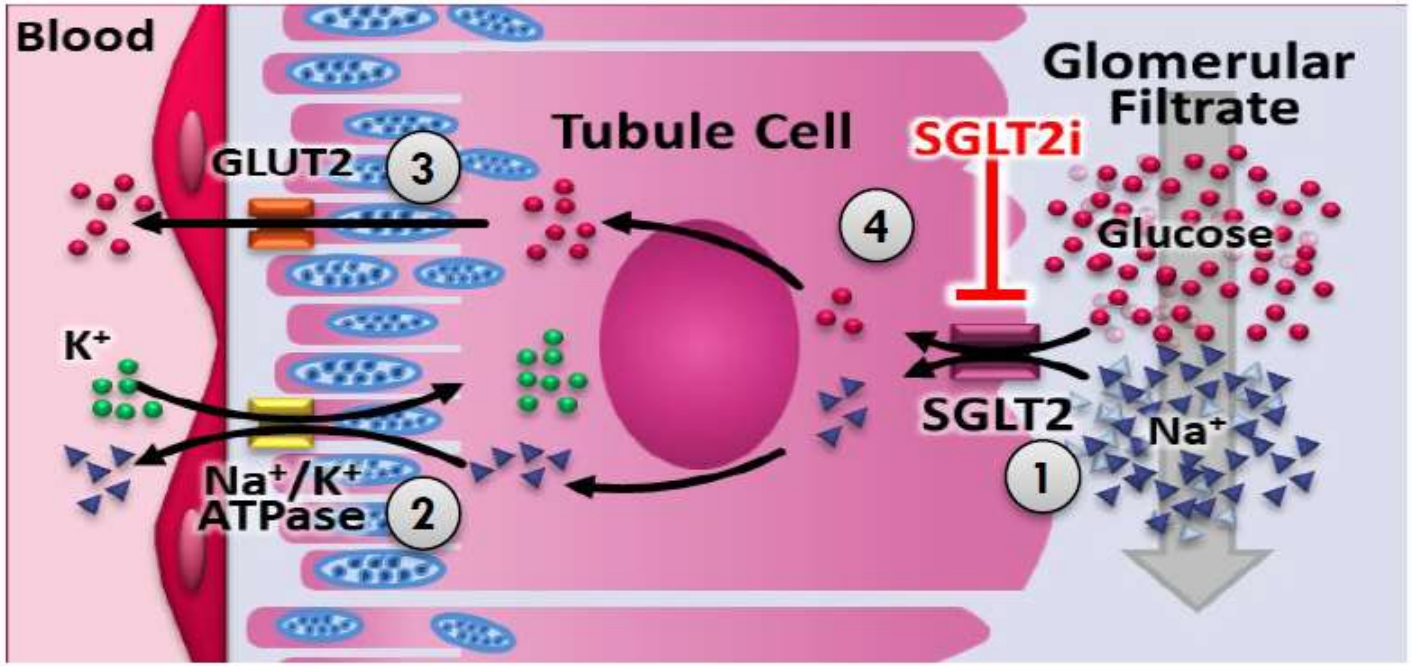
1. McMurray JJV et al. *N Engl J Med* 2014; 2. McMurray JJV et al. *N Engl J Med* 2019; 3. Armstrong PW et al. *N Engl J Med* 2020; 4. Packer M et al. *N Engl J Med* 2020; 5. Teerlink JT et al. *N Engl J Med* 2020; 6. Bhatt ML et al . *N Engl J Med* 2020

Emerging Treatment Strategies for HFrEF

- ARNI: sacubitril/valsartan
- **SGLT2 inhibitors:**
  - **Dapaglifozin**
  - Empaglifozin
  - Sotaglifozin
- Cardiac myosin activator: omecamtiv mecarbil
- Targeting the NO-sGC-cGMP Pathway in Heart Failure
  - sGC stimulator: vericiguat

Sodium GLucose coTransporter 2 inhibitors (SGLT2i) Prevent the Reabsorption of Glucose and Sodium in the Glomerular Filtrate

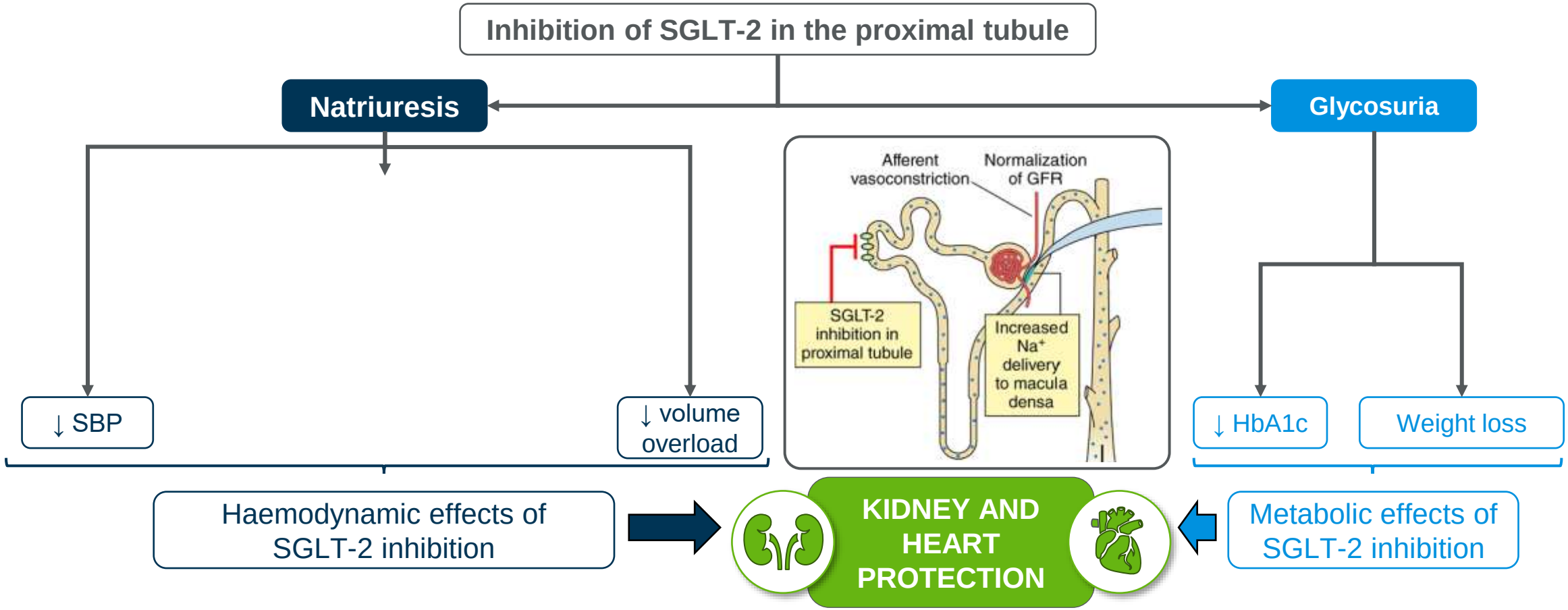
- **SGLT2** is a high-capacity, low-affinity transporter that accounts for 90% of the reabsorbed glucose from the glomerular filtrate back into circulation[1]
- Residual glucose is reabsorbed by **SGLT1**, a low-capacity, high-affinity transporter[1]
- **SGLT2 inhibitors (SGLT2i)** are a class of **antihyperglycemic medication** for the treatment of **type 2 diabetes:** they inhibit the physiological reabsorption of glucose in the kidneys resulting in excretion of glucose in the urine[1]



