Effect of Dapagliflozin in DAPA-HF According to Background Glucose-Lowering Therapy

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OBJECTIVE

To determine whether the benefits of dapagliflozin in patients with heart failure and reduced ejection fraction (HFrEF) and type 2 diabetes in the Dapagliflozin And Prevention of Adverse-Outcomes in Heart Failure trial (DAPA-HF) varied by background glucose-lowering therapy (GLT).

RESEARCH DESIGN AND METHODS

We examined the effect of study treatment by the use or not of GLT and by GLT classes and combinations. The primary outcome was a composite of worsening heart failure (hospitalization or urgent visit requiring intravenous therapy) or cardiovascular death.

RESULTS

In the 2,139 type 2 diabetes patients, the effect of dapagliflozin on the primary outcome was consistent by GLT use or no use (hazard ratio 0.72 [95% CI 0.58–0.88] vs. 0.86 [0.60–1.23]; interaction $P = 0.39$) and across GLT classes.

CONCLUSIONS

In DAPA-HF, dapagliflozin improved outcomes irrespective of use or no use of GLT or by GLT type used in patients with type 2 diabetes and HFrEF.

Although sodium–glucose cotransporter 2 inhibitors (SGLT2is) have been shown to improve cardiovascular outcomes in patients with type 2 diabetes, they are usually prescribed as second-line glucose-lowering therapy (GLT), most often in addition to metformin (1–3). Uncertainty about the place of SGLT2is in the management of patients with type 2 diabetes is reflected in the differing recommendations in recent guidelines (4–8). The placebo-controlled Dapagliflozin And Prevention of Adverse-Outcomes in Heart Failure trial (DAPA-HF), in which the SGLT2i dapagliflozin reduced the risk of worsening HF and cardiovascular mortality in patients with HF and reduced ejection fraction (HFrEF), provides a unique opportunity to examine the efficacy of SGLT2i alone and in combination with other GLTs in patients with type 2 diabetes (9).

RESEARCH DESIGN AND METHODS

DAPA-HF was a prospective, randomized, double-blind, placebo-controlled trial in patients with HFrEF that evaluated the efficacy and safety of 10 mg dapagliflozin once daily, compared with placebo, added to standard care (9,10).

In this post hoc analysis, we included randomized patients with either undiagnosed (defined as central laboratory $HbA_{1c} \geq 6.5\%$ [48 mmol/mol] at both screening and

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**A complete list of the DAPA-HF Investigators and Committees can be found in the supplementary material online.*

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randomization visits) or a medical history of type 2 diabetes. We examined the effect of dapagliflozin, compared with placebo, in subgroups (limited to those with >200 individuals to minimize the likelihood of type 1 errors) by the use or not of background GLT and by individual GLT classes: biguanides (hereafter referred to as metformin), sulfonylureas, dipeptidyl peptidase 4 (DPP-4) inhibitors, and insulin. We examined the primary outcome, a composite of an episode of worsening HF (either an unplanned hospitalization or an urgent visit resulting in intravenous therapy for HF) or cardiovascular death, along with the individual components of cardiovascular death and HF hospitalization, and the prespecified secondary end points of all-cause mortality and the composite of total (first and recurrent) HF hospitalizations and cardiovascular death.

The cumulative incidence of the primary end point by treatment group in subgroups of interest was plotted using the Kaplan-Meier method. The effect of dapagliflozin compared with placebo was examined using Cox proportional hazards models with history of hospitalization for HF and treatment-group assignment as fixed-effect factors (history of hospitalization for HF was not included in the models for all-cause mortality). An interaction test using a subgroup–by–randomized treatment interaction term was performed to assess for treatment effect modification within each subgroup. Analyses were performed using Stata, version 16 (StataCorp, College Station, TX). A P value <0.05 was considered statistically significant.

RESULTS

Of the 4,744 randomized patients in DAPA-HF, 1,983 (41.8%) had a documented medical history of type 2 diabetes, and 156 (3.3%) had undiagnosed type 2 diabetes. Therefore, 2,139 (45.1%) patients with type 2 diabetes were included in the analysis. Of these, 1,596 (74.6%) were treated with GLTs: metformin (47.7%), insulin (25.2%), sulfonylurea (20.6%), DPP-4 inhibitor (14.5%), and glucagon-like peptide 1 (GLP-1) receptor agonist (1.0%) (each alone or in combination). The baseline characteristics of patients by use of GLT and type of GLT are summarized in Supplementary Tables 1 and 2.

Supplementary Fig. 1 shows the cumulative incidence of the primary composite end point by randomized treatment in the subgroups of interest. The effect of dapagliflozin on the primary end point was consistent in patients taking GLT (hazard ratio 0.72; 95% CI 0.58–0.88) and in those who were drug-naive (0.86; 0.60–1.23; interaction $P = 0.39$) (Fig. 1). When considering individual GLT classes (Fig. 1) or combinations (Supplementary Fig. 2), there was no statistically significant interaction between background GLT and the effect of randomized therapy on the primary composite outcome.

