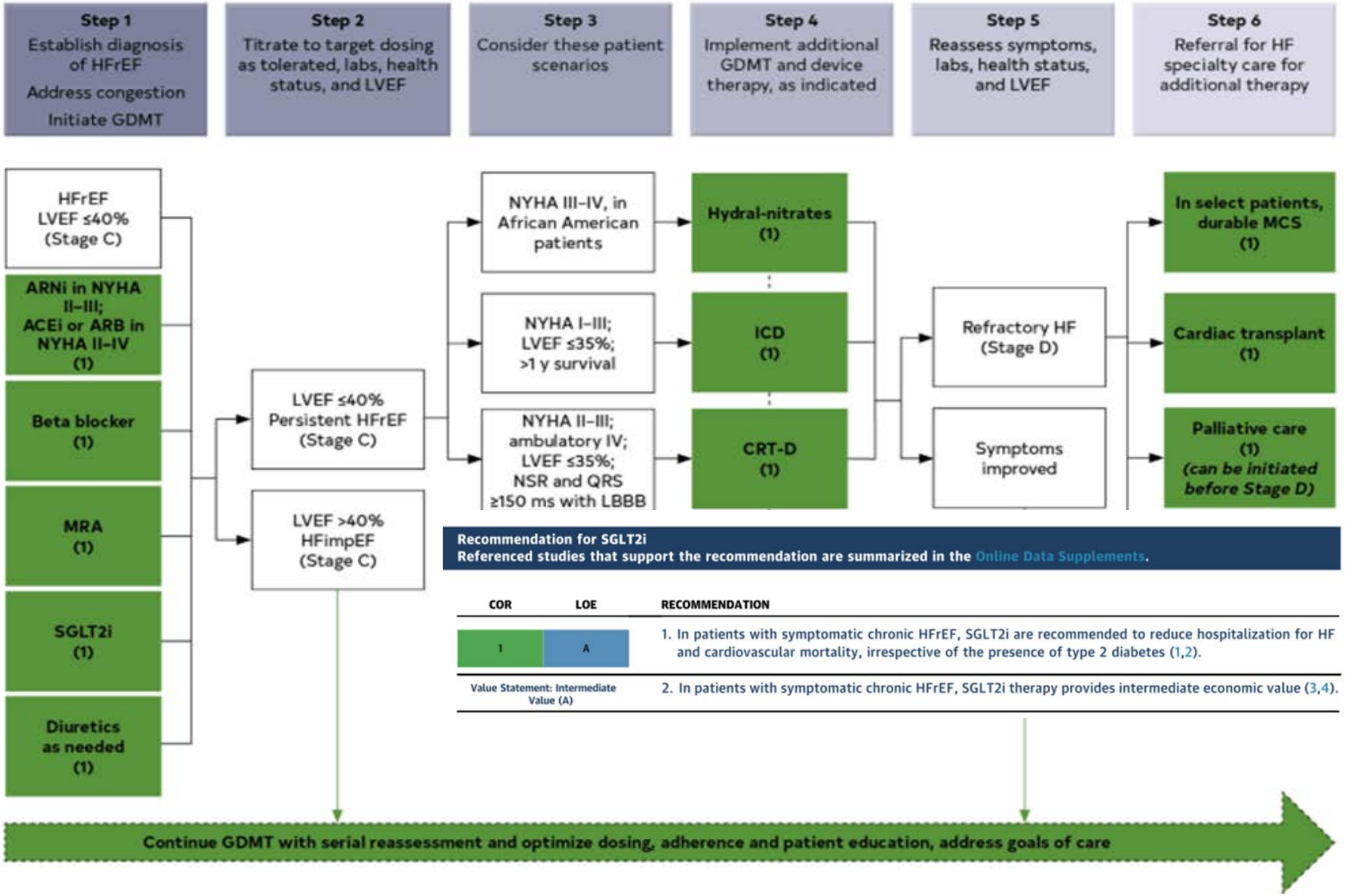
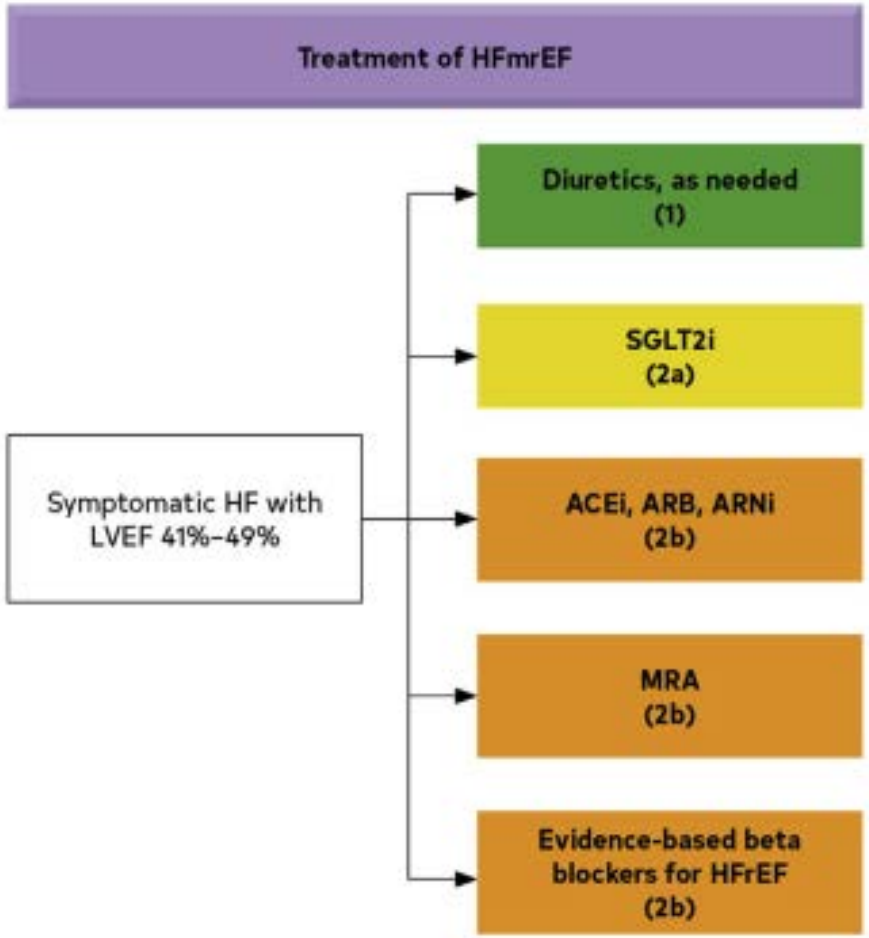
Ürəyimizin yeni xilaskarı Empagliflozin(EMPA)

