Cardiorenal Outcomes with Dapagliflozin by Baseline Glucose Lowering Agents - Post-hoc Analyses from DECLARE-TIMI 58

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ABSTRACT

Aims: To assess the associations between baseline glucose-lowering agents (GLA) and cardiorenal outcomes with dapagliflozin vs. placebo in the DECLARE-TIMI 58 study.

Methods: DECLARE-TIMI 58 assessed the cardiorenal outcomes of dapagliflozin vs. placebo in patients with type 2 diabetes. This post-hoc analysis elaborates the efficacy and safety outcomes by baseline GLA for treatment effect and GLA-based treatment interaction.

Results: At baseline 14,068 patients (82.0%) used metformin, 7322 (42.7%) sulfonylureas, 2888 (16.8%) DPP-4 inhibitors, 750 (4.4%) GLP-1 receptor agonists (GLP-1 RA) and 7013 (40.9%) insulin. Dapagliflozin reduced the composite of cardiovascular death and hospitalization for heart failure (CVD/HHF) vs. placebo regardless of baseline GLA, with greater benefit in the small group of patients with baseline use of GLP-1 RA (HR [95% CI] 0.37[0.18, 0.78] vs. 0.86[0.75,0.98] in GLP-1 RA users vs. non-users, $p_{interaction}$=0.03). The overall HR for major adverse cardiovascular events (CVD, myocardial infarction or ischemic stroke) was 0.93 (95% CI 0.84,1.03) with dapagliflozin vs placebo, with no interaction by baseline GLA ($p_{interaction}$ >0.05). The renal specific outcome was reduced with dapagliflozin vs. placebo in the overall cohort (HR [95%CI] 0.53[0.43-0.66]), with no interaction by baseline GLA ($p_{interaction}$ >0.05). All of these outcomes were similar in those with vs. without baseline metformin use.

Conclusions: The effects of dapagliflozin on cardiorenal outcomes were generally consistent regardless of baseline GLA, with consistent benefits regardless of baseline metformin use. The potential clinical benefit of combining SGLT-2 inhibitors with GLP-1 RA, given some evidence of cardiovascular risk reduction with both classes, should be further explored.

INTRODUCTION

Global prevalence of type 2 diabetes mellitus (T2DM) is steadily increasing and the number of people living with diabetes in 2019 has been estimated to be 463 million (1). The two recent decades have seen marked advancements in diabetes care with the inclusion of GLP-1 receptor agonists (GLP-1 RA), di-peptidyl-peptidase-4 (DPP-4) inhibitors and sodium glucose co-transporter 2 (SGLT-2) inhibitors in the treatment armamentarium of type 2 diabetes (2). In contrast to sulfonylureas or insulin, these agents do not lead to hypoglycemia or weight gain, and SGLT-2 inhibitors and GLP-1 RA in fact lead to weight loss (2). Cardiovascular outcome trials (CVOT) with DPP-4 inhibitors demonstrated no cardiovascular benefit, yet, more recent trials of SGLT-2 inhibitors and GLP-1 RA demonstrated marked cardiovascular and renal benefits – albeit with some heterogeneity within each class (3-7). Moreover, while a recent meta-analysis indicated the magnitude of benefit on major adverse cardiovascular events (MACE) was overall similar with GLP-1 RA and SGLT-2 inhibitors (HR 0.88, 95% CI 0.82-0.94 for both drug classes), effects on hospitalization for heart failure (HHF) and adverse renal outcomes differed markedly, with a more pronounced reduction observed with SGLT-2 inhibitors (5). Whether combining these two drug classes yields additive or synergistic cardiorenal outcomes is yet unclear and has been the focus of several observational and post-hoc analyses (8-11).

The vast majority of patients included in the CVOTs conducted over the last decade were not treatment naïve and had been taking at least one glucose lowering agent (GLA) at baseline. In the earlier trials, these consisted mostly of metformin, sulfonylureas and insulin, whereas in the more recent Dapagliflozin Effect on Cardiovascular Events (DECLARE) – TIMI 58 trial, incretin-based therapies (DPP-4 inhibitors and GLP-1 RA) were used as well (12, 13). While metformin is generally positioned as standard of care first line treatment for patients with T2DM, recent guidelines have challenged its status, due to lower quality of evidence supporting its cardio-protective role (14). The high prevalence of baseline metformin users in CVOTs of GLP-1 RA or SGLT-2 inhibitors argues against this approach, as the benefits observed were in a population with high background metformin use. Thus, it is clearly of interest to assess cardiorenal outcomes in patients with vs. without baseline metformin use (15, 16).

