Efficacy of dapagliflozin by baseline diabetes medications: A prespecified analysis from the DAPA-CKD study

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Abstract (232/250 words)

Objective: To determine whether the benefits of dapagliflozin in patients with chronic kidney disease (CKD) with or without type 2 diabetes in the Dapagliflozin And Prevention of Adverse Outcomes in CKD trial (DAPA-CKD) varied by background glucose-lowering therapy (GLT).

Research Design and Methods: We randomized 4304 adults with baseline eGFR 25–75 mL/min/1.73m^2 and urinary albumin:creatinine ratio 200–5000 mg/g to dapagliflozin 10mg or placebo once daily. The primary endpoint was a composite of ≥50% eGFR decline, end-stage kidney disease, and kidney or cardiovascular death. Secondary endpoints included a kidney composite endpoint (primary composite endpoint without cardiovascular death), a cardiovascular composite endpoint (hospitalized heart failure or cardiovascular death), and all-cause mortality. In this prespecified analysis, we investigated the effects of dapagliflozin on kidney, cardiovascular, and mortality outcomes according to baseline GLT class or number of GLTs.

Results: In 2,906 patients with type 2 diabetes included in DAPA-CKD, the effect of dapagliflozin on the primary composite outcome was consistent across GLT classes and according to the number of GLTs (all interaction P >0.08). Similarly, we found consistent benefit of dapagliflozin compared to placebo on the secondary endpoints regardless of background GLT class or number of GLTs. The same applied to the rate of decline in estimated glomerular filtration rate.

Conclusion: Dapagliflozin reduced kidney and cardiovascular events in patients with type 2 diabetes and CKD independent of baseline GLT class or number of GLTs.

Optimization of glycemic control in patients with diabetes reduces the risk of microvascular complications including kidney failure (1; 2). However, achieving optimal glucose control can be challenging in patients with type 2 diabetes and chronic kidney disease (CKD) because the presence of CKD restricts or prevents the use of several oral or injectable glucose lowering drugs (3). In particular, when kidney function declines, patients become more susceptible to experience hypoglycemia and therefore understanding the safety and tolerability of glucose-lowering therapies (GLT) is particularly important in patients with more severe CKD.

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) were originally developed for the treatment of type 2 diabetes. These agents also confer cardiovascular and kidney protection as demonstrated in clinical outcome trials in patients with type 2 diabetes, CKD or heart failure (4-9). In clinical practice SGLT2is are often prescribed as adjunct to other GLTs. The randomized, placebo-controlled Dapagliflozin and Prevention of Adverse outcomes in CKD (DAPA-CKD) trial, in which dapagliflozin reduced the risk of a composite kidney outcome of 50% eGFR decline, end-stage kidney disease, kidney or cardiovascular death (6), provided an opportunity to determine the efficacy and safety of dapagliflozin in patients with type 2 diabetes and CKD when administered in combination with different background GLTs.

Research Design and Methods

DAPA-CKD was a prospective, randomized, double-blind, placebo-controlled, multicenter trial in 4304 patients with CKD with eGFR of 25–75 mL/min/1.73m^3 and UACR of 200–5000 mg/g with or without type 2 diabetes that evaluated the effect of 10 mg dapagliflozin once daily, compared with placebo, on kidney and cardiovascular events (10).

In this prespecified analysis, we included randomized patients with type 2 diabetes defined by a medical history of type 2 diabetes or a central laboratory HbA_{1c} value ≥6.5% [48 mmol/mol] at both screening and randomization visits. We examined the effect of dapagliflozin, compared with placebo, by individual GLT classes: biguanides (hereafter referred to as metformin), sulfonylureas, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and insulin, and by the number of GLTs at baseline. We examined the primary outcome, a composite of sustained decline in eGFR of ≥50%, end-stage kidney disease, or death from kidney or cardiovascular causes. Secondary outcomes included a kidney-specific composite (the same as the primary without cardiovascular death), composite of hospitalizations for heart failure and cardiovascular mortality, and all-cause mortality.

