Pushing the boundaries of heart failure treatment with SGLT2i

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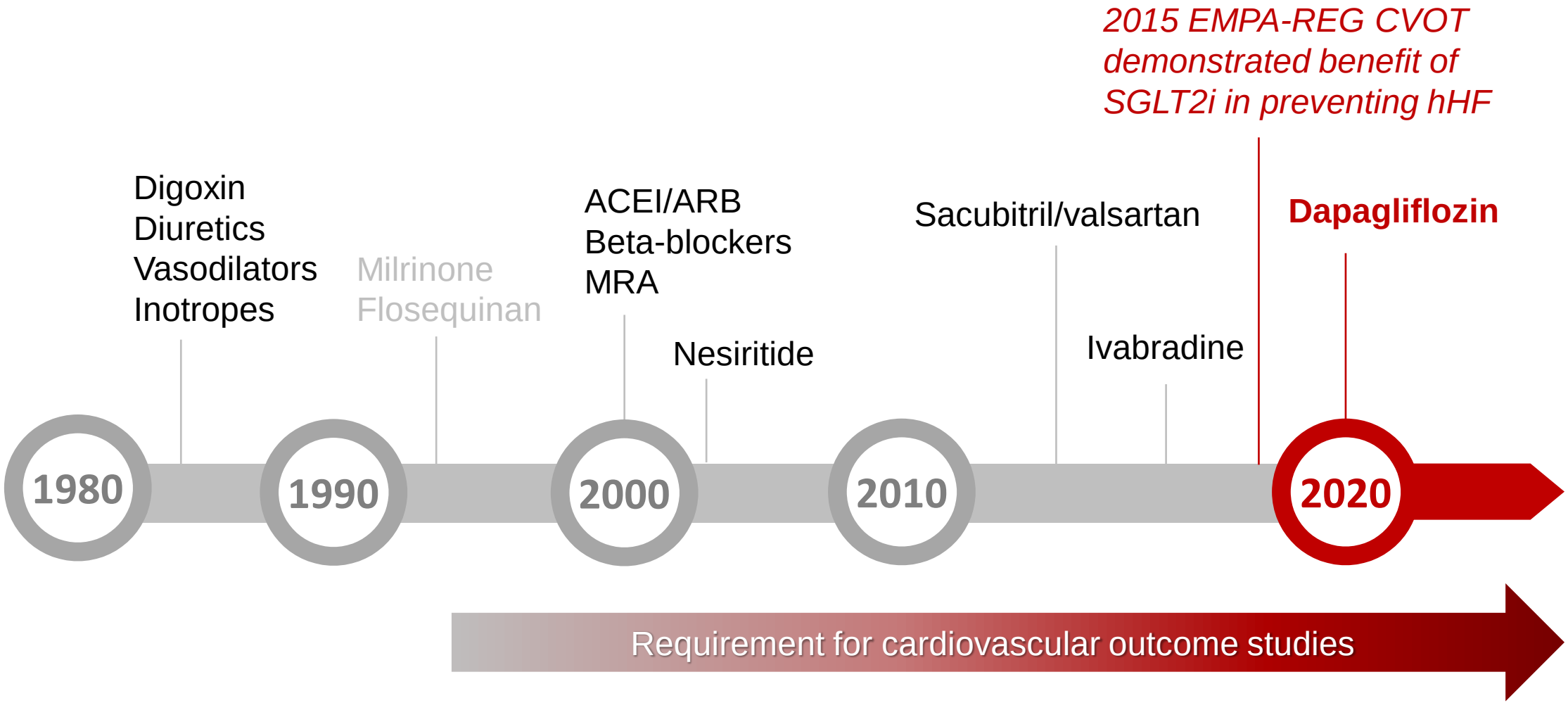
Disclosure

Consultancy and lecture honoraria from Astrazeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Johnson & Johnson, Merck, Novartis, Novo Nordisk, Pfizer

Breakthroughs in HF Pharmacotherapy



1. JACC Heart Fail. 2020;8:429-440. 2. https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-type-heart-failure

Summary of RCTs in HFrEF since 2010

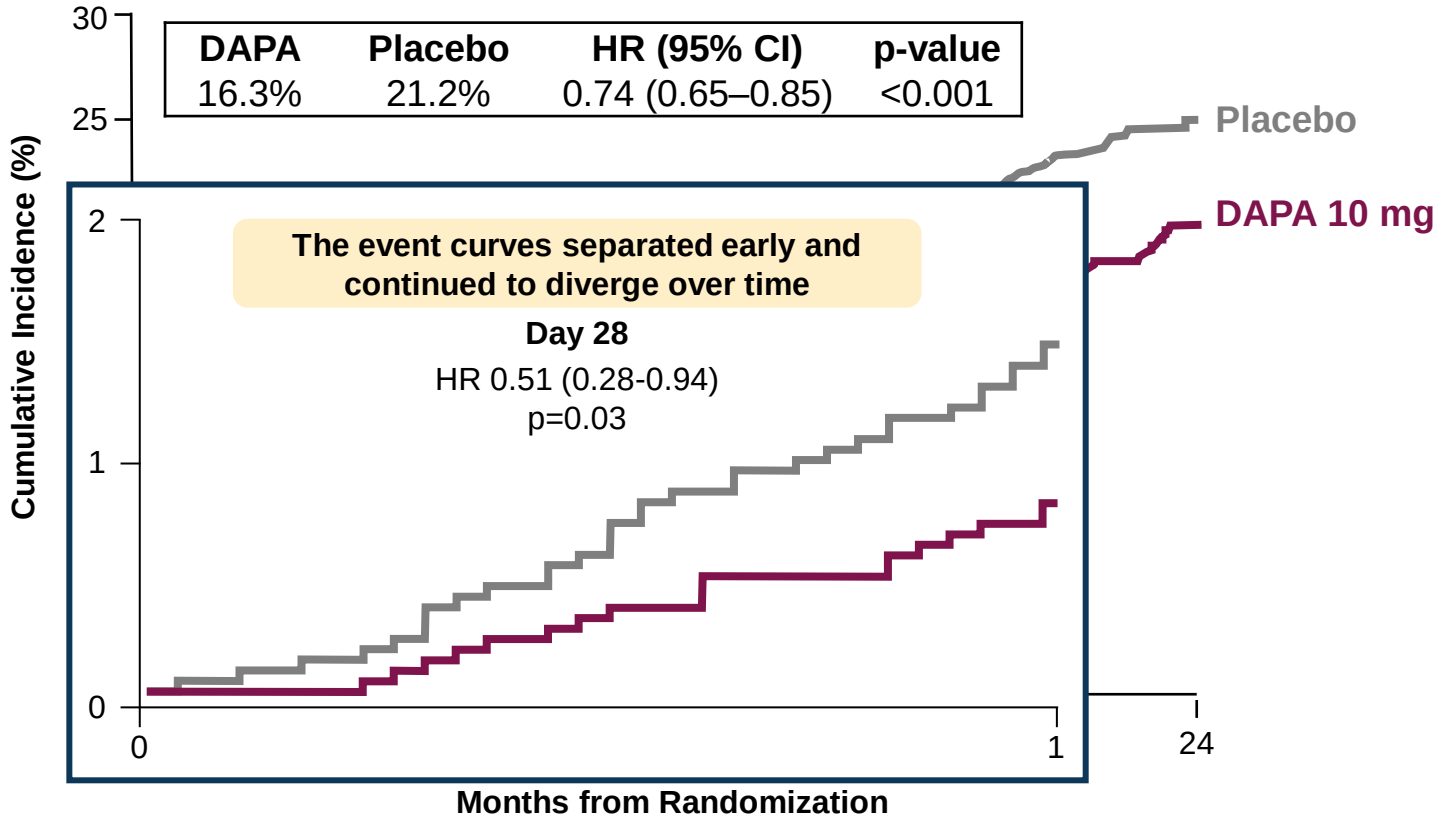
Trial (N; median follow-up month)	Drug	Background Rx.	CV death/HHF HR (95%CI)	HHF HR (95%CI)	CV death HR (95%CI)	All-cause mortality HR (95%CI)
EMPHASIS-HF (N=2737; 21 months)	Eplerenone vs placebo	ACEI/ARB 94% BB 87% MRA n/a	**0.66 (0.56–0.78)**	**0.61 (0.50–0.75)**	**0.77 (0.62–0.96)**	**0.78 (0.64–0.95)**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

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

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

DAPA-HF Primary Endpoint

CV Death or hHF or an Urgent HF Visit[1,2]



26% RRR

4.9% ARR

NNT=21

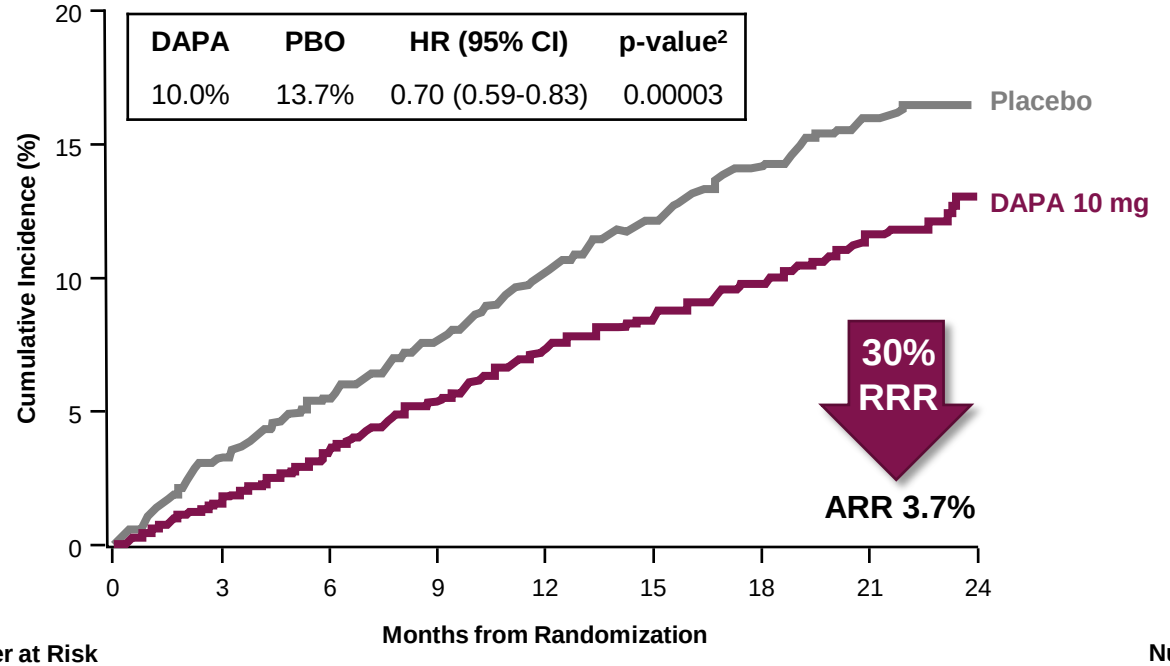
Number at Risk

DAPA 10 mg	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

1. McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008; 2. Berg DD et al. *JAMA Cardiol*. 2021;6:499-507.

DAPA-HF Components of the Primary Endpoint[1,2]

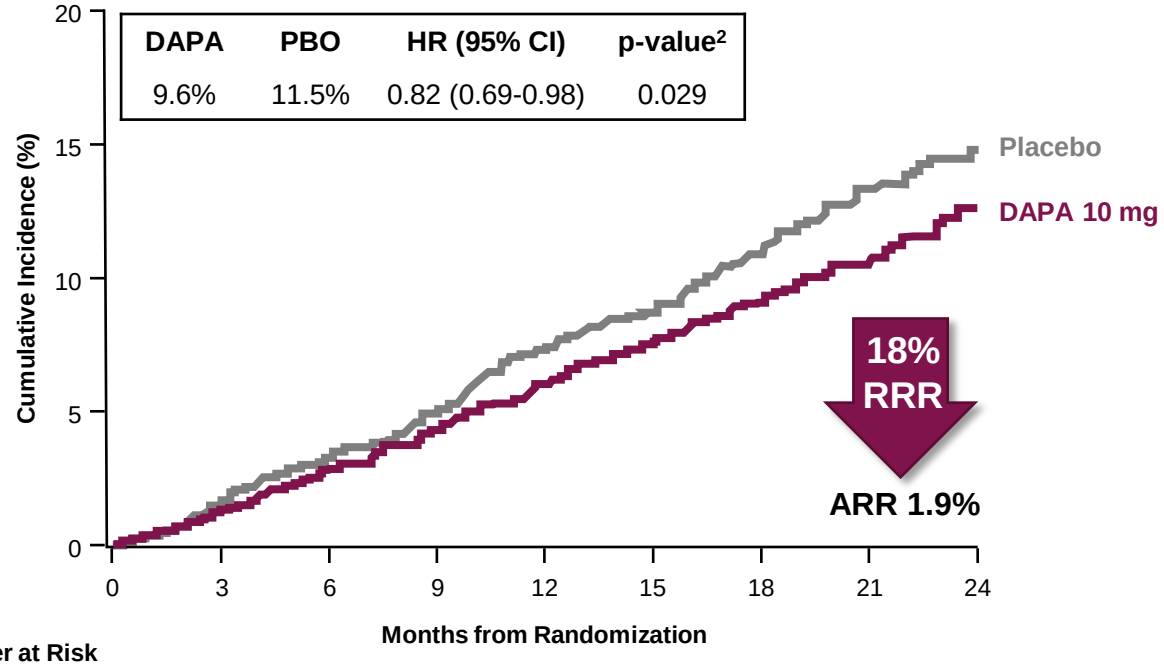
Worsening HF Event[a]



Number at Risk

DAPA 10 mg	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

CV Death



Number at Risk

DAPA 10 mg	2373	2339	2293	2248	2127	1664	1242	671	232
Placebo	2371	2330	2279	2230	2091	1636	1219	664	234

[a]Worsening HF includes hHF or urgent HF visit.

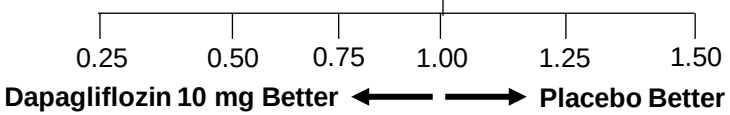
1. McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008; 2. McMurray J. Presented at: ESC Congress; Aug 31-Sep 4, 2019; Paris, France.

