ESC European Society of Cardiology
European Heart Journal (2021) **42**, 4887–4890
doi:10.1093/eurheartj/ehab704

VIEWPOINT
Heart failure and cardiomyopathies

Sodium glucose co-transporter inhibitors and heart failure outcomes across different patient populations

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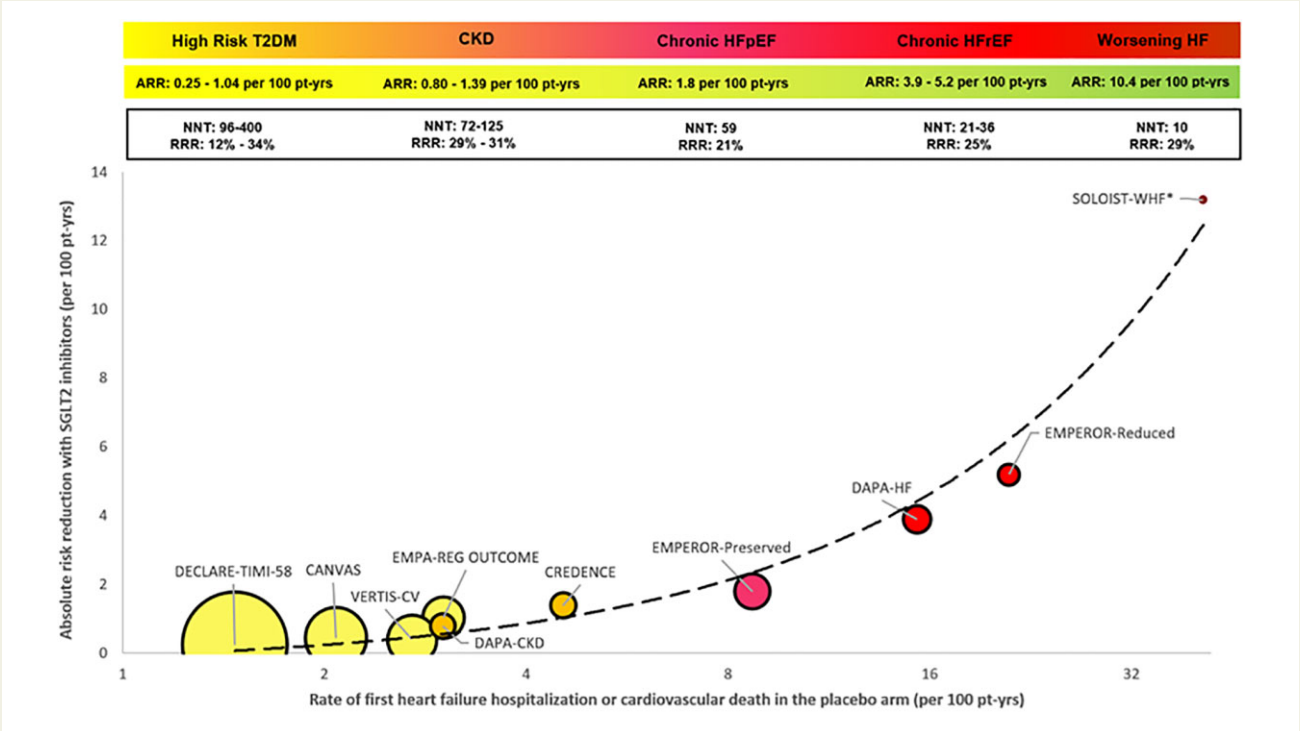
Received 30 July 2021; revised 3 September 2021; editorial decision 15 September 2021; accepted 30 September 2021; online publish-ahead-of-print 30 October 2021



Graphical Abstract These bubble plots demonstrate the consistent reductions in time to cardiovascular mortality or first heart failure hospitalization with SGLT2 inhibitors across all trials, with a greater absolute risk reduction in patients at higher risk. The size of the bubble represents the sample size of the trial. Number needed to treat (NNT) is estimated from the absolute risk reduction Event rates of first heart failure hospitalization or cardiovascular mortality were not reported in SOLOIST-WHF; we used 12-month Kaplan Meier event rates estimated by Cotter *et al.*[19]