The effect of dapagliflozin compared with placebo was examined using Cox proportional hazards models with treatment-group assignment as fixed-effect factor. An interaction test using a glucose lowering drug class–by–randomized treatment interaction term was performed to assess for effect modification within each GLT class subgroup. The effect of dapagliflozin as compared with placebo on the rate of decline in the eGFR from baseline to month 30 was analyzed with the use of a two-slope model as described in more detail elsewhere (6). Analyses were performed using R, version XXX (R Foundation, Vienna, Austria). A *P* value <0.05 was considered statistically significant.

Results

Of the 4,304 randomized patients in DAPA-CKD, 2,906 (68%) had a documented medical history of type 2 diabetes or had undiagnosed type 2 diabetes and were therefore included in the analysis. Of these, 1,244 (43%) were on metformin, 1,598 (55%) were on insulin, 774 (27%) on sulfonylureas, 742 (26%) on DPP-4 inhibitors, and 122 (4%) on GLP-1

receptor agonists. Other GLT such as glitazones and acarbose were uncommon. At baseline, 327 (11%) patients were without diabetes treatment, 1,442 (50%) were treated with one GLT, 943 (32%) with two, and 194 (7%) with three or more. The baseline characteristics of patients by number of GLTs at baseline are summarized in **Supplementary Table 1**.

The effect of dapagliflozin on the primary composite outcome was consistent across comparisons number of GLTs (hazard ratio 0.64; 95% CI 0.52–0.79; interaction *P* = 0.08) (**Figure 1A**). When considering individual GLT classes (**Figure 1B**), there was no statistically significant interaction between background GLT and the effect of randomized treatment on the primary composite outcome. Furthermore, no modification of treatment effect by background GLT class or number of GLT was observed for the kidney-specific composite end point, composite for heart failure and cardiovascular mortality, and all-cause mortality (**Supplementary Figure 1**).

The effect of dapagliflozin compared to placebo on the rate of eGFR decline is shown in **Supplementary Figure 2**. Overall, compared to placebo, dapagliflozin reduced the annual rate of change in eGFR from baseline to end of treatment (0.95 mL/min/1.73m^2 per year [95% CI 0.63–1.27]) with consistent effects regardless of number of GLTs or background GLT class.

Conclusions

In this prespecified analysis of the DAPA-CKD trial, we found that the benefit of dapagliflozin compared with placebo in reducing the risk of the primary and secondary kidney and cardiovascular outcomes among patients with type 2 diabetes and CKD was

consistent across all classes of commonly used GLTs, and according to the number of GLTs.

The KDIGO clinical practice guideline recommends metformin as first line GLT in patients with type 2 diabetes and CKD (11). Metformin was the most commonly used GLT next to insulin in the DAPA-CKD trial. However, the proportion of patients using metformin (43%) was less compared to other SGLT2 trials in patients with type 2 diabetes at high cardiovascular risk, most likely because guidelines do not recommend metformin in patients with eGFR <30 mL/min/1.73m^2 due to a perceived risk of lactic acidosis. The CANVAS trial suggested that the benefit of SGLT2 inhibitors may be attenuated in patients using metformin (12), but the present results of the DAPA-CKD trial and other trials did not confirm this finding (13-15).

Clinical practice guidelines also recommend GLP-1 receptor agonists in patients with atherosclerotic cardiovascular disease. An analysis from the CANVAS trial reported that the HbA_{1c}, body weight and blood pressure lowering effects of canagliflozin were accentuated in patients using versus not-using GLP-1 receptor agonists at baseline (16). In addition, the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial suggested that the effect of dapagliflozin in reducing the risk of heart failure hospitalizations or cardiovascular death was more pronounced in participants using GLP-1 receptor agonists compared to those not using these agents (13). We could not confirm this finding, however the number of patients using GLP-1 receptor agonists was low in our study. Meta-analyses are necessary to provide more definitive data on the combined use of SGLT2 inhibitors and GLP-1 receptor agonists.

