Systematic review of the effects of sodium-glucose cotransporter 2 inhibitors on hospitalization for heart failure and cardiac structure or function, and exploratory assessment of potential mechanisms

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Background and methods

In the past 5 years, there has been a profound shift in the therapeutic focus of trials of sodium-glucose cotransporter 2 inhibitors (SGLT2is).

Although initially explored and introduced as glucose-lowering agents for patients with type 2 diabetes mellitus (T2DM),[1] clinical investigation of these molecules has evolved towards heart failure (HF) and chronic kidney disease (CKD) outcomes in patients with and without T2DM.[2]

We systematically reviewed randomized controlled trial (RCT) data assessing the effects of SGLT2is compared with placebo on hospitalization for HF (HHF), cardiac structure and cardiac function, in a PRISMA-compliant manner (**Figure 1**).[2,3]

We also reviewed, in an exploratory manner, mechanistic evidence for how SGLT2is may exert their benefits (**Figure 1**).[2]

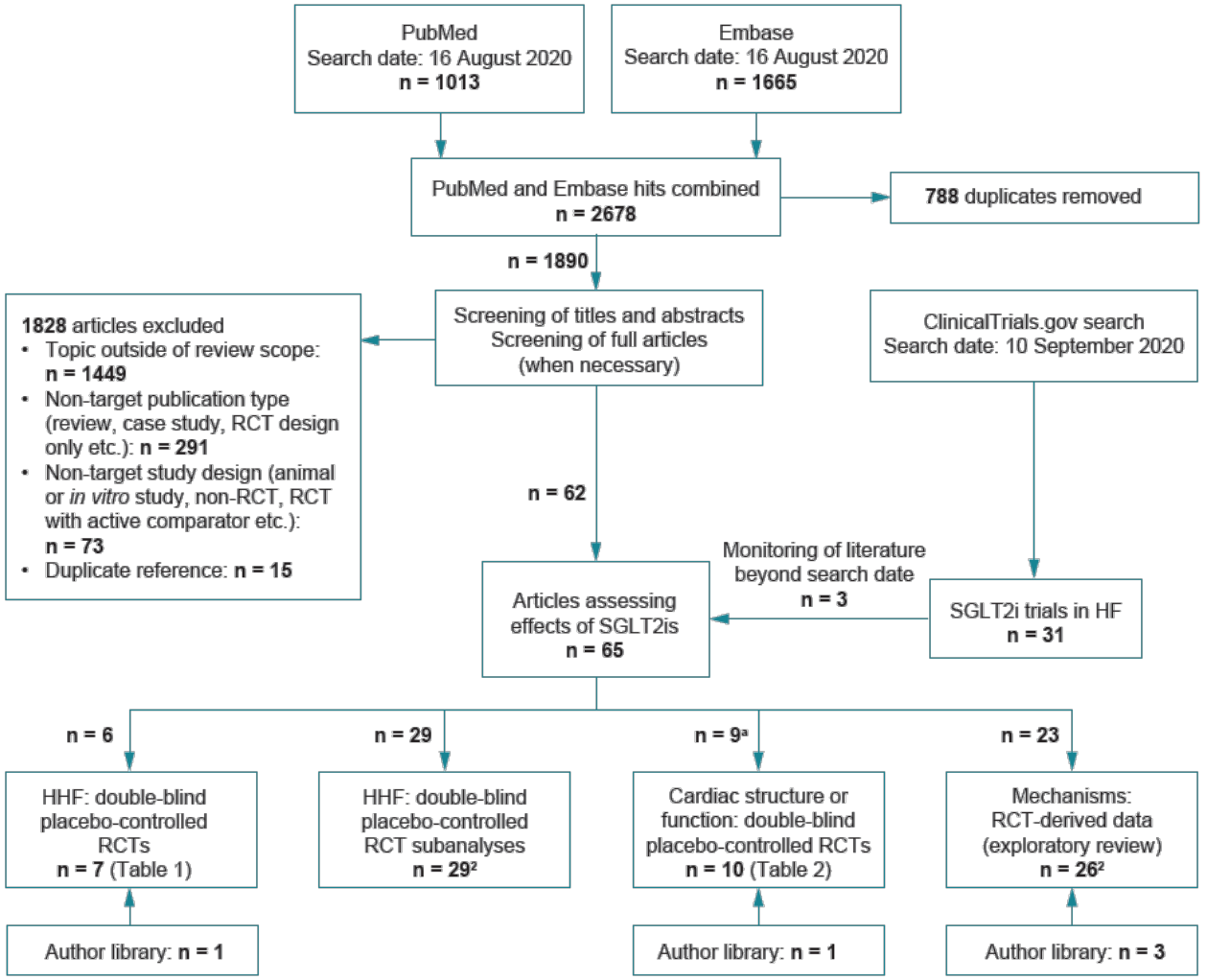

Figure 1. PRISMA summary of the literature searches. [a]Includes two studies also included in Table 1 (i.e. HHF: double-blind, placebo-controlled RCTs). Hence, the total number of studies across categories adds up to 67 rather than 65. HF, heart failure; HHF, hospitalization for heart failure; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; SGLT2, sodium-glucose cotransporter 2; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Trials assessing SGLT2i effects on HHF

