Full title: Effect of dapagliflozin in DAPA-HF according to background glucose-lowering therapy

Short title: Background glucose-lowering therapy in DAPA-HF

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Abstract

Objective: To determine whether the benefits of dapagliflozin in patients with heart failure and reduced ejection fraction (HFrEF) and type 2 diabetes in 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 HF (hospitalization or urgent visit requiring intravenous therapy) or cardiovascular death.

Results: In the 2139 type 2 diabetes patients, the effect of dapagliflozin on the primary outcome was consistent by GLT use/no use (hazard ratio 0.72 [95%CI 0.58-0.88] versus 0.86 [0.60-1.23]; P-interaction=0.39) and across GLT classes.

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

Trial Registration - ClinicalTrials.gov Identifier: NCT03036124

INTRODUCTION

Although sodium glucose cotransporter 2 inhibitors (SGLT2i) 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 SGLT2i in the management of patients with type 2 diabetes is reflected in 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 heart failure (HF) and cardiovascular mortality in patients with heart failure and reduced ejection fraction (HFrEF), provides a unique opportunity to examine the efficacy of SGLT2i alone and in combination with other GLT 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, which evaluated the efficacy and safety of dapagliflozin 10 mg 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 HbA1c ≥6.5% (48mmol/mol) at both screening and randomisation 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 error) 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 endpoints of all-cause mortality and the composite of total (first and recurrent) HF hospitalizations and cardiovascular death.

The cumulative incidence of the primary endpoint 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 adjusted for history of hospitalization for HF and treatment-group assignment. 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 (College Station, TX, USA). A p-value <0.05 was considered statistically significant.

RESULTS

Of the 4744 randomized patients in DAPA-HF, 1983 (41.8%) had a documented medical history of type 2 diabetes and 156 (3.3%) had undiagnosed type 2 diabetes. Therefore, 2139 (45.1%) patients with type 2 diabetes were included in the analysis. Of these, 1596 (74.6%) were treated with GLT: 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 summarised in Supplemental Table 1 and 2.

Supplemental Figure 1 shows the cumulative incidence of the primary composite endpoint by randomized treatment in the subgroups of interest. The effect of dapagliflozin on the primary endpoint was consistent in patients taking GLT (hazard ratio 0.72 95%CI 0.58-0.88), and in those who were drug-naïve (0.86, 0.60-1.23; interaction p=0.39) (Figure 1). When considering individual GLT classes (Figure 1) or combinations (Supplemental Figure 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 each of cardiovascular death and HF hospitalization, was similar for individual GLT (Supplemental Figure 3) and combinations of these (Supplement Figure 2). Furthermore, no modification of treatment effect by background GLT was observed for the composite endpoint of total (first and recurrent) HF hospitalizations and cardiovascular death (Supplement Figure 4) or all-cause mortality (Supplement Figure 5).

DISCUSSION

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-naïve patients and across all classes of commonly used GLT, including metformin.

Perhaps the most interesting group of participants were the approximately 25% of individuals with type 2 diabetes in DAPA-HF who were not prescribed any GLT at baseline i.e. those in which 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 endpoint 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 first-line GLT in patients with type 2 diabetes.[12] It has been suggested that the benefit of SLGT2i is contingent on metformin use, based upon a subgroup analysis of the CANVAS trials.[13] This is clearly not the case from the present analysis of DAPA-HF or a post-hoc analysis of the EMPA-REG OUTCOME trial. [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 to patients not taking insulin. Given the substantially higher event rate experienced by patients receiving insulin, compared to those

receiving other GLT, the *relative* risk reduction in insulin-treated individuals translated into an even larger *absolute* risk reduction and an NNT 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 (ADA) and European Association for the Study of Diabetes (EASD).[4-7] Both recommendations emphasised that the cardiovascular benefits of SGLT2i, and GLP-1 receptor agonists, are obtained independently of starting HbA1c, 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 receptor agonist at baseline prohibited further examination of this subgroup.

Conclusion

In patients with type 2 diabetes and HFrEF, the reductions in risk of worsening HF and cardiovascular death with dapagliflozin were consistent across a range of background of GLT, 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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Authors contributions: All authors contributed to the study design. KFD, PSJ, OB and JJVM contributed to the data analysis. All authors were involved in data interpretation and the writing or editing of the report. All authors read and approved the submitted version of the report.

Guarantor's statement: KFD and JJVM are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients With Heart Failure With and Without Diabetes. *JAMA* 2020; 2020; **323(14)**, 1353-1368.

FIGURE LEGENDS

Figure 1: Effect of dapagliflozin compared to placebo on the risk of the primary composite outcome by background glucose-lowering therapy in patients with diabetes

*Overall effect calculated in all randomized patients (n=4744)

The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or death from cardiovascular causes. Patients on multiple glucose-lowering medications are included in each individual medication subgroup.

DPP-4 = dipeptidyl peptidase-4; 12 patients were prescribed saxagliptin.
CI = confidence interval.