Currently under investigation in Phase 3 trials are **dapagliflozin** (HFrEF/HFpEF) and **empagliflozin** (HFrEF/HFpEF) from the SGLT2i class, and **sotagliflozin** (T2DM+HFrEF) from the SGLT1/2i class[2]

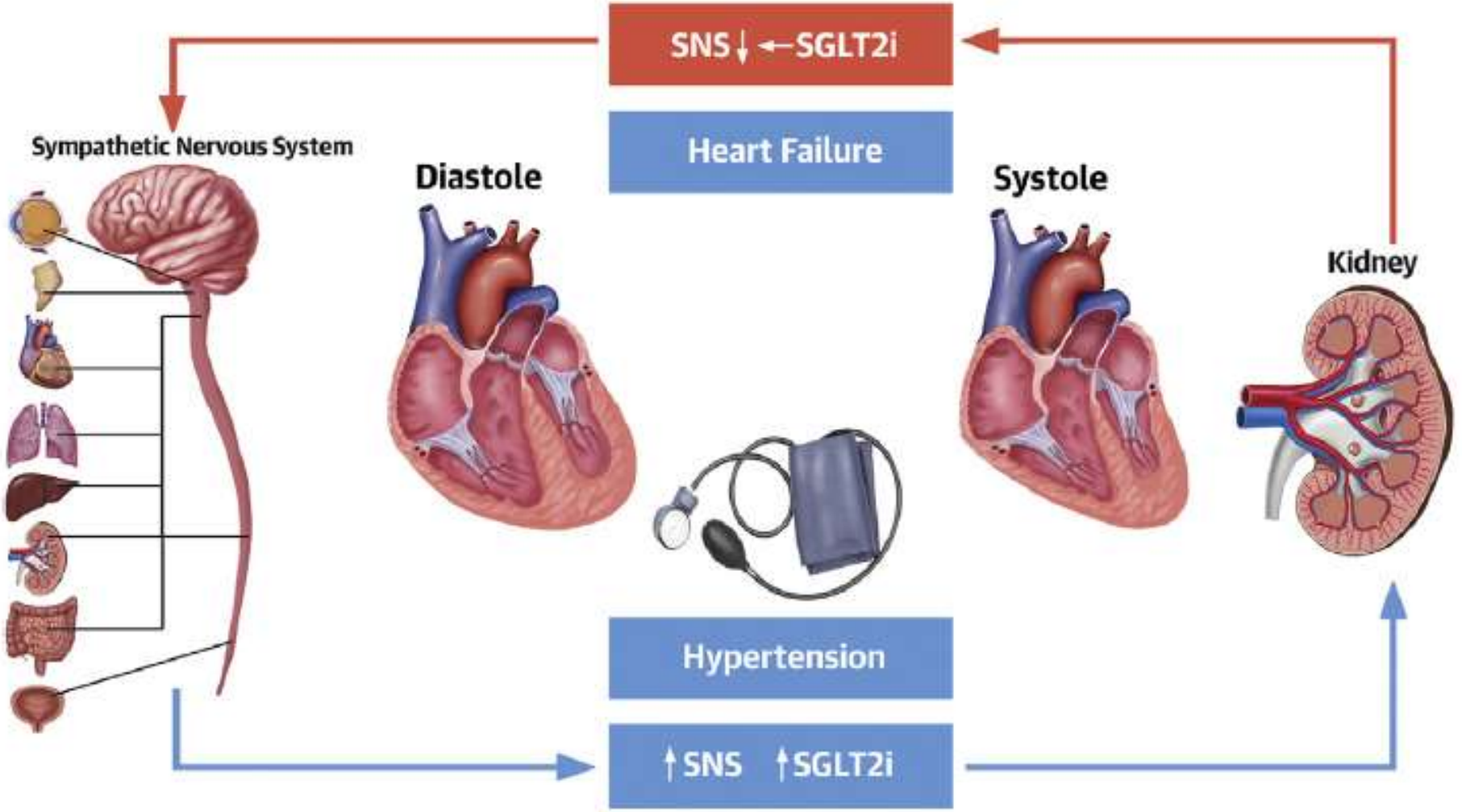
1. Zelniker TA and Braunwald E. *J Am Coll Cardiol*. 2018;72(15):1845-1855. 2. De Fronzo RA et al. *Nat Rev Nephrol*. 2017;13(1):11-26.

CV and Renoprotective Effects of SGLT-2 inhibition are Associated with Improvements in Haemodynamic and Metabolic Factors



Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2020;75:422–434

SGLT2i may reduce the SNS overdrive of HF



Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2020;75:422–434

Contraindications and Cautions for SGLT2 inhibitors

C) SGLT2 Inhibitors

Contraindications	Cautions

■ Not approved for use in patients with type I diabetes due to increased risk of diabetic ketoacidosis
■ Known hypersensitivity to drug
■ Lactation (no data)
■ On dialysis
	■ For HF care, dapagliflozin, eGFR <30 mL/min/1.73 m^2
	■ For HF care, empagliflozin, eGFR <20 mL/min/1.73 m^2
	■ Pregnancy
	■ Increased risk of mycotic genital infections
	■ May contribute to volume depletion. Consider altering diuretic dose if applicable
	■ Ketoacidosis in patients with diabetes:
	  ■ Temporary discontinuation before scheduled surgery is recommended to avoid potential risk for ketoacidosis
	  ■ Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis, regardless of blood glucose level
	■ Acute kidney injury and impairment in renal function: consider temporarily discontinuing in settings of reduced oral intake or fluid losses
	■ Urosepsis and pyelonephritis: evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated
	■ Necrotizing fasciitis of the perineum (Fournier's gangrene): rare, serious, life-threatening cases have occurred in both female and male patients; assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise

Maddox TM et al. *J Am Coll Cardiol*. 2021 Feb 16;77(6):772-810

DAPAHF

Dapagliflozin and Prevention of Adverse Outcomes in HF

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

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

This article was published on September 19, 2019, at NEJM.org.

N Engl J Med 2019;381:1995-2008.
DOI: 10.1056/NEJMoa1911303

Study Design

International, multicentre, parallel group, event-driven, randomized, double-blind, placebo-controlled phase 3 study

