ESC European Society of Cardiology

European Heart Journal (2021) **42**, 1199–1202
doi:10.1093/eurheartj/ehz916

VIEWPOINT
Heart failure and cardiomyopathies

The Dapagliflozin and Prevention of Adverse outcomes in Heart Failure trial (DAPA-HF) in context

John J.V. McMurray [1]*, Scott D. Solomon[2], Kieran F. Docherty [1], and Pardeep S. Jhund [1]

[1]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, UK; and [2]Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street Boston, MA 02115, USA

Received 26 November 2019; editorial decision 3 December 2019; accepted 4 December 2019; online publish-ahead-of-print 7 May 2020

The recently reported Dapagliflozin And Prevention of Adverse outcomes in Heart Failure trial (DAPA-HF) showed the sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin reduced the risk of hospital admission for worsening heart failure, increased survival and improved symptoms in patients with heart failure with reduced ejection fraction (HFrEF).[1–3] Although SGLT2 inhibitors had been developed as glucose-lowering treatments for patients with type 2 diabetes, approximately half the patients in DAPA-HF did not have type 2 diabetes.[1–3] The benefits of dapagliflozin in DAPA-HF were of a similar magnitude in participants without diabetes to the benefits obtained in individuals with diabetes. Importantly, in both groups of patients, dapagliflozin in patients with HFrEF were observed when dapagliflozin was added to excellent background disease-modifying therapy for heart failure.

In this brief commentary, we wish to put these findings into perspective. There are two principal contextual considerations—how the patients randomized in DAPA-HF and their event rates compare with those in the prior SGLT2 inhibitor trials and, second, how the effects of dapagliflozin compare with those of other pharmacological treatments for HFrEF.

DAPA-HF compared with prior sodium-glucose cotransporter 2 inhibitor trials

Table 1 compares the rates of heart failure hospitalization and the composite of heart failure hospitalization or cardiovascular death in the large randomized trials with SGLT2 inhibitors conducted before DAPA-HF and the rates of those outcomes in DAPA-HF.[4–7] The prior trials included few patients with known heart failure and in those patients, the heart failure phenotype was not characterized prospectively.[8,9] The rates of heart failure hospitalization (and the composite of heart failure hospitalization or cardiovascular death) were much lower in the prior trials with SGLT2 inhibitors, compared with DAPA-HF. Indeed, there was more than 10-fold difference between the rate of heart failure hospitalization in DAPA-HF and the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 trial (DECLARE–TIMI 58), the trial with the largest proportion of 'primary prevention' patients, also comparing dapaglifozin to placebo.[3,6] Moreover, the earlier trials included only patients with type 2 diabetes, whereas DAPA-HF also included patients without diabetes. If only the diabetes subgroup in DAPA-HF is examined, the rates of the events of interest are even higher still than in the prior SGLT2 inhibitor trials (*Table 1*). In summary, the patients in DAPA-HF were quite distinct and at much higher cardiovascular risk than patients in the prior SGLT2 inhibitor trials.

Effects of dapagliflozin compared with other pharmacological therapies for heart failure with reduced ejection fraction

It is also of interest to compare the benefits of dapagliflozin to those seen with other therapies. *Table 2* summarizes the effects of all pharmacological treatments shown to be effective over the last decade.[10–12] Because of the substantial and consistent benefit of a mineralocorticoid receptor antagonist (MRA) added to an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

* Corresponding author. Tel: +44 (141) 3303479, Fax: +44 (141) 3306955, Email: john.mcmurray@glasgow.ac.uk

Table 1 Event rates in SGLT2 inhibitor trials

Trial (year of publication)	SGLT2 inhibitor	Number of patients/ follow-up	Patients characteristics	Annual rate HFh per 1000 patient-years[a]	HR (95% CI)	Annual rate CV death/HFh per 1000 patient-years[a]	HR (95% CI)
DECLARE-TIMI 58 (2019)[6]	Dapagliflozin	17 160 4.2 years	T2D ASCVD/RFs	8.5	0.73 (0.61–0.88)	14.7	0.83 (0.73–0.95)
CANVAS (2017)[5]	Canagliflozin	10 142 2.4 years	T2D ASCVD/RFs	8.7	0.67 (0.52–0.87)	20.8	0.78 (0.67–0.91)
EMPA-REG (2015)[b4]	Empagliflozin	7020 3.1 years	T2D ASCVD	14.5	0.65 (0.50–0.85)	30.1	0.66 (0.55–0.79)
CREDENCE (2019)[7]	Canagliflozin	4401 2.6 years	T2D albuminuric CKD	25.3	0.61 (0.47–0.80)	45.4	0.69 (0.57–0.83)
DAPA-HF (2019)[3]	Dapagliflozin	4744 1.8 years	No T2D/T2D HFrEF	Overall: 98.3 No T2D: 79.7 T2D: 122.5	0.70 (0.59–0.83) 0.63 (0.48–0.81) 0.76 (0.61–0.95)	153.0 124.0 190.9	0.75 (0.65–0.85) 0.73 (0.60–0.89) 0.75 (0.63–0.90)

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; HFh, heart failure hospitalization; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio (for SGLT2 inhibitor vs. placebo); RFs, risk factors; SGLT2, sodium glucose co-transporter 2; T2D, type 2 diabetes mellitus.
[a]Placebo group.
[b]Excluding death from stroke.