In seven trials (3730–17 160 patients; all low risk of bias [RoB]), SGLT2is significantly reduced the relative risk of HHF by 27%–39% versus placebo (**Table 1**).[4–10]

These trial populations comprised patients with T2DM and high cardiovascular risk (four studies[4–7]), patients with T2DM and CKD (one study[8]), and patients with HF with reduced ejection fraction (HFrEF) with or without T2DM (two studies[9,10]) (**Table 1**).

Post hoc analyses of these trials suggest similar reductions in HHF risk regardless of demographics, blood glucose levels, degree of kidney function, HF medication or diuretic use, left ventricular ejection fraction, or presence of T2DM or HFrEF.[2]

Trials assessing SGLT2i effects on cardiac function

Five trials (56–105 patients; all low RoB) assessed the effects of 6–12 months of SGLT2i treatment on left ventricular structure/function; four[11–14] reported significant improvements compared with placebo and one[15] did not (**Supplemental Table 1**).

Five trials (all low RoB) assessed SGLT2i treatment effects on serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (**Supplemental Table 1**).

- Significant reductions in NT-proBNP compared with placebo were reported after 8–12 months of treatment in two studies (3730–4744 patients).[9,10]
- NT-proBNP was not significantly reduced compared with placebo after 12 weeks or less of treatment in three studies (80–263 patients).[16–18]

Table 1 . RCT data for effects of SGLT2is on HHF event rates. [a]All studies are double-blind, placebo-controlled RCTs that were determined to have a low risk of bias. [b]All doses are once daily. [c]Presented as means unless otherwise specified. [d]Summary statistics indicating a significant effect with an SGLT2i vs placebo are highlighted in bold text. CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HHF, hospitalization for heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; NR, not reported; RCT, randomized controlled trial; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus.

Study[a]	Median follow-up	Population	Interventions (n)[b]	Baseline characteristics: SGLT2i [placebo][c]	HR (95% CI) for HHF events (SGLT2i vs placebo)[d]
Zinman et al. 2015[4] EMPA-REG OUTCOME (NCT01131676)	3.1 years	T2DM with CVD (N = 7020)	Empagliflozin 10 mg or 25 mg (4687) or placebo (2333)	Age: 63.1 [63.2] years Women: 29% [28%]	0.65 (0.50, 0.85); ***P* = 0.002**
Neal et al. 2017[5] CANVAS and CANVAS-Renal (NCT01032629 and NCT01989754)	126 weeks	T2DM with high CVD risk (66% with established disease) (N = 10 142)	Canagliflozin 100 mg or 300 mg (5795) or placebo (4347)	Age: 63.2 [63.4] years Women: 35% [37%]	0.67 (0.52, 0.87); *P* = NR
Wiviott et al. 2018[6] DECLARE-TIMI 58 (NCT01730534)	4.2 years	T2DM with high atherosclerotic CVD risk (41% with established disease) (N = 17 160)	Dapagliflozin 10 mg (8582) or placebo (8578)	Age: 63.9 [64.0] years Women: 37% [38%]	0.73 (**0.61**, **0.88**); *P* = NR
Cannon et al. 2020[7] VERTIS CV (NCT01986881)	3.0 years	T2DM with established atherosclerotic CVD (N = 8246)	Ertugliflozin 5 mg or 15 mg (5499) or placebo (2747)	Age: 64.4 [64.4] years Women: 30% [31%]	0.70 (**0.54**, **0.90**); *P* = NR
Perkovic et al. 2019[8] CREDENCE (NCT02065791)	2.6 years	T2DM with albuminuric CKD (N = 4401)	Canagliflozin 100 mg (2202) or placebo (2199)	Age: 62.9 [63.2] years Women: 35% [33%]	0.61 (0.47, 0.80); ***P* < 0.001**
McMurray et al. 2019[9] DAPA-HF (NCT03036124)	18.2 months	HFrEF (N = 4744)	Dapagliflozin 10 mg (2373) or placebo (2371)	Age: 66.2 [66.5] years Women: 24% [23%]	0.70 (**0.59**, **0.83**); *P* = NR
Packer et al. 2020[10] EMPEROR-Reduced (NCT03057977)	16 months	HFrEF (N = 3730)	Empagliflozin 10 mg (1863) or placebo (1867)	Age: 67.2 [66.5] years Women: 24% [24%]	0.69 (**0.59**, **0.81**); *P* = NR