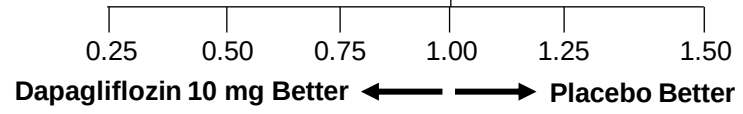
DAPA-HF Primary Endpoint by Background HF Therapy Subgroups[1]

Primary Endpoint- CV Death or hHF or an Urgent HF visit

Background Therapy, %	DAPA 10 mg	PBO	HR (95% CI)	Interaction p-value[a]
Overall Effect	16.3	21.2	0.74 (0.65, 0.85)	
ACE inhibitor/ARB target dose				
<50% (n=2435)	16.5	20.7	0.78 (0.65, 0.94)	0.21
≥50% (n=1517)	13.7	20.5	0.64 (0.50, 0.82)	
ARNI				
Yes (n=508)	16.4	21.7	0.75 (0.50, 1.13)	1.00
No (n=4236)	16.3	21.1	0.74 (0.65, 0.86)	
Beta-blocker target dose				
<50% (n=2209)	17.2	23.0	0.71 (0.59, 0.86)	0.76
≥50% (n=2349)	14.6	19.4	0.74 (0.61, 0.90)	
MRA				
Yes (n=3370)	16.6	21.6	0.74 (0.63, 0.87)	0.97
No (n=1374)	15.5	20.2	0.74 (0.57, 0.95)	
MRA target dose				
<50% (n=417)	15.3	20.9	0.71 (0.45, 1.12)	0.82
≥50% (n=2953)	16.8	21.7	0.74 (0.63, 0.88)	

Background Therapy, %	DAPA 10 mg	PBO	HR (95% CI)	Interaction p-value[a]
Overall Effect	16.3	21.2	0.74 (0.65, 0.85)	
Diuretic				
Yes (n=4008)	17.9	22.8	0.76 (0.66, 0.87)	0.27
No (n=736)	7.5	12.4	0.57 (0.36, 0.92)	
Digoxin				
Yes (n=887)	22.0	25.1	0.86 (0.66, 1.13)	0.21
No (n=3857)	14.9	20.3	0.71 (0.61, 0.83)	
Ivabradine				
Yes (n=228)	20.2	26.6	0.73 (0.42, 1.25)	0.94
No (n=4516)	16.1	20.9	0.74 (0.65, 0.85)	
ICD[b]				
Yes (n=1242)	18.3	23.4	0.77 (0.61, 0.99)	0.73
No (n=3502)	15.5	20.4	0.73 (0.63, 0.86)	
CRT[c]				
Yes (n=354)	18.4	22.0	0.85 (0.53, 1.36)	0.58
No (n=4390)	16.1	21.1	0.73 (0.64, 0.84)	





[a]A non-significant result for an interaction test can be interpreted as consistency of effect across the subgroup[2]; [b]Either ICD or CRT with a defibrillator; [c]CRT with or without a defibrillator.

1. Docherty KF et al. *Eur Heart J*. 2020;41:2379-2392; 2. Alosh M et al. *J Biopharm Stat*. 2015;25:1161-1178.

EMPEROR-Reduced Trial

- 3730 patients with HFrEF (LVEF ≤40%, NYHA Class II-IV) receiving recommended therapy
  - Patients enrolled based on varying thresholds for LVEF and NT-proBNP
  - 50% of the population did not have T2D

- Results:

Outcome	HR or Absolute Difference (95% CI)
Primary: composite of CV death or hHF	0.75 (0.65-0.86)
CV death	0.92 (0.75-1.12)
hHF	0.69 (0.59-0.81)
First secondary: total hHF	0.70 (0.58-0.85)
Second secondary: mean slope of change in eGFR	1.73[a] (1.10-2.37)
All-cause death	0.92 (0.77-1.10)

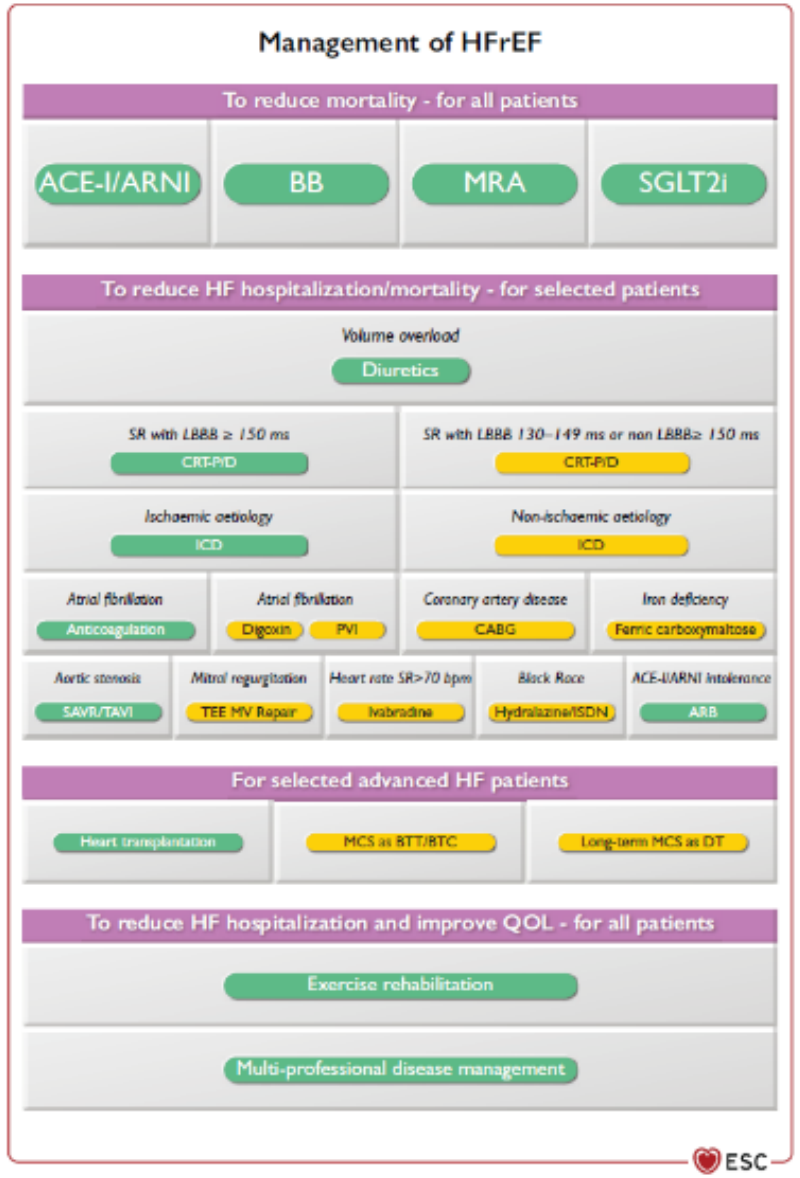
- Safety results were similar to the known safety profile of empagliflozin.

[a]Absolute difference reported as mL/min/1.73 m^2

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

ESC Heart Failure Guidelines 2021

SGLT2i is CLASS IA first line Rx for *all* patients with HFrEF from prevention to treatment

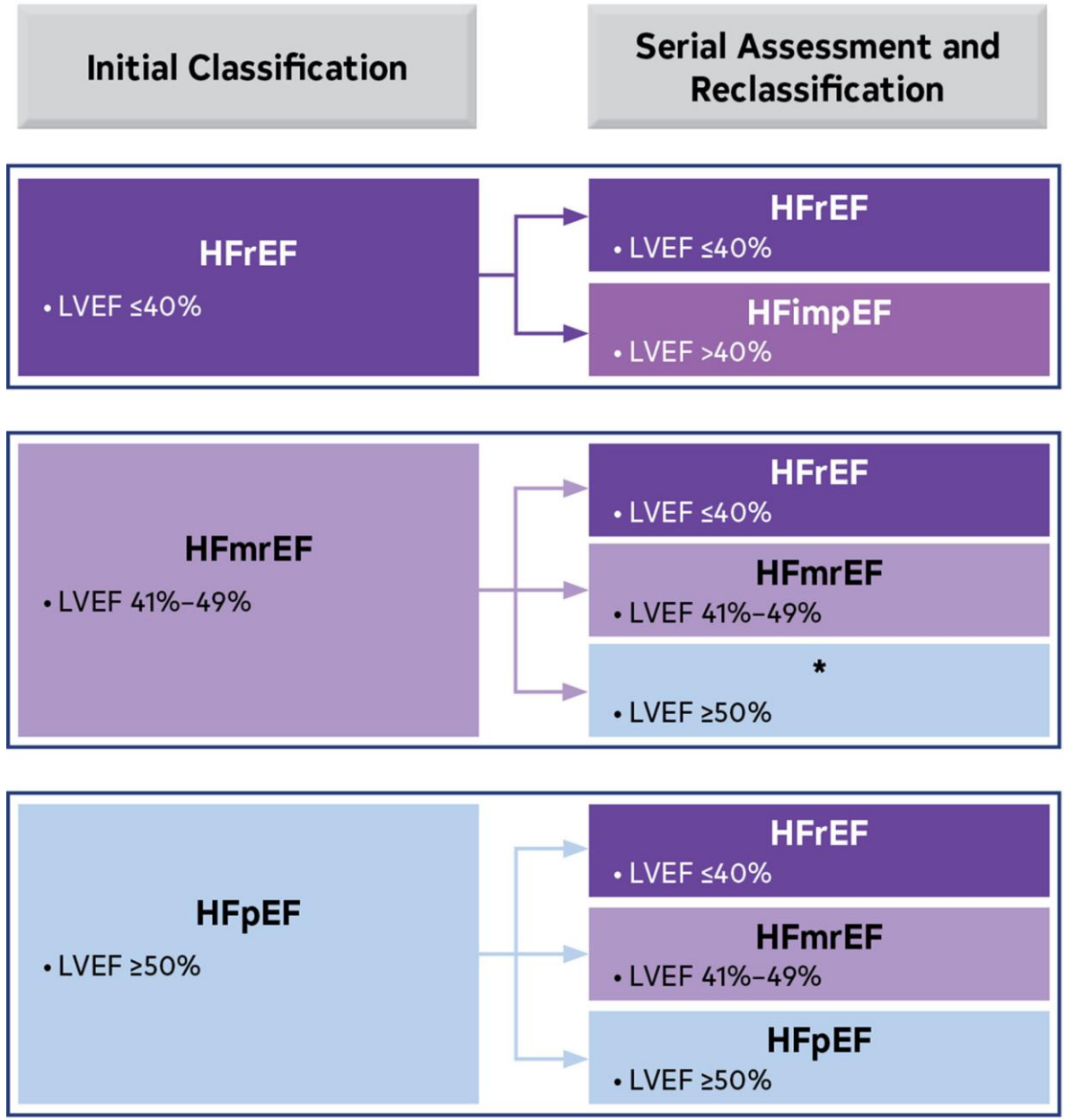


Recommendations for the prevention of chronic HF		
Treatment of hypertension is recommended to prevent or delay the onset of HF, and to prevent HF hospitalizations.	I	A
Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations.	I	A
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations.	I	A
Counselling against sedentary habit, obesity, cigarette smoking, and alcohol abuse is recommended to prevent or delay the onset of HF.	I	C

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

Recommendations for treatment 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	A
SGLT2 inhibitors (dapagliflozin, empagliflozin, and sotagliflozin) are recommended in patients with T2DM and HFrEF to reduce hospitalizations for HF and CV death.	I	A

Figure 3. Strategic phenotypic overview of the management of HFrEF
Green for Class of recommendation I; Yellow for Class of recommendation IIa



Heidenreich et al. AHA/ACC/HFSA Guideline for the Management of Heart Failure. Circulation. 2022;145:e895-e1032.

DELIVER Largest and Broadest Trial to Date in Patients with Heart Failure and Mildly Reduced or Preserved Ejection Fraction

International | Multicenter | Parallel-group | Event-driven | Randomized | Double-blind

Inclusion Criteria[1,2]

353 Sites

20 Countries

6263 Patients

- Age ≥40 with/without T2D
- Symptomatic HF
- LVEF >40%[a]
- Ambulatory or hospitalized
- Elevated NT-proBNP levels
- eGFR ≥25 mL/min/1.73 m^2

Randomized 1:1[b]

Stop when ~1117 primary events are reached

Dapagliflozin 10 mg | **Placebo**

Baseline Characteristics[2]

Older, Symptomatic Cohort

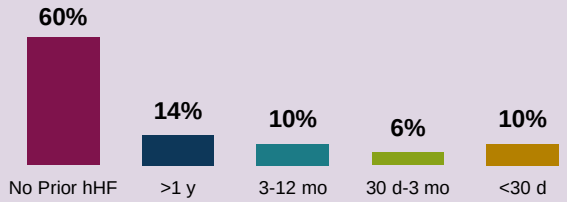
72 years Mean Age
44% Women
75% NYHA Class II
25% NYHA Class III
Moderate Symptomatic Impairment[c]

High Rate of Comorbidities

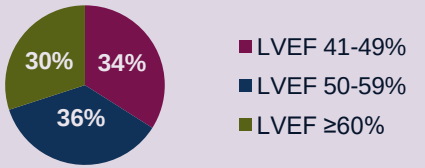
45% T2D
45% BMI ≥30 kg/m^2
89% Hypertension
57% History of AF/AFL
51% Coronary artery disease
61 mL/min/1.73 m^2 Mean eGFR

Elevated Risk

- Median NT-proBNP: **1011 pg/mL**
- **16%** enrolled during or <90 days of hospitalization
- History of hospitalization for HF:

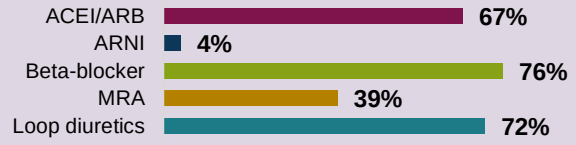


Well-represented LVEF Groups



- Mean LVEF: **54%**
- Patients with HFimpEF[3,d]: **18%**

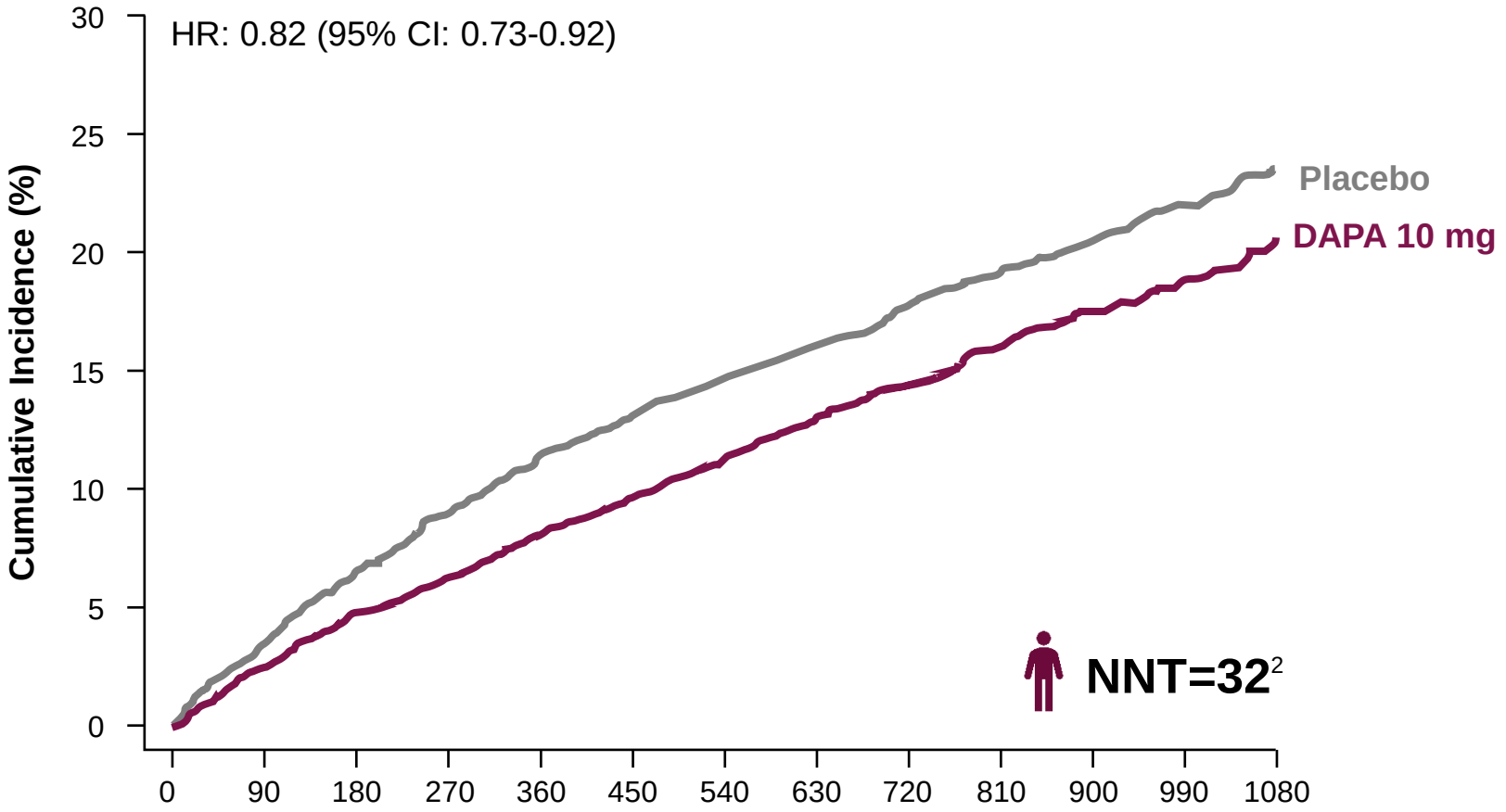
High Use of HF Medical Therapies



[a]Patients with prior LVEF ≤40% were also included; [b]Stratified by T2D status (established diagnosis/HbA1c ≥6.5% at enrollment); [c]Mean baseline KCCQ -CSS, -OSS, and -TSS were 68, 67, and 70, respectively; [d]Prior LVEF ≤40%.

1. Solomon SD et al. *Eur J Heart Fail*. 2021;23(7):1217-1225; 2. Solomon SD et al. *JACC Heart Fail*. 2022;10(3):184-197; 3. Vardeny O et al. *Nat Med*. 2022;28(12):2504-2511.

DELIVER Primary Composite of CV Death, hHF or Urgent HF Visit[1]



18% RRR

3.1% ARR

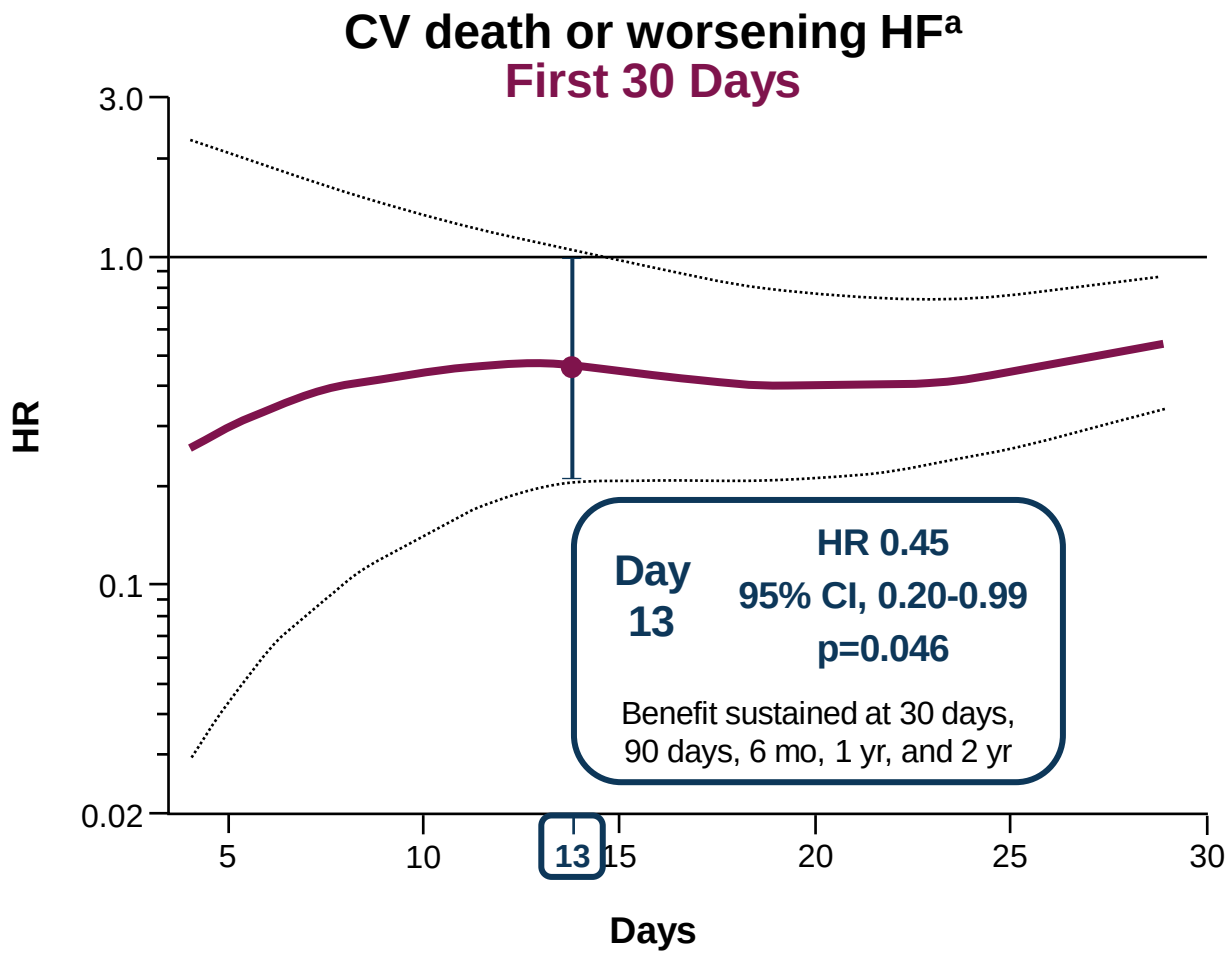
p=0.0008[2]

Number at Risk													
DAPA 10 mg	3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389
Placebo	3132	3007	2896	2799	2710	2608	2318	2080	1923	1554	1140	772	383

[a]Nominal significance at Day 13 (HR, 0.45; 95% CI, 0.20-0.99; p=0.046), with sustained statistical significance starting at Day 15.

1. Solomon SD et al. *N Engl J Med*. 2022;387(12):1089-1098; 2. Solomon SD. Presented at: ESC Congress; August 26-29, 2022; Barcelona, Spain; 3. Vaduganathan M et al. *JAMA Cardiol*. 2022;7(12):1259-1263.

DELIVER Benefit of Dapagliflozin on the Primary Composite Endpoint Occurred Within 2 Weeks

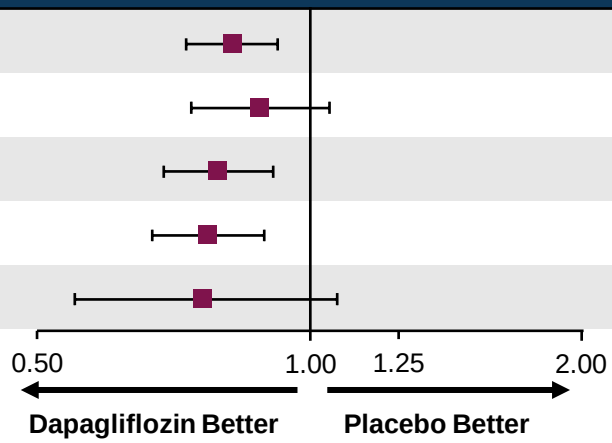


[a]Worsening HF includes hHF or urgent HF visit.

Vaduganathan M et al. *JAMA Cardiol*. 2022;7(12):1259-1263.

DELIVER Components of the Primary Endpoint[1]

Outcome, n (%)	DAPA 10 mg n=3131	Placebo n=3132	HR (95% CI)	p-value
CV death or worsening HF[a]	512 (16.4)	610 (19.5)	0.82 (0.73-0.92)	0.0008[2]
CV death[b]	231 (7.4)	261 (8.3)	0.88 (0.74-1.05)	
Worsening HF[a]	368 (11.8)	455 (14.5)	0.79 (0.69-0.91)	
hHF	329 (10.5)	418 (13.3)	0.77 (0.67-0.89)	
Urgent HF visit	60 (1.9)	78 (2.5)	0.76 (0.55-1.07)	



All individual components occurred less frequently in the dapagliflozin group

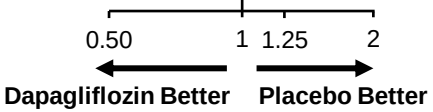
[a]Includes hHF or urgent HF visit; [b]Also a prespecified secondary endpoint.

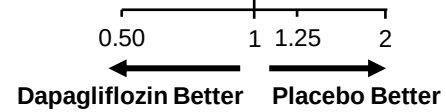
1. Solomon SD et al. *N Engl J Med*. 2022;387(12):1089-1098; 2. Solomon SD. Presented at: ESC Congress; August 26-29, 2022; Barcelona, Spain.

DELIVER Consistent Treatment Benefit Across All Prespecified Subgroups

Characteristic		DAPA n/N	PBO n/N	HR (95% CI)
Overall effect		512/3131	610/3132	0.82 (0.73-0.92)
Age, yr	≤72	247/1545	306/1604	0.82 (0.69-0.97)
	>72	265/1586	304/1528	0.81 (0.69-0.96)
Sex	Female	195/1364	243/1383	0.81 (0.67-0.97)
	Male	317/1767	367/1749	0.82 (0.71-0.96)
Race	Asian	97/630	106/644	0.91 (0.69-1.20)
	Black	21/81	19/78	1.08 (0.58-2.01)
	White	372/2214	461/2225	0.79 (0.69-0.90)
	Other	22/206	24/185	0.83 (0.46-1.48)
Region	Europe/ Saudi Arabia	261/1494	309/1511	0.83 (0.70-0.98)
	Asia	92/607	103/619	0.89 (0.67-1.18)
	Latin America	70/602	87/579	0.78 (0.57-1.07)
	North America	89/428	111/423	0.75 (0.57-1.00)
T2D	Yes	270/1401	317/1405	0.83 (0.70-0.97)
	No	242/1730	293/1727	0.81 (0.68-0.96)
AF/AFL on ECG	Yes	227/1327	271/1317	0.81 (0.68-0.97)
	No	285/1803	339/1814	0.82 (0.70-0.96)
BMI, kg/m²	<30	275/1734	302/1736	0.89 (0.75-1.04)
	≥30	236/1395	308/1392	0.74 (0.63-0.88)

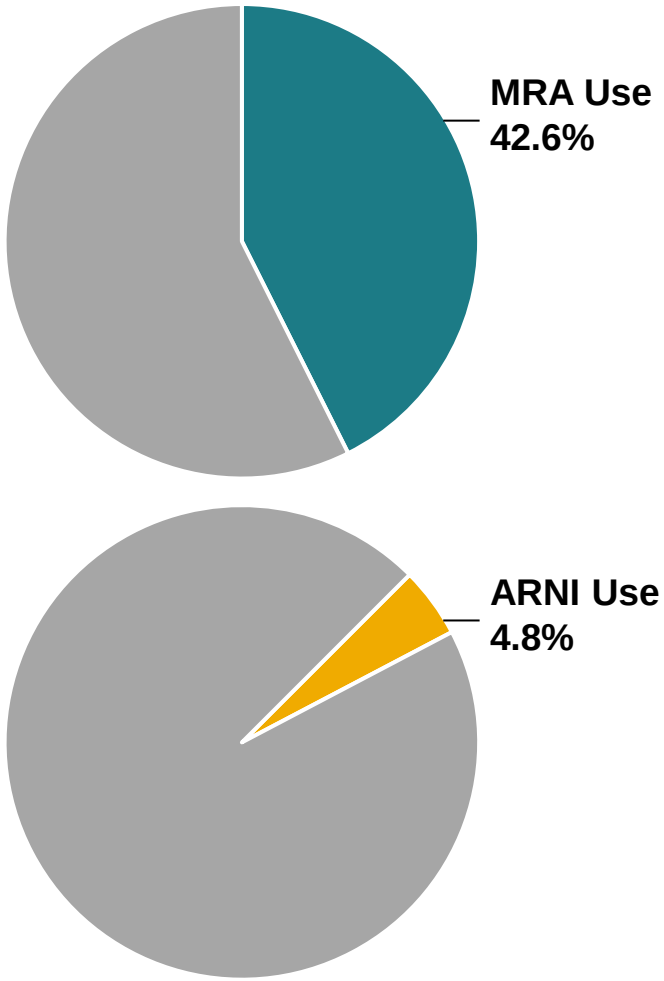
Characteristic		DAPA n/N	PBO n/N	HR (95% CI)
Overall effect		512/3131	610/3132	0.82 (0.73-0.92)
NYHA class	II	331/2314	411/2399	0.81 (0.70-0.94)
	III or IV	181/817	198/732	0.80 (0.65-0.98)
LVEF, %	≤49	207/1067	229/1049	0.87 (0.72-1.04)
	50-59	174/1133	211/1123	0.79 (0.65-0.97)
	≥60	131/931	170/960	0.78 (0.62-0.98)
NT-proBNP, pg/mL	≤1011	173/1555	208/1578	0.84 (0.68-1.02)
	>1011	339/1576	402/1553	0.79 (0.69-0.92)
Enrollment during or within 30 days of hHF	Yes	93/328	113/326	0.78 (0.60-1.03)
	No	419/2803	497/2806	0.82 (0.72-0.94)
Prior LVEF ≤40%	Yes	92/572	119/579	0.74 (0.56-0.97)
	No	420/2559	491/2553	0.84 (0.73-0.95)
eGFR, mL/min/1.73 m²	<60	289/1516	355/1554	0.81 (0.69-0.94)
	≥60	223/1615	255/1577	0.84 (0.70-1.00)
SBP, mmHg	≤128	280/1568	300/1590	0.93 (0.79-1.10)
	>128	232/1563	310/1542	0.71 (0.60-0.85)