Table 2 Recent positive trials with pharmacological therapy in patients with heart failure and reduced ejection fraction

	Background therapy	CV death/HF hospitalization HR (95% CI)	HF hospitalization HR (95% CI)	CV death HR (95% CI)	All-cause death HR (95% CI)
EMPHASIS-HF (n = 2737)[10] placebo vs. eplerenone	ACEi/ARB 94% BB 87% MRA NA	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)[11] placebo vs. ivabradine	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)[12] enalapril vs. sacubitril/valsartan (control vs. neprilysin inhib.)	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)[3] placebo vs. dapagliflozin	ACEi/ARB[a] 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)

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; NA, not applicable.
[a]Including sacubitril/valsartan.

blocker (ARB) and beta-blocker, use of these drugs had become the optimum combination in patients who could tolerate them (*Table 2*).[10,13] Therefore, it is important that dapagliflozin was added to background treatment with an MRA in most (71%) patients randomized in DAPA-HF. Despite this, the benefits of dapagliflozin compared favourably with all the other treatments described, including the only other novel therapy for HFrEF shown to reduce mortality, neprilysin inhibition.[12] As with dapagliflozin, a neprilysin inhibitor was beneficial even when added to an ACEi or ARB, beta-blocker, and an MRA. The incremental absolute, as well as relative, risk reductions with both treatments are substantial as shown in *Table 3*. As can be seen, the absolute risk reduction with dapagliflozin in DAPA-HF was at least as large as with neprilysin inhibition in PARADIGM-HF. Although only a small proportion (around 11%) of patients were treated with sacubitril/valsartan at baseline in DAPA-HF, a non-prespecified subgroup analysis showed an almost identical reduction in risk of the primary composite outcome with dapagliflozin in patients treated with a neprilysin inhibitor compared to those not treated with a neprilysin inhibitor.[3] Specifically, the hazard ratio for the comparison of dapagliflozin and placebo for the primary

Table 3 Absolute benefit of treatment—expressed as reduction in events per 1000 person-years of treatment

Trial	Background therapy	CV death/HF hospitalization	HF hospitalization	CV death
PARADIGM-HF (n = 8399)[12] enalapril vs. sacubitril/valsartan (control vs. neprilysin inhibition)	ACEi/ARB 100% BB 93% MRA 56%	26.7	15.9	15.0
DAPA-HF (n = 4744)[3] placebo vs. dapagliflozin	ACEi/ARB[a] 94% BB 96% MRA 71%	38.7	29.2	14.0

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CV, cardiovascular; HF, heart failure; MRA, mineralocorticoid receptor antagonist.
[a]Including sacubitril/valsartan.

outcome in patients talking sacubitril/valsartan was 0.75 (95% confidence interval 0.50–1.13), compared to 0.74 (0.65–0.86) among those not taking sacubitril/valsartan (P for interaction 1.00).[3] From first principles, it is not surprising that these two treatments have independent, additive, benefits.[14,15] The goal of therapeutic inhibition of the enzyme neprilysin is to reduce the breakdown of a variety of vasoactive peptides, particularly the natriuretic peptides.[14] Sodium-glucose cotransporter 2 inhibitors target a sodium-glucose cotransporter in the proximal renal tubule and although the precise ways in which these drugs bring about their benefits in HFrEF are unknown, there is no suggestion that the possible mechanisms involved include augmentation of natriuretic peptides; indeed, the evidence to date suggests that SGLT2 inhibitors actually reduce levels of these peptides.[3,15,16] The crucial message for patients is that in the past 5 years two complementary, life-saving therapies have been identified and these should be added to the existing three already known to be of benefit. Although the thought of having to use five life-saving therapies in HFrEF will inevitably raise questions about polypharmacy, two of these treatments are already combined in a single pill (an ARB and neprilysin inhibitor in sacubitril/valsartan) and the fields of hypertension and preventive Cardiology (with the 'polypill') have already embraced the idea of combination therapy.[17–21] Arguably, dapagliflozin as a single dose, once-daily, remarkably well-tolerated treatment lends itself to such combination therapy. Even if combination therapies are to be developed, this will take time and there will also need to be discussion, in the interim, about how best to sequence the variety of treatments now available for our patients with HFrEF. Two critical considerations will be blood pressure (little effect from an MRA and SGLT2 inhibitor) and renal function (no worsening, or even improvement, with a neprilysin inhibitor and SGLT2 inhibitor). It is clear, however, that using all these drugs together is eminently feasible, as evidenced by DAPA-HF, and that the best chance of a patient with HFrEF feeling well, avoiding hospitalization and staying alive is to receive treatment with a renin–angiotensin system blocker, a neprilysin inhibitor, a beta-blocker, an MRA, and a SGLT2 inhibitor.

Funding

The DAPA-HF trial was funded by AstraZeneca.