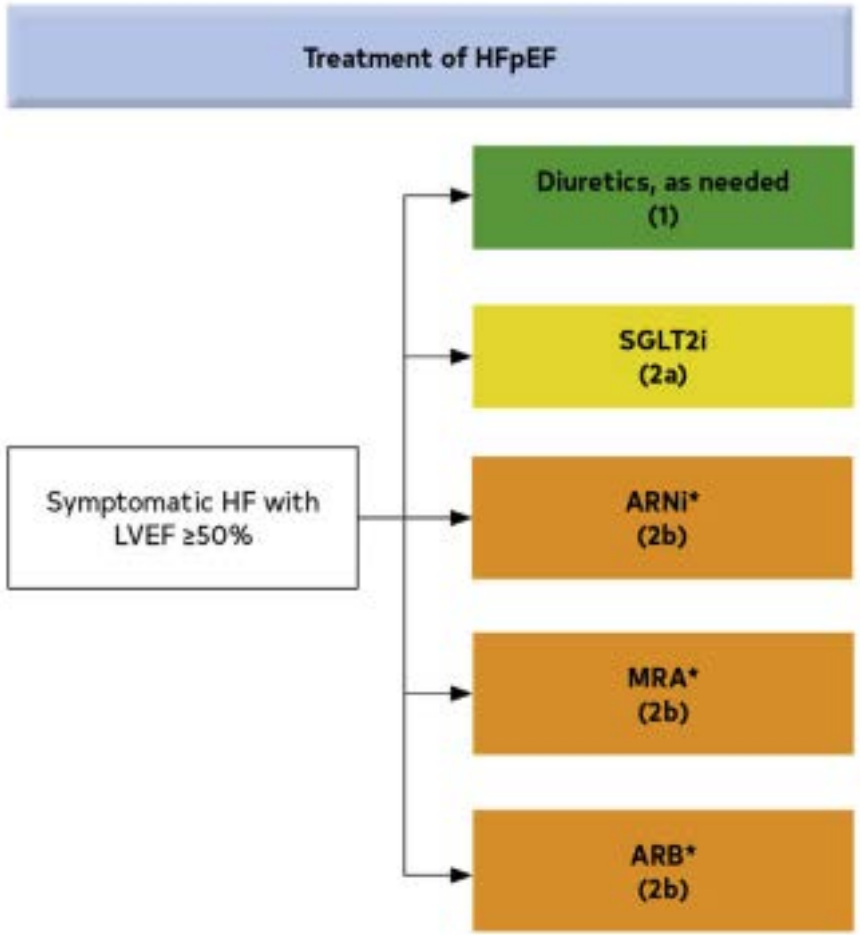
Fuad Səmədov

II ÜÇYK, 11.06.2023

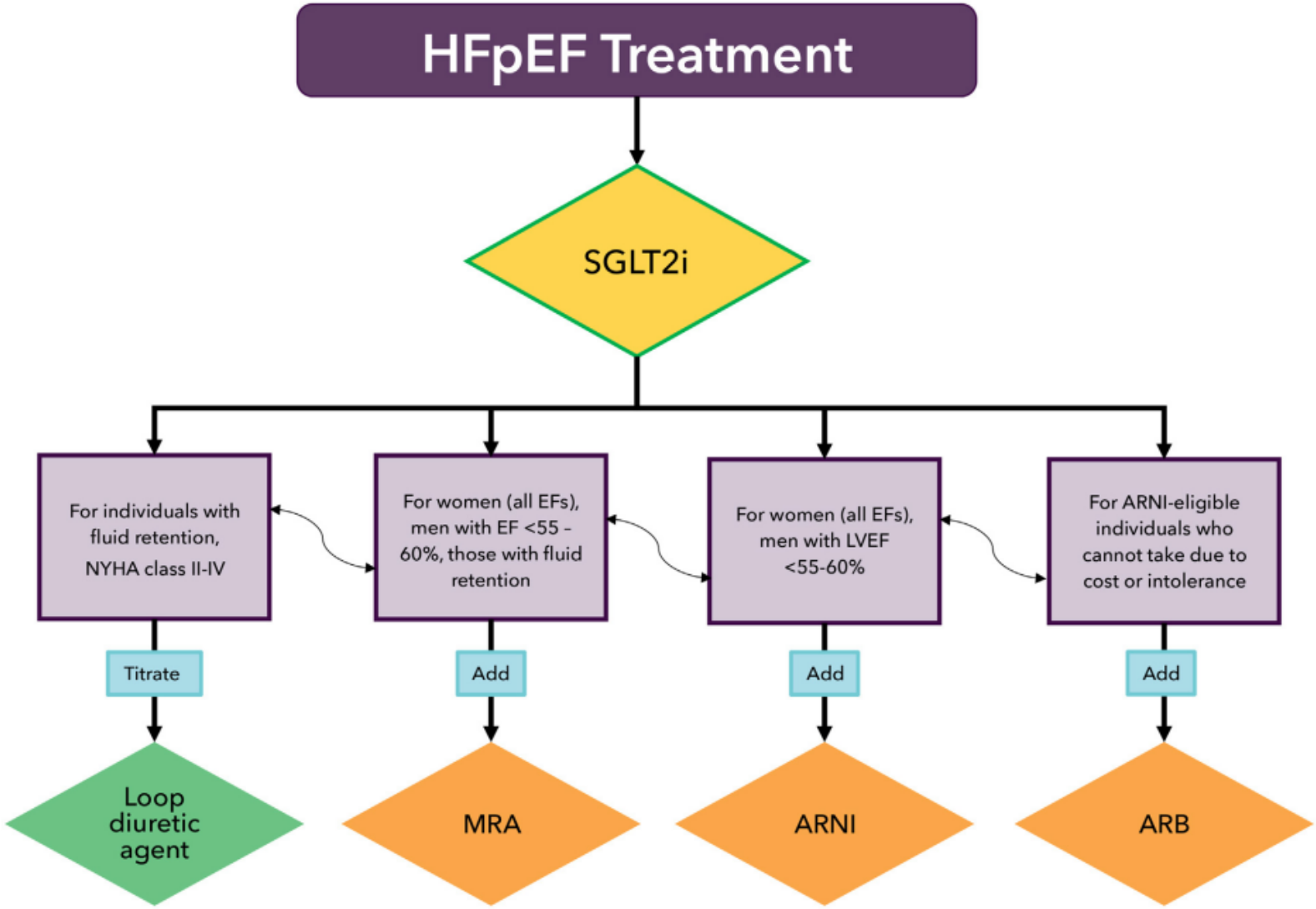


2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure

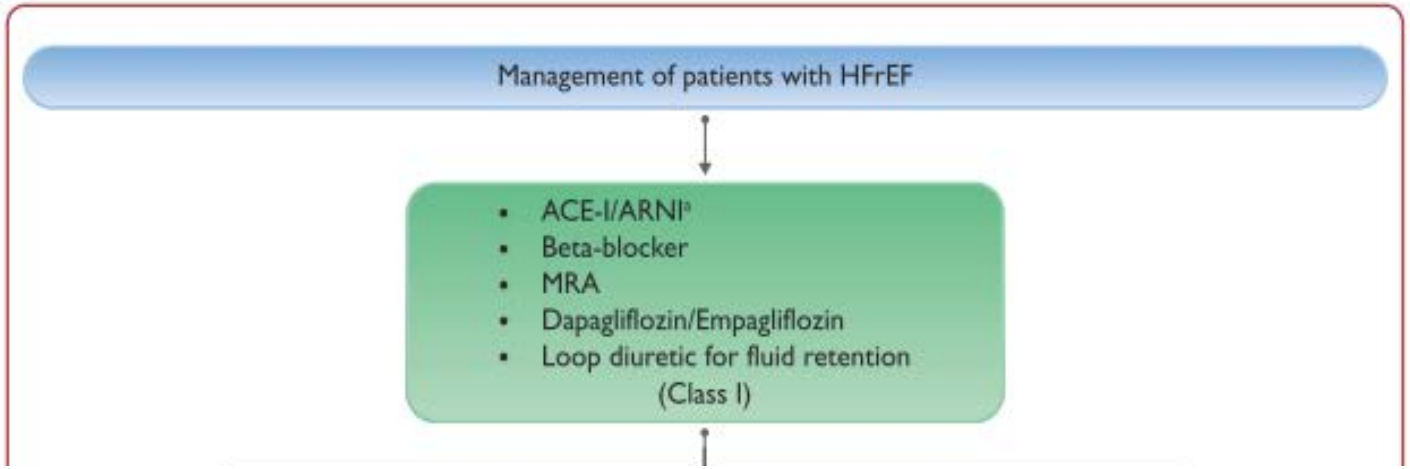




2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure



2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction

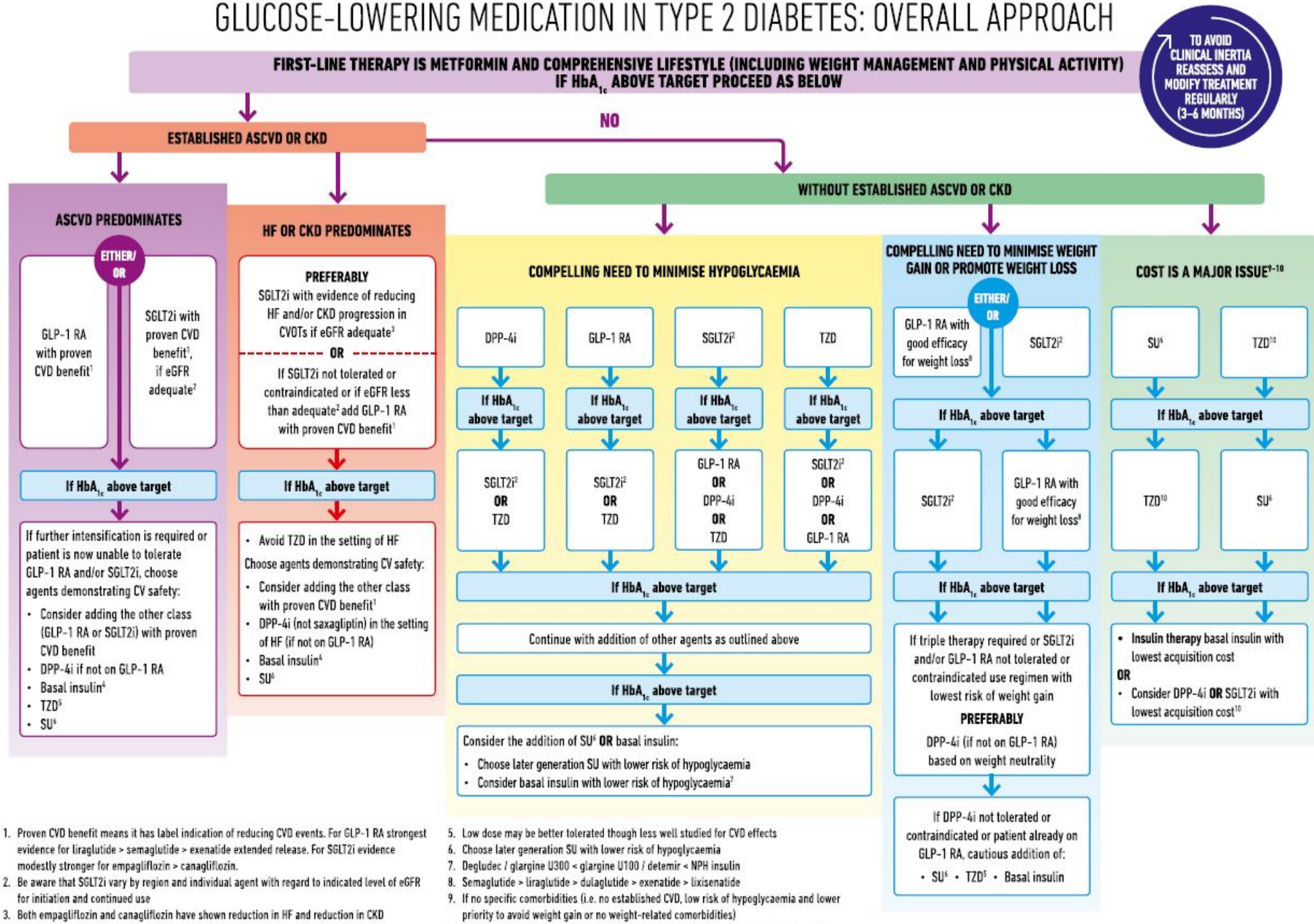


Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

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

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

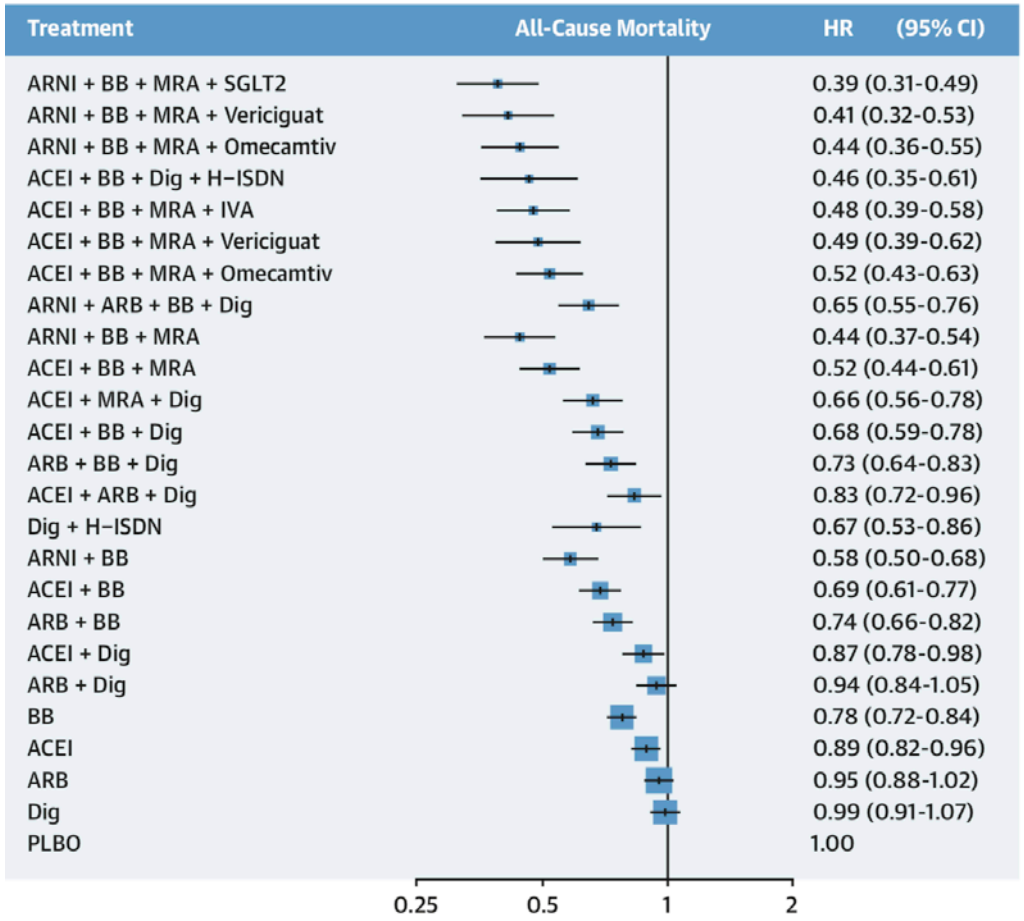
GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

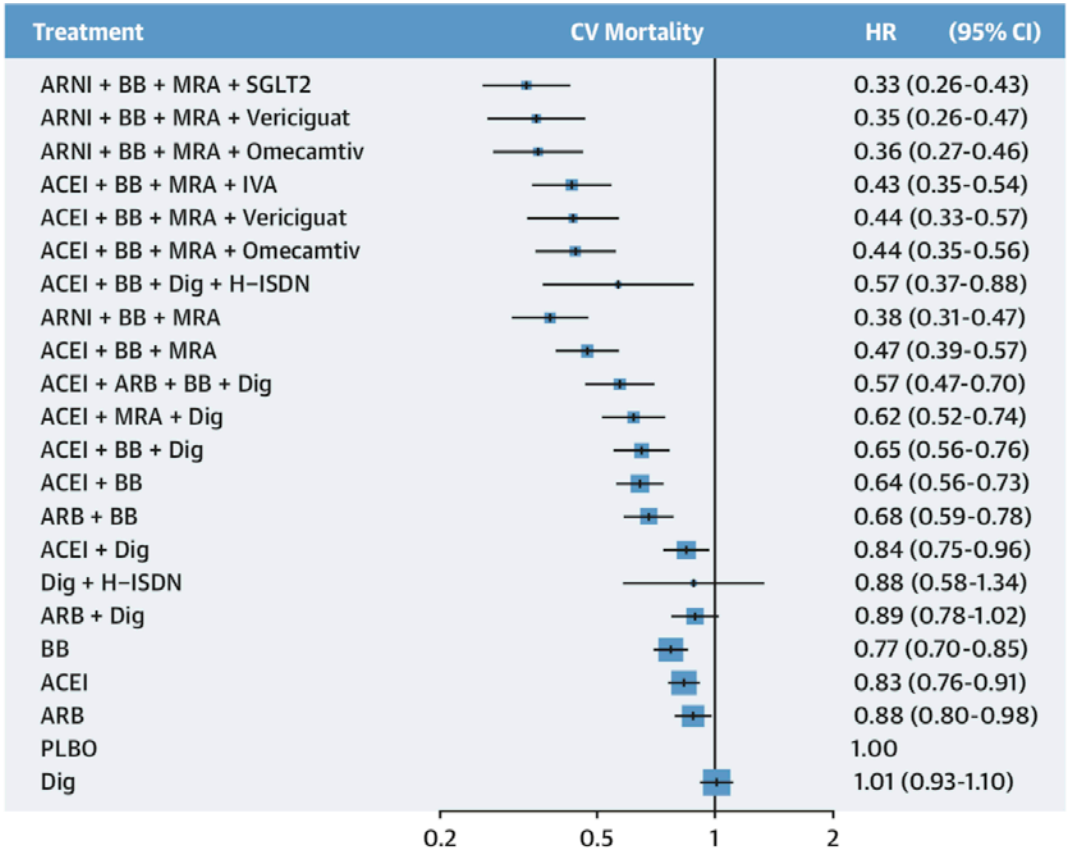


1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

A Systematic Review and Network Meta-Analysis of Pharmacological Treatment of Heart Failure With Reduced Ejection Fraction

Our analyses on patients from large multiethnic HF registries found that comprehensive pharmacological therapy (ARNi, BB, MRA, and SGLT2i) can collectively extend life-expectancy in HFrEF by 7.9 years in a 50-year-old and by 5.0 years in a 70-year-old patient compared with no treatment



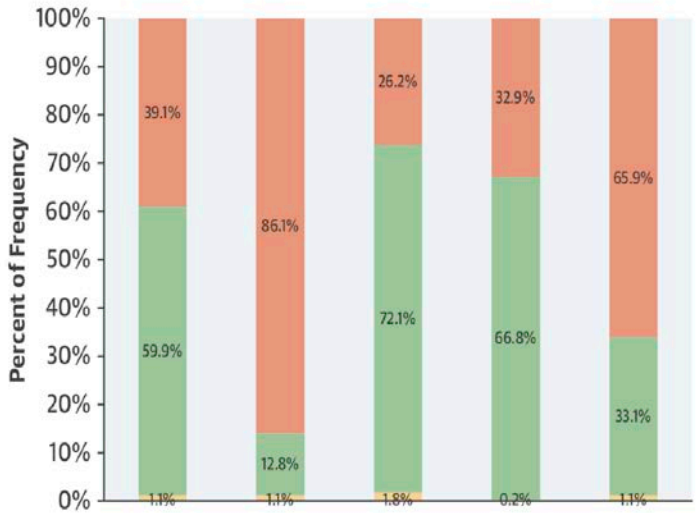


Tromp, J. et al. J Am Coll Cardiol HF. 2022;10(2):73–84.

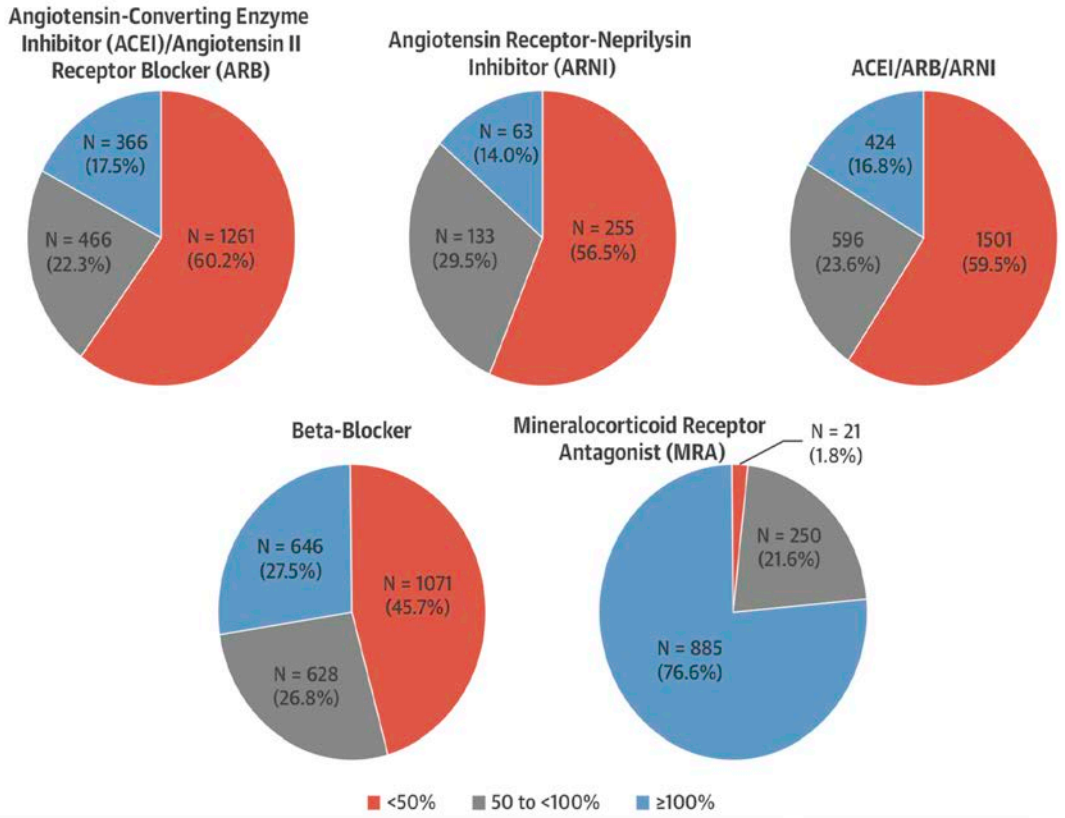
Medical Therapy for Heart Failure With Reduced Ejection Fraction

The CHAMP-HF Registry

A



	ACEI/ARB	ARNI	ACEI/ARB/ ARNI	Beta-Blocker	MRA
Without Contraindication and Not Treated	1374	3029	920	1159	2317
Treated	2107	452	2536	2351	1163
With Contraindication	37	37	62	8	38



RESULTS Overall, 3,518 patients from 150 primary care and cardiology practices were included. Mean age was 66 ± 13 years, 29% were female, and mean EF was 29 ± 8%. Among eligible patients, 27%, 33%, and 67% were not prescribed ACEI/ARB/ARNI, beta-blocker, and MRA therapy, respectively. When medications were prescribed, few patients were receiving target doses of ACEI/ARB (17%), ARNI (14%), and beta-blocker (28%), whereas most patients were receiving target doses of MRA therapy (77%). Among patients eligible for all classes of medication, 1% were simultaneously receiving target doses of ACE/ARB/ARNI, beta-blocker, and MRA. In adjusted models, older age, lower blood pressure, more severe functional class, renal insufficiency, and recent HF hospitalization generally favored lower medication utilization or dose. Social and economic characteristics were not independently associated with medication use or dose.

Greene, S.J. et al. J Am Coll Cardiol. 2018;72(4):351–66.