Exploratory assessment of SGLT2i mechanisms in HF

Limited available RCT-derived evidence suggests various possible, and largely glucose-independent, cardiorenal protective SGLT2i mechanisms (**Figure 2**).[2]

Some mechanisms, such as haemodynamic effects, may contribute to early separation of SGLT2i and placebo HHF event curves, while others, such as reversal of adverse ventricular remodelling, may contribute to later separation (**Figure 3**).[2]

Diuretics also have haemodynamic effects in patients with HF; however, unlike diuretics, SGLT2is may cause natriuresis and reduced interstitial fluid without detrimental blood volume contraction or neurohormonal activation.[2]

Indeed, numerous differences in the physiological effects of SGLT2is compared with diuretics have been observed (**Table 2, slide 4**).[2]

Figure 2. Potential cardiorenal protective mechanisms that have been proposed to contribute to benefits observed with SGLT2is in patients with HF. AMPK, adenosine monophosphate-activated protein kinase; HF, heart failure; NHE, sodium-hydrogen exchanger; RAAS, renin–angiotensin–aldosterone system; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SIRT1, sirtuin 1.

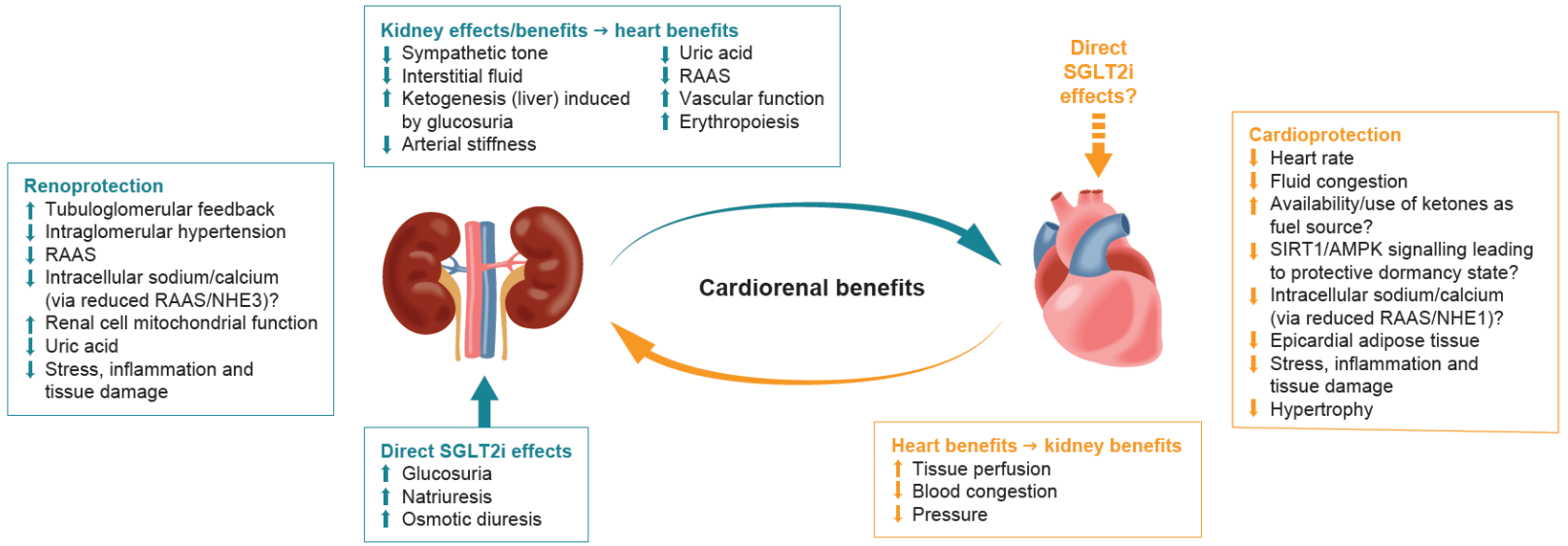

Figure 3. Potential mechanisms that may account for early versus later benefits observed with SGLT2is in patients with HF (adapted from McMurray *et al*. 2019[9]). AMPK, adenosine monophosphate-activated protein kinase; HF, heart failure; HHF, hospitalization for heart failure; NHE, sodium-hydrogen exchanger; RAAS, renin–angiotensin–aldosterone system; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SIRT1, sirtuin 1.