In terms of safety, our data suggest that dapagliflozin can be safely administered and poses no risk for hypoglycemia regardless of background GLTs or number of GLTs.

As reported previously, dapagliflozin only reduced HbA_{1c} in DAPA-CKD participants by 0.1% (17). This is probably caused by less filtration of glucose in patients with CKD, attenuating glycemic efficacy and causing a low risk of hypoglycemia. The current data provides further evidence that the low risk of hypoglycemia remains present regardless of background GLTs.

Perhaps the most interesting subgroup in terms of number of medications were the 327 (12%) patients who did not use any other GLT. In these patients dapagliflozin was used as first-line glucose-lowering pharmacotherapy. Despite that the glycemic effects of SGLT2 inhibitors are attenuated in patients with CKD, there was no evidence that the effect of dapagliflozin in reducing the relative risks of the primary and secondary trial outcomes was different compared to the overall population. The finding that dapagliflozin was well tolerated irrespective of the number of GLTs provide reassurance that this therapy can be initiated in many patients with type 2 diabetes and CKD, including people with numerous anti-hyperglycemic agents.

A limitation of this analysis is that background GLT was not stratified and some of the subgroups were small, limiting statistical power. In addition, background GLT was based on patient-specific characteristics, prescriber patterns, and regional guidelines and recommendations. These factors may determine clinical outcomes and the results should be interpreted with this in mind.

In patients with type 2 diabetes and CKD, the reductions in the risk of kidney and CV events were consistent across a range of background of GLTs and according to the number of GLTs. Our data provide support for the use of dapagliflozin as first-line or add-on therapy in patients with type 2 diabetes and CKD.

Declaration of interests

JMB

FP has served as a consultant, on advisory boards or as educator for AstraZeneca, Novo Nordisk, Boehringer Ingelheim, Sanofi, Mundipharma, MSD, Novartis, Amgen and has received research grants to institution from Novo Nordisk, Boehringer Ingelheim, Amgen and AstraZeneca

NJ declares no conflicts of interest.

GDL

GMC has received fees from AstraZeneca for service on the DAPA-CKD trial steering committee. He serves on the Board of Directors for Satellite Healthcare. He has served on other trial steering committees for Akebia, AstraZeneca, Gilead, Sanifit, and Vertex, and on data safety monitoring boards for Angion, Bayer, Mineralys, and ReCor. He has served as an advisor and received fees and/or stock options from Ardelyx, CloudCath, Cricket, DiaMedica, Durect, DxNow, Miromatrix, Outset, Physiowave, and Unicycive. He has received research grants from NIDDK, NHLBI, and NIAID.

JJVM has received payments to his employer, Glasgow University, for his work on clinical trials, consulting and other activities from AstraZeneca, Cytokinetics, KBP Biosciences, Amgen, Bayer, Theracos, Ionis Pharmaceuticals, Dalcor Pharmaceuticals, Novartis, GlaxoSmithKline, Bristol Myers Squibb, Boehringer Ingelheim, Cardurion and Alnylam, and has received personal lecture fees from Abbott, Alkem Metabolics, Eris Life Sciences, Hickma, Lupin, Sun Pharmaceuticals, Medscape/Heart.org, ProAdWise Communications, Radcliffe Cardiology, Servier and the Corpus.

AML, CDS, are employees and stockholders of AstraZeneca.

RC-R has received honoraria from AbbVie, AstraZeneca, GlaxoSmithKline, Medtronic, and Boehringer Ingelheim, and has lectured for Amgen, Janssen, Takeda, AstraZeneca, and Boehringer Ingelheim and has received research support from GlaxoSmithKline, Novo Nordisk and AstraZeneca.

PR has received honoraria to Steno Diabetes Center Copenhagen for: steering group membership and/or lectures and advice from AstraZeneca, Novo Nordisk, Bayer and Eli Lilly; advisory board participation from Sanofi Aventis and Boehringer ingelheim; steering group participation from Gilead.