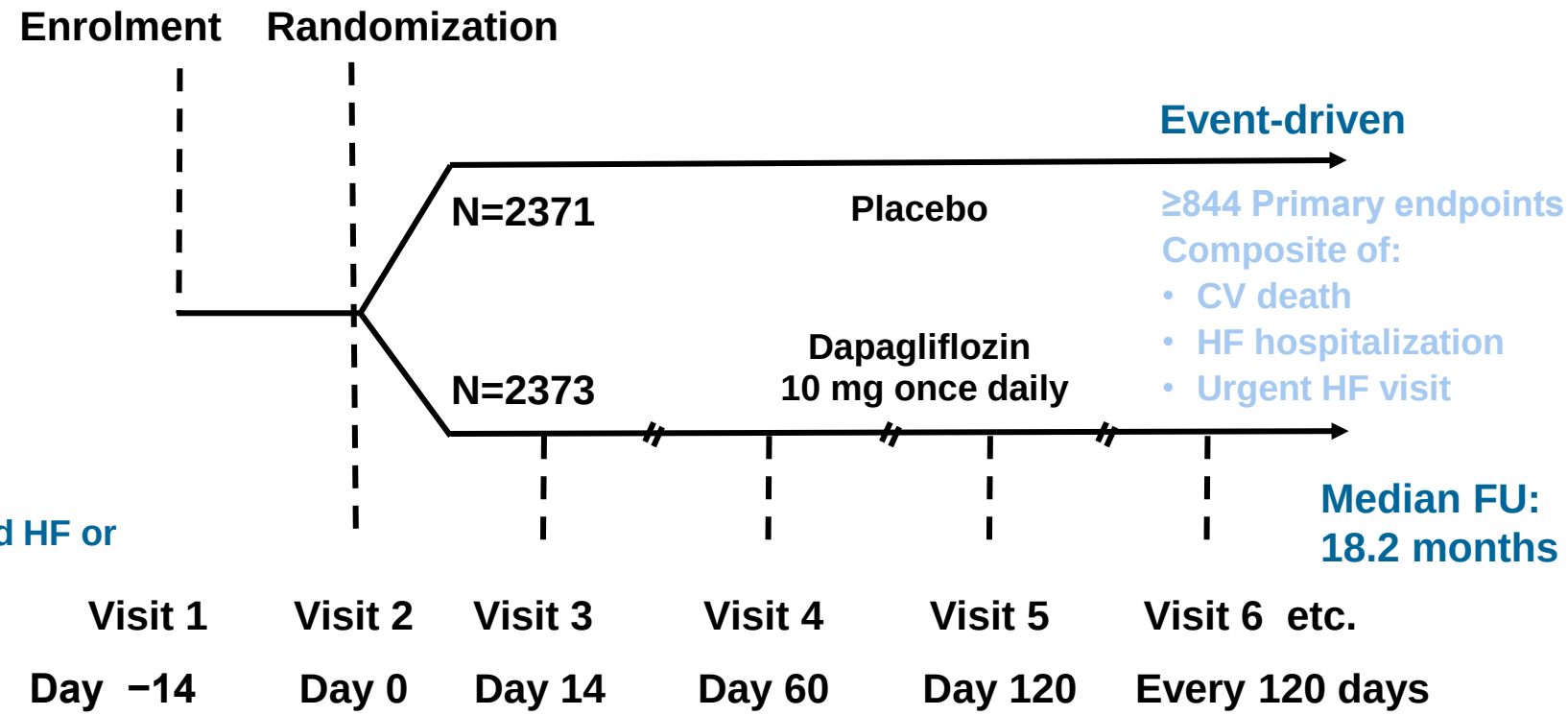
4744 patients; 20 countries (2017-2018)

Key inclusion criteria:

- LVEF ≤40%
- NYHA class II-IV
- NT-proBNP ≥600 pg/ml*
- On top of HF SoC^

Key exclusion criteria:

- Recent treatment or previous intolerance to SGLT2i
- Type 1 diabetes
- SBP <95 mmHg
- Current acute decompensated HF or HFH<4 weeks before visit 1
- eGFR <30 ml/min/1.73 m^2



* ≥400 pg/ml if HF hospitalization within ≤12 months; ≥900 pg/ml if atrial fibrillation/flutter

^ Optimized and stable for ≥4 weeks before visit 1 and include: ACEi or ARB or ARNI, Beta-blocker, MRA

Randomization will be stratified by T2D status at randomization (2 levels: with T2D; without T2D). T2D for stratified randomization is defined as established diagnosis of T2D or HbA1c ≥6.5% (48 mmol/mol) shown at central laboratory test at visit 1

McMurray JJV et al. *N Engl J Med* 2019;381:1995-2008

Primary and Secondary Outcomes

Primary Outcome

Time to the first occurence of any of the components of the composite:

1. CV death
2. Worsening HF event
    1. Hospitalization for HF
    2. An urgent HF visit resulting in IV therapy

Secondary Outcomes

- Time to the first occurence of either of the components of the composite:
    1. CV death
    2. Hospitalization for HF
- Total number of (first and recurrent) HF hospitalization and CV death
- Change from baseline measured at 8 months in the total symptom score of the KCCQ, a specific PRO outcome questionnaire
- Time to the first occurence of any of the components of the composite:
    1. ≥50% sustained decline in eGFR
    2. ESRD*
    3. Renal death
- Time to death to any cause

* Sustained <15 ml/min/1.73 m2 or Chronic dialysis treatment or receiving a renal transplant

McMurray JJV et al. *N Engl J Med* 2019;381:1995-2008

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Safety and Tolerability

Safety Outcome

1. Serious adverse events
2. Discontinuation due to adverse events
3. Changes in clinical/haematology parameters
4. Adverse events of interest (volume depletion, renal events, major hypoglycaemic events, fractures, diabetic ketoacidosis, AEs leading to amputation and to a risk for lower limb amputations)

McMurray JJV et al. *N Engl J Med* 2019;381:1995-2008

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Key Baseline Characteristics

	Dapaglifozin (n=2373)	Placebo (n=2371)
Mean age (yr)	66.2±11	66.5±10.8
NYHA functional classification (n, %)		
II	1606 (67.7)	1597 (67.4)
III	747 (31.5)	751 (31.7)
IV	20 (0.8)	23 (1.0)
Median NT-proBNP (pg/ml)	1428	1446
Systolic BP (mmHg)	122±16.3	121.6±16.3
LVEF (%)	31.2±6.7	30.9±6.9
Mean eGFR (ml/min/1.73m^2)	66±19.6	65.5±19.3
eGFR <60 ml/min/1.73m^2 (%)	40.6	40.7
Prior heart failure hospitalization (n, %)	1124 (47.4)	1127 (47.5)
Atrial fibrillation (n, %)	916 (38.6)	902 (38)
Diabetes mellitus (n, %)	993 (41.8)	990 (41.8)