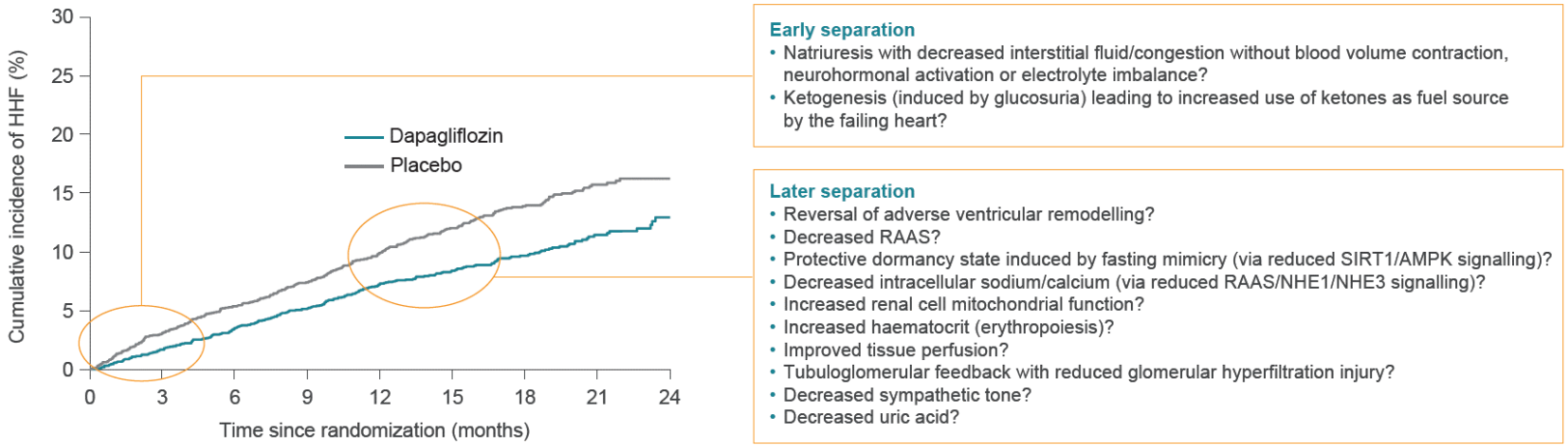

Table 2. Physiological effects of SGLT2is versus diuretics. ↓ = decrease in physiological parameter; ↑ = increase in physiological parameter; ↔ = no notable change in physiological parameter. eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Physiological parameter	SGLT2is	Diuretics
Sodium	↔	↓
Potassium	↔	↓
Magnesium	↔	↓
Uric acid	↓	↑
LDL cholesterol	↔	↑
Plasma glucose	↓	↑
Haematocrit	↑	↔
Heart rate	↓	↑
Systolic blood pressure	↓	↓
Intravascular volume	↓	↓
Interstitial volume	↓	↔
Myocardial infarction	↔	↔
Stroke	↔	↓
eGFR	↓ then ↔	↓
Intraglomerular pressure	↓	↔
Tubuloglomerular feedback	↑	↔
Renin/angiotensin II	↓	↑
Aldosterone	↓	↑
Sympathetic tone	↓	↑
Arginine vasopressin	↔	↑

Conclusions

SGLT2is consistently reduce HHF rates in clinical trials, including in patients with HFrEF with or without T2DM.

Reversal of adverse ventricular remodelling likely contributes to improved HF outcomes, although the magnitude of this contribution is unknown.

Several intriguing and convincing hypotheses have been proposed to explain the benefits of SGLT2is in patients with HF; hypothesis-driven RCT data are sparse, but numerous trials are ongoing.[2]

Continued education around the glucose-independent benefits of SGLT2is is of paramount importance to maximizing patient care, even if a sound mechanistic framework is currently lacking.

References: **1.** Chao EC *et al. Nat Rev Drug Discov* 2010;9:551–9. **2.** Rasalam R *et al. ESC Heart Fail* 2021;doi: 10.1002/ehf2.13483. **3.** Moher D *et al. BMJ* 2009;339:b2535. **4.** Zinman B *et al. N Engl J Med* 2015;373:2117–28. **5.** Neal B *et al. N Engl J Med* 2017;377:644–57. **6.** Wiviott SD *et al. N Engl J Med* 2019;380:347–57. **7.** Cannon CP *et al. N Engl J Med* 2020;383:1425–35. **8.** Perkovic V *et al. N Engl J Med* 2019;380:2295–306. **9.** McMurray JJV *et al. N Engl J Med* 2019;381:1995–2008. **10.** Packer M *et al. N Engl J Med* 2020;383:1413–24. **11.** Brown AJM *et al. Eur Heart J* 2020;41:3421–32. **12.** Lee MMY *et al. Circulation* 2020;143:516–25. **13.** Santos-Gallego CG *et al. J Am Coll Cardiol* 2020;77:243–55. **14.** Verma S *et al. Circulation* 2019;140:1693–702. **15.** Singh JSS *et al. Diabetes Care* 2020;43:1356–9. **16.** Damman K *et al. European Journal of Heart Failure.* 2020;22:713–22. **17.** Jensen J *et al. Am Heart J* 2020;228:47–56. **18.** Nassif ME *et al. Circulation* 2019;140:1463–76.

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