EMPEROR-Reduced Trial

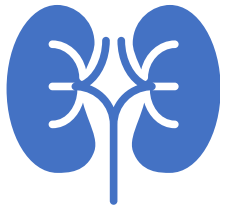
Effect of Empagliflozin on Cardiovascular and Renal Events in Heart Failure With a Reduced Ejection Fraction

Milton Packer MD and Faiez Zannad MD, on behalf of the EMPEROR-Reduced Executive Committee, Trial Committees, Investigators and Coordinators

EMPEROR-Reduced Trial Specified Only Three Endpoints to be Tested in Hierarchical Manner

Primary Endpoint
Composite of cardiovascular death or heart failure hospitalization

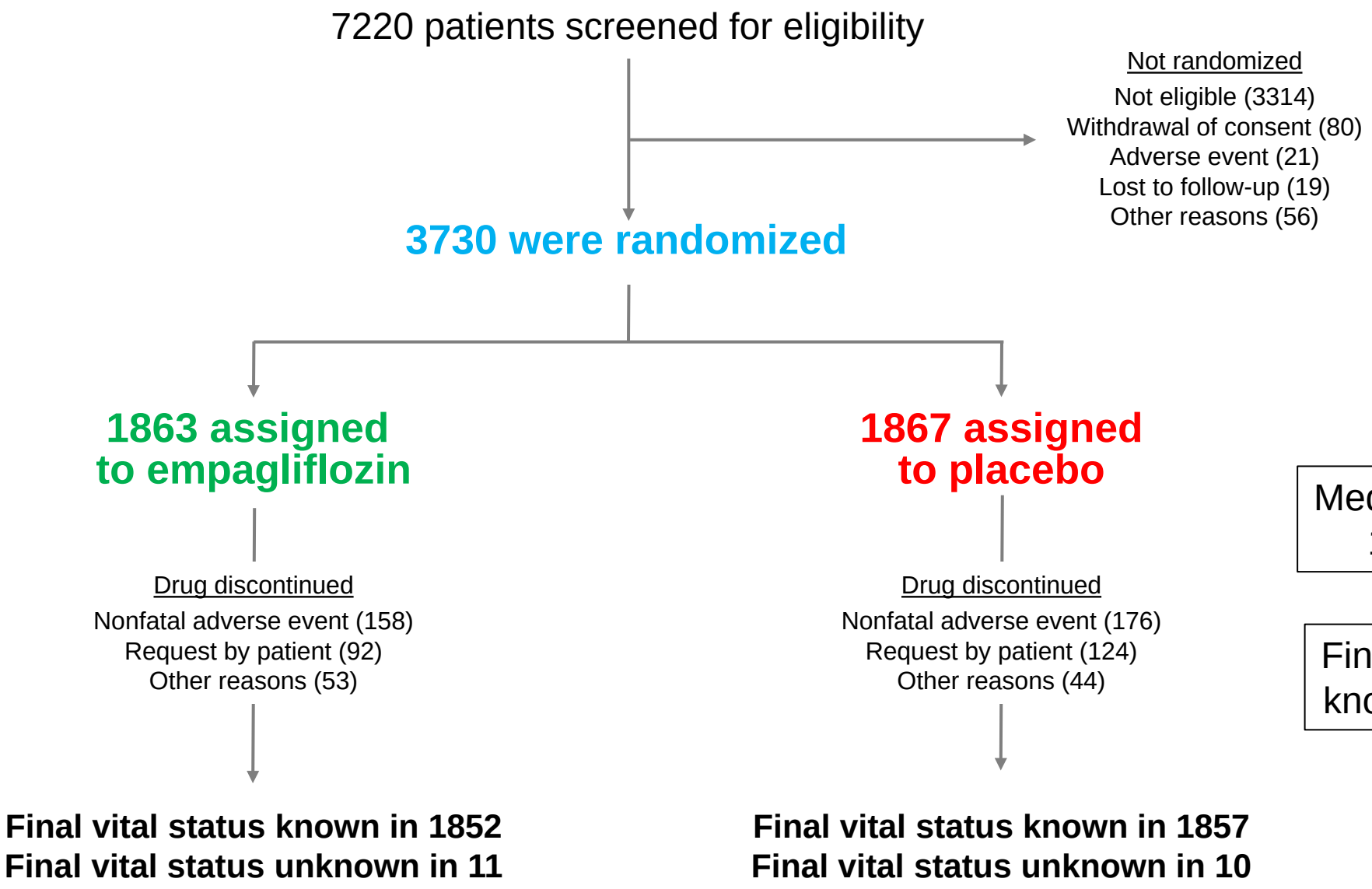
First Secondary Endpoint
Total (first and recurrent heart failure hospitalizations)



Second Secondary Endpoint
Slope of decline in glomerular filtration rate over time

Other prespecified endpoints: Composite renal endpoint, KCCQ clinical summary score, total number of hospitalizations for any reason, all-cause mortality, new onset diabetes

EMPEROR-Reduced: Patient Disposition



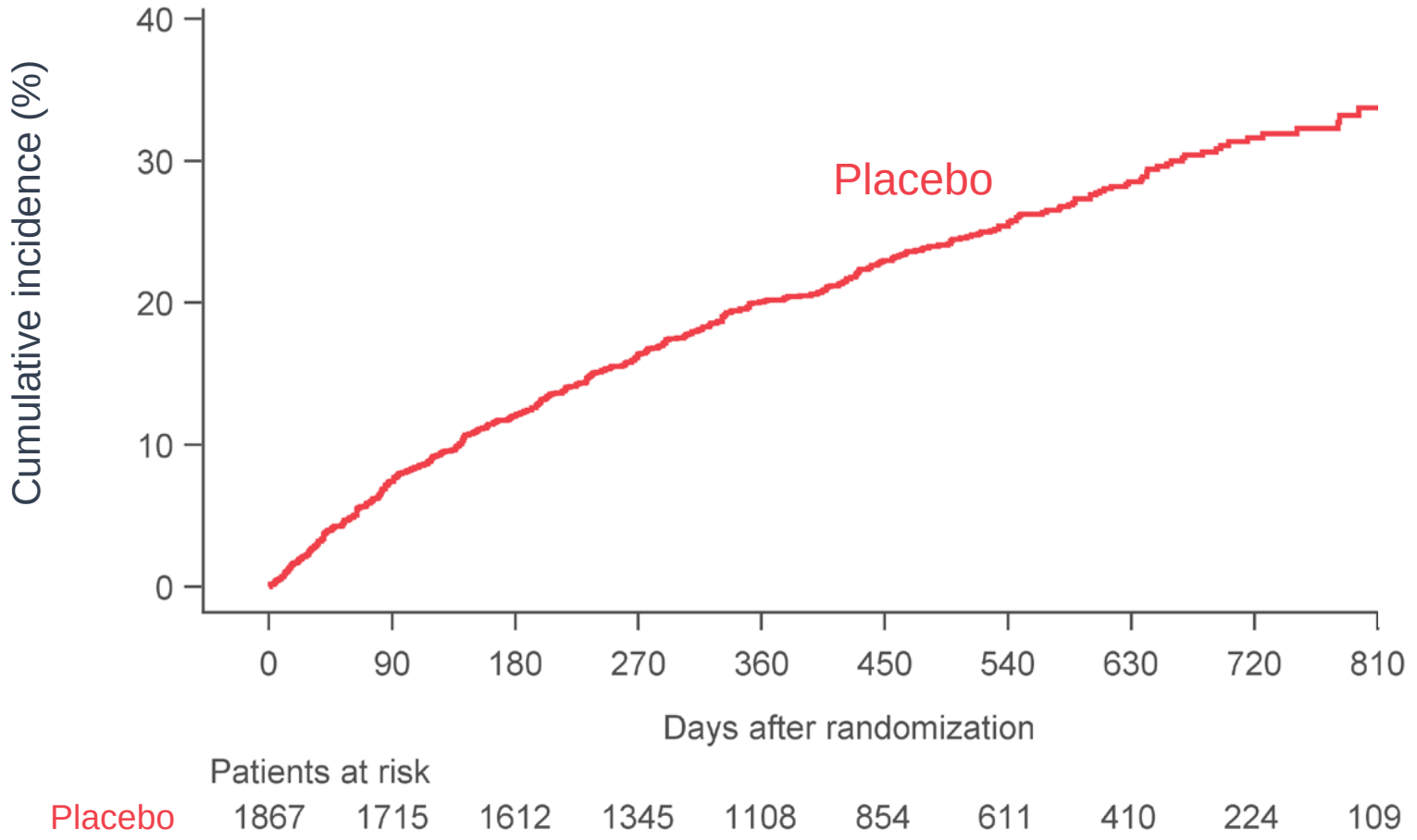
Median follow-up 16 months

Final vital status known in 99.4%

Baseline Characteristics

	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 m^2)	**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%)

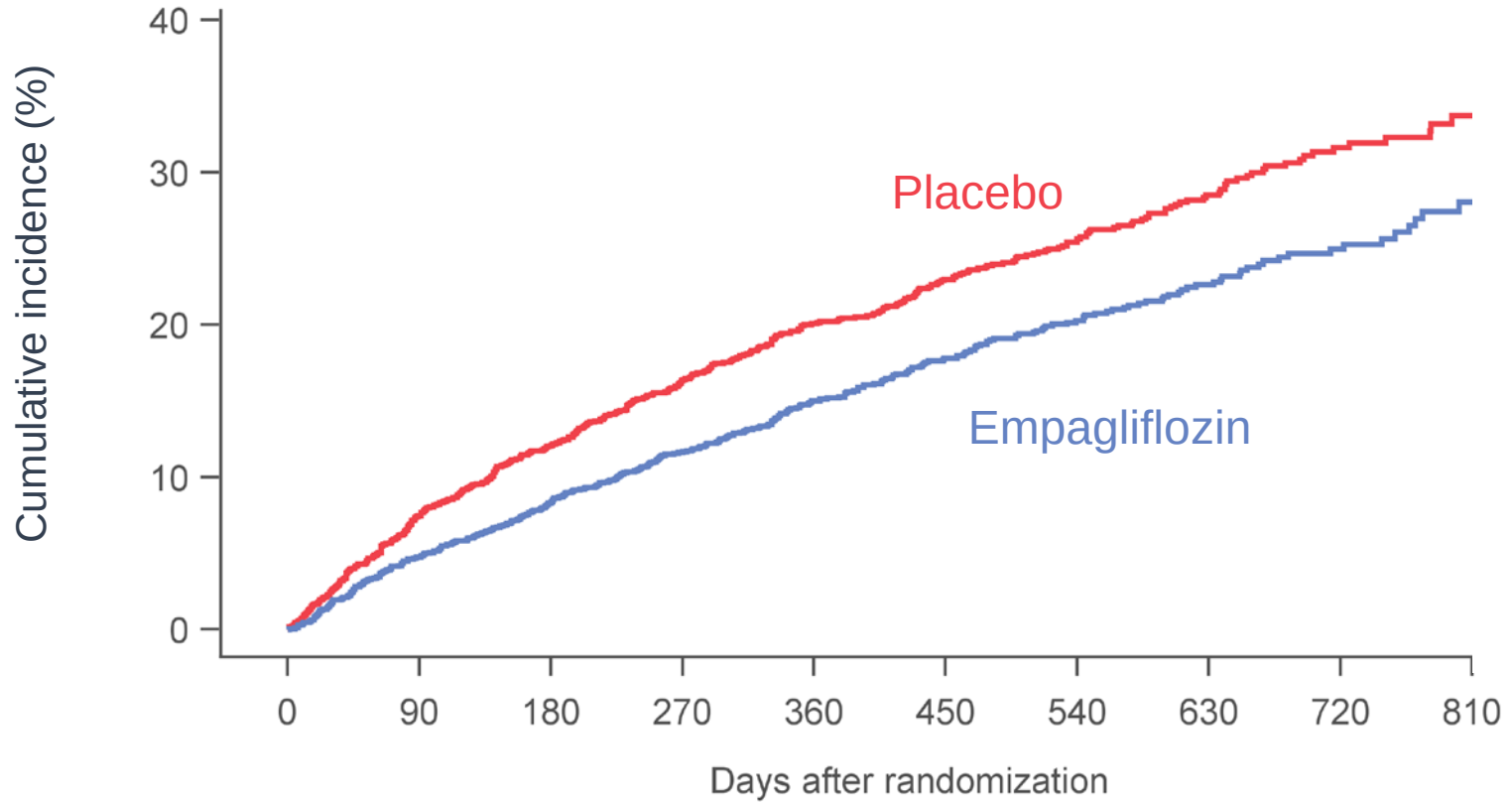
EMPEROR-Reduced: Time to Cardiovascular Death or Hospitalization for Heart Failure (Primary Endpoint)



462 patients with event
Rate: 21.0/100 patient-years

40% higher than in DAPA-HF

EMPEROR-Reduced: Time to Cardiovascular Death or Hospitalization for Heart Failure (Primary Endpoint)



462 patients with event
Rate: 21.0/100 patient-years

361 patients with event
Rate: 15.8/100 patient-years

HR 0.75
(95% CI 0.65, 0.86)
P < 0.0001

RRR 25%

ARR 5.2%

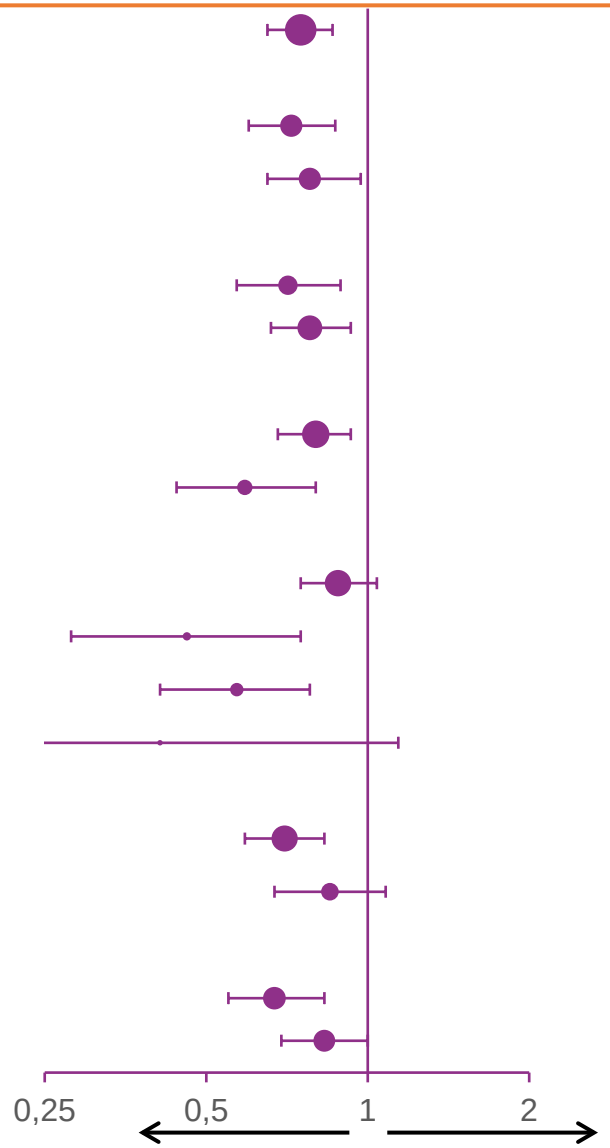
NNT = 19

EMPEROR-Reduced:
Effect on Individual Components of the Primary Endpoint

	Empagliflozin (n=1863)		Placebo (n=1867)		Hazard ratio (95% CI)	P value
	Number of events (%)	Events/100 patient-yr	Number of events (%)	Events/100 patient-yr		
Primary composite outcome	361 (19.4%)	15.8	462 (24.7%)	21.0	0.75 (0.65 – 0.86)	<0.0001
First hospitalization for heart failure	246 (13.2%)	10.7	342 (18.3%)	15.5	0.69 (0.59 – 0.81)	
Cardiovascular death	187 (10.0%)	7.6	202 (10.8%)	8.1	0.92 (0.75 – 1.12)	

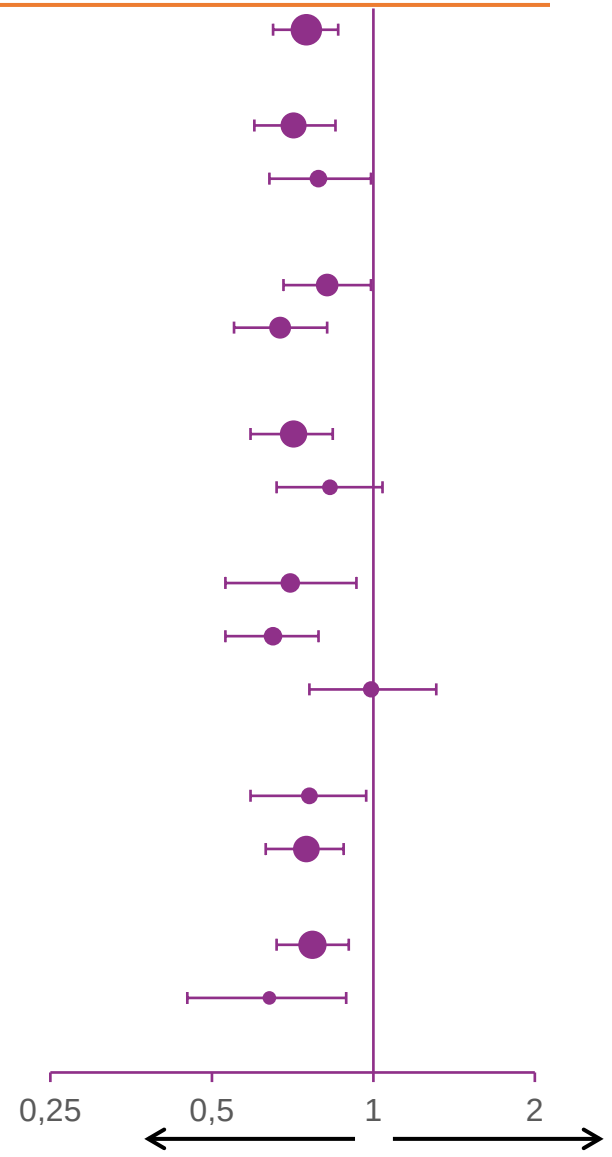
EMPEROR-Reduced: Primary Endpoint Subgroups