McMurray JJV et al. *N Engl J Med* 2019;381:1995-2008

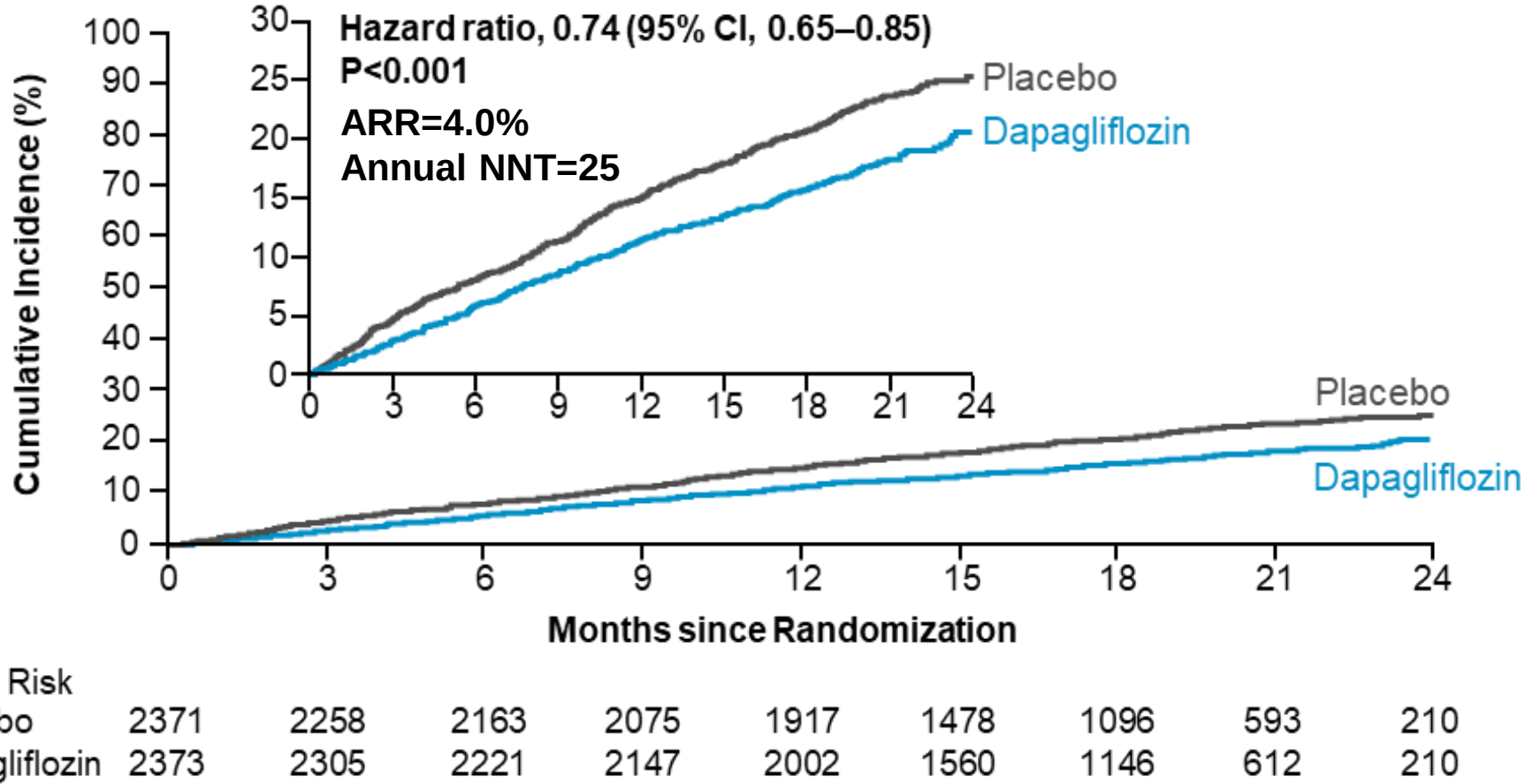
Key Baseline Treatment

	Dapaglifozin (n=2373)	Placebo (n=2371)
Heart failure medication (n, %)		
Diuretic	2216 (93.4)	2217 (93.5)
ACE inhibitor	1332 (56.1)	1329 (56.1)
ARB	675 (28.4)	632 (26.7)
Sacubitril/valsartan	250 (10.5)	258 (10.9)
Beta-blocker	2278 (96)	2280 (96.2)
MRA	1696 (71.5)	1674 (70.6)
Device therapy (n, %)		
Implantable cardioverter–defibrillator	622 (26.2)	620 (26.1)
Cardiac resynchronization therapy	190 (8)	164 (6.9)

Patients with type 2 diabetes continued to take their glucose lowering medications: biguadine, sulfonylurea, DPP-4 inhibitor; GLP-1 receptor agonist, insulin

McMurray JJV et al. *N Engl J Med* 2019;381:1995-2008

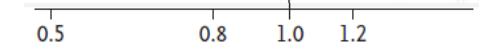
Primary Outcome: Worsening HF or Death from CV Causes



McMurray JJV et al. *N Engl J Med.* 2019;381:1995–2008.

Primary Composite Outcome According to Prespecified Subgroup (I)

Subgroup	Dapagliflozin (N=2373)	Placebo (N=2371)	Hazard Ratio (95% CI)
	no. of patients/total no.		Dapagliflozin Better / Placebo Better
All patients	386/2373	502/2371	0.74 (0.65–0.85)
Age			
≤65 yr	162/1032	196/998	0.78 (0.63–0.96)
>65 yr	224/1341	306/1373	0.72 (0.60–0.85)
Sex			
Male	307/1809	406/1826	0.73 (0.63–0.85)
Female	79/564	96/545	0.79 (0.59–1.06)
Race			
White	275/1662	348/1671	0.78 (0.66–0.91)
Black	26/122	32/104	0.62 (0.37–1.04)
Asian	78/552	118/564	0.64 (0.48–0.86)
Other	7/37	4/32	
Geographic region			
Asia	77/543	114/553	0.65 (0.49–0.87)
Europe	193/1094	218/1060	0.84 (0.69–1.01)
North America	54/335	73/342	0.73 (0.51–1.03)
South America	62/401	97/416	0.64 (0.47–0.88)
NYHA class			
II	190/1606	289/1597	0.63 (0.52–0.75)
III or IV	196/767	213/774	0.90 (0.74–1.09)
LVEF			
≤Median	222/1230	307/1239	0.70 (0.59–0.84)
>Median	164/1143	195/1132	0.81 (0.65–0.99)
NT-proBNP			
≤Median	100/1193	155/1179	0.63 (0.49–0.80)
>Median	286/1179	347/1191	0.79 (0.68–0.92)



Although the patients in NYHA functional class III or IV appeared to have less benefit than those in class II

McMurray JJV et al. *N Engl J Med.* 2019;381:1995–2008.

DAPAHF

Safety and Tolerability: Results

Variable	Dapagliflozin (N=2373)		Placebo (N=2371)		Hazard or Rate Ratio or Difference (95% CI)	P Value
	values	*events/100 patient-yr*	*values*	*events/100 patient-yr*		
Safety outcomes						
Discontinuation due to adverse event — no./total no. (%)	111/2368 (4.7)	—	116/2368 (4.9)	—	—	0.79
Adverse events of interest — no./total no. (%)						
Volume depletion	178/2368 (7.5)	—	162/2368 (6.8)	—	—	0.40
Renal adverse event	153/2368 (6.5)	—	170/2368 (7.2)	—	—	0.36
Fracture	49/2368 (2.1)		50/2368 (2.1)	—	—	1.00
Amputation	13/2368 (0.5)	—	12/2368 (0.5)	—	—	1.00
Major hypoglycemia**	4/2368 (0.2)	—	4/2368 (0.2)	—	—	NA
Diabetic ketoacidosis††	3/2368 (0.1)	—	0	—	—	NA
Fournier's gangrene	0	—	1/2368 (<0.1)	—	—	NA

** Major hypoglycemia was defined as hypoglycemia requiring the assistance of another person to actively administer carbohydrates or glucagon or to take other corrective action. All cases occurred in patients with diabetes at baseline.
†† All cases of diabetic ketoacidosis occurred in patients with diabetes at baseline.

There was no notable excess of any serious adverse events in the dapagliflozin group.

Change in systolic blood pressure from baseline were significantly higher for dapagliflozin vs placebo: -1.92±14.92 vs -0.38±15.27 (HR -1.27; 95% CI: -2.09 to -0.45; *P*<0.002)

McMurray JJV et al. *N Engl J Med.* 2019;381:1995–2008.

Dapagliflozin and Prevention of Adverse Outcomes in HF

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CONCLUSIONS

Among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes. (Funded by AstraZeneca; DAPA-HF ClinicalTrials.gov number, NCT03036124.)