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Table 1 Study and baseline characteristics

	Diabetes cardiovascular outcome								Chronic kidney disease						Heart failure							
									DM + non-DM		DM only				Reduced EF				Worsening HF		Preserved EF	
	CANVAS		EMPA-REG OUTCOME		DECLARE-TIMI 58		VERTIS-CV		DAPA-CKD		CREDENCE		SCORED		EMPEROR-Reduced		DAPA-HF		SOLOIST-WHF		EMPEROR-Preserved	
	Cana	Pla	Empa	Pla	Dapa	Pla	Ertu	Pla	Dapa	Pla	Cana	Pla	Sota	Pla	Empa	Pla	Dapa	Pla	Sota	Pla	Empa	Pla
N	5795	4347	4687	2333	8582	8578	5499	2747	2152	2152	2202	2199	5292	5292	1863	1867	2373	2371	608	614	2997	2991
Age (years)	63 (8)	63 (8)	63 (9)	63 (9)	64 (7)	64 (7)	64 (8)	64 (8)	62 (12)	62 (12)	63 (9)	63 (9)	69 (63-74)	69 (63-74)	67 (11)	67 (11)	66 (11)	67 (11)	69 (63-76)	70 (64-76)	71 (9)	72 (10)
HF, *n* (%)																						
Total	803 (13.9)	658 (15.1)	462 (9.9)	244 (10.5)	852 (9.9)	872 (10.2)	1286 (23.4)	672 (24.5)	235 (10.9)	233 (10.8)	329 (14.9)	323 (14.7)	1640 (31.0)	1643 (31.0)	1863 (100)	1867 (100)	2373 (100)	2371 (100)	608 (100)	614 (100)	2997 (100)	2991 (100)
HFrEF	*	*	*	*	318 (3.7)	353 (4.1)	680 (12.4)	327 (11.9)	*	*	*	*	505 (9.5)	528 (10.0)	1863 (100)	1867 (100)	2373 (100)	2371 (100)	481 (79.1)	485 (79.0)	–	-
HFpEF	*	*	*	*	399 (4.6)	409 (4.7)	319 (5.8)	159 (5.8)	*	*	*	*	1133 (21.4)	819 (21.1)	–	–	–	-	127 (20.9)	129 (21.0)	2997 (100)	2991 (100)
Diabetes, (%)[‡]	100	100	100	100	100	100	100	100	68	67	100	100	100	100	50	50	42	42	100	100	49	49
eGFR, mL/min per 1.73 m^2[§], mean (SD)	77 (20)	76 (21)	74 (22)	74 (21)	85 (16)	85 (16)	76 (21)	76 (21)	43 (12)	43 (12)	56 (18)	56 (18)	44 (37-51)	45 (37-52)	62 (23)	62 (22)	66 (20)	66 (19)	49 (39-61)	51 (41-65)	61 (20)	61 (20)
Outcomes (events/rate)																						
First HHF/CVM, events	*	*	198	265	417	496	444	250	110	138	179	253	*	*	361	462	382	495	*	*	415	511
First HHF/CVM, rate (no. per 1000 pt-yrs)	16.3	20.8	19.7	30.1	12.2	14.7	23.0	27.0	22.0	30.0	31.5	45.4	*	*	158	210	114	153	*	*	69	87
First HHF, events	*	*	126	95	212	286	139	99	*	*	89	141	152	219	246	342	231	318	234	254	259	352
First HHF, rate (no. per 1000 pt-yrs)	5.5	8.7	9.4	14.5	6.2	8.5	7.0	11.0	*	*	15.7	25.3	*	*	107	155	69	98	*	*	43	60
Outcomes (effect sizes)																						
First CVM/HHF, HR (95% CI)																						
Overall	0.78 (0.61, 0.91)		0.66 (0.55, 0.79)		0.83 (0.73, 0.95)		0.88 (0.75, 1.03)		0.71 (0.55, 0.92)		0.69 (0.57, 0.83)		0.77 (0.66, 0.91)		0.75 (0.65, 0.86)		0.75 (0.65, 0.85)		0.71 (0.56, 0.90)		0.79 (0.69-0.90)	
HF	0.61 (0.46, 0.80)		0.72 (0.50, 1.04)		HFrEF: 0.62 (0.45, 0.86) HFpEF: 0.88 (0.66, 1.17)		*		*		0.81 (0.57, 1.17)		*		0.75 (0.65, 0.86)		0.75 (0.65, 0.85)		0.71 (0.56, 0.90)		*	
Non-HF	0.87 (0.72, 1.06)		0.63 (0.51, 0.78)		0.88 (0.74, 1.03)		*		*		0.63 (0.51, 0.80)		*		*		*		*		*	
First HHF, HR (95% CI)																						
Overall	0.67 (0.52, 0.87)		0.65 (0.50, 0.85)		0.73 (0.61, 0.88)		0.70 (0.54, 0.90)		*		0.61 (0.47, 0.80)		*		0.69 (0.59, 0.81)		0.70 (0.59, 0.83)		*		0.71 (0.63-0.83)	
HF	0.51 (0.33, 0.78)		0.75 (0.48, 1.19)		HFrEF: 0.64 (0.43, 0.95) HFpEF: 0.72 (0.50, 1.04)		All: 0.63 (0.44, 0.90) HFrEF: 0.48 (0.30, 0.76) HFpEF: 0.86 (0.58, 1.29)		*		0.76 (0.48, 1.22)		*		0.69 (0.59, 0.81)		0.70 (0.59, 0.83)		*		*	
Non-HF	0.79 (0.57, 1.09)		0.59 (0.43, 0.82)		0.77 (0.60, 0.97)		0.79 (0.54, 1.15)		*		0.54 (0.39, 0.75)		*		*		*		*		*	
Total HHF, rate ratio (95% CI)																						
Overall	*		*		*		0.70 (0.56, 0.87)		*				0.67 (0.55, 0.82)		0.70 (0.58, 0.85)		*		0.64 (0.49, 0.83)		0.73 (0.61-0.88)	