In these post-hoc analyses of the DECLARE-TIMI 58 trial, we assessed the associations between baseline GLA and cardiorenal outcomes.

MATERIALS AND METHODS

Study overview

In the DECLARE - TIMI 58 trial, a total of 17,160 patients, including 6,974 with established atherosclerotic cardiovascular disease (ASCVD) and 10,186 with multiple risk factors (MRF) but without ASCVD, were randomly assigned to receive dapagliflozin 10 mg daily or placebo and followed for a median of 4.2 years. All patients were treated according to regional standards of care for cardiovascular risk factors - blood pressure, lipids, antithrombotic treatment and HbA1c. The design, baseline characteristics and principal results of this study have been previously published (12, 13, 17).

Assessment of outcomes

The dual composite efficacy endpoints were cardiovascular death or hospitalization for heart failure (CVD/HHF) and major adverse cardiovascular events (MACE; the composite of cardiovascular death, myocardial infarction [MI] or ischemic stroke). Additional prespecified efficacy outcomes included a renal specific composite outcome (sustained decrease of 40% or more in estimated glomerular filtration rate [eGFR] to less than 60 ml/min/1.73m2, new end-stage renal disease [ESRD], or death from renal causes), and the individual components of the primary endpoints. New onset confirmed sustained albuminuria was defined as the development of micro- or macro- albuminuria in people with normoalbuminuria at baseline which was observed over two consecutive visits at least 4 weeks apart.

Statistical analysis

Baseline characteristics are reported as frequencies and percentages for categorical variables and as mean and standard deviation (SD), or median and interquartile range (IQR) for continuous variables. Analyses were performed on an intention-to-treat basis. Within each subgroup, we calculated the effect of dapagliflozin on the incidence of the efficacy outcome using Cox regression models.

To test for heterogeneity of efficacy, hazard ratios (HRs) and 95% confidence intervals (CI) were determined from Cox regression models with stratification factor (ASCVD or MRF status and baseline hematuria) as strata in models comparing treatment in baseline GLA groups with formal statistical testing for interaction. Of note, due to a numerical imbalance in the early development program of dapagliflozin regarding bladder cancer events, all patients were screened for hematuria at trial entry, and patients in whom bladder cancer could not be ruled out were excluded from the study.

To increase the robustness of our findings, multivariate analyses were conducted for each outcome and baseline GLA adjusting for baseline differences within each GLA. Baseline insulin subgroup was adjusted for baseline BMI, eGFR (CKD-EPI), diabetes duration, HbA1c, ASCVD vs. MRF, history of heart failure, history of myocardial infarction and all other baseline GLA. Baseline metformin was adjusted for baseline age, sex, baseline BMI, eGFR (CKD-EPI), ASCVD vs. MRF, diabetes duration, HbA1c, history of heart failure, history of MI, and all other baseline GLA. Baseline sulfonylureas subgroup was adjusted for baseline BMI, eGFR (CKD-EPI), diabetes duration, ASCVD vs. MRF, history of MI, and all other baseline GLA. Baseline DPP-4 inhibitors subgroup was adjusted for sex, baseline BMI, UACR, eGFR (CKD-EPI), diabetes duration, HbA1c, history of heart failure, history of MI, and all other baseline GLA. Baseline GLP-1 RA was adjusted for baseline BMI, age, sex, diabetes duration, history of heart failure, and all other baseline GLA.

As a sensitivity analysis, we considered all outcomes by the use of each GLA at any time during the trial (defined as “ever” vs. “never” users).

Mixed models for repeated measures in HbA1c, weight, systolic blood pressure (SBP), eGFR and UACR were analyzed to produce least-squares mean estimates and 95% CIs in each treatment and baseline GLA group. Three-way interactions were calculated assessing the interaction of baseline GLA status, visit and treatment allocation to dapagliflozin vs. placebo.