DCW has received consultancy fees from AstraZeneca and personal fees from Bayer, Boehringer Ingelheim, Astellas, GlaxoSmithKline, Janssen, Napp, Mundipharma, Reata, Vifor Fresenius and Tricida.

HJLH has received honoraria (paid to his institution [University Medical Center Groningen]) for participation in steering committees from AstraZeneca, Janssen, Gilead, Bayer, Chinook, and CSL Pharma; honoraria for participation in advisory boards from Merck, Mitsubishi Tanabe, Janssen, and Mundipharma; fees for consultancy from AstraZeneca, AbbVie, Retrophin, Boehringer Ingelheim, and Novo Nordisk; and research grant support from AstraZeneca, AbbVie, Janssen, and Boehringer Ingelheim.

Data sharing

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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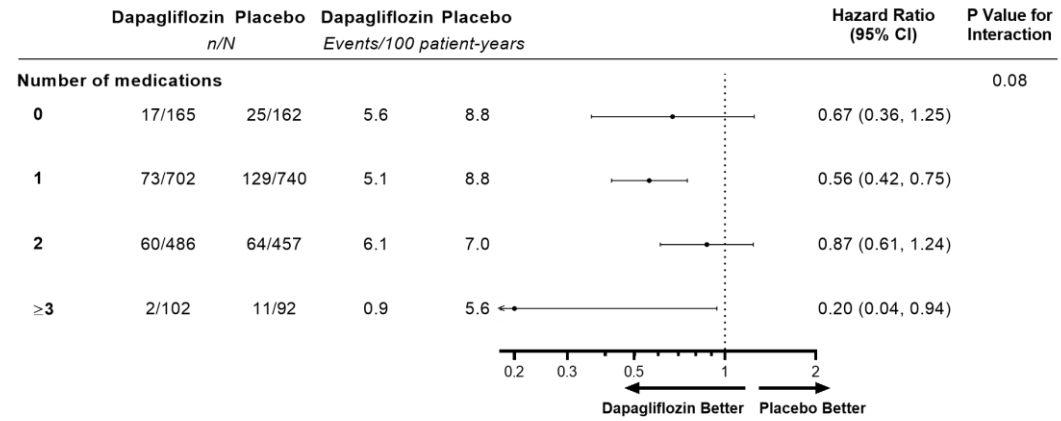
Table 1: Baseline characteristics by number of glucose-lowering therapies

	Dapagliflozin 10 mg				Placebo			
Number of GLTs	**0**	**1**	**2**	**≥3**	**0**	**1**	**2**	**≥3**
Age, years, mean (SD)	63.4 (11.6)	64.3 (10.1)	64.0 (9.1)	65.1 (8.3)	64.5 (10.7)	65.2 (9.4)	64.2 (9.2)	64.1 (9.8)
Female sex, n (%)	43 (26.1)	249 (35.5)	169 (34.8)	33 (32.4)	45 (27.8)	269 (36.4)	130 (28.4)	27 (29.3)
Weight, kg, mean (SD)	81.1 (20.9)	82.2 (20.6)	84.5 (21.1)	87.2 (21.5)	78.0 (17.8)	84.0 (21.5)	85.6 (21.6)	83.7 (20.9)
BMI, kg/m^2, mean (SD)	29.1 (5.8)	29.9 (6.2)	30.8 (6.3)	31.3 (5.9)	28.4 (5.2)	30.6 (6.5)	30.7 (6.4)	30.3 (5.7)
Blood pressure, mmHg, mean (SD)								
Systolic	135.7 (17.5)	139.2 (17.5)	139.0 (17.8)	140.4 (17.2)	138.2 (17.5)	140.0 (17.7)	140.1 (16.3)	136.9 (14.9)
Diastolic	76.8 (11.5)	76.2 (10.7)	77.0 (9.7)	75.9 (9.6)	76.8 (10.7)	76.4 (10.1)	76.7 (9.5)	75.8 (8.3)
eGFR, mL/min/1.73m^2, mean (SD)	39.4 (11.7)	42.0 (12.0)	47.3 (12.9)	49.5 (10.8)	39.2 (11.1)	41.7 (12.2)	47.2 (12.6)	48.2 (12.5)
UACR, mg/g, median (IQR)	972.0 (498.5–1769.0)	1025.8 (449.9–2245.0)	1069.2 (491.6–2304.4)	777.8 (431.0–1643.1)	1054.0 (566.8–1918.1)	1000.8 (497.2–2018.5)	1026.5 (460.5–2010.5)	869.0 (484.1–2021.1)
HbA1c, %, mean (SD)	6.8 (1.4)	7.7 (1.6)	8.1 (1.7)	8.3 (1.4)	6.8 (1.3)	7.7 (1.6)	8.1 (1.6)	8.5 (1.8)
HbA1c, mmol/mol, mean (SD)	51 (15)	61 (18)	65 (19)	67 (15)	51 (14)	61 (18)	65 (18)	69 (20)
CV history, n (%)	65 (39.4)	319 (45.4)	213 (43.8)	43 (42.2)	59 (36.4)	344 (46.5)	211 (46.2)	27 (29.3)