	Empagliflozin	Placebo	Hazard ratio (95% CI)
	n with event/N analysed		
Overall	361/1863	462/1867	0.75 (0.65, 0.86)
Baseline diabetes status			
Diabetic	200/927	265/929	0.72 (0.60, 0.87)
Non-diabetic	161/936	197/938	0.78 (0.64, 0.97)
Age, years			
<65	128/675	193/740	0.71 (0.57, 0.89)
≥65	233/1188	269/1127	0.78 (0.66, 0.93)
Sex			
Male	294/1426	353/1411	0.80 (0.68, 0.93)
Female	67/437	109/456	0.59 (0.44, 0.80)
Race			
White	264/1325	289/1304	0.88 (0.75, 1.04)
Black/African-American	24/123	48/134	0.46 (0.28, 0.75)
Asian	62/337	99/335	0.57 (0.41, 0.78)
Other	5/51	14/63	0.41 (0.15, 1.14)
Body mass index (kg/m^2)			
<30	226/1263	322/1300	0.70 (0.59, 0.83)
≥30	135/600	140/567	0.85 (0.67, 1.08
Baseline eGFR (CKD-EPI), ml/min/1.73 m^2			
<60	159/969	224/960	0.67 (0.55, 0.83)
≥60	202/893	237/906	0.83 (0.69, 1.00)

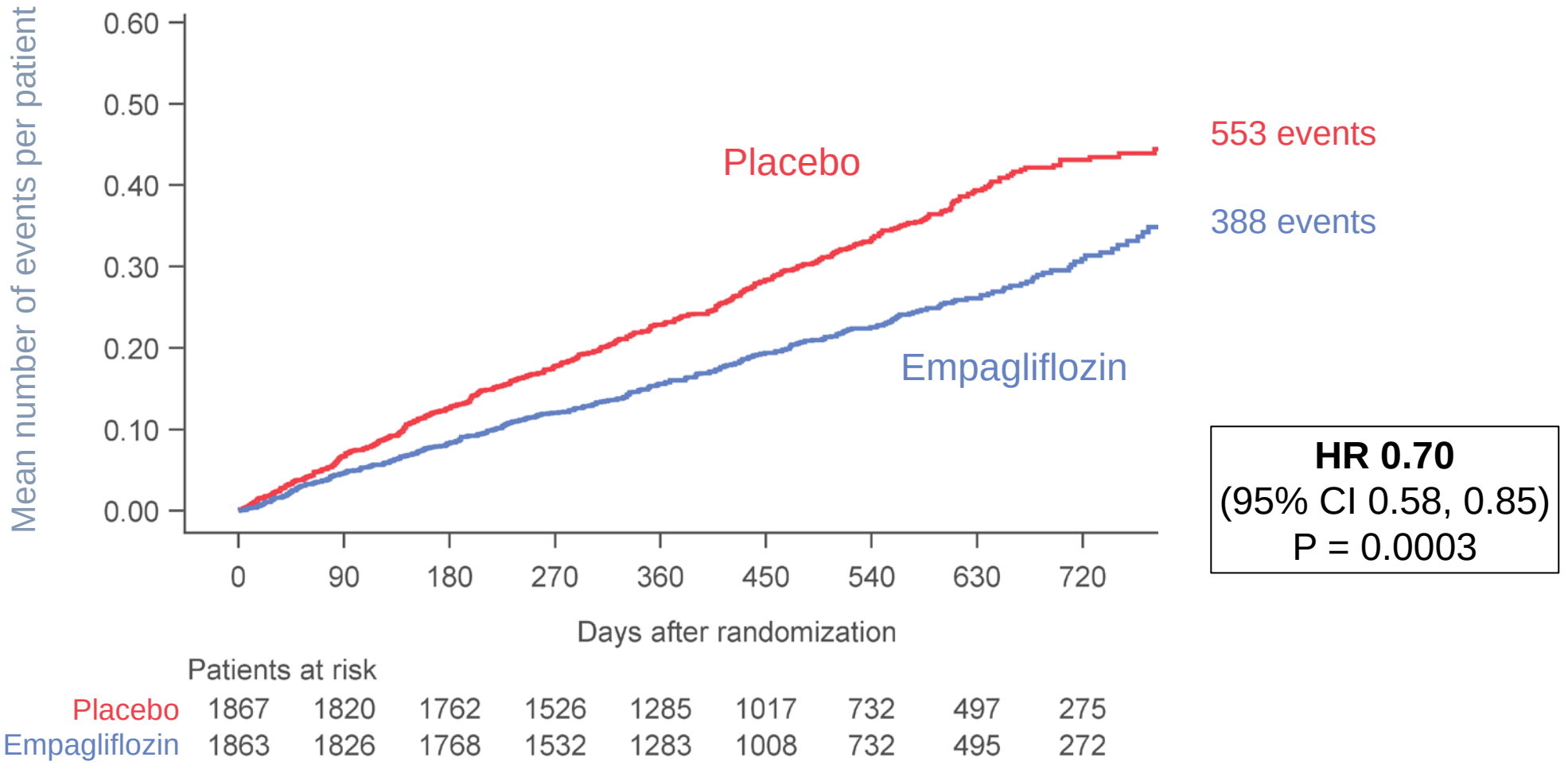


EMPEROR-Reduced: Primary Endpoint Subgroups

	Empagliflozin	Placebo	
	n with event/N analysed		HR (95% CI)
Overall	361/1863	462/1867	0.75 (0.65, 0.86)
Heart failure hospitalization within 12 months			
No	208/1286	285/1293	0.71 (0.60, 0.85)
Yes	153/577	177/574	0.79 (0.64, 0.99)
Etiology of heart failure			
Ischaemic	207/983	236/946	0.82 (0.68, 0.99)
Non-ischaemic	154/880	226/921	0.67 (0.55, 0.82)
Baseline NYHA functional class			
II	220/1399	299/1401	0.71 (0.59, 0.84)
III/IV	141/464	163/466	0.83 (0.66, 1.04)
Heart failure physiology			
LVEF ≤30% and NTproBNP <median	80/699	115/724	0.70 (0.53, 0.93)
LVEF ≤30% and NTproBNP ≥median	169/631	249/661	0.65 (0.53, 0.79)
LVEF >30%	108/526	97/475	0.99 (0.76, 1.31)
Use of mineralocorticoid receptor antagonist			
No	118/557	132/512	0.76 (0.59, 0.97)
Yes	243/1306	330/1355	0.75 (0.63, 0.88)
Use of angiotensin receptor neprilysin inhibitor			
No	310/1523	369/1480	0.77 (0.66, 0.90)
Yes	51/340	93/387	0.64 (0.45, 0.89)

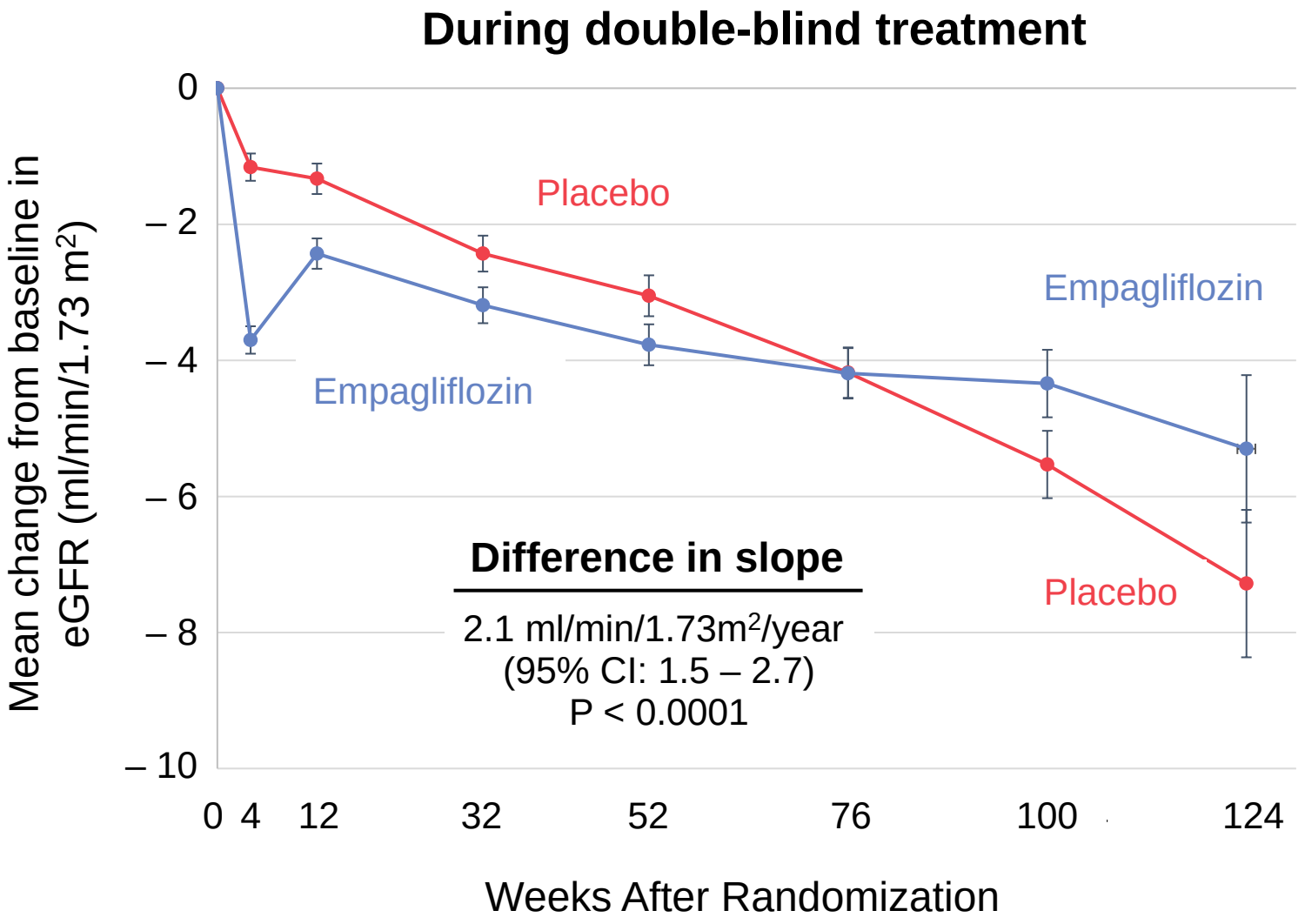


EMPEROR-Reduced: Total Hospitalizations for Heart Failure (First and Recurrent) — Hierarchical Endpoint #2



HR 0.70
(95% CI 0.58, 0.85)
P = 0.0003

EMPEROR-Reduced: Slope of Decline in Glomerular Filtration Rate — Hierarchical Endpoint #3



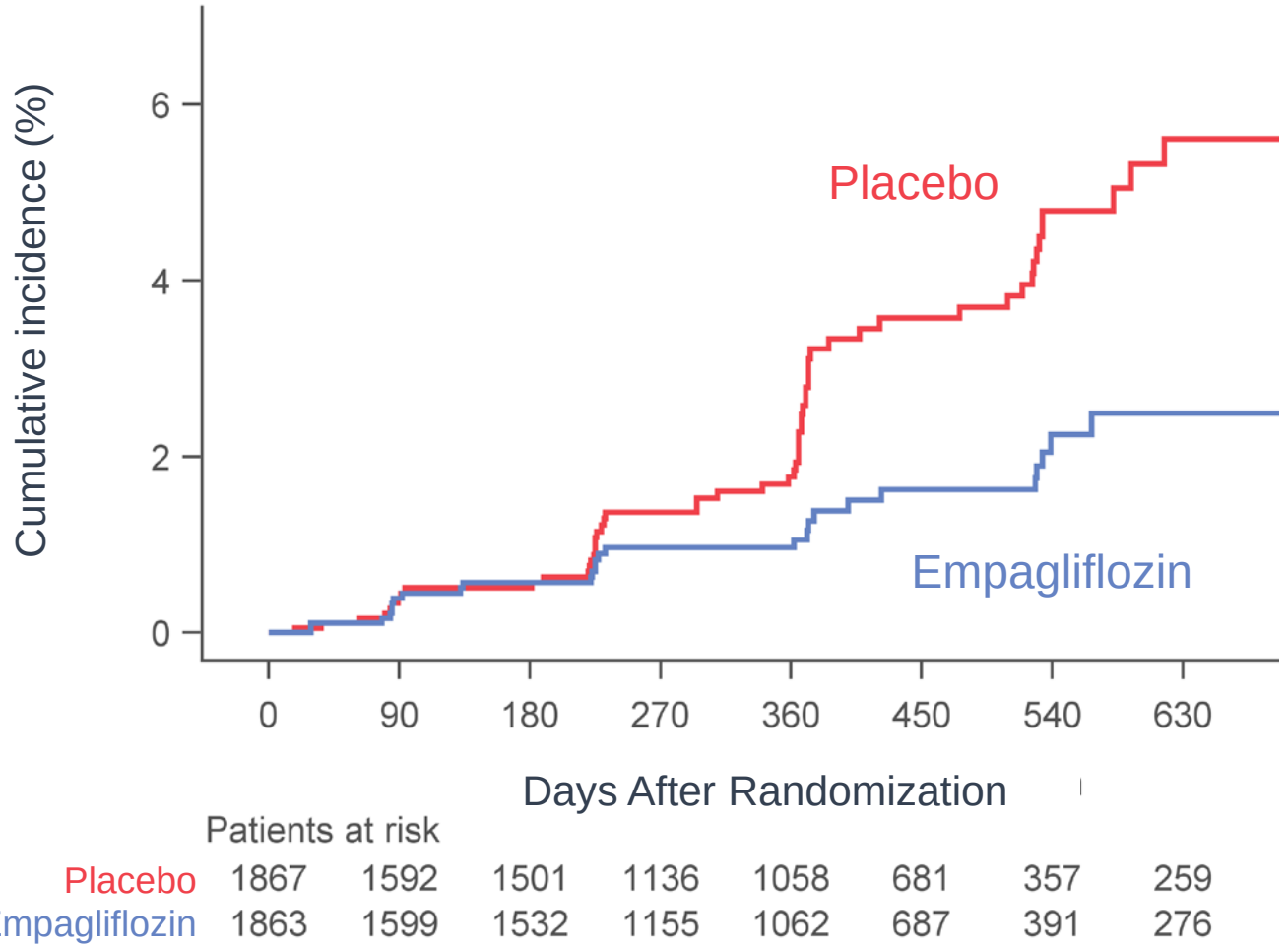
In 966 patients, eGFR was reassessed at the end of the trial 23-42 days after the withdrawal of double-blind therapy, thus allowing unconfounded assessment of the effects of treatment. Over 16 months, eGFR deteriorated by