This study should be considered as hypothesis generating, and there was no statistical adjustment for multiple comparisons. A p-value <0.05 was considered statistically significant.

All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata version 14.2 (College Station, TX, USA).

RESULTS

Baseline characteristics

In the DECLARE-TIMI 58 trial, metformin was used by 14068 (82.0%) of the patients, sulfonylureas by 7322 (42.7%), DPP-4 inhibitors by 2888 (16.8%), GLP-1 RA by 750 (4.4%) and insulin by 7013 (40.9%) of the patients at baseline. Baseline characteristics of patients by medication use are shown in supplementary tables 1A-E. As expected, multiple differences were noted when comparing baseline users vs. non-users of each drug class. In short, patients using metformin or GLP-1 RA were younger than non-users. HbA1c levels were higher with baseline insulin or sulfonylurea use vs. non-use whereas metformin or DPP-4 inhibitors were associated with lower baseline HbA1c levels compared with non-users. Body mass index (BMI) was markedly higher in patients with baseline use of GLP-1 RA (35.4 ± 6.8 kg/m^2) vs. those without GLP-1 RA use at baseline (31.9 ± 5.9 kg/m^2). Baseline eGFR levels were lower in insulin users yet higher in metformin or sulfonylureas users. Use vs. non-use of DPP-4 inhibitors was associated with lower levels of urinary albumin creatinine ratio (UACR) and insulin users had higher UACR compared with non-users. Patients with baseline insulin use had longer disease duration and higher prevalence of established cardiovascular disease or prior myocardial infarction (MI) compared with non-users, while opposite trends were observed with baseline use of metformin or sulfonylureas.

Cardiovascular outcomes

Dapagliflozin reduced the composite of CVD/HHF (HR [95% CI] 0.83 [0.73, 0.95]) regardless of baseline GLA (interaction p-values >0.05), though the effect appeared to be particularly large in the small group of patients with baseline use of GLP-1 RA (interaction p-value 0.03; Figure 1A). This was driven by a marked reduction in HHF in patients with baseline use of GLP-1 RA (HR 0.2 (95% CI 0.07, 0.60), Figure 1B). These effects were not observed in analysis by use of GLP-1 RA at any time during the study, whereby the HRs for CVD/HHF and for HHF in GLP-1 RA users were in line with those seen in the overall study population, and no interaction was observed between use or non-use of GLP-1 RA during the trial

and reduction in CVD/HHF and in HHF with dapagliflozin vs. placebo (interaction p-values >0.05; supplementary figures 1A-B).

The overall HR for MACE was 0.93 (95% CI 0.84, 1.03) with dapagliflozin vs placebo, and this was consistent regardless of the different GLA used at baseline (figure 2). A tendency toward greater benefit with dapagliflozin was observed in baseline insulin users (interaction p-value 0.06), yet not in those using insulin at any time during the study (interaction p-value 0.28, supplementary figure 1C).

The individual components of MACE (CVD, myocardial infarction, ischemic stroke) and all-cause mortality with dapagliflozin vs. placebo are shown in supplementary figures 2A-H for baseline GLA use and by use of GLA at any time during the trial. Generally, these outcomes were balanced in the overall study population and consistently by GLA subgroups.

Adjustment of all outcomes for baseline characteristics maintained these results (supplementary tables 2A-G). Moreover, baseline number of GLA used revealed consistent outcomes as in the overall population (i.e. reduction of CVD/HHF and HHF with dapagliflozin vs. placebo and balanced for MACE and its components, supplementary table 3).

Renal outcomes

The prespecified composite renal specific outcome was reduced with dapagliflozin vs placebo in the overall study population (HR [95% CI] 0.53 [0.43, 0.66]) with no interaction by baseline GLA (interaction p values >0.05; Figure 3). New onset albuminuria (confirmed sustained) in patients without albuminuria at baseline was reduced with dapagliflozin vs. placebo (HR [95% CI] 0.79 [0.72, 0.87]) regardless of baseline GLA (interaction p values >0.05; Figure 4). Adjustment of these two outcomes for baseline characteristics maintained these results (Supplementary table 2H-I). These observations were consistent regardless of the number of baseline GLA used (interaction p values >0.05; supplementary table 3).