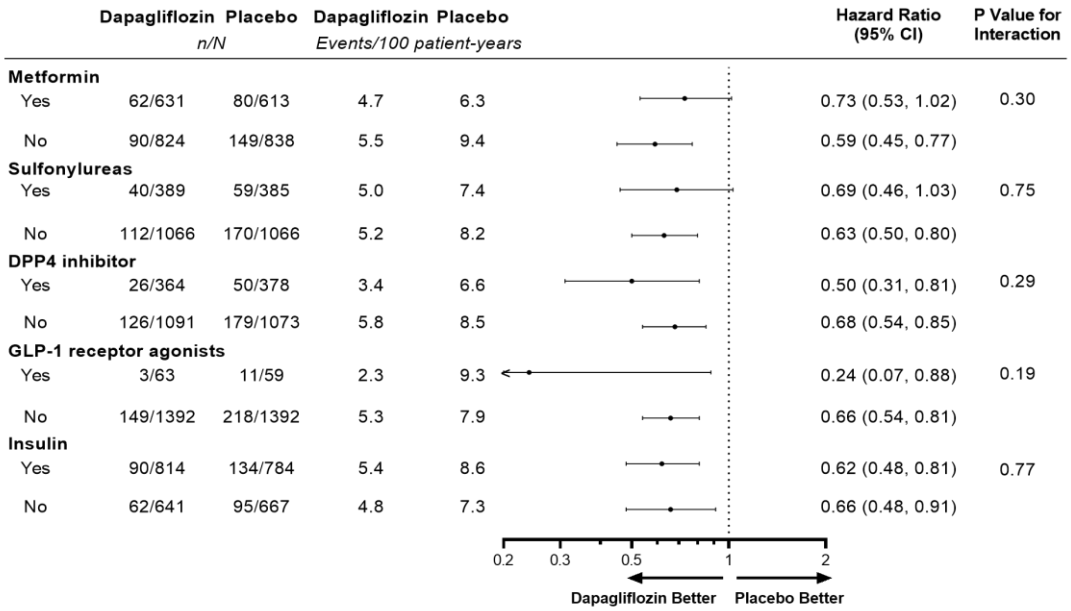
BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GLT, glucose-lowering therapies; UACR, urinary albumin:creatinine ratio

Figure 1: The primary endpoint by (A) number of baseline glucose-lowering therapies and by (B) type of glucose-lowering therapy at baseline