– 4.2 ml/min/1.73 m² on placebo

– 0.9 m/min/1.73 m² on empagliflozin

P < 0.0001

EMPEROR-Reduced: Composite Renal Endpoint

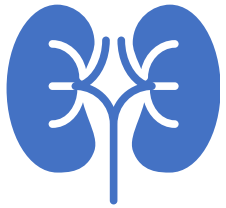


58 patients with event
Rate: 3.1/100 patient-years

30 patients with event
Rate: 1.6/100 patient-years

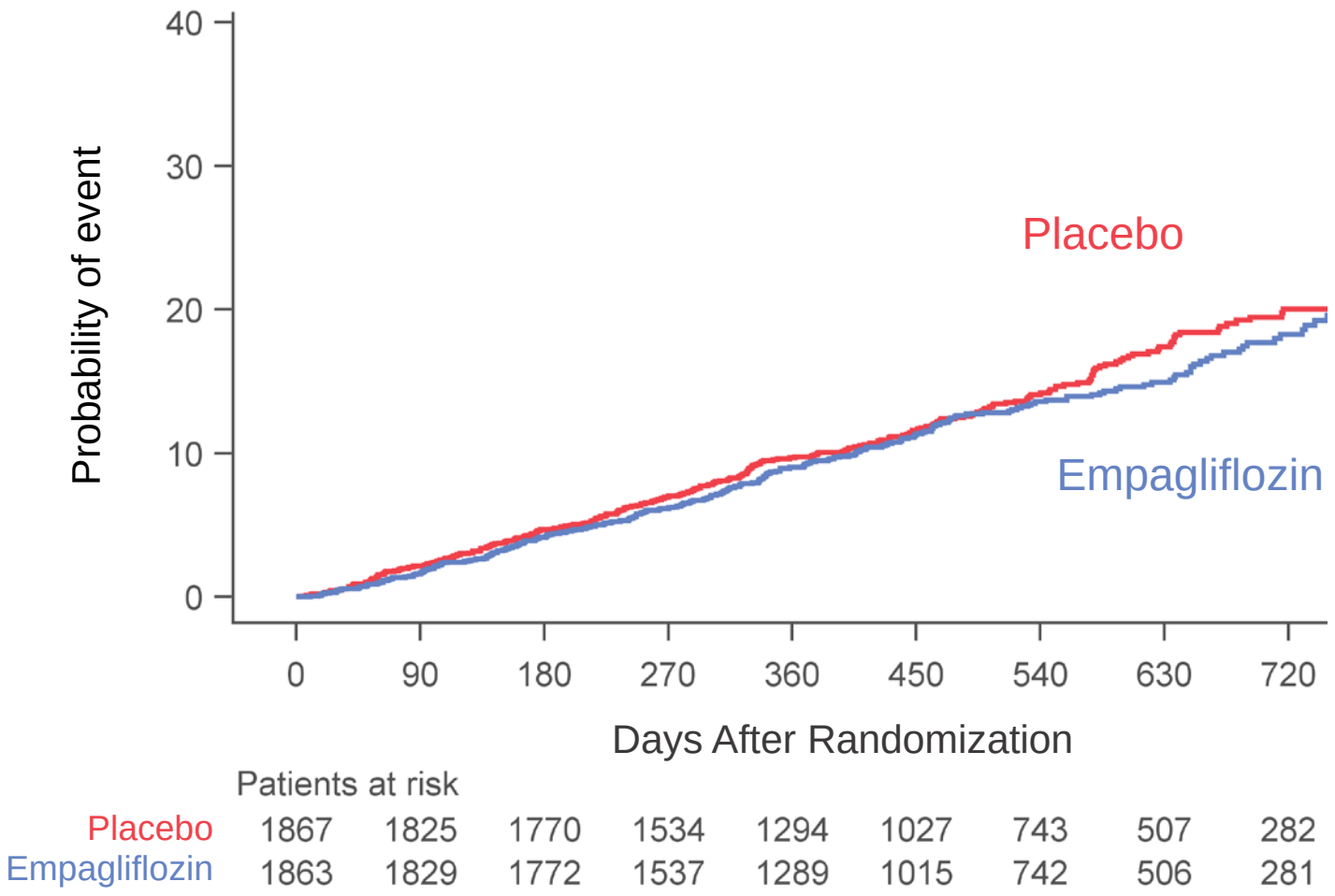
HR 0.50
(95% CI 0.32, 0.77)

EMPEROR-Reduced Achieved All Three Hierarchically Specified Endpoints at P < 0.001

	**Primary Endpoint** Composite of cardiovascular death or heart failure hospitalization	**Achieved** **P < 0.001**
	**First Secondary Endpoint** Total (first and recurrent heart failure hospitalizations)	**Achieved** **P < 0.001**
	**Second Secondary Endpoint** Slope of decline in glomerular filtration rate over time	**Achieved** **P < 0.001**

Also achieved success on composite renal endpoint, KCCQ clinical summary score, and total number of hospitalizations for any reason (all nominal P < 0.01)

EMPEROR-Reduced: All-Cause Mortality



266 patients with event
Rate: 10.7/100 patient-years

249 patients with event
Rate: 10.1/100 patient-years

HR 0.92
(95% CI 0.77, 1.10)

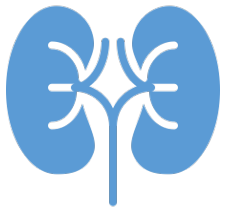
EMPEROR-Reduced: Vital Signs and Biomarkers

	Empagliflozin	Placebo	Treatment Difference
Glycated hemoglobin (%) in patients with diabetes– mean (SE)	– 0.28 ± 0.03	– 0.12 ± 0.03	– 0.16 (–0.25 to – 0.08)
Hematocrit (%) – mean (SE)	1.98 ± 0.10	– 0.38 ± 0.10	2.36 (2.08 to 2.63)
NT-proBNP (pg/ml) – median (IQR)	–244 (-890, 260)	–141 (-787, 585)	0.87 (0.82 to 0.93)
Body weight (kg) – mean (SE)	– 0.73 ± 0.13	0.08 ± 0.13	– 0.82 (–1.18 to –0.45)
Systolic blood pressure (mm Hg) – mean (SE)	– 2.4 ± 0.4	– 1.7 ± 0.4	– 0.7 (–1.8 to 0.4)

EMPEROR-Reduced: Adverse Events

	Empagliflozin (n=1863)	Placebo (n=1863)
Serious adverse events	772 (41.4)	896 (48.1)
Related to cardiac disorder	**500 (26.8)**	**634 (34.0)**
Related to worsening renal function	**59 (3.2)**	**95 (5.1)**
Selected adverse events of special interest		
Volume depletion	197 (10.6)	184 (9.9)
Hypotension	176 (9.4)	163 (8.7)
Symptomatic hypotension	106 (5.7)	103 (5.5)
Hypoglycemia	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)
Lower limb amputations	13 (0.7)	10 (0.5)

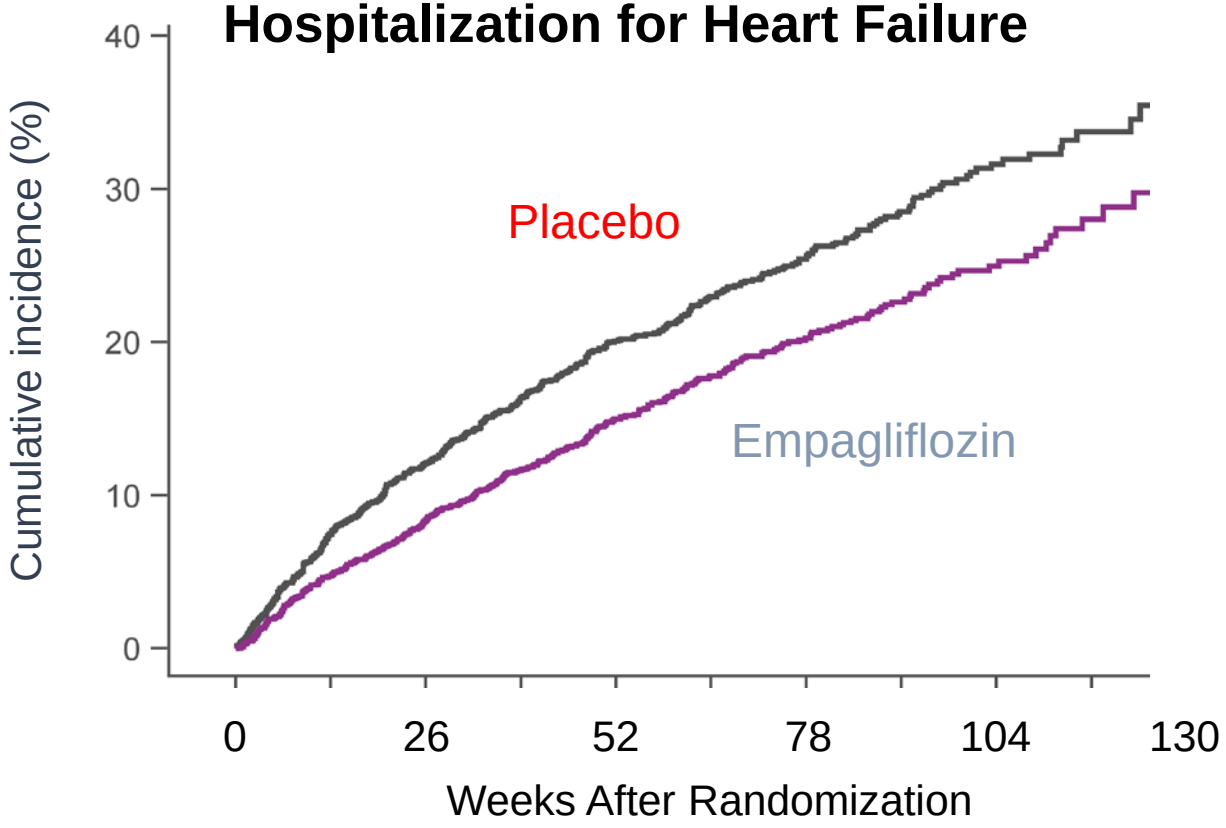
SGLT2 Inhibition With Empagliflozin Is Effective in Heart Failure With a Reduced Ejection Fraction With or Without Diabetes

	**Primary Endpoint** Composite of cardiovascular death or heart failure hospitalization	**25% ↓ in risk** **P < 0.001**
	**First Secondary Endpoint** Total (first and recurrent heart failure hospitalizations)	**30% ↓ in risk** **P < 0.001**
	**Second Secondary Endpoint** Slope of decline in glomerular filtration rate over time	**P < 0.001** **(50% ↓ in renal events)**

Also achieved success on composite renal endpoint, KCCQ clinical summary score, and total number of hospitalizations for any reason (all nominal P < 0.01)

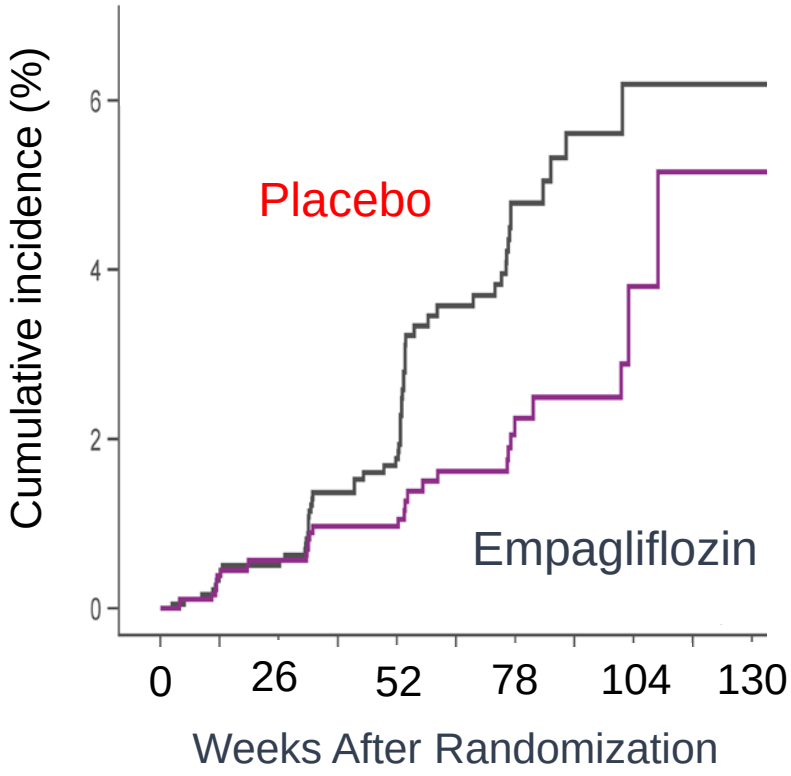
Empagliflozin Prevented Both Serious Heart Failure and Serious Kidney Failure Events

Cardiovascular Death or Hospitalization for Heart Failure



Hazard ratio 0.75 (25% reduction in risk)
(95% CI 0.65, 0.86), P < 0.0001

Composite Renal Endpoint



Hazard ratio 0.50 (50% reduction in risk)
(95% CI 0.32, 0.77), P = 0.0019

EMPEROR-Preserved Trial

Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction

Stefan D. Anker, MD PhD & Javed Butler, MD on behalf of the EMPEROR-Preserved Executive Committee, Trial Committees, Investigators & Coordinators

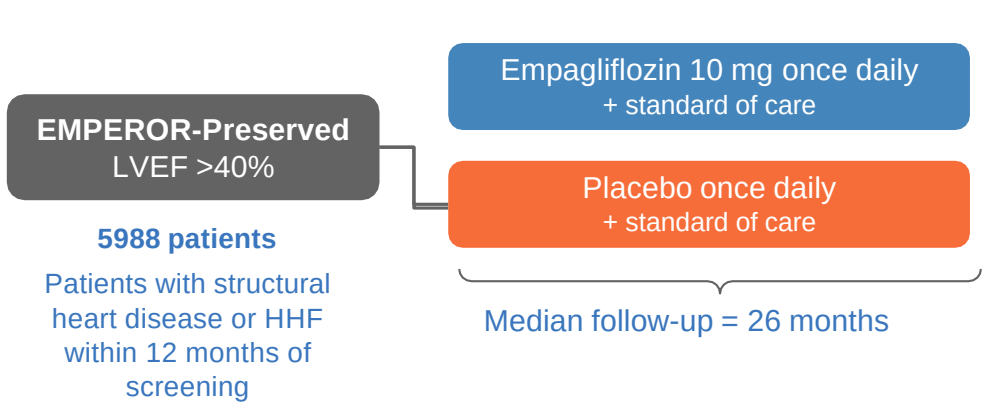
Dept. of Cardiology & BCRT (CVK), Charité Berlin, Germany
University of Mississippi Medical Center, Jackson, Mississippi, USA

EMPEROR-Preserved – Study Design

Phase III randomised double-blind placebo-controlled trial

Aim: to evaluate efficacy and safety of empagliflozin versus placebo, on top of standard of care, in **patients with HFpEF** with or without diabetes

Population: T2DM & non-T2DM, aged ≥18 years, chronic HF (NYHA class II–IV), eGFR≥20



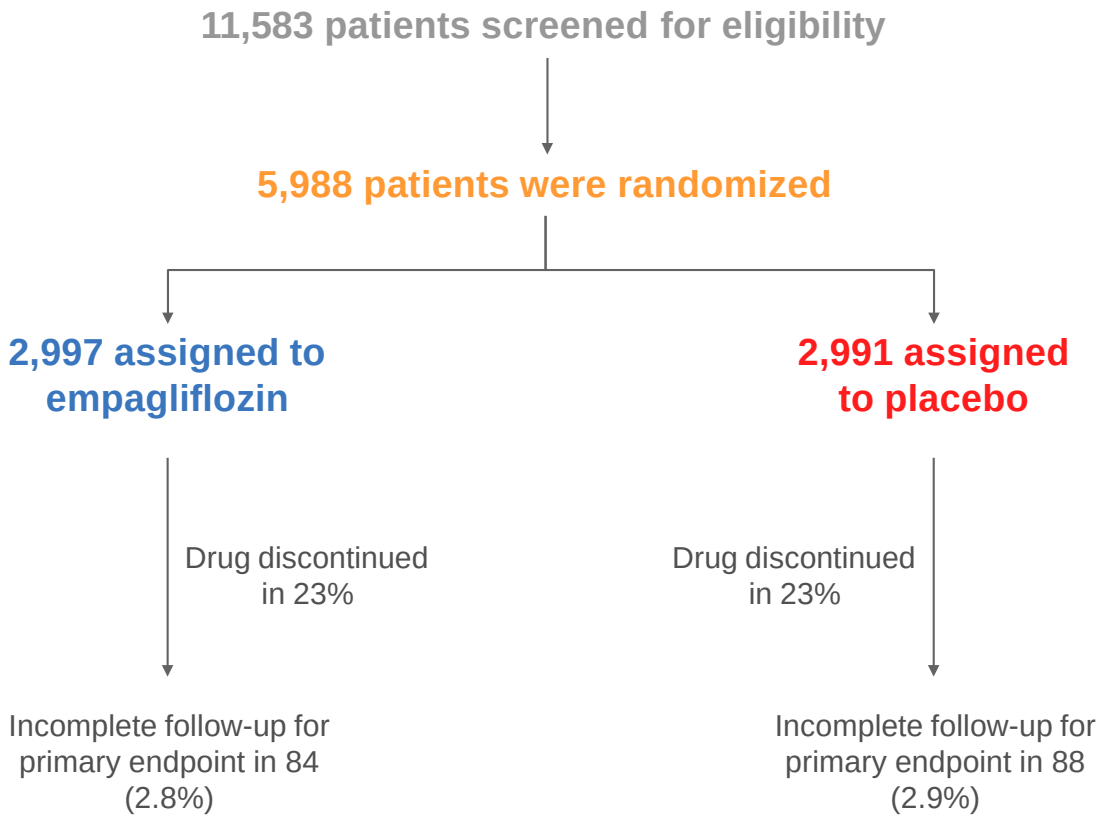
COMPOSITE PRIMARY ENDPOINT

Time to first event of adjudicated cardiovascular death or adjudicated HHF

SECONDARY ENDPOINTS

- **First and recurrent adjudicated HF hospitalisation events**
- **Slope of change in eGFR (CKD-EPI)**