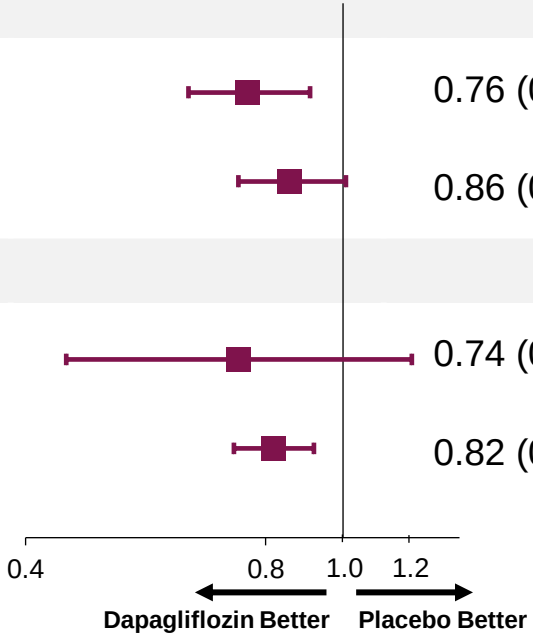
Solomon SD et al. *N Engl J Med*. 2022;387(12):1089-1098.

DELIVER Dapagliflozin Consistently Reduced the Primary Endpoint, Regardless of MRA or ARNI Use[1]



CV Death or Worsening HF[a]

Background Therapy, %	DAPA 10 mg	PBO	HR (95% CI)	Interaction p-value[b]
MRA use				
Yes (n=2667)	15.9	20.1	0.76 (0.64-0.91)	0.30
No (n=3596)	16.7	19.1	0.86 (0.74-1.01)	
ARNI use				
Yes (n=301)	18.8	22.8	0.74 (0.45-1.22)	0.75
No (n=5962)	16.2	19.3	0.82 (0.73-0.92)	



AEs occurred at a similar rate between DAPA and PBO, regardless of MRA or ARNI use

[a]Includes hHF or urgent HF visit; [b]A non-significant result for an interaction test can be interpreted as consistency of effect across the subgroup.[2]

1. Yang M et al. *Eur J Heart Fail*. 2022;24(12):2307-2319; 2. Alosh M et al. *J Biopharm Stat*. 2015;25(6):1161-1178.

DELIVER Safety Outcomes[1]

Event, n (%)	Dapagliflozin 10 mg n=3126[a]	Placebo n=3127[a]
Any serious AE[b]	1361 (43.5)	1423 (45.5)
AE leading to treatment discontinuation	182 (5.8)	181 (5.8)
AE leading to treatment interruption	436 (13.9)	494 (15.8)
AE of interest		
Amputation	19 (0.6)	25 (0.8)
Major hypoglycemic event	6 (0.2)	7 (0.2)
Diabetic ketoacidosis[c]	2 (0.1)	0 (0)
Volume depletion serious AE or treatment discontinuation AE	42 (1.3)	32 (1.0)
Renal serious AE or treatment discontinuation AE	73 (2.3)	79 (2.5)
Fournier's gangrene	0 (0.0)	0 (0.0)

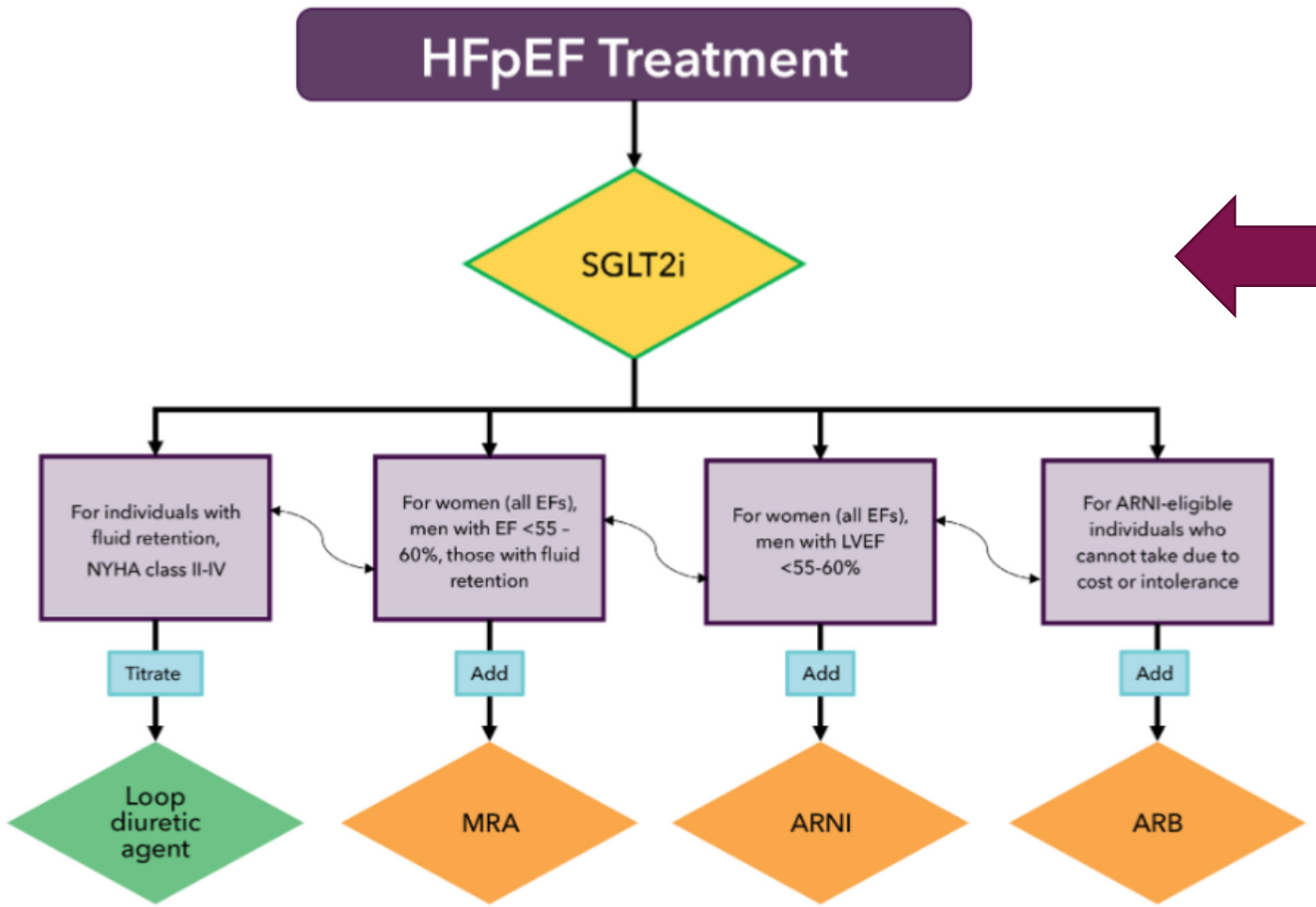
Major hypoglycemia and diabetic ketoacidosis[c] events were rare and only occurred in patients with T2D[2]

[a]Includes all patients who underwent randomization and received at least 1 dose of study medication; [b]Including death; [c]All cases were adjudicated as definite or probable.

1. Solomon SD et al. Article and supplementary appendix. *N Engl J Med*. 2022;387(12):1089-1098; 2. Inzucchi SE et al. *Lancet Diabetes Endocrinol*. 2022;10(12):869-881.

SGLT2i as First Line Therapy for HFpEF

FIGURE 9 Treatment Algorithm for Guideline-Directed Medical Therapy in HFpEF*

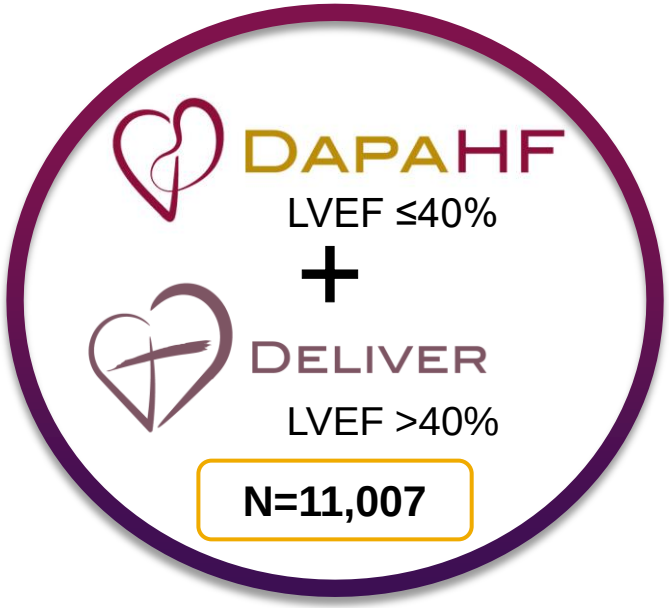


*Green color identifies a Class 1 therapy from clinical practice guidelines,[14] yellow color indicates a Class 2a therapy, and orange color denotes a Class 2b therapy. SGLT2is receive a Class 2a indication in the 2022 AHA/ACC/HFSA HF Guidelines,[14] but the benefit, now confirmed in 2 randomized trials,[60,61] suggests that SGLT2is may receive a stronger class of recommendation in future guidelines, and thus the box is shaded yellow with a green border. AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; EF = ejection fraction; HFpEF = heart failure with preserved ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid antagonist; NYHA = New York Heart Association; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

SGLT2is receive a **Class 2a** indication in the 2022 AHA/ACC/HFSA HF Guidelines, but **the benefit**, now **confirmed** in 2 randomized trials, **suggests that SGLT2is may receive a stronger class of recommendation in future guidelines**, and thus the box is shaded yellow with a green border.

ACC Expert Consensus Decision Pathway on Management of HFpEF 2023

DAPA-HF and DELIVER Pooled Analysis[1]



Pre-specified
Prior to unblinding of the DAPA-HF trial[2]

Patient-level

Purpose
Provide an estimate of the overall treatment effect by increasing the statistical power to analyze components of the primary endpoint and key secondary endpoints

Key Outcomes

- CV death
- All-cause death
- Total[a] hHF
- CV death or hHF
- MACE[b]

[a]First and recurrent; [b]Composite of CV death, myocardial infarction, or stroke.

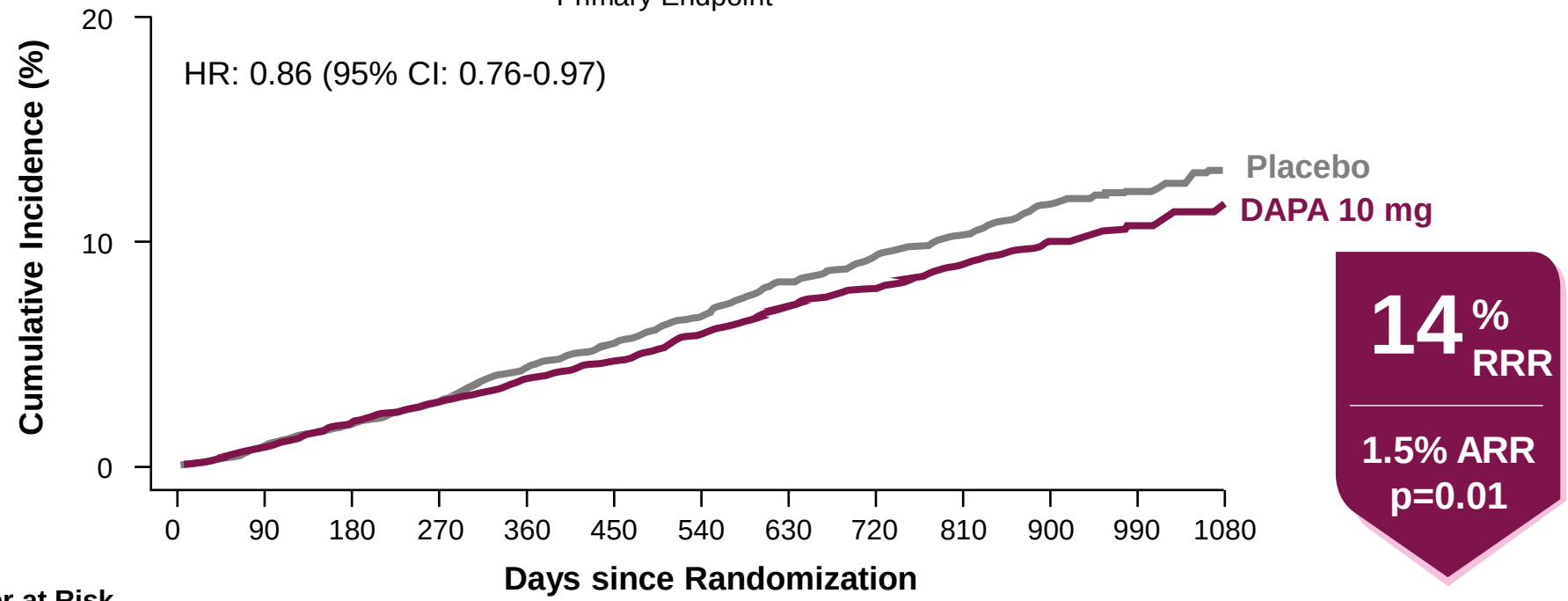
1. Jhund PS et al. Article and supplementary online content. *Nat Med*. 2022;28(9):1956-1964; 2. Solomon SD et al. *Eur J Heart Fail*. 2021;23:1217-1225.