Emerging Treatment Strategies for HFrEF

- ARNI: sacubitril/valsartan
- **SGLT2 inhibitors:**
  - Dapaglifozin
  - **Empaglifozin**
  - Sotaglifozin
- Cardiac myosin activator: omecamtiv mecarbil
- Targeting the NO-sGC-cGMP Pathway in Heart Failure
  - sGC stimulator: vericiguat

Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction: EMPEROR-Reduced

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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*

EMPEROR-Reduced study design

Design: Randomised, double-blind, placebo-controlled, phase III study

Objective: Investigate the safety and efficacy of empagliflozin versus placebo on top of SOC in patients with HFrEF

Eligibility criteria

- Age ≥18 years*
- Diagnosed HF (NYHA class II–IV)
- LVEF ≤40%
- Elevated NT-proBNP#
- Receipt of SOC for HF and stable for ≥1 week before visit 1
- Written consent provided

Median follow-up: 16 months

Primary endpoint: Time to first event of CV death or HFH

*For Japan only: Age ≥20 years; #NT-proBNP cut-off was double in patients with atrial fibrillation
CV, cardiovascular; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFH, heart failure hospitalisation; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; od, once daily; SOC, standard of care

Packer M et al. *N Engl J Med*. 2020;383:1413–1424

Heart Failure

Exclusion criteria and Outcomes

Main Exclusion Criteria

- Acute decompensated HF treated within 1 wk at screening
- SBP ≥180 mmHg at randmz; if SBP ≥151-179 pts should receive ≥3 antihypertensive drugs
- Symptomatic hypotension and/or a SBP ≤100 mmHg
- Indication of liver disease
- Impaired renal function: eGFR <20 Ml/min/1.73m2
- Current use or prior use of a SGLT1-2 also in combo, 12 weeks prior randmz/screening; discontinuation for the pourpose of study enrollment not permitted

Primary Outcome

- Composite of adjudicated cardiovascular death or hospitalization for heart failure, analyzed as the time to the first event.

Secondary Outcome

- Occurrence of all adjudicated hospitalizations for HF, including first and recurrent
- Events rate of the decline in the estimated GFR

Packer M et al. Engl J Med. 2020 Oct 8;383(15):1413-1424.

NYHA pts Class II were 75.1%, 24.4% Class III; LVEF ≤30% pts were 71.8%

Characteristics	Empagliflozin (N = 1863)	Placebo (N = 1867)
Age — yr	67.2±10.8	66.5±11.2
Female sex — no. (%)	437 (23.5)	456 (24.4)
NYHA functional class — no. (%)		
II	1399 (75.1)	1401 (75.0)
III	455 (24.4)	455 (24.4)
IV	9 (0.5)	11 (0.6)
Body-mass index	28.0±5.5	27.8±5.3
Heart rate — beats/min	71.0±11.7	71.5±11.8
Systolic blood pressure — mm Hg	122.6±15.9	121.4±15.4
Left ventricular ejection fraction		
Mean value	27.7±6.0	27.2±6.1
Value of ≤30% — no. (%)	1337 (71.8)	1392 (74.6)

Packer M et al. Engl J Med. 2020 Oct 8;383(15):1413-1424.

Median NT-proBNP was 1906, 31% of pts were Hospitalizad fo HF, whereas pts with <60 ml eGFR were 48 %

Characteristic	Empagliflozin (N = 1863)	Placebo (N = 1867)
NT-proBNP		
Median value (IQR) — pg/ml	1887 (1077–3429)	1926 (1153–3525)
Value of ≥1000 pg/ml — no./total no. (%)	1463/1862 (78.6)	1488/1866 (79.7)
Cause of heart failure — no. (%)		
Ischemic	983 (52.8)	946 (50.7)
Nonischemic	880 (47.2)	921 (49.3)
Cardiovascular history — no. (%)		
Hospitalization for heart failure in ≤12 mo	577 (31.0)	574 (30.7)
Atrial fibrillation	664 (35.6)	705 (37.8)
Diabetes mellitus	927 (49.8)	929 (49.8)
Hypertension	1349 (72.4)	1349 (72.3)
Estimated glomerular filtration rate		
Mean value — ml/min/1.73 m2	61.8±21.7	62.2±21.5
Value of <60 ml/min/1.73 m2 — no./total	893/1862 (48.0)	906/1866 (48.6)

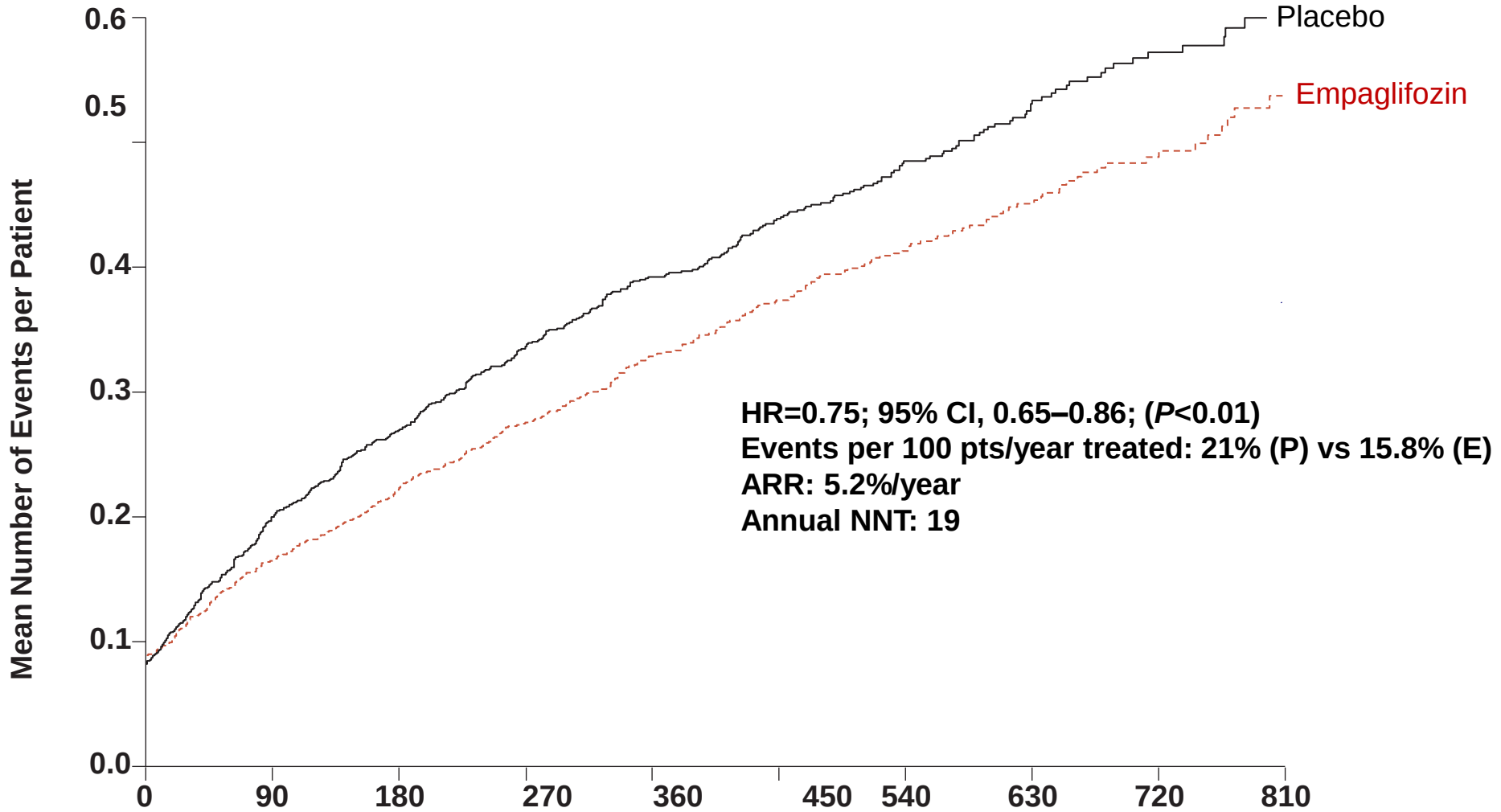
Packer M et al. Engl J Med. 2020 Oct 8;383(15):1413-1424.