The overall pattern of eGFR changes with dapagliflozin vs. placebo throughout the trial was consistent across all baseline GLA. There was no interaction between treatment, visit, and use or non-use of each GLA at baseline ($p>0.05$ for all GLA). An initial decline in eGFR was observed with dapagliflozin vs. placebo with subsequent stabilization of levels, and final eGFR levels at month 48 were generally higher with dapagliflozin vs. placebo (Table 1, supplementary figure 3A). UACR levels were also generally lower after 48 months with dapagliflozin vs. placebo across the different GLA categories (Table 1).

Cardiometabolic efficacy

There was greater decline in HbA1c, weight and systolic blood pressure with dapagliflozin vs. placebo across all subgroups of GLA with all parameters significantly lower with dapagliflozin at month 48 (Table 1, supplementary figures 3B-D).

DISCUSSION

The current analyses of the DECLARE-TIMI 58 trial demonstrate overall consistent cardiovascular, renal and metabolic benefits with dapagliflozin vs. placebo regardless of type or number of baseline GLA. Cardiorenal outcomes did not differ irrespective of baseline use of metformin. CVD/HHF was more prominently reduced with dapagliflozin vs. placebo in the small subset of patients who used GLP-1 RA at baseline compared with those who did not, yet the magnitude of CVD/HHF reduction with dapagliflozin was similar when comparing those using vs. not using GLP-1 RA at any time during the study. Adverse renal outcomes were less frequent with dapagliflozin vs. placebo regardless of baseline GLA, moreover, new onset albuminuria was less frequent with dapagliflozin consistently across all subgroups assessed.

In our study, 3092 patients were not using metformin at baseline. This population was older, with longer standing diabetes and a higher prevalence of cardiovascular disease, CHF and chronic kidney disease compared with metformin users. Nevertheless, the impact of dapagliflozin on the cardiovascular, renal and metabolic outcomes of this cohort did not significantly differ from its effect in patients who had been using metformin at baseline. This observation persisted after adjusting for baseline characteristics. These data support the notion that the beneficial effect of dapagliflozin is consistent irrespective of baseline metformin use. Notably, analysis of data from the EMPA-REG OUTCOME trial also did not reveal heterogeneity of cardiovascular outcomes by baseline use vs. non-use of metformin (18). Thus, the role of metformin as first line treatment is further challenged, whereas early treatment with an SGLT-2 inhibitor may be a better therapeutic choice for many patients.

Current treatment algorithms promote the early use of SGLT-2 inhibitors or GLP-1 RA in the care of patients with T2DM with or at high risk for atherosclerotic cardiovascular disease (2,14). The cardiometabolic benefits of combining GLP-1 RA and SGLT-2 inhibitors have been assessed in several trials demonstrating further improvement in cardiometabolic parameters when intensifying therapy with one class in addition to the other (19-24). Post-hoc analysis of the CANVAS program revealed a greater reduction of HbA1c, systolic blood pressure and body weight with canagliflozin vs. placebo in patients with baseline use of GLP-1 RA compared to those without (24).

Combined use of GLP-1 RA and SGLT-2 inhibitors is advocated in patients at high CV risk, if HbA1c remains above target, yet the cardiorenal outcomes of this combination require further study (9, 10). Post-hoc analysis of the CANVAS program noted a similar effect of canagliflozin on the primary cardiovascular outcome and the composite adverse renal outcome in those with vs. without baseline use of GLP-1 RA (24). Observational real world data analysis with propensity score matching of patients using GLP-1 RA who added SGLT-2 inhibitors vs. sulfonylureas demonstrated reduced cardiovascular events and hospitalization for heart failure in those adding SGLT-2 inhibitors (8). Our study enrolled a significant number of patients with baseline use of incretin-based therapies, to an SGLT-2 inhibitor vs. placebo and thus enables analyses of the cardio-renal outcomes of this treatment combination.

All DPP-4 inhibitors have been neutral with respect to MACE, while a reduction in MACE has been demonstrated with most GLP-1 RA (liraglutide, semaglutide, albiglutide and dulaglutide), and within the SGLT-2 inhibitors class it had been shown for canagliflozin and empagliflozin yet did not reach statistical significance with dapagliflozin or ertugliflozin (5, 25). In our study, treatment with dapagliflozin vs. placebo did not significantly reduce MACE irrespective of baseline use of DPP-4 inhibitors or GLP-1 RA.