Pooled Analysis Dapagliflozin Significantly Reduced CV Death

DAPA-HF → Pre-specified patient-level pooled analysis ← DELIVER

CV Death

Primary Endpoint



Number at Risk

DAPA 10 mg	5504	5430	5339	5254	5087	4556	3826	3010	2403	1781	1312	903	441
Placebo	5503	5426	5333	5238	5048	4508	3789	2978	2391	1767	1306	910	451

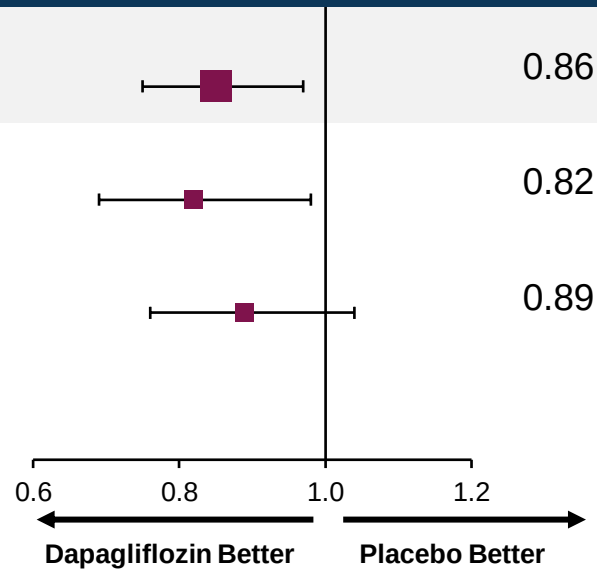
Results were unchanged when undetermined deaths were excluded from the definition of CV death or if the definition of CV death used in each trial was examined.

Jhund PS et al. *Nat Med*. 2022;28(9):1956-1964.

Both DAPA-HF and DELIVER Contributed to Reduction in CV Death

DAPA-HF ← Pre-specified patient-level pooled analysis → DELIVER

CV death, n/N	Dapagliflozin 10 mg	Placebo	HR (95% CI)	HR (95% CI)	p-value
DAPA-HF + DELIVER Pooled[a]	525/5504	607/5503		0.86 (0.76-0.97)	0.01
DAPA-HF population (LVEF ≤40%)	227/2373	273/2371		0.82 (0.69-0.98)	*Interaction p-value* 0.52
DELIVER population (LVEF >40%)	298/3131	334/3132		0.89 (0.76-1.04)	

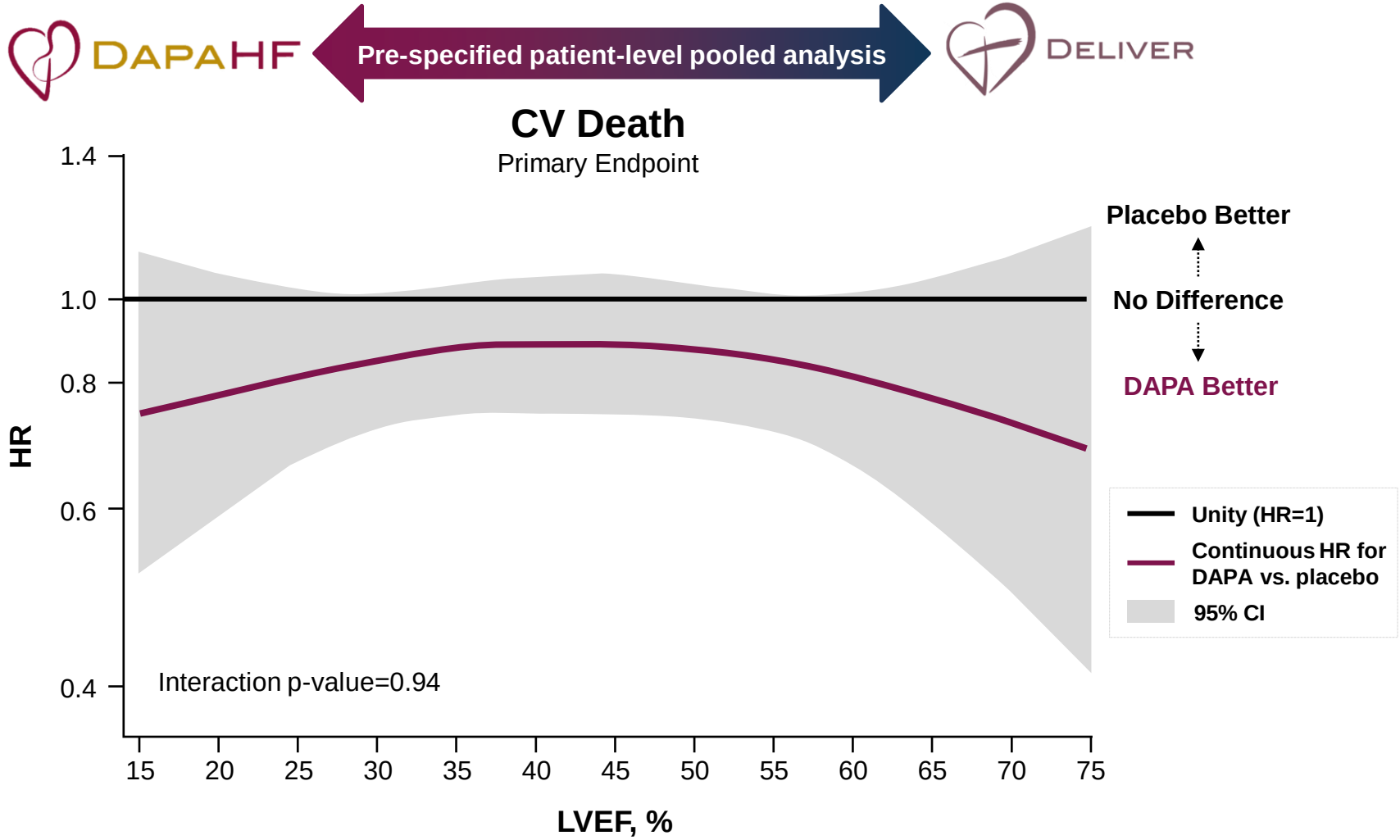


Between-trial heterogeneity for the effect of treatment on the primary endpoint of CV death was tested before the DAPA-HF and DELIVER trials were pooled together using the I^2 statistic.[1] There was no heterogeneity found as evidenced by an I^2 of 0%.[2]

[a]Results include deaths of undetermined causes.

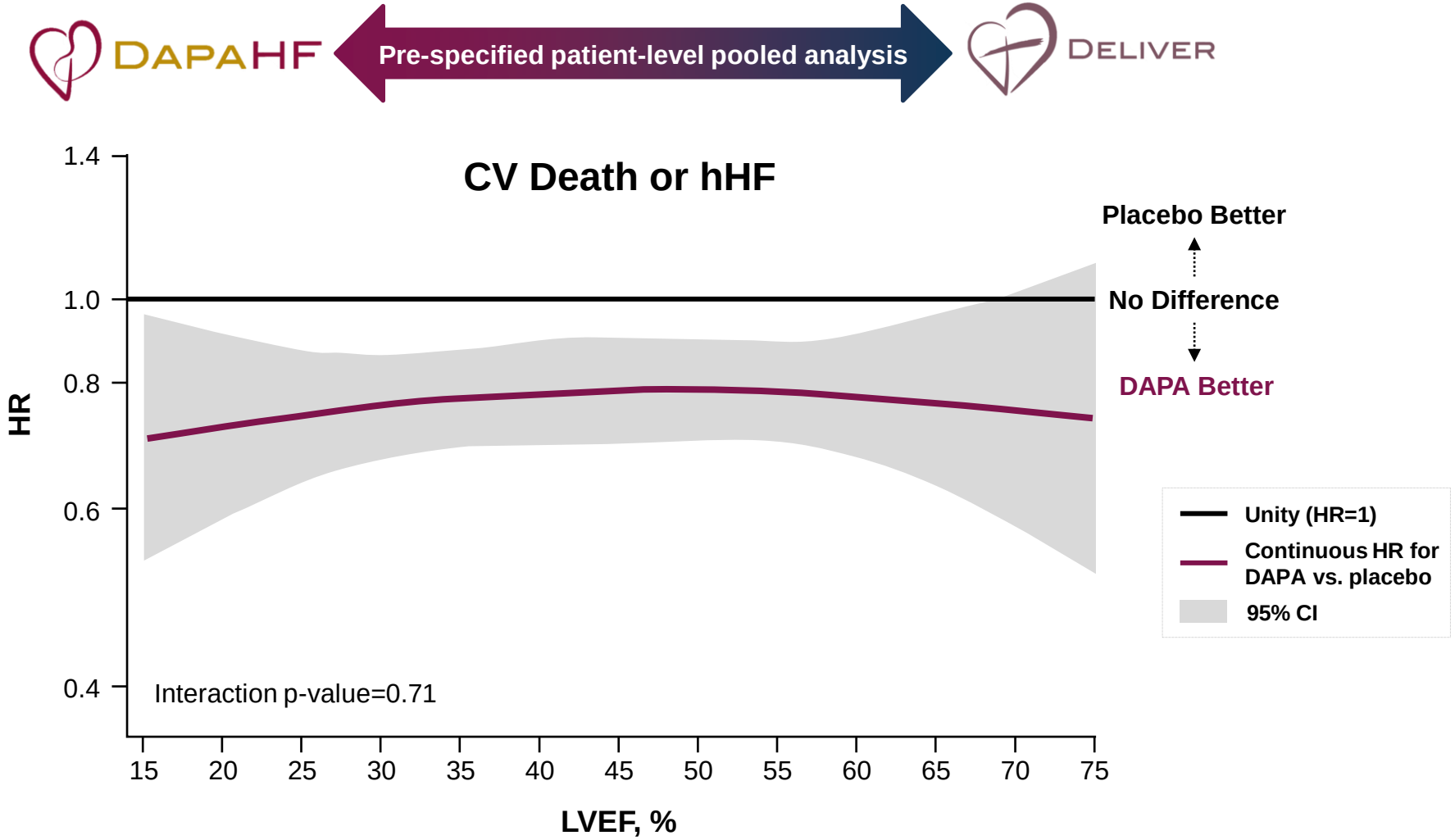
1. Jhund PS et al. *Nat Med*. 2022;28(9):1956-1964; 2. Melson WG et al. *Clin Microbiol Infect*. 2014;20(2):123-129.

Benefit in CV Death is Maintained Across the Range of LVEF



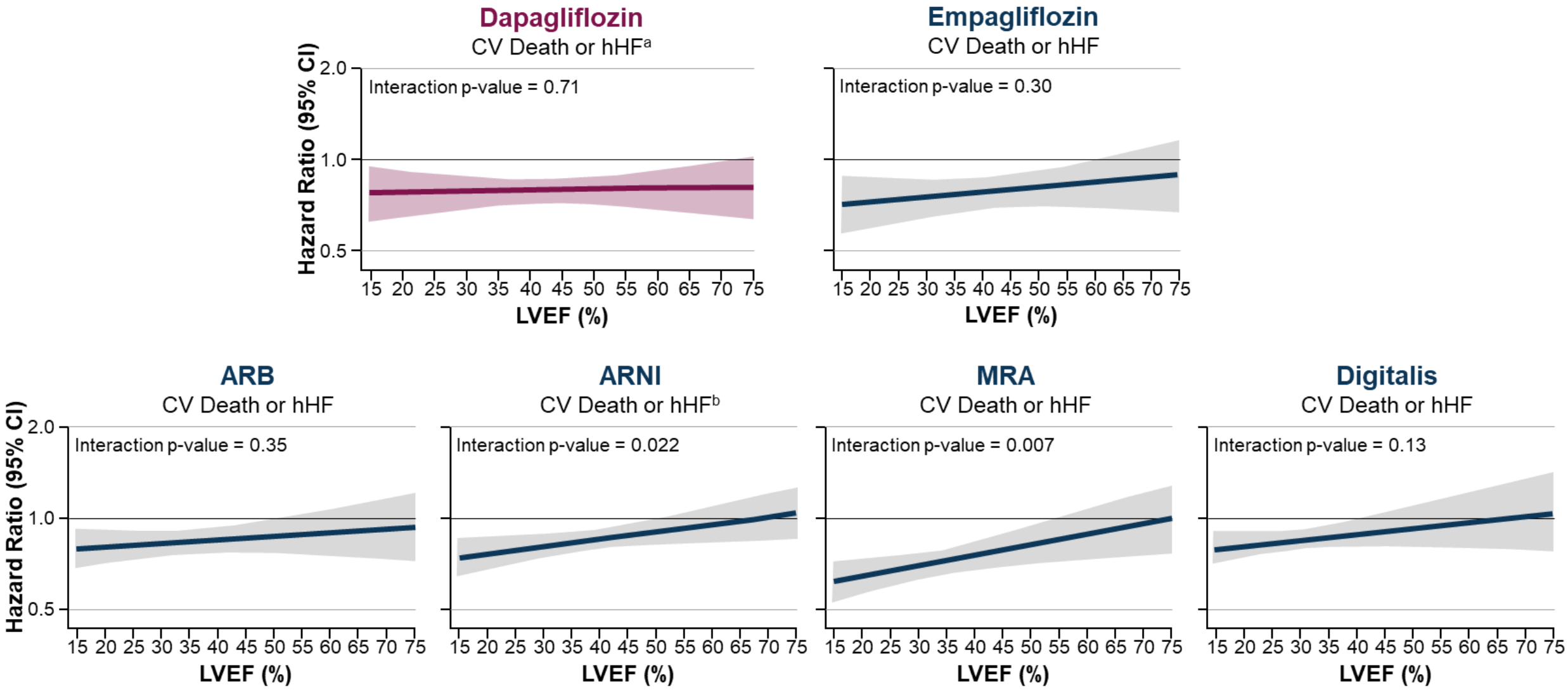
Jhund PS et al. *Nat Med*. 2022;28(9):1956-1964.