*Data not published.

Hospitalization for heart failure marks a fundamental change in the natural history of the disease and portends a poor prognosis for the patients. For those without a history of heart failure, a hospitalization signals development of new onset heart failure that is associated with 40–50% 5-year mortality risk.[1] Amongst those with a previous history of heart failure, worsening symptoms leading to hospitalization are associated with ~20–25% 1 year mortality risk, a ~20% 4-week readmission risk and a ~50% 6-month readmission risk.[1] In observational studies, these risks are apparent whether a person has heart failure with reduced or preserved ejection fraction.[2] Recent clinical trials have demonstrated that worsening heart failure is associated with the highest absolute risk of heart failure hospitalization, followed by chronic heart failure with reduced ejection fraction, and then chronic heart failure with preserved ejection fraction in the outpatient setting. Relative to patients with manifest heart failure, the absolute risk of heart failure hospitalizations is lower in populations with chronic kidney disease and diabetes without prevalent heart failure, but these patients nevertheless are at a higher risk than those without these comorbidities. Indeed, in patients with diabetes mellitus, the risk for heart failure has been shown to be higher and less amenable to reduction with risk factor control than myocardial infarction and diabetes.[3] Besides portending risk, these hospitalizations are associated with high costs, both to an individual as well as the society, accounting for most of the overall annual direct cost of care related to heart failure.[1] Thus, prevention of hospitalizations for heart failure is an important clinical, patient-centric and societal goal.