Most DPP-4 inhibitors are neutral with respect to HHF, although a significant increased risk has been observed with saxagliptin (3). GLP-1 RA have been shown to have a modest benefit on reducing HHF, with a HR of 0.91 (0.84–1.00) in a recently published meta-analysis, albeit reduced HHF was not observed in the individual studies (5). To the contrary, SGLT-2 inhibitors have an established benefit in reducing HHF and current guidelines and consensus society recommendations, as well as drug product labeling, promote the use of dapagliflozin for the prevention of HHF in patients with T2DM with risk factors for or established atherosclerotic cardiovascular disease (2, 6, 14, 26). Results from the present analyses suggest greater benefit with the combined use of GLP-1 RA and dapagliflozin regarding CVD/HHF, implying a possible synergistic effect. However, the number of evaluable events are small (only 34 events of CVD/HHF among baseline GLP-1 RA users), confidence intervals are wide, and this observation did not persist when analyzing by use of GLP-1 RA at any time during the trial implying this may be a chance observation.

Our analyses further clarify the long-term renal outcomes of combining of SGLT-2 inhibitors – a class with established robust renal benefits, with incretin based therapies – which have also shown some favorable renal outcomes. DPP-4 inhibitors have been shown to reduce albuminuria in most but not all studies, with no effect on eGFR (27-30). GLP-1 RA have shown a larger and more consistent effect on albuminuria compared to DPP-4 inhibitors, and a slowing of eGFR decline has been demonstrated with dulaglutide and liraglutide in patients with eGFR<60 ml/min/1.73m^2 (31-32). Dulaglutide has also demonstrated reduced rates of eGFR decline by ≥40% or ≥50% compared to placebo (33). The renal benefits observed with incretin based therapies, particularly GLP-1 RA have been attributed to anti-inflammatory effects, alteration of renal hemodynamics due to inhibition of sodium reabsorption as well as effects secondary to weight loss, improved glycemic control and reduced blood pressure (10). SGLT-2

inhibitors convey renal protection by multiple mechanisms including alteration of renal hemodynamics and restoration of tubulo-glomerular feedback, reduction in tubular workload and metabolic stress and reduced blood pressure, weight, glucose and vascular stiffness (34-36). Many of the reno-protective effects of incretin based therapies and SGLT-2 inhibitors are probably complementary and therefore an added benefit of dapagliflozin on top of these agents may be expected (10).

In our cohort, patients using DPP-4 inhibitors at baseline had lower levels of albuminuria compared with non-users. Whether this is reflective of other baseline characteristics or of the drug itself cannot be determined from these analyses. Nevertheless, the renal benefits of dapagliflozin occurred irrespective of baseline DPP-4 inhibitors use indicating an added renal benefit of prescribing dapagliflozin on top of DPP-4 inhibitors, though probably not a synergistic effect. Adding dapagliflozin to patients using GLP-1 RA maintained the renal benefits observed in the overall DECLARE-TIMI 58 study population, with lower rates of the renal specific endpoint and of new onset albuminuria, and lower UACR at month 48. Although differences in the renal outcomes did not reach statistical significance in the small group of GLP-1 RA users, the trends were similar with no heterogeneity by GLP-1 RA use. Thus, the benefit of dapagliflozin was not altered by baseline GLP-1 RA use, promoting their combined use in renal protection.

Patients using insulin at baseline experienced lower rates of MACE with dapagliflozin vs. placebo (HR [95% CI] 0.84 [0.74, 0.97]), yet this was not observed in patients not using insulin at baseline (interaction p-value 0.06). Notably, insulin users were more likely to have prior MI and longer disease duration – both of which we have previously demonstrated to be associated with reduced rates of MACE with dapagliflozin vs. placebo (37, 38). Thus, it may be possible that patient characteristics and not insulin use in itself underlie this observation. Moreover, analysis by use of insulin at any time during the trial did not demonstrate a differential effect on MACE of dapagliflozin vs. placebo by insulin use.