Patient Disposition



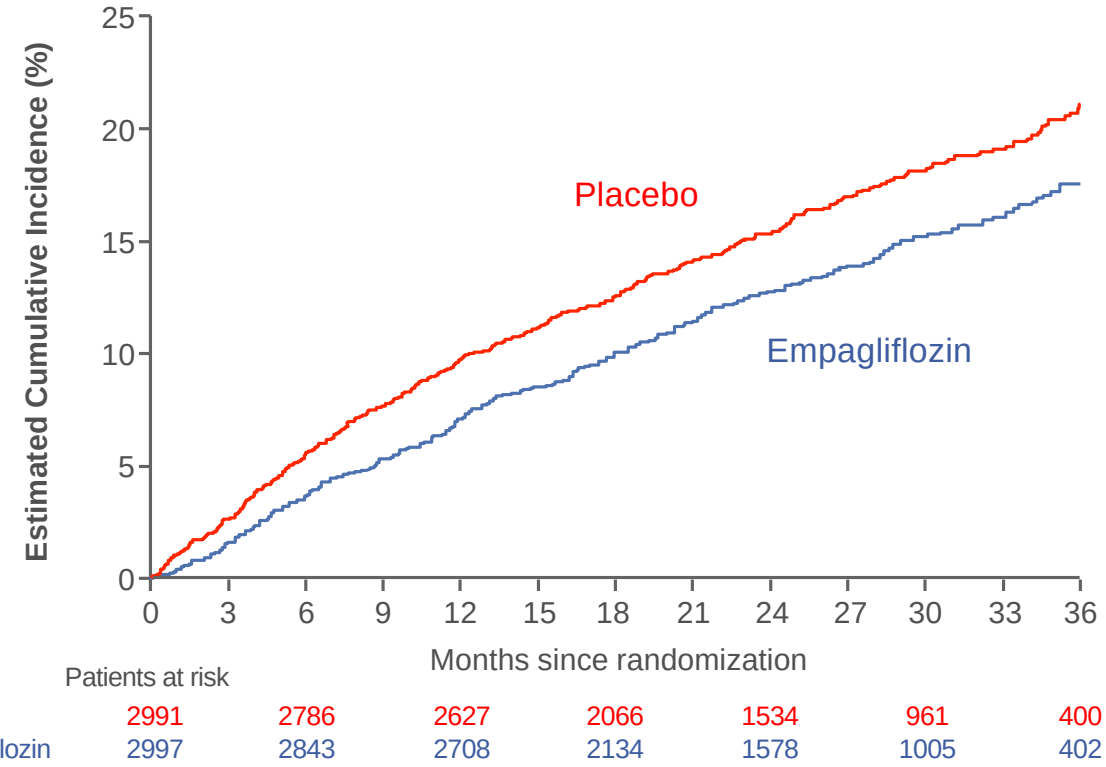
Median follow-up 26 months

Final vital status known in 99.4%
(all but 36 patients)

Demographics and Baseline Characteristics

	Empagliflozin (n=2997)	Placebo (n=2991)
Age (yr)	71.8 ± 9.3	71.9 ± 9.6
Women (%)	1338 (45)	1338 (45)
Diabetes mellitus (%)	1466 (49)	1472 (49)
Ischaemic HF (%)	1079 (36)	1038 (35)
NYHA functional class II (%)	2432 (81)	2451 (82)
LV ejection fraction (%)	54.3 ± 8.8	54.3 ± 8.8
NT-proBNP (median, IQR), pg/mL	994 (501, 1740)	946 (498, 1725)
Atrial fibrillation	1543 (51)	1514 (51)
Glomerular filtration rate (mL/min/1.73 m^2)	60.6 ± 19.8 (50% <60)	60.6 ±19.9 (50% <60)
Co-medications of interest		
RAASi ± ARNI	2428 (81)	2404 (80)
MRA	1119 (37)	1125 (38)
Beta blocker	2598 (87)	2569 (86)
Statins	2042 (68)	2089 (70)

Primary Endpoint
Composite of Cardiovascular Death or HF Hospitalization



HR 0.79
(95% CI 0.69, 0.90)
P = 0.0003

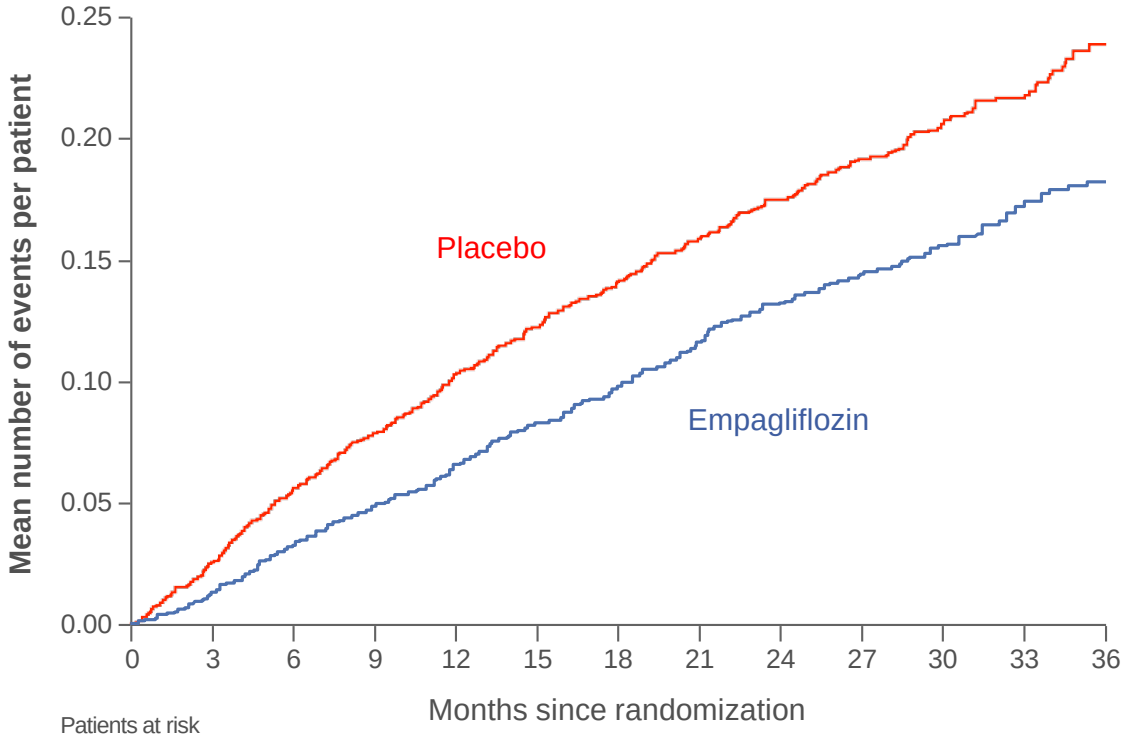
Placebo:
511 patients with event
Rate: 8.7 per 100 patient-years

Empagliflozin:
415 patients with event
Rate: 6.9 per 100 patient-years

Primary endpoint: individual components

	Empagliflozin (n=2997)		Placebo (n=2991)		Hazard ratio (95% CI)	P value
	Number of events (%)	Events/100 patient-yrs	Number of events (%)	Events/100 patient-yrs		
Primary composite outcome	415 (13.8%)	6.9	511 (17.1%)	8.7	0.79 (0.69 – 0.90)	0.0003
First hospitalization for heart failure	259 (8.6%)	4.3	352 (11.8%)	6.0	0.71 (0.60 – 0.83)	
Cardiovascular death	219 (7.3%)	3.4	244 (8.2%)	3.8	0.91 (0.76 – 1.09)	

First Secondary Endpoint: Total (First and Recurrent) HF Hospitalizations



Patients at risk

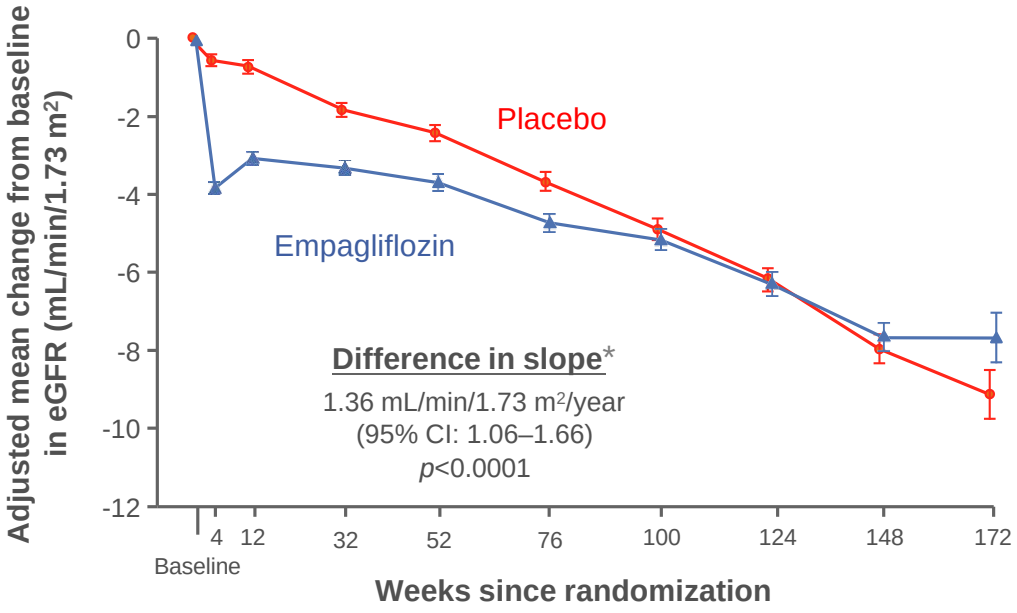
Placebo	2991	2901	2816	2258	1695	1061	448
Empagliflozin	2997	2913	2817	2247	1684	1081	446

HR 0.73
(95% CI 0.61, 0.88)
P = 0.0009

Empagliflozin:
407 heart failure hospitalisation events

Placebo:
541 heart failure hospitalisation events

Second Secondary Endpoint: Slope of Decline in GFR Over Time



In 3176 patients, eGFR was reassessed 23-42 days after the withdrawal of double-blind therapy.** Over 28 months, eGFR deteriorated by

– 3.3 mL/min/1.73 m² on Empagliflozin

– 5.7 mL/min/1.73 m² on placebo

P < 0.0001

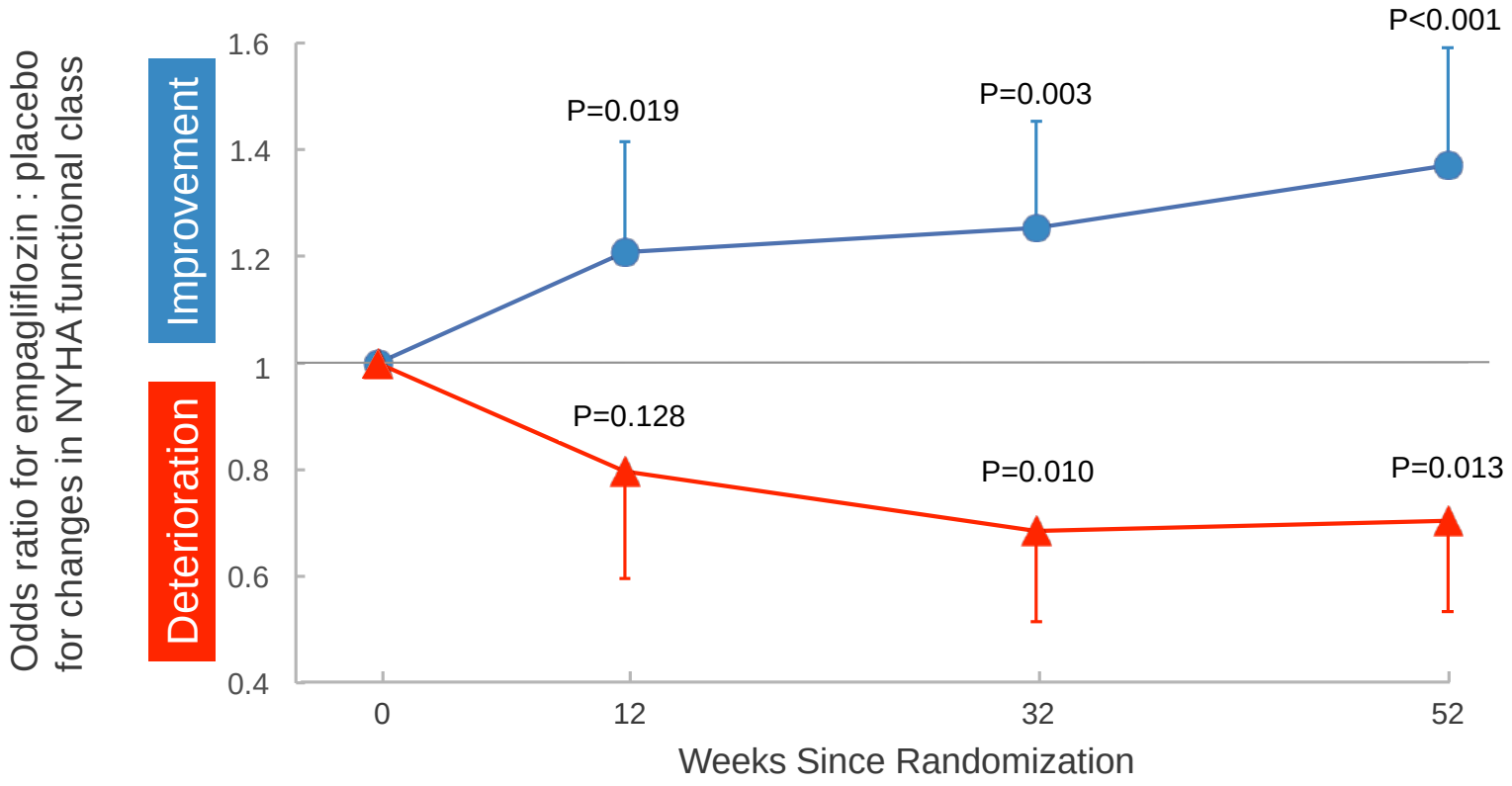
** The eGFR slope is analyzed on the basis of on-treatment data*

*** this represents the unconfounded assessment of the treatment effect*

Success on all 3 prespecified hierarchical endpoints

	**Primary Endpoint** Composite of cardiovascular death or heart failure hospitalization	**21% ↓ in risk** **P = 0.0003**
	**First Secondary Endpoint** Total (first and recurrent) heart failure hospitalizations	**27% ↓ in risk** **P = 0.0009**
	**Second Secondary Endpoint** Slope of decline in glomerular filtration rate over time	**P < 0.0001** Difference: 1.36 mL/min/1.73 m^2 per year

Effects of Empagliflozin on NYHA Class



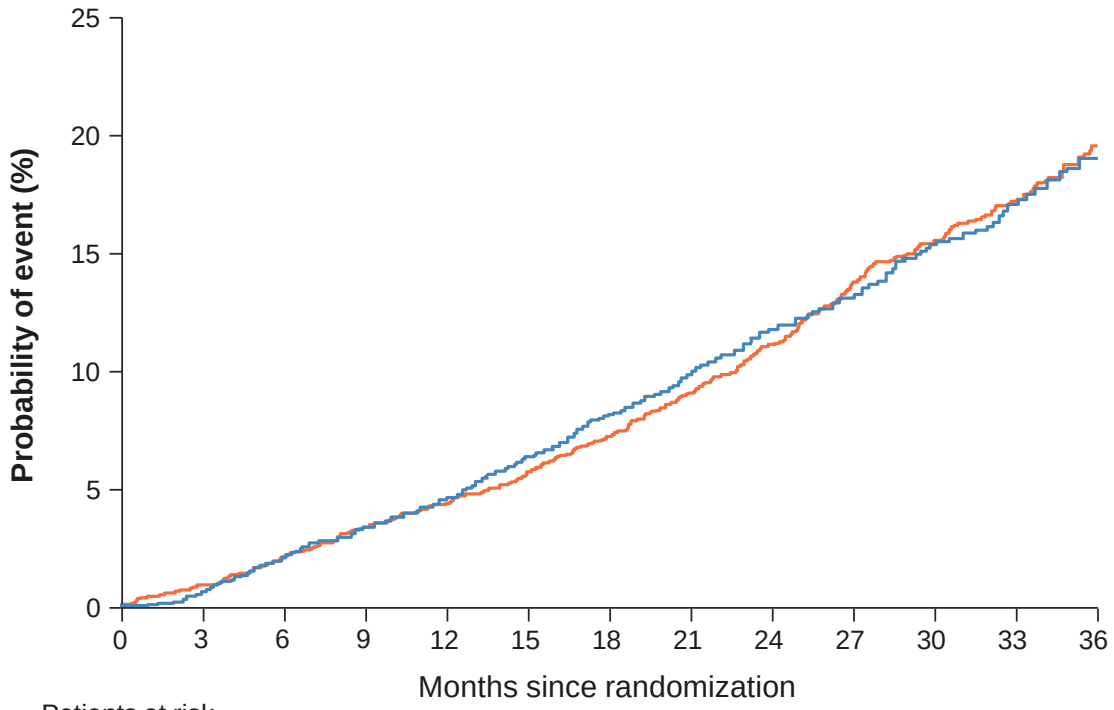
Vital Signs and Biomarkers

	Empagliflozin	Placebo	Treatment Difference	P-value
Glycated hemoglobin (%) in patients with diabetes– mean (SE)	– 0.16 ± 0.02	0.03 ± 0.02	– 0.19 (–0.25 to –0.14)	<0.0001
Hematocrit (%) – mean (SE)	1.94 ± 0.07	– 0.41 ± 0.07	2.36 (2.17 to 2.54)	<0.0001
NT-proBNP (pg/mL) – median (IQR)	– 29 (-335, 263)	– 9 (-286, 322)	0.95* (0.91 to 0.99)	0.0071
Body weight (kg) – mean (SE)	– 1.39 ± 0.09	– 0.11 ± 0.09	– 1.28 (–1.54 to –1.03)	<0.0001
Systolic blood pressure (mm Hg) – mean (SE)	– 1.8 ± 0.3	– 0.6 ± 0.3	– 1.2 (–2.0 to –0.5)	0.0071