Conflict of interest: J.J.V.M., K.F.D. and P.S.J.'s employer the University of Glasgow has been paid by AstraZeneca for their time working on the DAPA-HF trial and travel and accommodation for some meetings related to this trial. The University of Glasgow is also paid for J.J.V.M.'s participation in the DAPA-CKD, DELIVER and DETERMINE trials with dapagliflozin and the PRIORITIZE trial with sodium zirconium cyclosilicate, and for advisory boards and presentations related to dapagliflozin, diabetes and heart failure. J.J.V.M.'s employer has also received grants/other payments from Alnylam, Amgen, Bayer, BMS, Cardurion, GSK, Novartis and Theracos. P.S.J. has also received grant support from Boehringer Ingelheim and fees for serving on an advisory board from Cytokinetics. S.D.S. reports grants paid to his institution from Alnylam, Amgen, AstraZeneca, Bayer, Bellerophon, BMS, Celladon, Cytokinetics, Gilead, Celladon, Eidos, GSK, Ionis, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Novartis, Sanofi Pasteur, and Theracos; and consulting fees from Alnylam, Amgen, AoBiome, AstraZeneca, Bayer, BMS, Cardiac Dimensions, Corvia, Cytokinetics, Daichi-Sankyo; Gilead, GSK, Ironwood, Janssen, Merck, MyoKardia, Novartis, Quantum Genomics, Roche, Takeda, Tenaya, and Theracos. M.V. reports consulting fees from Amgen, AstraZeneca, Baxter Healthcare, Bayer AG, and Boehringer Ingelheim.

References

1. McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sabatine MS, Sjöstrand M, Solomon SD; DAPA-HF Committees and Investigators. A trial to evaluate the effect of the sodium glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail* 2019;**21**:665–675.
2. McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sabatine MS, Sjöstrand M, Solomon SD; DAPA-HF Committees and Investigators. The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics. *Eur J Heart Fail* 2019;**21**:1402.
3. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang C-E, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde A-M; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995.
4. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; 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, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. 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, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM,

Sabatine MS; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**:347–357.
7. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;**380**:2295–2306.
8. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RH, Kuder J, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JP, Bonaca MP, Ruff CT, Desai AS, Goto S, Johansson PA, Gause-Nilsson I, Johanson P, Langkilde AM, Raz I, Sabatine MS, Wiviott SD; DECLARE–TIMI 58 Investigators. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation* 2019;**139**:2528–2536.
9. Figtree GA, Rådholm K, Barrett TD, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Matthews DR, Shaw W, Neal B. Effects of canagliflozin on heart failure outcomes associated with preserved and reduced ejection fraction in type 2 diabetes mellitus. *Circulation* 2019;**139**:2591–2593.
10. Zannad F, McMurray JJV, Krum H, Van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21.
11. Swedberg K, Komajda M, BöHm M, Borer JS, Ford I, Dubost- Brama A, Lerebours G, Tavazzi L. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–885.
12. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Me* 2014;**371**:993–1004.
13. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–717.
14. McMurray JJ. Neprilysin inhibition to treat heart failure: a tale of science, serendipity, and second chances. *Eur J Heart Fai* 2015;**17**:242–247.
15. Wojcik C, Warden BA. Mechanisms and evidence for heart failure benefits from SGLT2 inhibitors. *Curr Cardiol Rep* 2019;**21**:130.
16. Januzzi JL Jr, Butler J, Jarolim P, Sattar N, Vijapurkar U, Desai M, Davies MJ. Effects of canagliflozin on cardiovascular biomarkers in older adults with type 2 diabetes. *J Am Coll Cardiol* 2017;**70**:704–712.
17. Volpe M, Gallo G, Tocci G. New approach to blood pressure control: triple combination pill. *Trends Cardiovasc Med* 2019;pii: S1050-1738 (19) 30031-3. doi: 10.1016/j.tcm.2019.03.002.
18. Düsing R, Waeber B, Destro M, Santos Maia C, Brunel P. Triple-combination therapy in the treatment of hypertension: a review of the evidence. *J Hum Hypertens* 2017;**31**:501–510.
19. Ibañez B, Castellano JM, Fuster V. Polypill strategy at the heart of cardiovascular secondary prevention. *Heart* 2019;**105**:9–10.
20. Roshandel G, Khoshnia M, Poustchi H, Hemming K, Kamangar F, Gharavi A, Ostovaneh MR, Nateghi A, Majed M, Navabakhsh B, Merat S, Pourshams A, Nalini M, Malekzadeh F, Sadeghi M, Mohammadifard N, Sarrafzadegan N, Naemi-Tabiei M, Fazel A, Brennan P, Etemadi A, Boffetta P, Thomas N, Marshall T, Cheng KK, Malekzadeh R. Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): a pragmatic, cluster-randomised trial. *Lancet* 2019;**394**:672–683.
21. Muñoz D, Uzoije P, Reynolds C, Miller R, Walkley D, Pappalardo S, Tousey P, Munro H, Gonzales H, Song W, White C, Blot WJ, Wang TJ. Polypill for cardiovascular disease prevention in an underserved population. *N Engl J Med* 2019;**381**:1114–1123.