A

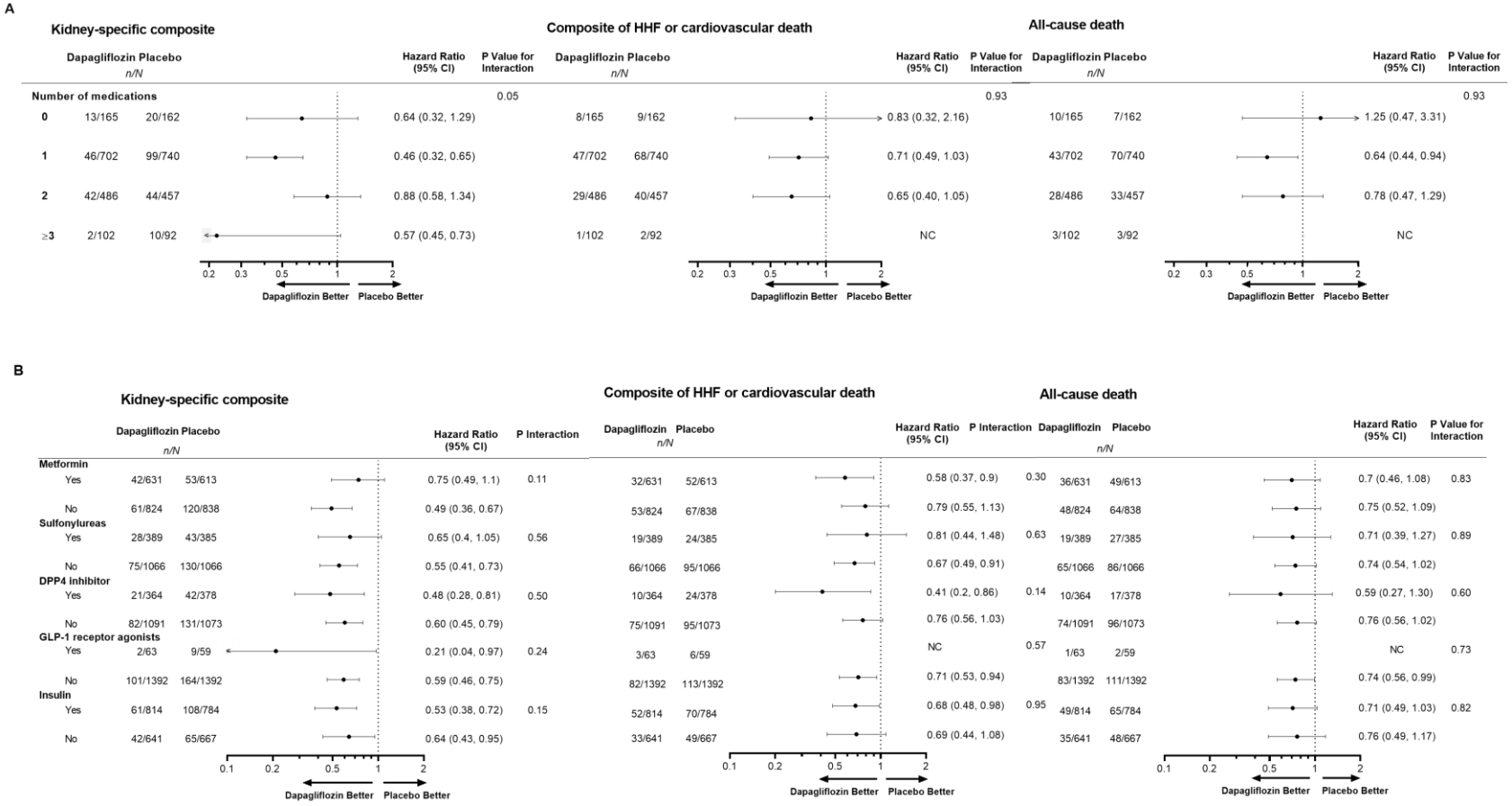


B



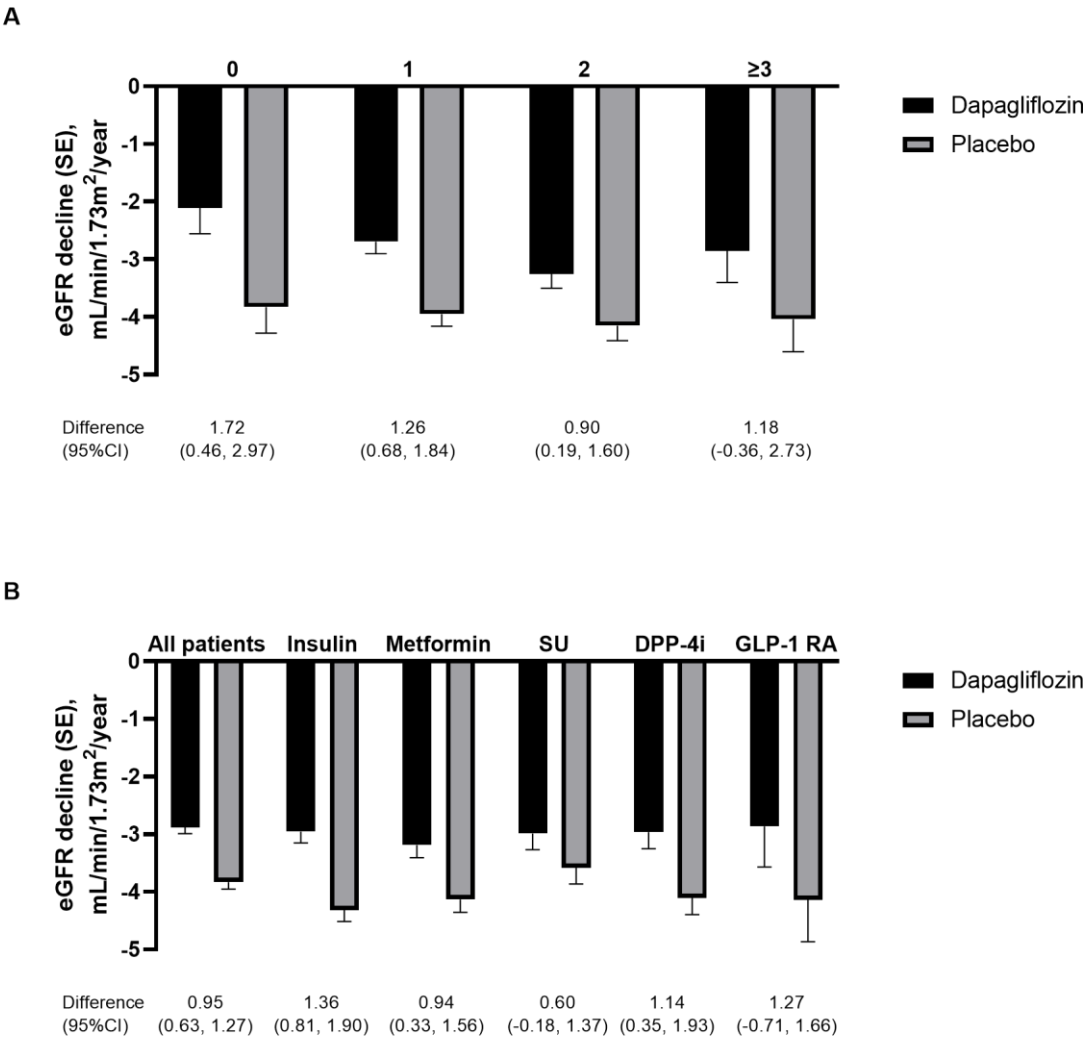
DPP4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide -1.

Supplemental Figure 1: Secondary endpoints by glucose-lowering therapy at baseline by (A) number of baseline glucose-lowering therapies and by (B) type of glucose-lowering therapy at baseline



DPP4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide -1; HHF, hospitalization for heart failure.

Supplemental Figure 2: eGFR decline over the study by (A) the number of glucose-lowering therapies and (B) type of glucose-lowering therapy at baseline



DPP4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, glucagon-like peptide -1 receptor agonist; SU, sulphonylurea.