Pts were Submitted to Optimal GDMT: 18.3% Received Neprilysin Inhibitor

Characteristic	Empagliflozin (N = 1863)	Placebo (N = 1867)
Renin–angiotensin inhibitor §		
Without neprilysin inhibitor	1314 (70.5)	1286 (68.9)
With neprilysin inhibitor	340 (18.3)	387 (20.7)
Mineralocorticoid receptor antagonist	1306 (70.1)	1355 (72.6)
Beta-blocker	1765 (94.7)	1768 (94.7)
Device therapy — no. (%)		
Implantable cardioverter–defibrillator	578 (31.0)	593 (31.8)
Cardiac resynchronization therapy‖	220 (11.8)	222 (11.9)

Packer M et al. Engl J Med. 2020 Oct 8;383(15):1413-1424.

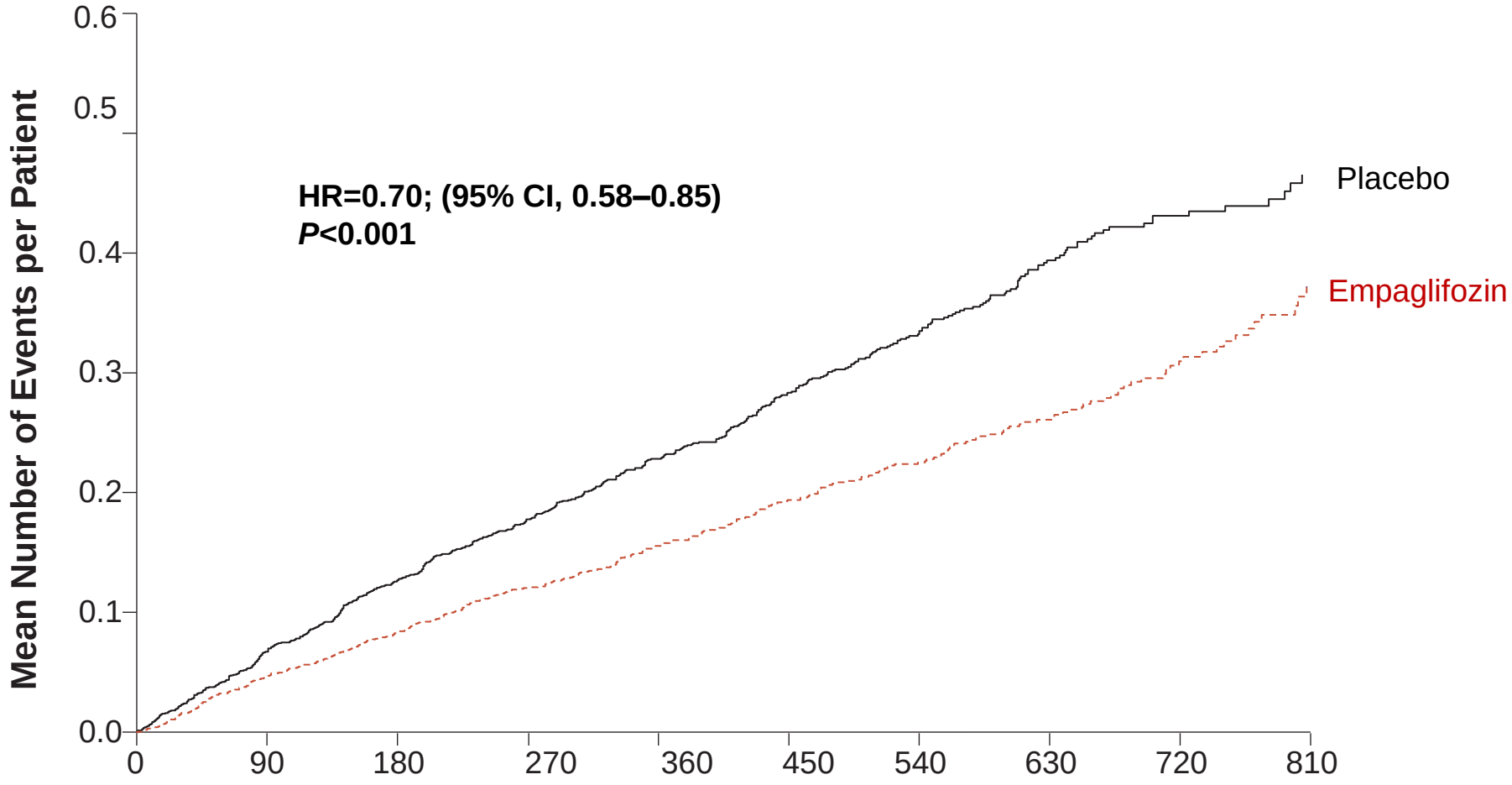
EMPAGLIFOZIN was More Effective than placebo in Reducing Risk of CV Death or Hospitalization



No. at Risk										
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

Packer M et al. Engl J Med. 2020 Oct 8;383(15):1413-142.