Benefit in CV Death or hHF is Maintained Across the Range of LVEF



Jhund PS et al. *Nat Med*. 2022;28(9):1956-1964.

Dapagliflozin Benefit is Consistent, With no Attenuation, Across LVEF[1,2]



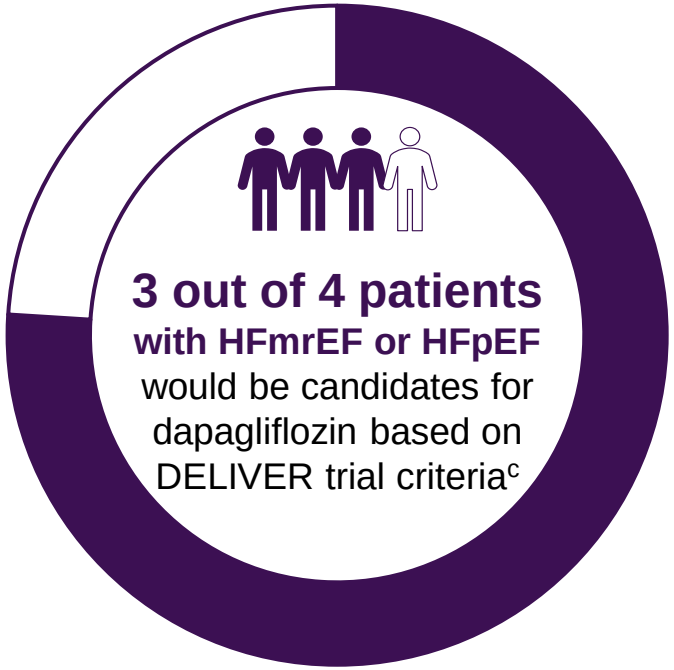
[a]Linear regression model of CV death (including undetermined death) and hHF to ensure consistency across trials; [b]All data is in comparison to placebo, except for ARNI which is in comparison to enalapril or valsartan.

1. Kondo T et al. *Eur Heart J.* 2022;43(5):427-429; 2. In House Data, AstraZeneca. Data on file 161903.

Real-world Application of DAPA-HF and DELIVER[1,2]

GWTG-HF Registry[a] Population[1]
LVEF ≤40%
January 2014-September 2019
n=154,714 hospitalized at 406 centers

GWTG-HF Registry[a] Population[2]
LVEF >40%
January 2014-December 2018
n=52,964 hospitalized at 363 centers

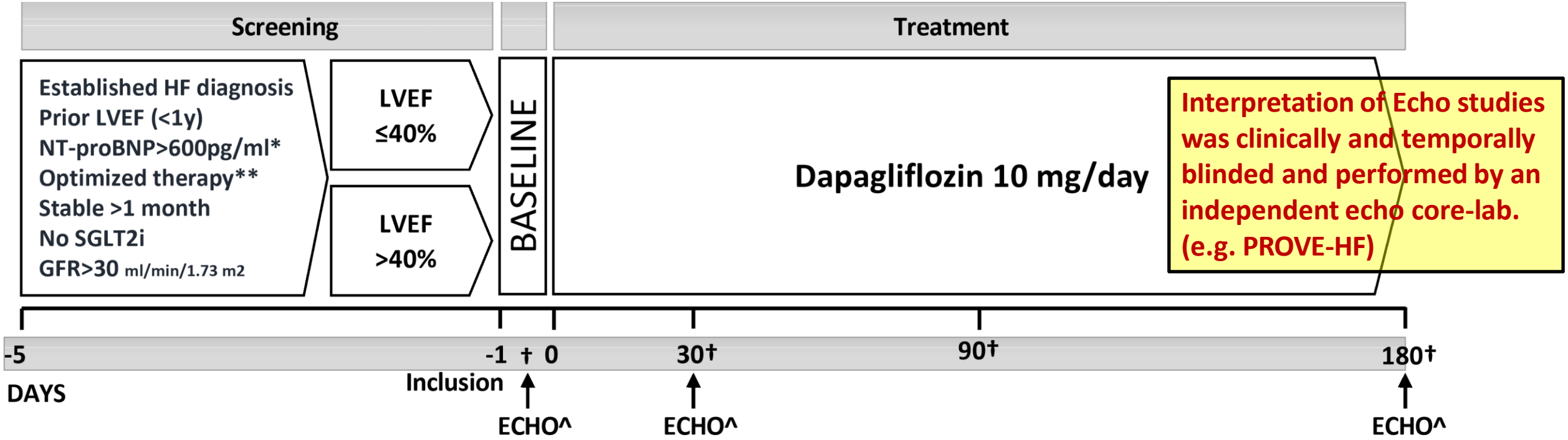


[a]Hospital-based quality improvement registry at participating centers across the US that prospectively collects data from patients hospitalized for HF or who develop HF during hospitalization[1,2]; [b]Patients were excluded based on the following criteria: eGFR <30 mL/min/1.73 m^2 at discharge, dialysis (chronic or during hospitalization), or T1D. Dapagliflozin is not contraindicated in patients with an eGFR <30 mL/min/1.73 m^2 for the treatment of HFrEF in US Prescribing Information[3]; [c]Patients were excluded based on the following criteria: eGFR <25 mL/min/1.73 m^2 at discharge, dialysis (chronic or during hospitalization), SBP <95 mmHg or >180 mmHg at discharge, non-elevated natriuretic peptide levels, BMI >50 kg/m^2 or T1D.

1. Vaduganathan M et al. *JAMA Cardiol*. 2021;6:267-275; 2. Vaduganathan M et al. Presented at: HFSA Annual Scientific Meeting; September 30-October 3, 2022; Washington, DC;
3. FARXIGA® (dapagliflozin) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; May 2023.

DAPA MODA Design

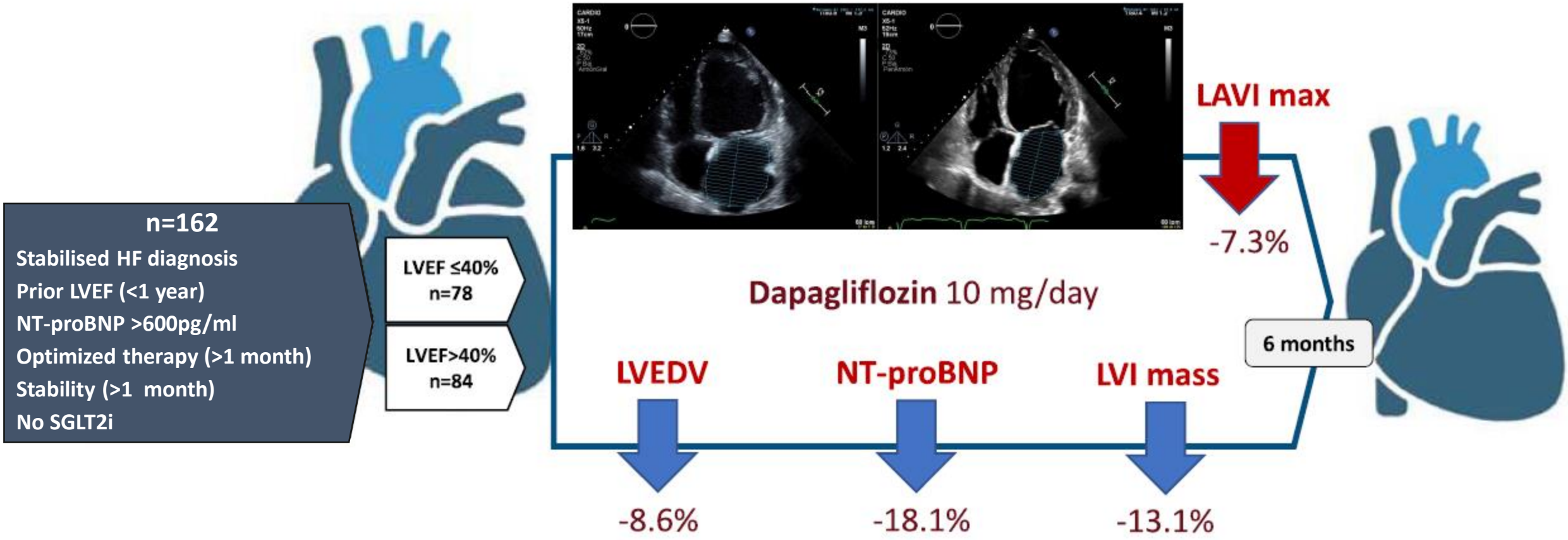
DAPA-MODA trial (NCT04707352) is a multicenter, single-arm, open-label, prospective and interventional study, specifically designed to assess the effect of dapagliflozin in cardiac remodeling parameters over a period of 6 months, in stable patients with chronic HF irrespective of LVEF and diabetes status.



* ≥400 pg/ml if hospitalized for HF within the previous 12 months; ≥900 pg/ml if concomitant atrial fibrillation at screening irrespective of time to last HF hospitalization.
** According with ESC HF guidelines and with stable doses of all of them, including oral loop diuretics for at least 1 month.
† Follow-up visits of the study: blood samples, clinical and vital signs, quality of life and adverse events were obtained in all of them.
^ Interpretation of echo studies was clinically and temporally blinded and performed by an independent echo core-lab.

- Pascual-Figal DA, et al. [published online ahead of print May 21, 2023]. Eur J Heart Fail. 2023.

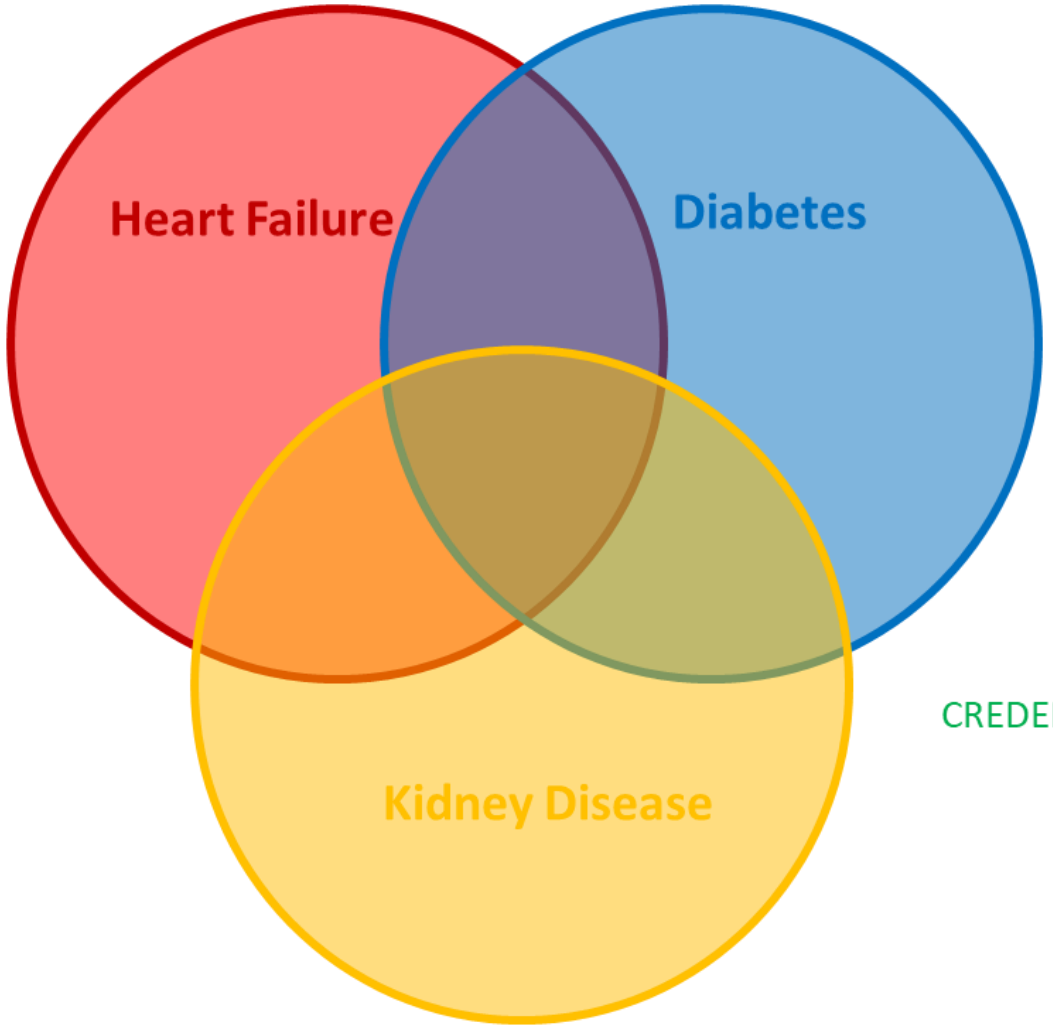
DAPA-MODA trial



Pascual-Figal DA, et al. [published online ahead of print May 21, 2023]. Eur J Heart Fail. 2023.