In general, the effect of dapagliflozin on cardiovascular death and HF hospitalization was similar for individual GLTs (Supplementary Fig. 3) and combinations of these (Supplementary Fig. 2). Furthermore, no modification of treatment effect by background GLT was observed for the composite end point of total (first and recurrent) HF hospitalizations and cardiovascular death (Supplementary Fig. 4) or all-cause mortality (Supplementary Fig. 5).

CONCLUSIONS

In this post hoc analysis of DAPA-HF, we found that the benefit of dapagliflozin compared with placebo in patients with type 2 diabetes and HFrEF was not influenced by background GLT use. The benefit of dapagliflozin was consistent in drug-naive patients and across all classes of commonly used GLTs, including metformin.

Perhaps the most interesting group of participants was the ~25% of individuals with type 2 diabetes in DAPA-HF who were not prescribed any GLT at baseline, i.e., those in whom randomized dapagliflozin became first-line GLT and pharmacological monotherapy. Despite limited power for subgroup analysis due to a relatively small number of patients and a lower event rate, the benefit of dapagliflozin on the primary end point seemed to be consistent with the effect in type 2 diabetes patients overall.

Metformin was the most commonly used GLT in DAPA-HF, taken by approximately half of patients with type 2 diabetes and HFrEF, despite limited evidence for its cardiovascular safety in this patient group (11). Nevertheless, international HFrEF management guidelines support the use of metformin as the first-line GLT in patients with type 2 diabetes (12). It has been suggested that the benefit of SGLT2i is modified by metformin use based on a subgroup analysis of the Canagliflozin Cardiovascular Assessment Study (CANVAS) trials (13). This is clearly not the case from the present analysis of DAPA-HF or a post hoc analysis of the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) (14).

Examination of outcomes in patients receiving the other major classes of GLT was also of interest. After metformin, insulin was the most widely used GLT, and dapagliflozin was as effective in these participants as compared with patients not taking insulin. Given the substantially higher event rate experienced by patients receiving insulin compared with those receiving other GLTs, the relative risk reduction in insulin-treated individuals translated into an even larger absolute risk reduction and a number needed to treat of only 16 to prevent one patient having the primary outcome over the median 18.2 months of follow-up. Furthermore, the benefits of dapagliflozin were again consistent whether added to a sulfonylurea or a DDP-4 inhibitor.

We believe our findings are relevant to the discussion that followed recent updated guidance on management of diabetes issued by the European Society of Cardiology (ESC) and jointly by the American Diabetes Association and the European Association for the Study of Diabetes (4–7). Both recommendations emphasized that the cardiovascular benefits of SGLT2i and GLP-1 receptor agonists are obtained independently of starting HbA_{1c}, an approach supported by the strategy employed in DAPA-HF. More controversially, the ESC guidance supported the use of SGLT2i and GLP-1 receptor agonists as first-line GLT and not necessarily as an adjunct to metformin, which had previously been the recommended initial GLT in most patients with cardiovascular disease (7). Our data also support this recommendation, at least in patients with HFrEF, and provide further evidence, along with the evidence of benefit in HFrEF patients without diabetes, to the view that the mechanisms of action underlying the cardiovascular benefits of dapagliflozin are independent of any glucose-lowering effect (15).

As with all studies of this nature, there are inherent limitations. The analyses were not prespecified and some had limited power, despite only including subgroups with >200 individuals. The small number of patients taking a GLP-1