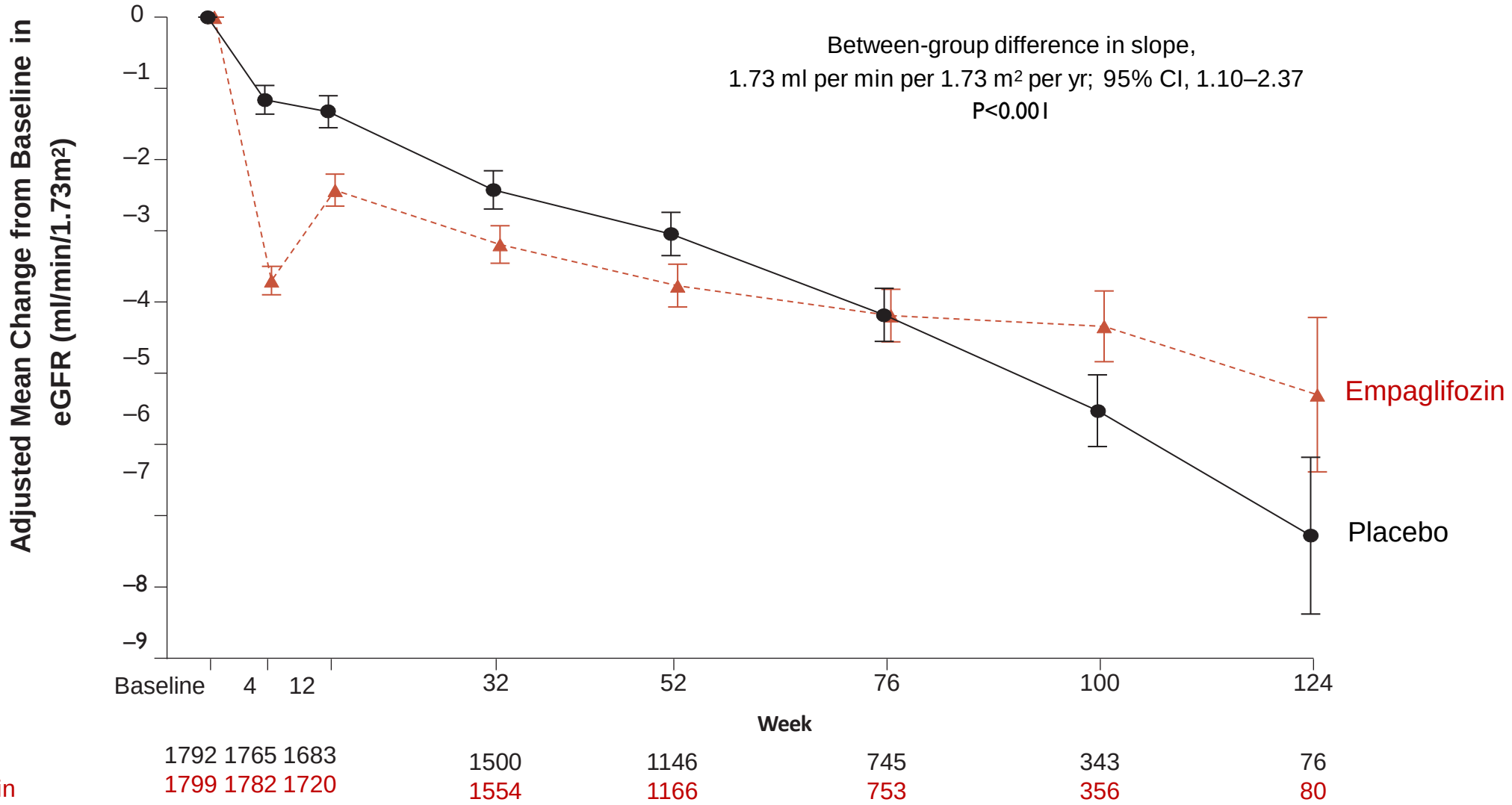
EMPAGLIFOZIN was More Effective than placebo in Reducing Risk of Recurrent Hospitalizations



No. at Risk										
Placebo	1867	1820	1762	1526	1285	1017	732	497	275	135
Empagliflozin	1863	1826	1768	1532	1283	1008	732	495	272	118

Packer M et al. Engl J Med. 2020 Oct 8;383(15):1413-1424.

The Annual Rate of Decline in the eGFR was Slower in the Empagliflozin Group than in the Placebo Group



No. at Risk							
Placebo	1792	1765	1683	1500	1146	745	343	76
Empagliflozin	1799	1782	1720	1554	1166	753	356	80

Packer M et al. Engl J Med. 2020 Oct 8;383(15):1413-1424.

Primary & Secondary Outcomes

Table 2. Primary and Secondary Cardiovascular Outcomes.*

Variable	Empagliflozin (N=1863)	events/100 patient-yr	Placebo (N=1867)	events/100 patient-yr	Hazard Ratio or Absolute Difference (95% CI)†	P Value
Primary composite outcome — no. (%)	361 (19.4)	15.8	462 (24.7)	21.0	0.75 (0.65 to 0.86)	<0.001
Hospitalization for heart failure	246 (13.2)	10.7	342 (18.3)	15.5	0.69 (0.59 to 0.81)	
Cardiovascular death	187 (10.0)	7.6	202 (10.8)	8.1	0.92 (0.75 to 1.12)	
Secondary outcomes specified in hierarchical testing procedure						
Total no. of hospitalizations for heart failure	388	—	553	—	0.70 (0.58 to 0.85)	<0.001
Mean slope of change in eGFR — ml/min/1.73 m^2 per year‡	−0.55±0.23	—	−2.28±0.23	—	1.73 (1.10 to 2.37)	<0.001
Other prespecified analyses						
Composite renal outcome — no. (%)§	30 (1.6)	1.6	58 (3.1)	3.1	0.50 (0.32 to 0.77)	
Change in quality-of-life score on KCCQ at 52 weeks¶	5.8±0.4	—	4.1±0.4	—	1.7 (0.5 to 3.0)	
No. of hospitalizations for any cause	1364	—	1570	—	0.85 (0.75 to 0.95)	
Death from any cause — no. (%)	249 (13.4)	10.1	266 (14.2)	10.7	0.92 (0.77 to 1.10)	
Onset of new diabetes in patients with prediabetes — no./total no. (%)	71/632 (11.2)	9.3	80/636 (12.6)	10.6	0.86 (0.62 to 1.19)	
Laboratory and other measurements (adjusted change from baseline to 52 wk)						
Glycated hemoglobin in patients with diabetes — %	−0.28±0.03	—	−0.12±0.03	—	−0.16 (−0.25 to −0.08)	
Hematocrit (%)	1.98±0.10	—	−0.38±0.10	—	2.36 (2.08 to 2.63)	
Median NT-proBNP (IQR) — pg/ml‖	−244 (−890 to 260)		−141 (−784 to 585)	—	0.87 (0.82 to 0.93)	
Body weight — kg	−0.73±0.13	—	0.08±0.13	—	−0.82 (−1.18 to −0.45)	
Systolic blood pressure — mm Hg	−2.4±0.4	—	−1.7±0.4	—	−0.7 (−1.8 to 0.4)	

Packer M et al. Engl J Med. 2020 Oct 8;383(15):1413-1424.

EMPAGLIFOZIN showed a Good Safety Profile

Characteristic	Empagliflozin (N = 1863)	Placebo (N = 1863)
Pts with any serious adverse events	772 (41.4)	896 (48.1)
Pts with any adverse events	1470 (76.2)	1463 (78.5)
Selected adverse events of interest		
Volume depletion	197 (10.6)	184 (9.9)
Symptomatic hypotension	106 (5.7)	103 (5.5)
Hypoglycemic events	27 (1.4)	28 (1.5)
Ketoacidosis	0 (0.0)	0 (0.0)
Urinary tract infections	91 (4.9)	83 (4.5)
Genital tract infections	31 (1.7)	12 (0.6)
Bone fractures	45 (2.4)	42 (2.3)
Events leading to lower limb amputations	13 (0.7)	10 (0.5)
Bone fractures	45 (2.4)	42 (2.4)

Packer M et al. Engl J Med. 2020 Oct 8;383(15):1413-1424. SUPPLEMENTARY

Among Patients Receiving Recommended Therapy for Heart Failure, those in the Empagliflozin Group…

Had a lower risk of cv death or hospitalization for HF than those in the placebo group, regardless of the presence or absence of diabetes, 25% RR (HR: 0.75; [CI] 0.65 to 0.86; *P*<0.001)

Had a lower total number of hospitalizations for HF, 30% RRR (HR: 0.70; [CI] 0.58 to 0.85; *P*<0.001)

Annual rate of decline in the estimated glomerular filtration rate was slower in the empagliflozin group than in the placebo group

Uncomplicated genital tract infection was reported more frequently with empagliflozin

Packer M et al. Engl J Med. 2020 Oct 8;383(15):1413-1424.