SGLT2i in the Cardio-Reno-Metabolic Space

EMPEROR-Reduced
EMPEROR-Preserved
DAPA-HF
DELIVER



EMPA-REG
CANVAS Program
DECLARE

CREDENCE

DAPA-CKD
EMPA-KIDNEY

DAPA-CKD Dapagliflozin in Patients With Chronic Kidney Disease[1,2]

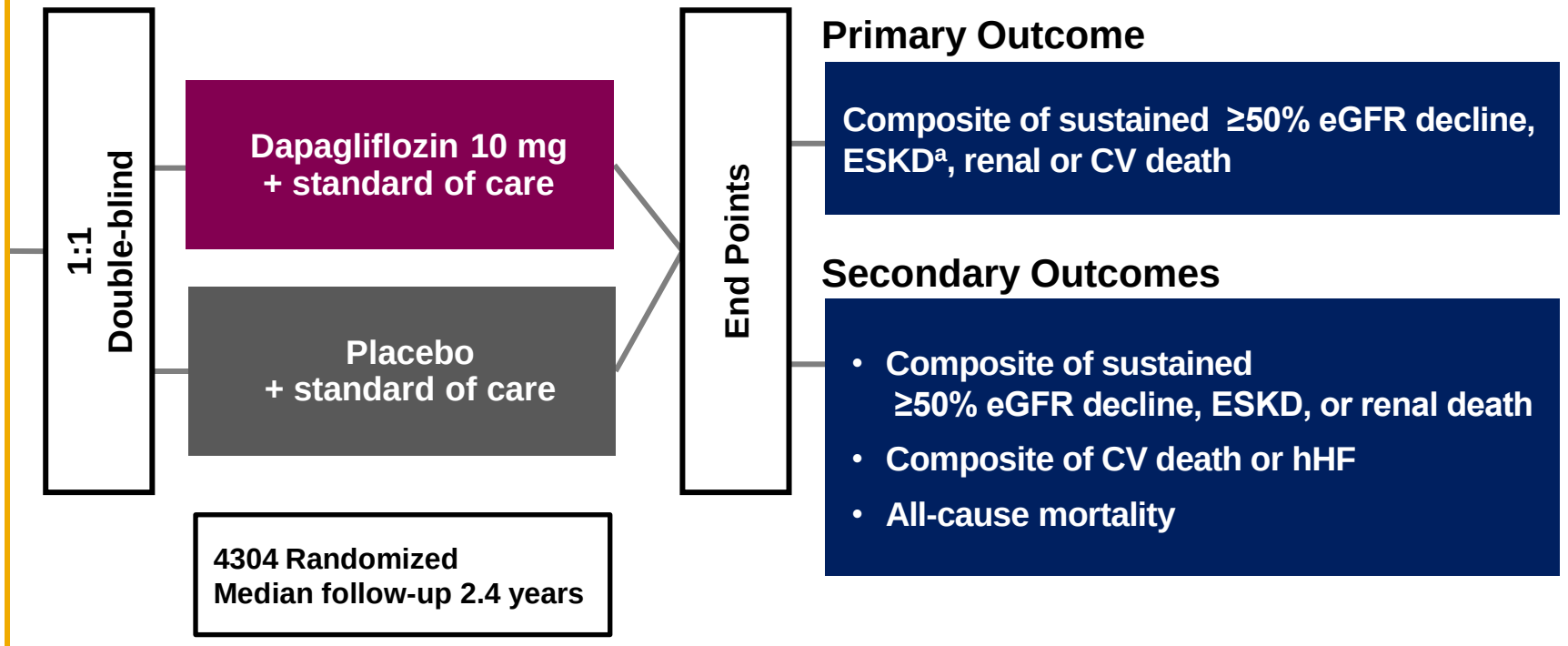
Objective To assess whether treatment with dapagliflozin, compared with placebo, reduced the risk of renal and CV events in patients with CKD with or without T2D, and who were receiving standard of care including a maximum tolerated dose of an ACEi or ARB

Key Inclusion Criteria

- ≥18 years of age
- eGFR ≥25 to ≤75 mL/min/1.73m^2
- UACR ≥200 to ≤5000 mg/g
- Stable max tolerated dose of ACEi/ARB for ≥4 weeks
- With and without T2D

Key Exclusion Criteria

- T1D
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy ≤6 months prior to enrollment



[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for more than 28 days, renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days.

1. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282; 2. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446.

Dapagliflozin significantly reduced the risk of the primary composite outcome in DAPA-CKD[1]

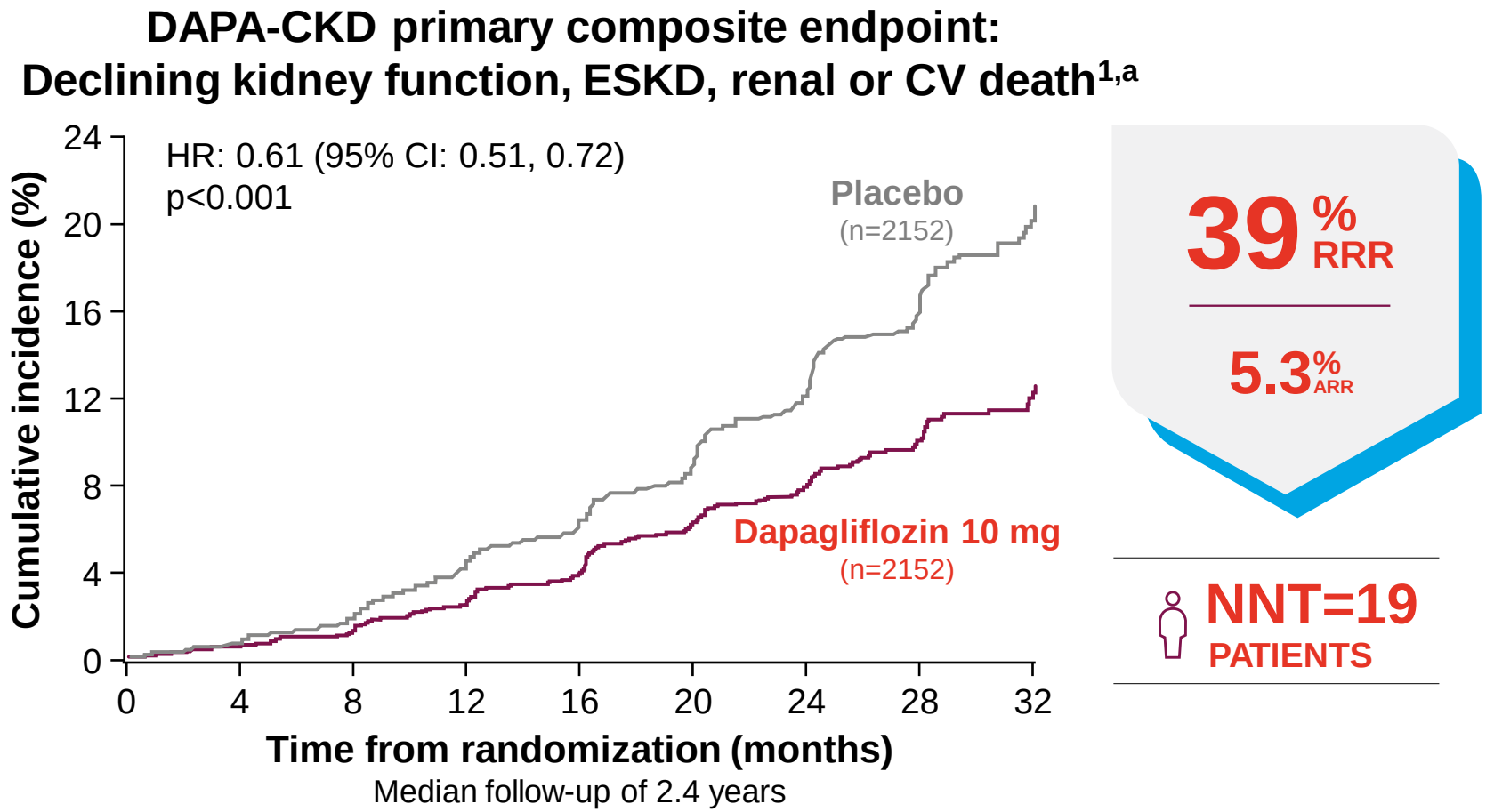
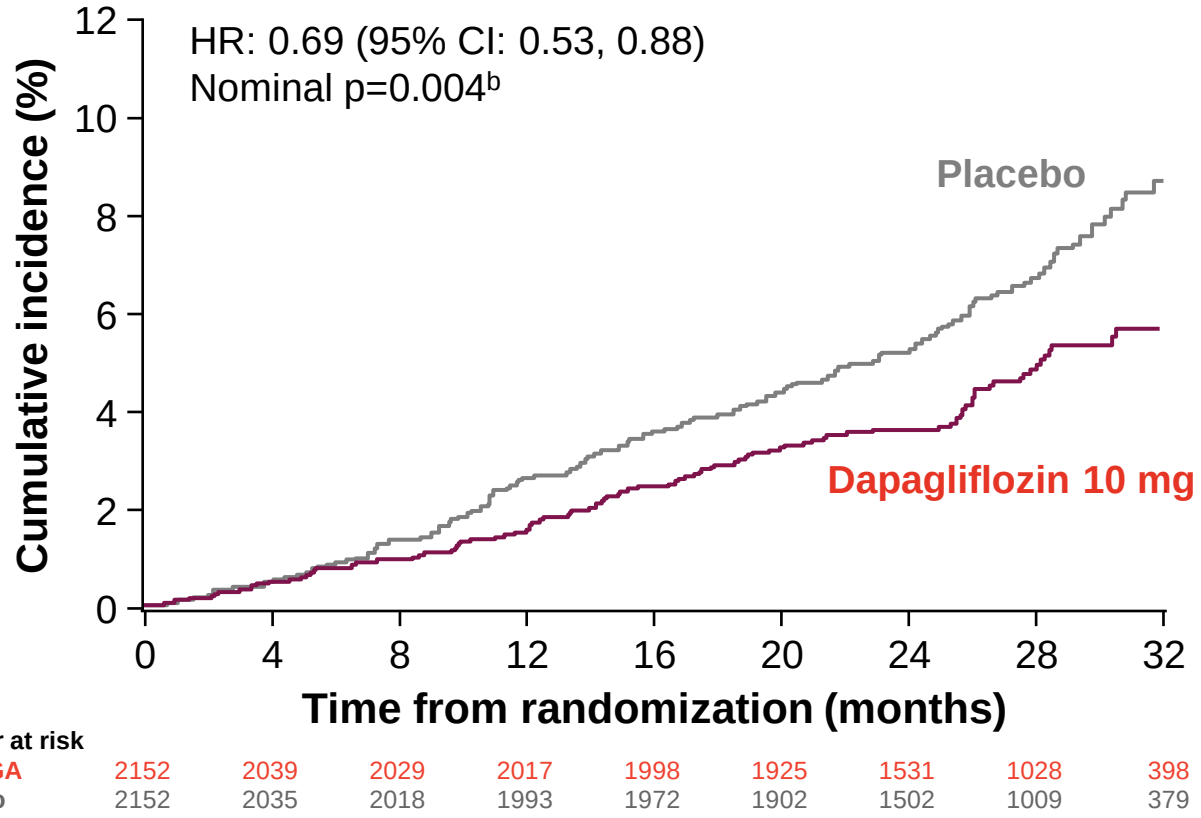


Figure adapted from Heerspink HJL, et al. 2020.[1] [a]Primary composite endpoint of ≥50% sustained decline in eGFR, reaching ESKD, renal or CV death. ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days, renal transplantation or sustained eGFR <15 mL/min/1.73 m^2 for at least 28 days[1]

1. Heerspink HJL, et al. *N Engl J Med* 2020;383:1436–1446

Mortality benefit seen with dapagliflozin in patients with CKD with or without T2D[1–5]

DAPA-CKD secondary endpoint: Risk of all-cause mortality[1,a]



31% RRR

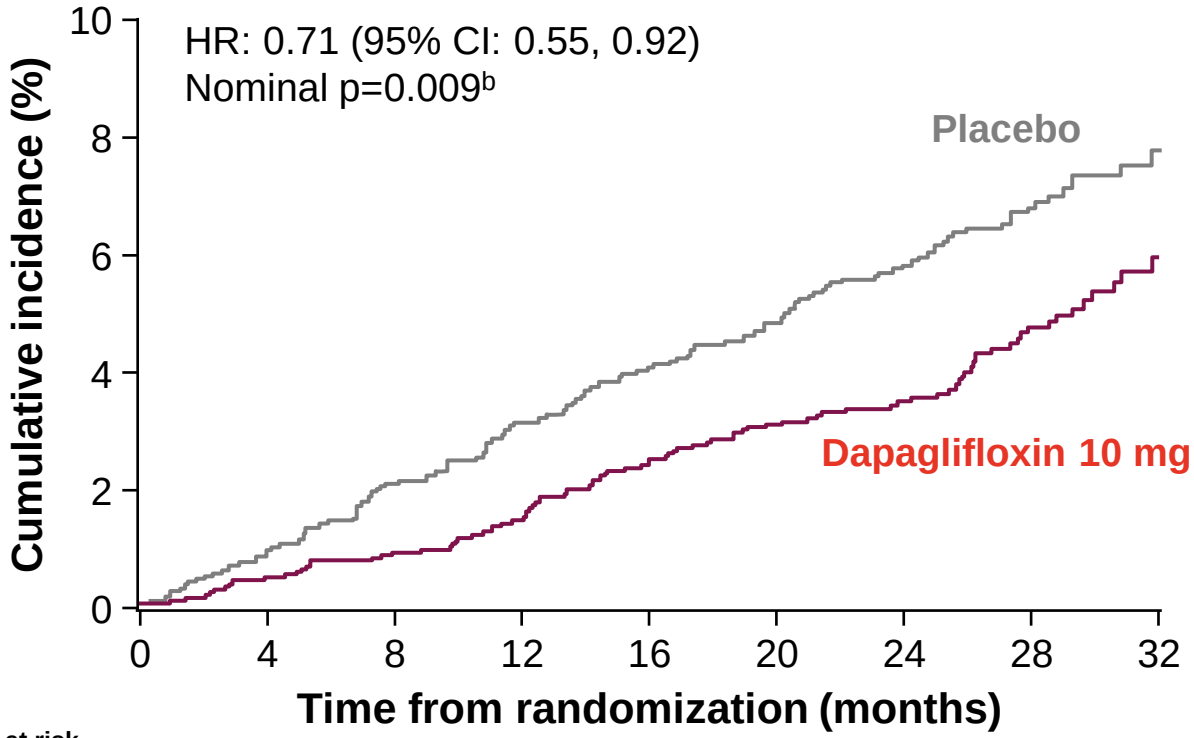
2.1% ARR

Consistent efficacy in patients with or without T2D[6,a]

Figure adapted from Heerspink HJL, et al. 2020[1] [a]There was no significant subgroup interaction of the effect on the secondary endpoint by diabetes status (all-cause mortality; *P* for interaction = 0.85);[6] [b]DAPA-CKD was stopped early due to efficacy benefit.[1] Because of the unplanned early stop, this secondary endpoint is considered nominal.