*Value given is geometric mean ratio

Change from baseline to 52 weeks

All-Cause Mortality



Patients at risk

Placebo	2991	2923	2849	2302	1738	1107	471
Empagliflozin	2997	2930	2847	2287	1725	1118	462

HR 1.00
(95% CI 0.87, 1.15)
P = 0.99

Empagliflozin:
422 patients with event
Rate: 6.6 / 100 patient-years

Placebo:
427 patients with event
Rate: 6.7 / 100 patient-years

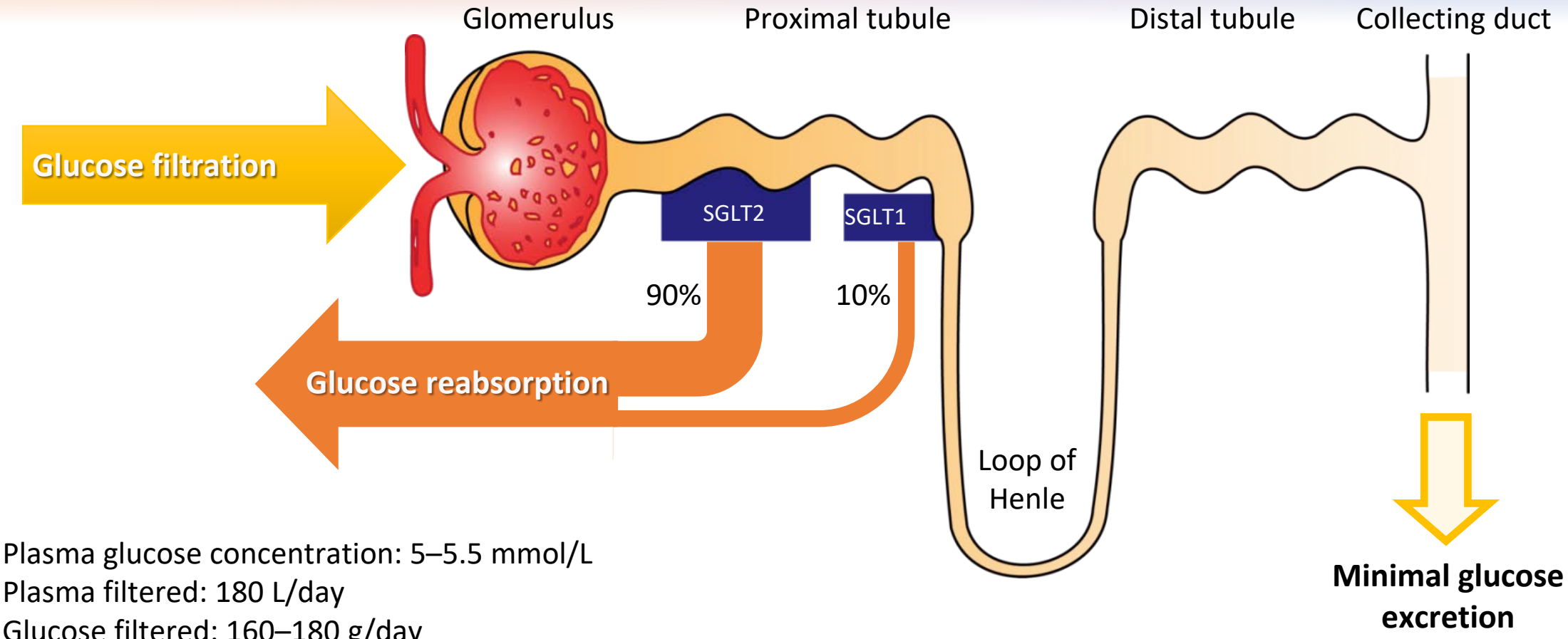
Safety: Selected Adverse Events

	Empagliflozin (N=2996) n (%)	Placebo (N=2989) n (%)
Serious adverse events	1436 (47.9)	1543 (51.6)
Selected adverse events of special interest		
Hypotension	311 (10.4)	257 (8.6)
Symptomatic hypotension	197 (6.6)	156 (5.2)
Hypoglycemia	73 (2.4)	78 (2.6)
Ketoacidosis	4 (0.1)	5 (0.2)
Bone fractures	134 (4.5)	126 (4.2)
Lower limb amputations	12 (0.4)	17 (0.6)
Urinary tract infections	297 (9.9)	243 (8.1)
Genital infections	67 (2.2)	22 (0.7)

EMPEROR-Preserved in the Context of Other Studies

	DELIVER[6]	EMPEROR-PRESERVED[7]	TOPCAT*[16]	PARAGON-HF[19]	CHARM-PRESERVED[24]
Size	N = 6,263	N = 5,988	N = 3,445	N = 4,822	N = 3,023
Agent	Dapagliflozin	Empagliflozin	Spironolactone	Sacubitril/valsartan	Candesartan
Median age, y	72	72	69†	73	67
Female sex	44%	45%	52%	52%	40%
Median follow-up, y	2.3	2.2	3.3	2.9	3.1
EF entry criteria	>40%	>40%	≥45%	≥45%	>40%
Mean baseline LVEF	54%	54%	56%†	58%	54%
Proportion with T2DM	45%	49%	33%	43%	29%
HF medical therapy					
Diuretic agent	77%	NR	82%	95%	75%
ACE inhibitor or ARB	73%	81%	84%	86%	19%‡
ARNI	5%	2%	N/A	N/A	N/A
Beta-blocker	83%	86%	78%	80%	56%
MRA	43%	37%	N/A	26%	12%
Primary composite outcome, HR or rate ratio (95% CI)	Worsening HF and CV death: HR: 0.82 (0.73-0.92)	Hospitalization for HF and CV death: HR: 0.79 (0.69-0.90)	Hospitalization for HF, aborted cardiac arrest, CV death: HR: 0.89 (0.77-1.04)	Total hospitalizations for HF and CV death: Rate ratio: 0.87 (0.75-1.01)	Hospitalization for HF and CV death: HR: 0.86 (0.74-1.00)
Hospitalization for HF, HR or rate ratio (95% CI)	HR: 0.77 (0.67-0.89)	HR: 0.71 (0.60-0.83)	HR: 0.83 (0.69-0.99)	Rate ratio: 0.85 (0.72-1.00)	HR: 0.84 (0.70-1.00)
Urgent visit for HF, HR (95% CI)	0.76 (0.55-1.07)	NR	NR	NR	NR
CV death, HR (95% CI)	0.88 (0.74-1.05)	0.91 (0.76-1.09)	0.90 (0.73-1.12)	0.95 (0.79-1.16)	0.95 (0.76-1.18)

Renal glucose handling in the nephron of the healthy individual

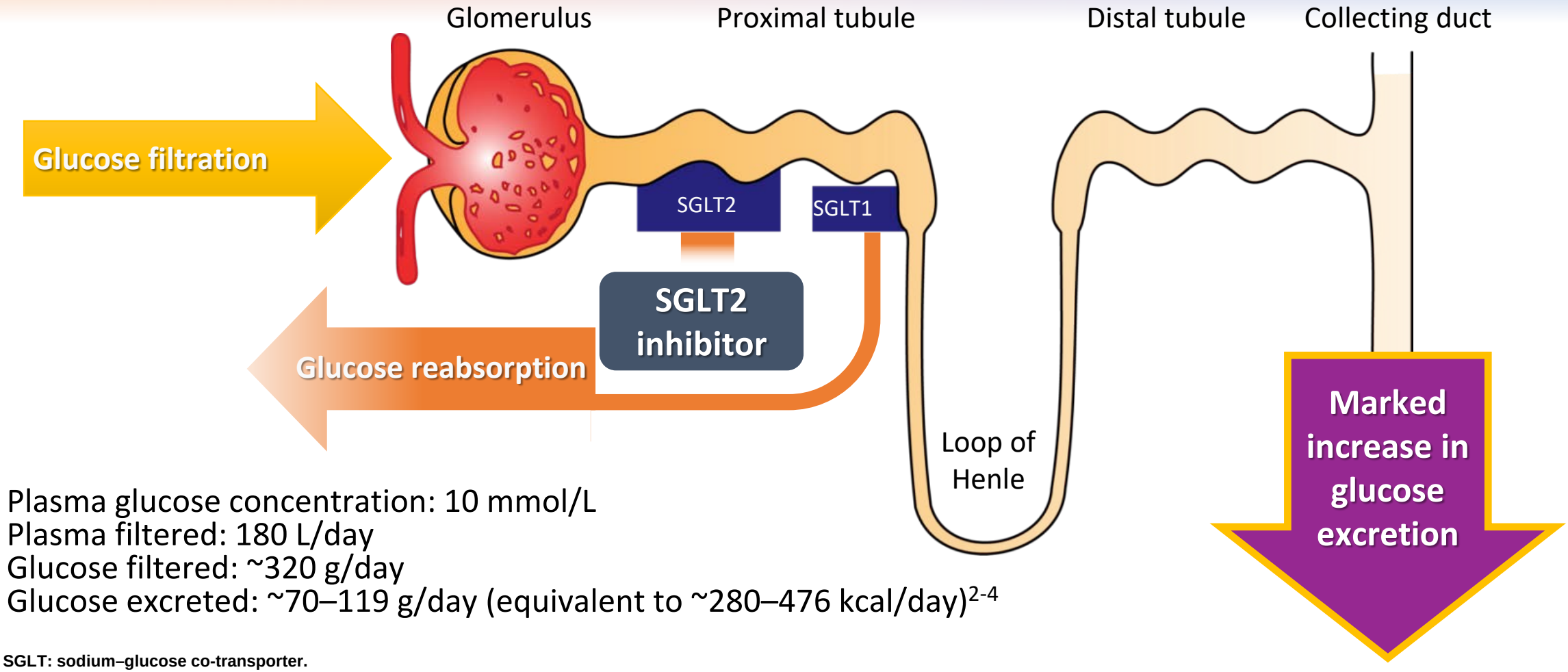


- Plasma glucose concentration: 5–5.5 mmol/L
- Plasma filtered: 180 L/day
- Glucose filtered: 160–180 g/day
- Glucose excreted: Minimal

SGLT: sodium–glucose co-transporter.

Figure adapted from: Bailey CJ. *Trends Pharmacol Sci.* 2011;32:63–71.

SGLT2 inhibition lowers the elevated renal threshold for glucose in type 2 diabetes



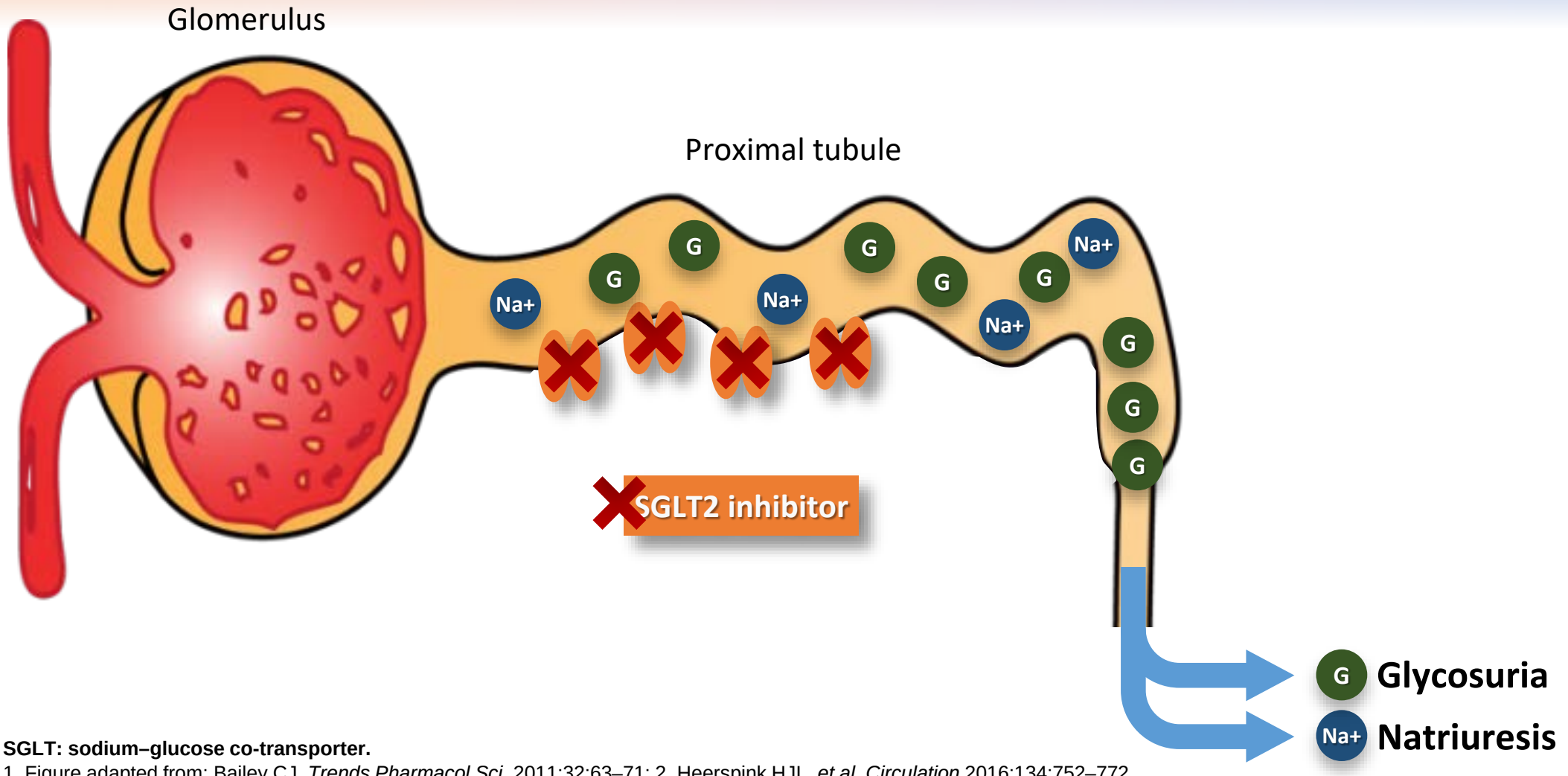
- Plasma glucose concentration: 10 mmol/L
- Plasma filtered: 180 L/day
- Glucose filtered: ~320 g/day
- Glucose excreted: ~70–119 g/day (equivalent to ~280–476 kcal/day)[2-4]

SGLT: sodium–glucose co-transporter.

Figure adapted from: Bailey CJ. *Trends Pharmacol Sci.* 2011;32:63–71.