Putting data into context

Key details of the DAPA-HF and EMPEROR-Reduced studies

		DAPA-HF (N=4744)[1–3] Dapagliflozin	EMPEROR-Reduced (N=3730)[4] Empagliflozin
Inclusion/ exclusion criteria	NT-proBNP cut-off (pg/ml)	≥600 or ≥400 if HFH within 12 months or ≥900 if AF	EF ≤30%: ≥600, or ≥1200 if AF EF 31–35%: ≥1000, or ≥2000 if AF EF 36–40%: ≥2500, or ≥5000 if AF EF ≤40% and HFH within 12 months: ≥600, or ≥1200 if AF
	Recent HF decompensation	No current ADHF or hospitalisation due to decompensated HF <4 weeks prior to enrolment	Chronic HF ≥3 months No current ADHF requiring IV diuretics, vasodilators, inotropic agents or mechanical support within 1 week of screening and during the screening period prior to randomisation
Baseline characteristics	Median NT-proBNP, pg/ml	1437	1907
	NYHA class III or IV	32%	25%
	Prior HFH	16% within 6 months	31% within 12 months
	Mean eGFR, ml/min/1.73 m^2	66	62
	eGFR <60 ml/min/1.73 m^2	41%	48%
Primary endpoint event rate (control arm)		15.6 events/100 PY	21.0 events/100 PY

EMPEROR-Reduced included a higher-risk patient population than DAPA-HF

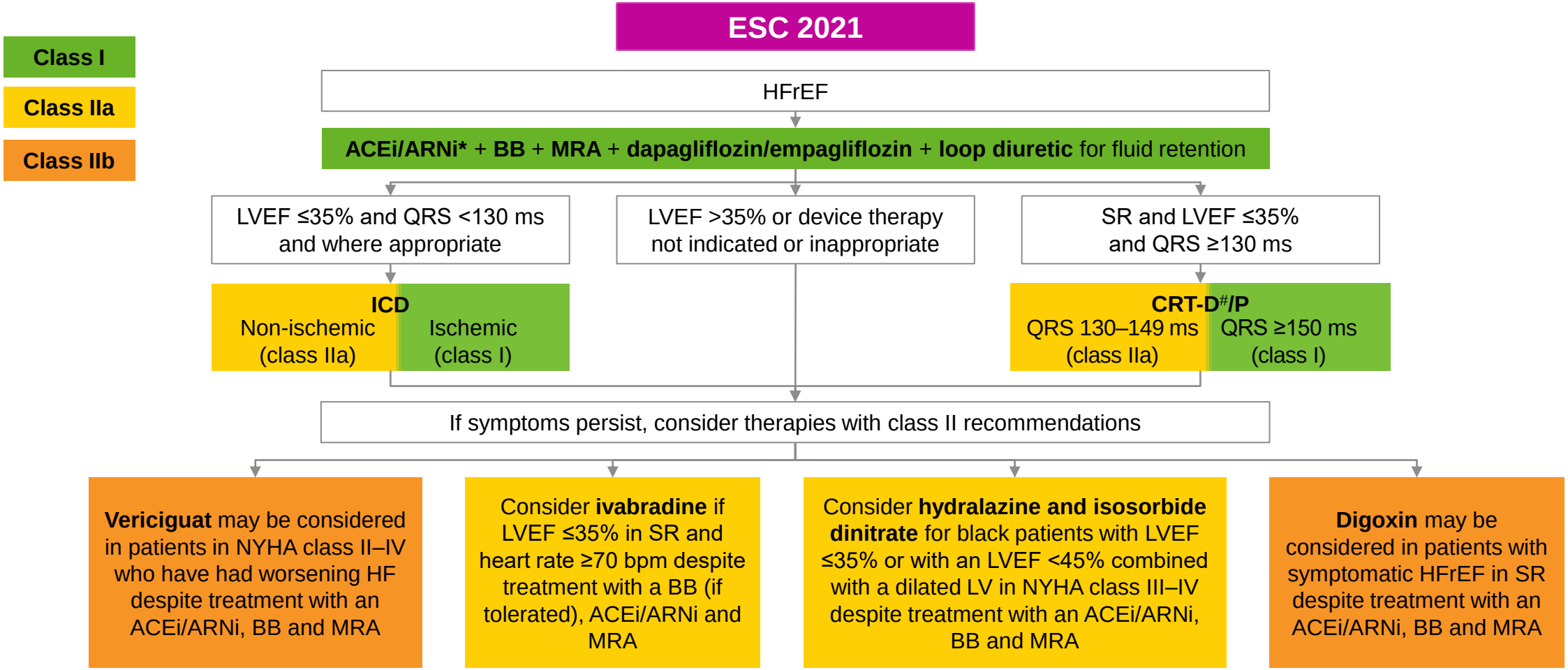
Note: The total population values have not been reported for EMPEROR-Reduced, so the average of the mean or median values from the individual study arms was calculated in some cases. Each study was conducted independently, and no head-to-head studies have been completed that allow for direct comparison of the efficacy and/or safety of one drug vs another
AF, atrial fibrillation; ADHF, acute decompensated heart failure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFH, heart failure hospitalisation; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PY, patient-years

1. McMurray JJV et al. *N Engl J Med.* 2019;381:1995–2008; 2. McMurray JJV et al. *Eur J Heart Fail.* 2019;21:1402–1411; 3. McMurray JJV et al. *Eur J Heart Fail.* 2019;21:665–675;
4. Packer M et al. *N Engl J Med*. 2020;383:1413–1424

Heart Failure

	PARADIGM-HF[1]		DAPA-HF[1]		EMPEROR-Reduced[1]	
	Control	Sacubitril/ valsartan	Control	Dapa-gliflozin	Control	Empa-gliflozin
Primary endpoint	13.2	10.5	15.6	11.6	21.0	15.8
ARR	2.7		4.0		5.2	
CV death	7.5	6.0	7.9	6.5	8.1	7.6
ARR	1.5		1.4		0.6	
First HF hospitalisation	7.7[4]	6.2[4]	9.8	6.9	15.5	10.7
ARR	1.6		2.9		4.8	

ESC 2021 recommendations for the treatment of patients with HFrEF[1]



*ARNi recommended as a replacement for ACEi; an ARB is recommended in patients unable to tolerate an ACEi or ARNi (class I, level B). # Where appropriate.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P,cardiac resynchronization therapy with pacemaker; ESC, European Society of Cardiology; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; QRS, Q, R and S waves; SR, sinus rhythm.

Reference: 1. McDonagh TA *et al. Eur Heart J* 2021; doi:10.1093/eurheartj/ehab368.

ESC 2021 guidelines: Drugs recommended in all patients with HFrEF[1]

Recommendations	Class	Level
ACEi 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 is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death	I	A
Sacubitril/valsartan is recommended as a replacement for ACEi in patients with HFrEF to reduce the risk of HF hospitalization and death	I	B

ACEi, angiotensin-converting enzyme inhibitor; ESC, European Society of Cardiology; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.

Reference: 1. McDonagh TA *et al. Eur Heart J* 2021; doi:10.1093/eurheartj/ehab368.