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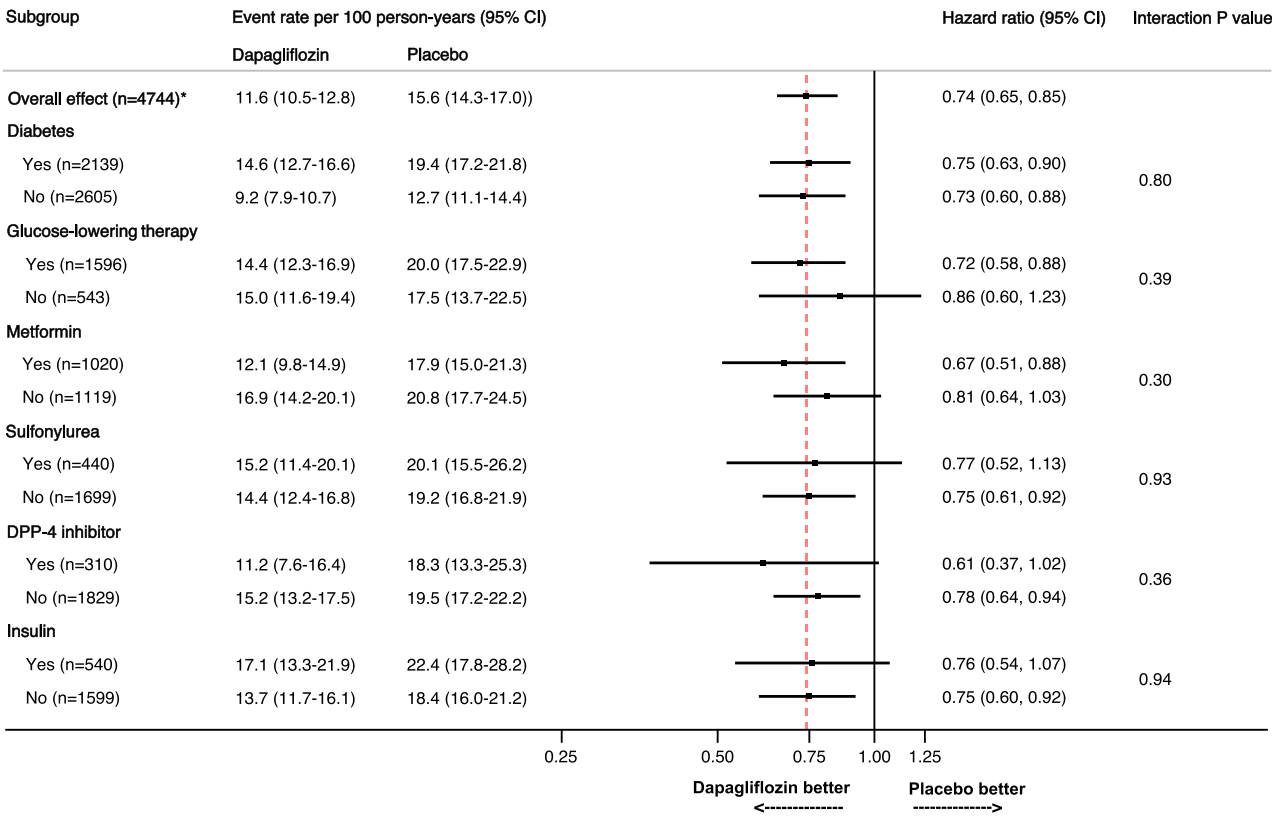

Figure 1—Effect of dapagliflozin compared with placebo on the risk of the primary composite outcomes by background GLT in patients with diabetes. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for HF) or death from cardiovascular causes. Patients on multiple glucose-lowering medications are included in each individual medication subgroup. A total of 12 patients were prescribed saxagliptin. *The overall effect was calculated in all randomized patients (n = 4,744).

receptor agonist at baseline prohibited further examination of this subgroup.

Conclusion

In patients with type 2 diabetes and HFrEF, the reductions in the risk of worsening HF and cardiovascular death with dapagliflozin were consistent across a range of background of GLTs and in patients receiving no GLT. Our data provide support for the use of dapagliflozin as first-line monotherapy in type 2 diabetes, at least in patients with HFrEF.

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References

1. NHS Digital. Prescribing for diabetes, England 2008/09 to 2018/19, 2019. Accessed 15 May 2020. Available from https://digital.nhs.uk/data-and-information/publications/statistical/prescribing-for-diabetes/2008-09---2018-19

2. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019; 393:31–39

3. 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

4. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2018;61:2461–2498

5. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Association of clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2020 executive summary. Endocr Pract 2020;26:107–139

6. Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2020;63:221–228

7. Cosentino F, Grant PJ, Aboyans V, et al.; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2020;41:255–323

8. Sattar N, McMurray JJ, Cheng AY. Cardiorenal risk reduction guidance in diabetes: can we reach consensus? Lancet Diabetes Endocrinol 2020;8: 357–360

9. McMurray JJV, Solomon SD, Inzucchi SE, et al.; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019; 381:1995–2008

10. McMurray JJV, DeMets DL, Inzucchi SE, et al.; 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

11. MacDonald MR, Eurich DT, Majumdar SR, et al. Treatment of type 2 diabetes and outcomes in patients with heart failure: a nested case-control study from the U.K. General Practice Research Database. Diabetes Care 2010;33:1213–1218

12. Ponikowski P, Voors AA, Anker SD, et al.; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–2200

13. Neuen B, Heerspink HJL, Neal B, et al. Cardiovascular and renal outcomes with canagliflozin in people with type 2 diabetes according to baseline use of metformin. Endocr Pract 2019;25: 99–100

14. Inzucchi SE, Fitchett D, Jurišić-Eržen D, et al.; EMPA-REG OUTCOME® Investigators. Are the cardiovascular and kidney benefits of empagliflozin influenced by baseline glucose-lowering therapy? Diabetes Obes Metab 2020;22:631–639

15. Petrie MC, Verma S, Docherty KF, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. JAMA 2020;323: 1353–1368

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