Dapagliflozin significantly improved CV outcomes[1]

DAPA-CKD secondary composite endpoint: Risk of CV death or hHF[1,a]



Number at risk									
FORXIGA	2152	2035	2021	2003	1975	1895	1502	1003	384
Placebo	2152	2023	1989	1957	1927	1853	1451	976	360

29% RRR

1.8% ARR

Consistent efficacy in patients with or without T2D[2,a]

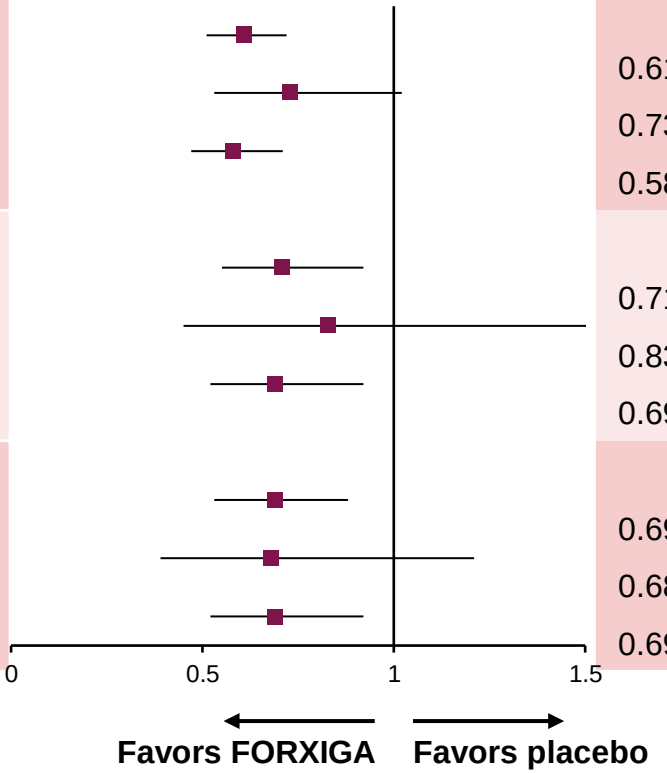
There were comparable rates of the individual component of CV death vs placebo (3.0% vs 3.7%; HR: 0.81; 95% CI: 0.58, 1.12)[1]

Figure adapted from Heerspink HJL, et al. 2020.[1] [a]There was no significant subgroup interaction of the effect on the secondary endpoint by diabetes status (composite of CV death or hHF; *P* for interaction = 0.11);[2] [b]DAPA-CKD was stopped early due to efficacy benefit.[1] Because of the unplanned early stop, this secondary endpoint is considered nominal

1. Heerspink HJL, et al. *N Engl J Med* 2020;383:1436–1446; 2. Wheeler DC, et al. *Lancet Diabetes Endocrinol* 2021;9:22–31

DAPA-CKD Consistent benefit observed for primary outcome, CV death or hHF, and all-cause mortality in patients with CKD stages 2/3 and stage 4[1]

	FORXIGA 10 mg	Placebo	FORXIGA 10 mg	Placebo	Hazard ratio (95% CI)	P_{int}
	n/N		Events/100 patient-years			
Primary outcome: ≥50% eGFR decline, ESKD, or kidney or CV death[a]						
Overall	197/2152	312/2152	4.6	7.5	0.61 (0.51, 0.72)	
Stage 4	59/293	87/331	11.1	14.9	0.73 (0.53, 1.02)	0.22
Stage 2/3	138/1859	225/1821	3.7	6.2	0.58 (0.47, 0.71)	
CV death or hHF[b]						
Overall	100/2152	138/2152	2.2	3.0	0.71 (0.55, 0.92)	
Stage 4	18/293	24/331	2.9	3.6	0.83 (0.45, 1.53)	0.63
Stage 2/3	82/1859	114/1821	2.0	2.9	0.69 (0.52, 0.92)	
All-cause mortality[b]						
Overall	101/2152	146/2152	2.2	3.1	0.69 (0.53, 0.88)	
Stage 4	19/293	31/331	3.0	4.6	0.68 (0.39, 1.21)	0.95
Stage 2/3	82/1859	115/1821	2.0	2.9	0.69 (0.52, 0.92)	



Consistent effects by CKD stage on the component of progression to ESKD[1]

Prespecified analysis. CKD stage 4: eGFR <30 mL/min/1.73 m^2; CKD stage 2/3: eGFR ≥30 mL/min/1.73 m^2
[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15 mL/min/1.73 m^2 for at least 28 days;[2] [b]DAPA-CKD was stopped early due to efficacy benefit.[2] Because of the unplanned early stop, these secondary endpoints are considered nominal
CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; hHF, hospitalization for heart failure; P_{int}, *P* value for interaction

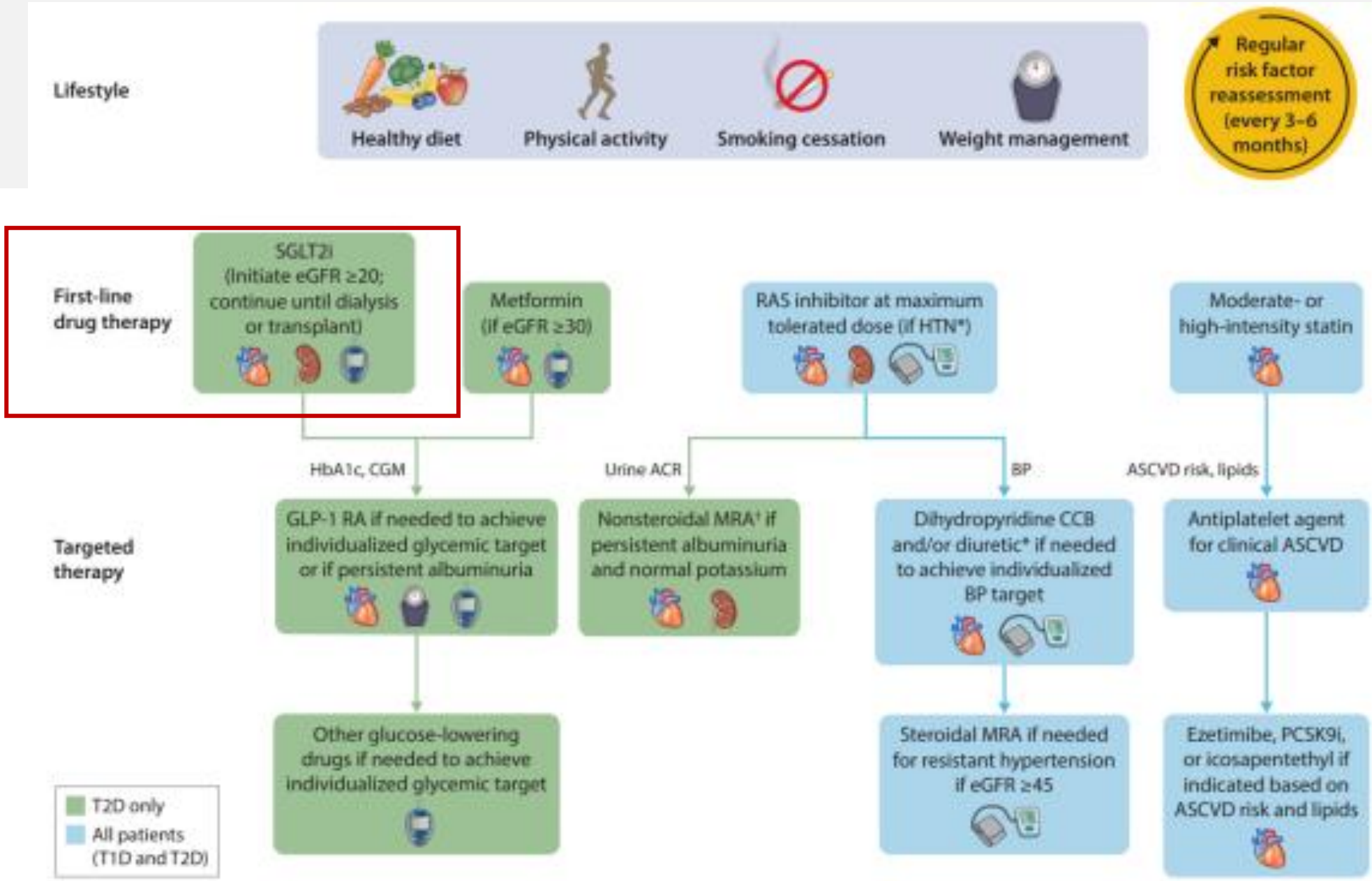
1. Chertow G, et al. *J Am Soc Nephrol* 2021. doi:10.1681/ASN.2021020167 [Epub ahead of print]; 2. Heerspink HJL, et al. *N Engl J Med* 2020;383:1436–1446

UK Kidney Association CPG SGLT2-i in Adults with Kidney Disease

RECOMMENDATIONS FOR USE IN PEOPLE WITH AN eGFR ≥25mL/min/1.73m^2		
Section 2	**PEOPLE WITH TYPE 2 DM**	**Grade**
1.	We recommend initiating SGLT-2inhibition* in those with: (a) uACR of ≥25 mg/mmol attributed to diabetic nephropathy (b) Established coronary disease or stable symptomatic heart failure (irrespective of ejection fraction).	**1A**
2.	We recommend initiating SGLT-2 inhibition in those with a uACR of ≥25 mg/mmol attributable to a non-diabetic cause‡	**1B**
3.	We suggest initiating SGLT-2 inhibition to modify cardiovascular risk in those with an eGFR 25-60 mL/min/1.73m^2 and uACR <25 mg/mmol, recognising effects on glycaemic control will be limited.	**2B**
Section 3	**PEOPLE WITHOUT DM**	
1.	We recommend initiating SGLT-2 inhibition* in those with stable symptomatic heart failure (irrespective of ejection fraction).	**1A**
2.	We recommend initiating SGLT-2 inhibition* in those with a uACR of ≥25 mg/mmol, excluding people with polycystic kidney disease or on immunological therapy for renal disease.‡	**1B**
** See section 4 for summary of indications/licensed uses* *‡ DAPA-CKD provides the key clinical evidence and excluded people with a kidney transplant, polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis, and those receiving immunological therapy for renal disease in the last 6 months.*		

https://ukkidney.org/sites/renal.org/files/UKKA%20guideline_SGLT2i%20in%20adults%20with%20kidney%20disease%20v1%2020.10.21.pdf, Access on [8 Apr 2022]

KDIGO 2022 CPG for Diabetes Management in CKD



ACEi or ARB should be first-line therapy for hypertension when albuminuria is present, otherwise dihydropyridine CCB or liuretic can also be considered; all three classes often needed to attain BP targets.

		Outcomes	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
T2DM			CANVAS[1]	DECLARE TIMI-58[2]	EMPA REG[3]	VERTIS CV[9]
	Risk factors of ASCVD	*Heart Failure Hospitalization*	✓ 39% RRR (CI 0.39, 0.96), *NR*	✓ 36% RRR (CI 0.46, 0.88), *NR*	*Not Studied*	*Not Studied*
		Renal Outcome	✓ 31% RRR (CI 0.54, 0.88), *NR*	✓ 49% RRR (CI 0.37, 0.69), *NR*		
	With ASCVD	*Heart Failure Hospitalization (HHF)*	✓ 39% RRR (CI 0.44, 0.85), *NR*	✓ 22% RRR (CI 0.63, 0.97), *NR*	✓ 35% RRR (CI 0.50, 0.85), *P=0.002*	✓ 30%RRR (CI, 0.54, 0.90), P=0.006%
		Renal Outcome	✓ 30% RRR (CI 0.56, 0.88), *NR*	✓ 45% RRR (CI 0.41, 0.75), *NR*	✓ 46% RRR (CI 0.40, 0.75), *P<0.001*	✗ 19%RRR (CI, 0.63, 1.04), P=0.08%
Local registration			*T2DM treatment reduces the risk of MACE in patient w/ T2DM & ASCVD*	*T2DM treatment, respect to outcome result for reduce HHF and renal risk*	*T2DM Treatment, Risk reduction of CV death in patients w/ type 2 DM & ASCVD*	*T2DM treatment*
HFrEF			*NA*	DAPA-HF[4]	Emperor-Reduced[5]	*NA*
		Primary outcome for HF outcome	*Not Studied*	✓ 26% RRR (CI 0.65-0.85), *p*<0.001	✓ 25% RRR (CI 0.65-0.86), *p*<0.001	*Not Studied*
		CV Death		✓ 18% RRR (CI 0.69- 0.98), *NR*	✗ 18% RRR (CI 0.75-1.12), *NR*	
		All-Cause Death		✓ 17% RRR (CI 0.71-0.97), *NR*	✗ 18% RRR (CI 0.77-1.10), *NR*	
HFpEF			*NA*	***DELIVER[10]***	Emperor-Preserved[6]	*NA*
		Primary outcome for HF outcome	*Not Studied*	✓ *18%RRR [CI 0.73 -0.92), P<0.001*	✓ 21% RRR (CI 0.69-0.90), P<0.001	*Not Studied*
		Renal Outcome		*Not Studied*	✗ 5% RRR (CI 0.69-1.24), NR	
CKD			Credence[7]	DAPA-CKD[8]	***EMPA-KIDNEY***	***NA***
	Diabetes	*Primary outcome for CKD progression*	✓ 30% RRR (CI 0.59-0.82), *P<0.001*	✓ 46% RRR (CI 0.52-0.79), *NR*	✓ 36% RRR (CI 0.54–0.77) P= NR	*NA*
		All- Cause death	✗ 17% RRR (CI 0.68-1.02), *NR*	✓ 26% RRR (CI 0.56-0.98), *NR*	✗ Main result 0.87 (0.70–1.08) p=N.S Sub-analysis not available yet	
	Non Diabetes	*Primary outcome for CKD progression*	*Not Studied*	✓ 50% RRR (CI 0.35-0.72), *NR*	✓ 18%RRR (CI 0.68-0.99) P=NR	
		All- Cause death		✓ 48% RRR (CI 0.29-0.93), NR	✗ Main result 0.87 (0.70–1.08) p=N.S Sub-analysis not available yet	
Local registration			***Treatment for Diabetes Kidney Disease***	**Treatment for Chronic Kidney disease**	*N/A*	*NA*

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Conclusions

- SGLT2i confer HF and kidney benefits in both T2DM and non-T2DM patients; HF- and reno-protective effects extend across a wide range of LVEF and renal function, respectively
- Current guidelines recommend initiation of SGLT2i early in the treatment of T2DM and non-T2DM patients with HF and CKD
- Use of SGLT2i is well tolerated, and can be maintained into advanced CKD
- Among SGLT2i, dapagliflozin has demonstrated consistent additional mortality benefits
- Many real-world patients are eligible for, and will derive significant CV, renal and mortality benefits with, dapagliflozin