Sodium glucose co-transporter (SGLT2) inhibitors were originally developed for glycemic control in patient with type-2 diabetes. These drugs subsequently have been shown to have a remarkably consistent benefit in reducing the risk of adverse heart failure outcomes across diverse patient populations (*Table 1*). Furthermore, the absolute risk reduction in heart failure outcomes with SGLT2 inhibitors is higher in patients who are at a higher risk for adverse outcomes (*Graphical Abstract*).

Type-2 diabetes mellitus

All four cardiovascular outcomes trials in patients with type 2 diabetes—EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), CANVAS (Canagliflozin Cardiovascular Assessment Study), DECLARE-TIMI 58 (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events), and VERTIS-CV (Evaluation Of Ertugliflozin Efficacy And Safety Cardiovascular Outcomes Trial) trials—showed remarkably consistent effect on hospitalization for heart failure (27–35% relative risk reduction), even though they showed inconsistent effects on other cardiovascular and renal events.[4–7] These benefits were observed in those with and without a history of atherosclerotic cardiovascular disease. Similarly, these benefits were consistent in the majority of those who did not have a history of heart failure, as well as those who did.

Chronic kidney disease

Three trials have studied the effect of these drugs in patients with chronic kidney disease, i.e. CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy); DAPA CKD (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease); and SCORED (Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk).[8–10] In these high-risk patients for heart failure hospitalizations, a consistent risk reduction was observed, ranging from ~25% to 30%. The CREDENCE trial enrolled ~15% of patients with a history of heart failure, and reported consistent results in both patients with and without heart failure. DAPA CKD enrolled patients with (68%) and without (32%) diabetes and reported benefits in both groups (P interaction = 0.78).[11] These data are the first to suggest the primary prevention of heart failure in patients without diabetes with SGLT inhibitors.

Heart failure with reduced ejection fraction

The DAPA-HF (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure) trial and EMPEROR-Reduced (Empagliflozin Outcome Trial In Patients With Chronic Heart Failure With Reduced Ejection Fraction) trial evaluated the effects of dapagliflozin and empagliflozin, respectively, in patients with heart failure and reduced ejection fraction.[12–14] Both trials showed reduction in time to cardiovascular death or heart failure hospitalization, time to first heart failure hospitalization, total (first and recurrent) heart failure hospitalization, and all worsening heart failure events (heart failure hospitalization or need for intensification of diuretics in non-hospitalized settings).[15–16] These benefits were seen in patients regardless of diabetes status, chronic kidney disease, or baseline therapy. The magnitude of benefit for heart failure hospitalization was near identical in both trials at ~30%.

Worsening heart failure

SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure) trial studied the effects of sotagliflozin, a combined SGLT2/SGLT1 inhibitor, in a population comprising of both heart failure with reduced or preserved ejection fraction, who had diabetes and worsening heart failure.[17] There was a 36% relative risk reduction observed for hospitalization or urgent visits for heart failure with sotagliflozin; benefits were consistent across major patient subgroups.

Heart failure with preserved ejection fraction

In the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction), empagliflozin reduced the risk of cardiovascular death and heart failure hospitalization in patients with heart failure and preserved ejection fraction.[18] There was a 30% relative risk reduction for total heart failure hospitalizations. Consistent with heart failure and reduced

ejection fraction data, benefits were seen regardless of diabetes status or chronic kidney disease. In the SOLOIST trial, there was a small group of patients with heart failure and preserved ejection fraction; this group also benefitted in terms of hospitalization or urgent visits for heart failure risk.

In total, so far this experience represents over 75 000 randomized patients and over 3000 first heart failure events. (*Graphical Abstract*) The effect of SGLT2i on heart failure hospitalization risk reduction is remarkably consistent in both the primary prevention and secondary prevention cohorts. The primary prevention risk reduction is seen in both patients with or without diabetes and with or without atherosclerotic cardiovascular disease and in those with chronic kidney disease. The secondary prevention benefit has now been demonstrated in patients with heart failure and reduced ejection fraction and preserved ejection fraction and in patients with stable or with worsening heart failure. While the link between heart failure hospitalization and mortality has been well associated, the lack of consistent mortality benefit in these trials despite robust consistent heart failure hospitalization risk reduction is intriguing. It may be related to a need for longer follow-up, as there was non-statistically significant favourable directional benefit seen in most trials for cardiovascular mortality. This issue will require further studies.