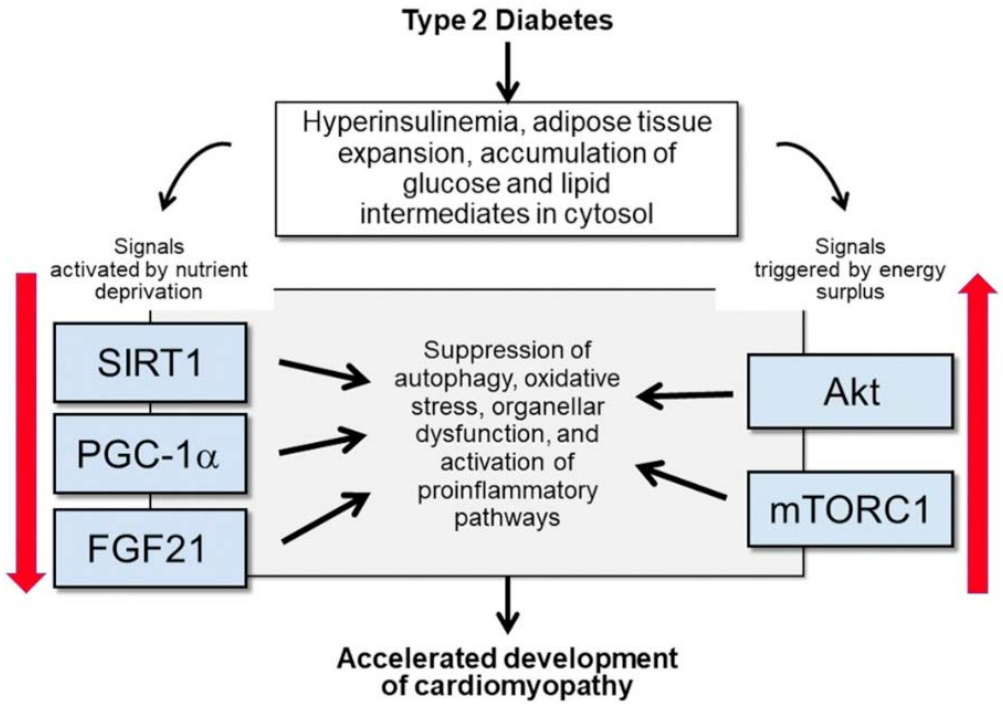
1. DeFronzo RA *et al. Diabetes Obes Metab.* 2012;14:5–14; 2. Invokana (canagliflozin). Summary of Product Characteristics; 3. Jardiance (empagliflozin). Summary of Product Characteristics; 4. Forxiga (dapagliflozin). Summary of Product Characteristics. All SmPCs available at: https://www.medicines.org.uk/emc/ (accessed April 2018).

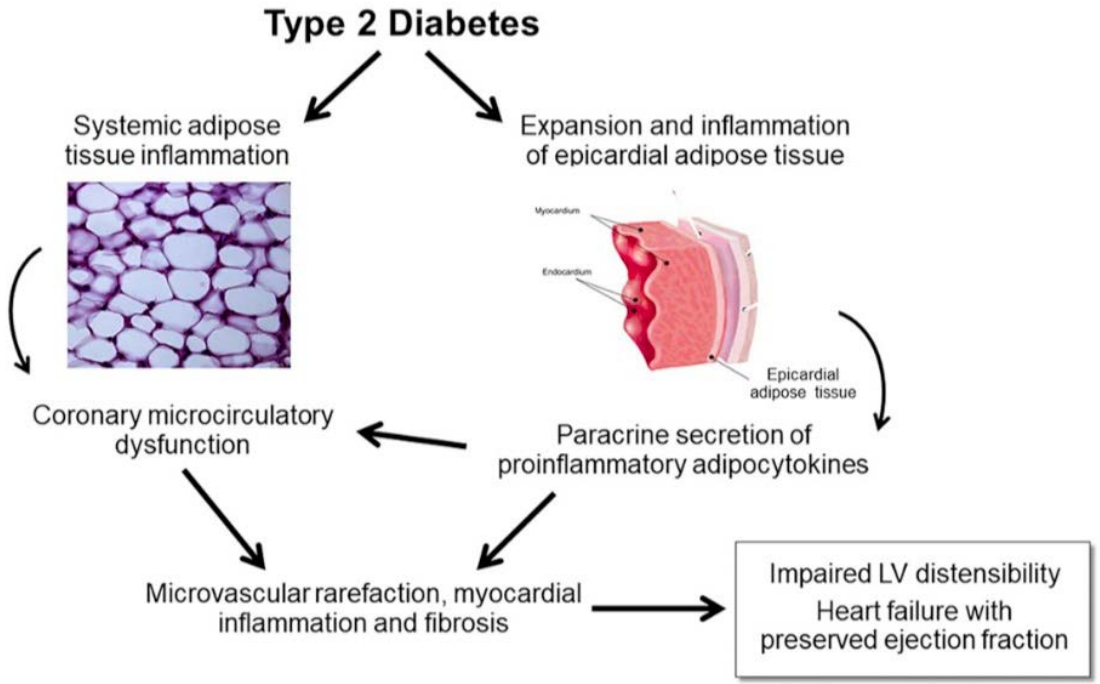
SGLT2 inhibitors lead to dual inhibition



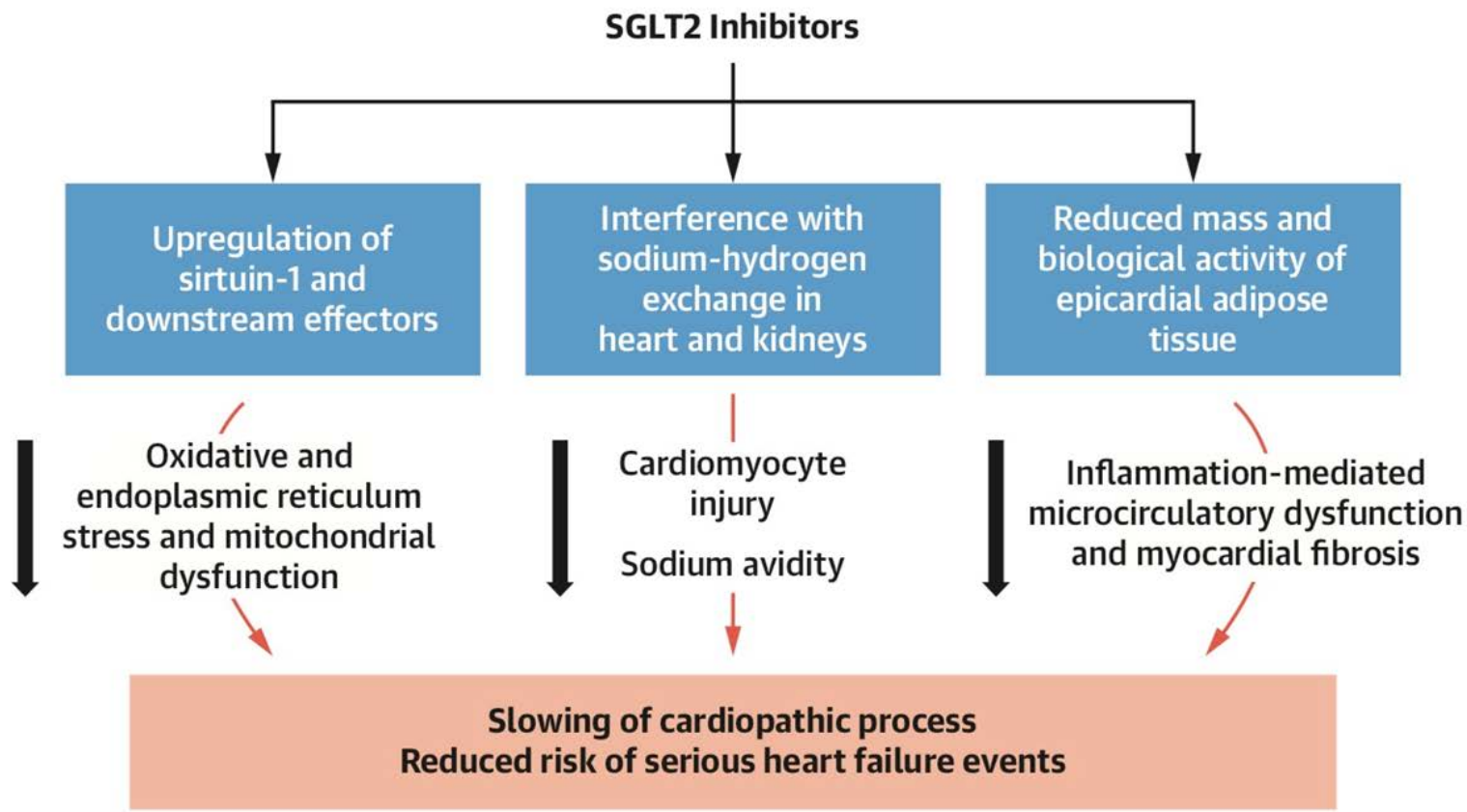
SGLT: sodium–glucose co-transporter.

1. Figure adapted from: Bailey CJ. *Trends Pharmacol Sci.* 2011;32:63–71; 2. Heerspink HJL, *et al. Circulation* 2016;134:752–772.


Type 2 Diabetes
Hyperinsulinemia, adipose tissue expansion, accumulation of glucose and lipid intermediates in cytosol
Signals activated by nutrient deprivation
Signals triggered by energy surplus
SIRT1
PGC-1α
FGF21
Suppression of autophagy, oxidative stress, organellar dysfunction, and activation of proinflammatory pathways
Akt
mTORC1
Accelerated development of cardiomyopathy

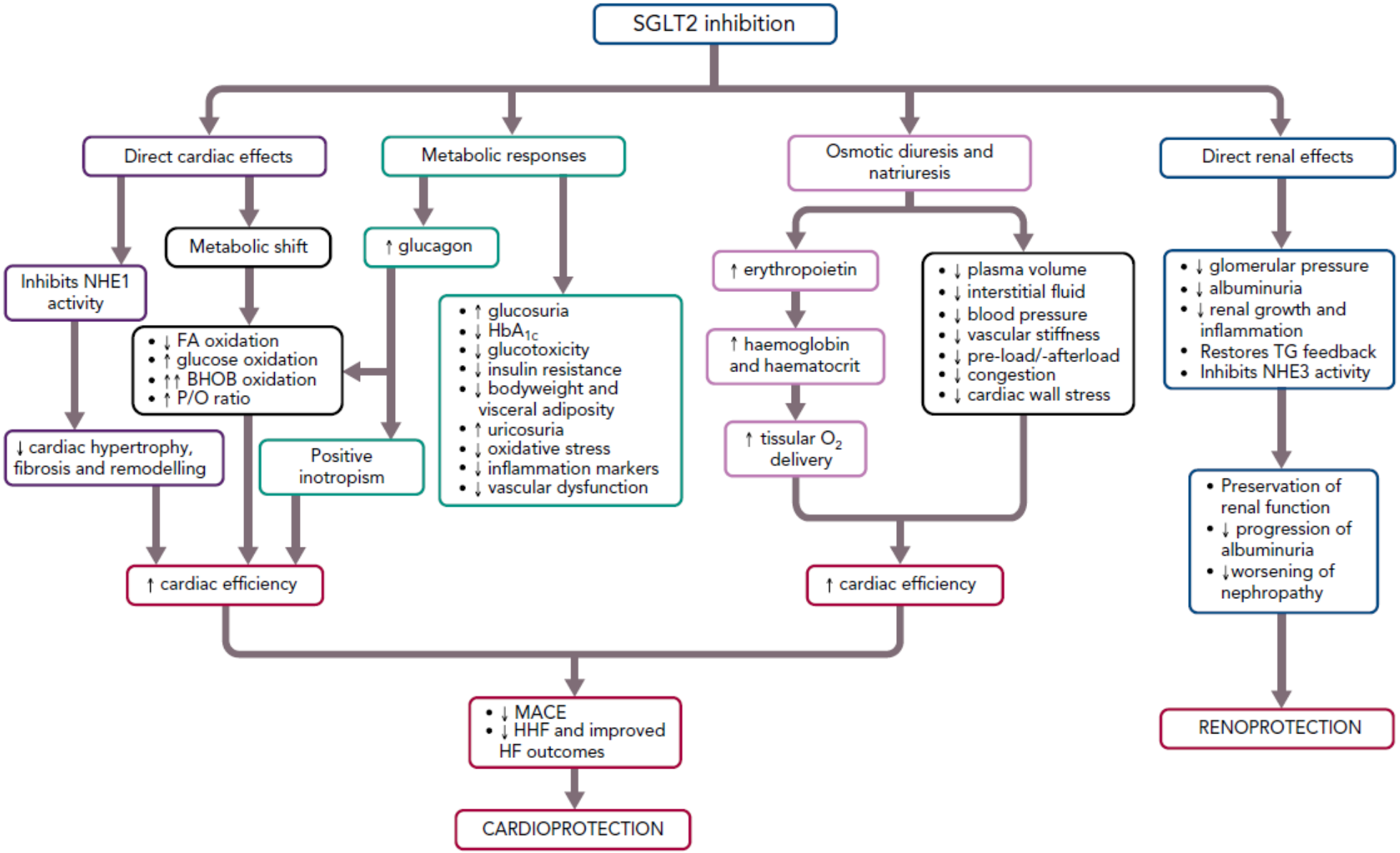

Type 2 Diabetes
Systemic adipose tissue inflammation
Expansion and inflammation of epicardial adipose tissue
Myocardium
Endocardium
Epicardial adipose tissue
Coronary microcirculatory dysfunction
Paracrine secretion of proinflammatory adipocytokines
Microvascular rarefaction, myocardial inflammation and fibrosis
Impaired LV distensibility
Heart failure with preserved ejection fraction

CENTRAL ILLUSTRATION **Sodium-Glucose Cotransporter 2 Inhibitors Interfere With the Principal Mechanisms by Which Diabetes Can Promote the Development and Progression of Cardiomyopathy**



Packer, M. J Am Coll Cardiol HF. 2021;9(8):535-549.

Sodium-glucose cotransporter 2 inhibitors are capable of interfering with all 3 of the primary pathophysiological mechanisms by which type 2 diabetes can lead to heart failure with a reduced or preserved ejection fraction. These include the following actions: 1) up-regulating nutrient deprivation signaling (eg, sirtuin-1 and its downstream effectors); 2) interfering with the actions of sodium-hydrogen exchangers in the heart and kidneys; and 3) reducing the mass and proinflammatory activity of epicardial adipose tissue. The net result of all 3 effects is to slow the development of cardiomyopathy and reduce the risk of serious heart failure events.



European Cardiology Review 2019;14(1):23-32

Hansı pasientlərdə Empagliflozin təyin edilə bilər ?

- HFrEF ✓
- HFpEF ✓
- HFmrEF ✓

- DM (-) ✓
- Tip 2 DM ✓
- Tip 1 DM ✗

- Hospitalizasiya ✓
- Ambulator ✓
- Kəskin ÜÇ ✓
- Xroniki ÜÇ ✓

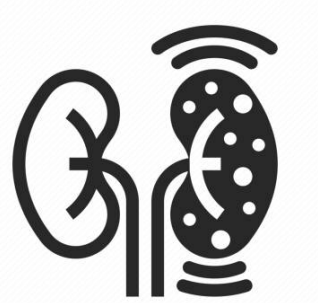
Empagliflozinin əks-göstərişləri varmı?

Tip 1 DM / Ketoasidoz anamnezi

Hamiləlik/südvermə

AT<100-60mmHg

Təkrarlayan genital/urinar inf.



Dializ xəstələri
Empa eGFR<20ml/dəq/1.73m2

Kəskin ÜÇ – son 24 saatda
inotrop + / IV diuretik eskalasiya

Empagliflozin necə qəbul olunmalıdır ?

Gündə 1 dəfə 1 tab 10mg

ElDash RM, et al. F1000Res. 2021 Apr 26;10:321

Nələrə diqqət olunmalıdır ?

- Böyrək testləri – başlayarkən və 2 həftə sonra
- Qan şəkəri – yanaşı insulin/sulfoniurea qəbul edirsə
- Kəskin xəstəlik/cərrahiyyə olarsa dərmana fasilə verilməsi

Pasientləri məlumatlandır !

- Gündəlik genital gigiyenanın əhəmiyyəti
- Urogenital infeksiya simptomları
- Hipovolemiya simptomları
- Diabetik ketoasidoz simptomları
- Qidalanma
  - Dehidratasiyadan çəkinmək
  - Aşağı karbohidratlı pəhrizlərdən imtina etmək (ketogen)
  - Aşırı alkoqol qəbulundan imtina etmək

Euqlikemik DKA