This success in reducing the risk of heart failure event by SGLT inhibitors across patient populations to a clinically important and remarkably consistent degree is not only a moment for celebration, but also an opportunity for humility, recognizing the serendipity that these strikingly effective drugs were originally and primarily developed to lower blood glucose.

Conflict of interest: J.B. is a consultant to Abbott, Adrenomed, Amgen, Applied Therapeutics, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Cardior, CVRx, G3 Pharma, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, Sequana Medical, and Vifor. S.D.A. reports grants from Vifor; personal fees from Vifor, Bayer, Boehringer Ingelheim, Novartis, Servier, Impulse Dynamics, Cardiac Dimensions, and Thermo Fisher Scientific; Abbott Vascular. G.F. reports receiving payment from Boehringer Ingelheim, Medtronic, Vifor, Servier, and Novartis.J.P.F. reports personal fees from Boehringer Ingelheim. F.Z. reports personal fees from Janssen, Novartis, Boehringer Ingelheim, Boston Scientific, Amgen, CVRx, AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmacuetical, Applied Therapeutics, Merck, Bayer, and Cellprothera and other support from CVCT and Cardiorenal. M.P. reports personal fees from AbbVie, Akcea, Amarin, AstraZeneca, Amgen, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Johnson & Johnson, Lilly, Novartis, Pfizer, Relypsa, Sanofi, Synthetic Biologics, Theravance, and NovoNordisk. M.S.U. has not relationships to declare.

References

1. Virani SS, Alonso A, Aparicio HJ et al.; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. *Circulation* 2021;**143**:e254–e743.
2. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006;**355**:251–259.
3. Rawshani A, Rawshani A, Franzén S et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2018;**379**:633–644.
4. Zinman B, Wanner C, Lachin JM et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–2128.
5. Neal B, Perkovic V, Mahaffey KW et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644–657.
6. Wiviott SD, Raz I, Bonaca MP et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**:347–357.
7. Cannon CP, Pratley R, Dagogo-Jack S et al.; VERTIS CV Investigators. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med* 2020;**383**:1425–1435.
8. Perkovic V, Jardine MJ, Neal B et al.; CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 2019;**380**:2295–2306.
9. Heerspink HJL, Stefánsson BV, Correa-Rotter R et al.; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**:1436–1446.
10. Bhatt DL, Szarek M, Pitt B et al.; SCORED Investigators. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med* 2021;**384**:129–139.
11. Wheeler DC, Stefánsson BV, Jongs N et al.; DAPA-CKD Trial Committees and Investigators. Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial. *Lancet Diabetes Endocrinol* 2021;**9**:22–31.
12. McMurray JJV, Solomon SD, Inzucchi SE et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008.
13. Packer M, Anker SD, Butler J et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**:1413–1424.
14. Zannad F, Ferreira JP, Pocock SJ et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 2020 Sep 19;**396**:819–829.
15. Packer M, Anker SD, Butler J et al.; for the EMPEROR-Reduced Trial Committees and Investigators. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-reduced trial. *Circulation* 2021;**143**:326–336.
16. Jhund PS, Ponikowski P, Docherty KF et al. Dapaglifloin and recurrent heart failure hospitalizations in heart failure with reduced ejection fraction: an analysis of DAPA-HF. *Circulation* 2021;**143**:1962–1972.
17. Bhatt DL, Szarek M, Steg PG et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021;**384**:117–128.
18. Anker SD, Butler J, Filippatos G et al.; for the EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; doi:10.1056/NEJMoa2107038.
19. Cotter G, Davison, BA, Edwards C et al. Acute heart failure treatment: a light at the end of the tunnel? *Eur J Heart Fail* 2021;**23**:698–702.