Dapagliflozin led to greater decline in HbA1c, weight and SBP and compared to placebo. These changes were largely unaffected by baseline GLA in line with previously published data, further supporting the favorable metabolic impact of adding dapagliflozin to any prevailing glucose-lowering regimen (39). The

addition of dapagliflozin to patients with vs. without baseline use of incretin based GLA led to comparable HbA1c reductions (Table 1, supplementary figure 3B), in line with data from most studies demonstrating the glycemic efficacy of this combination (19-23).

Some limitations of our analyses should be noted. First, while analyses by baseline GLA were generally pre-specified, the specific analytic plan as well as analysis of the metabolic outcomes were largely post-hoc. Second, baseline use or non-use of a particular GLA may have been determined by local guidelines, cost, availability of treatment or patient preference and not by true biological variation and the results should thus be interpreted in this context. Moreover, the impact of this confounder is even more substantial in the sensitivity analyses by medication use at any time during the study. This post-randomization analysis may be affected by treatment allocation as well and thus is more subject to potential bias than the primary one by baseline medications. Third, we did not account for the particular agents used within each class or for drug dosages. Finally, no correction for multiplicity was performed, thus although some of the interaction p-values were indeed <0.05 these must be considered as hypothesis generating alone.

In conclusion, in this study, the cardiovascular and renal benefits of dapagliflozin were observed regardless of baseline GLA. Benefit is maintained, when combining classes of CV and renal protecting agents, and there is no evidence to support a role of metformin in mediating the observed benefits of dapagliflozin.

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CONFLICT OF INTEREST

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LEGENDS TO FIGURES

Figure 1A – CVD/HHF with dapagliflozin vs. placebo by baseline glucose lowering agents

Figure 1B – HHF with dapagliflozin vs. placebo by baseline glucose lowering agents

Figure 2 – Major adverse cardiovascular events with dapagliflozin vs. placebo by baseline glucose lowering agents

Figure 3 – Renal specific outcome with dapagliflozin vs. placebo by baseline glucose lowering agents

Legend: The renal specific outcome was a composite of: sustained decrease of 40% or more in eGFR to less than 60 ml/min/1.73m^2, new end-stage renal disease, or death from renal causes

Figure 4 – New onset albuminuria with dapagliflozin vs. placebo by baseline glucose lowering agents

Legend: New onset, sustained, albuminuria (micro or macro) in patients with normoalbuminuria at baseline.

Table 1 – Metabolic parameters at 48 months with dapagliflozin and placebo by baseline glucose lowering agent

Baseline glucose lowering agent		HbA1c (%)		Weight (kg)		SBP (mmHg)		eGFR		UACR	
		DAPA	PBO	DAPA	PBO	DAPA	PBO	DAPA	PBO	DAPA	PBO
Metformin	YES	7.83±0.02*	8.08±0.02	86.73±0.08*	88.77±0.08	132.51±0.21*	135.03±0.21	77.61±0.18*	75.80±0.18	128.74±6.33*	185.42±6.42
	NO	7.95±0.04+	8.14±0.04	88.17±0.20*	89.58±0.21	132.26±0.47+	133.97±0.49	73.45±0.40	72.67±0.41	170.99±16.38	195.12±16.77
SUR	YES	7.90±0.03*	8.17±0.03	84.36±0.11*	86.46±0.11	131.67±0.29*	134.71±0.29	78.01±0.25*	76.38±0.25	111.37±8.45*	161.41±8.49
	NO	7.82±0.02*	8.03±0.02	88.96±0.11*	90.77±0.11	133.06±0.26*	134.94±0.26	76.03±0.22*	74.39±0.23	153.23±7.22*	200.25±7.39
DPP-4 i	YES	7.84±0.04+	8.02±0.04	85.65±0.15*	88.14±0.15	130.36±0.45*	133.57±0.46	77.87±0.38*	75.75±0.38	101.89±10.01	126.81±10.08
	NO	7.86±0.02*	8.11±0.02	87.22±0.07*	89.07±0.07	132.91±0.21*	135.11±0.22	76.69±0.18*	75.15±0.19	140.49±6.73*	195.71±6.87
GLP-1 RA	YES	7.93±0.08¶	8.19±0.09	99.44±0.46¶	100.97±0.50	131.11±0.87¶	133.72±0.94	78.04±0.76	76.14±0.82	106.00±23.16¶	178.02±25.08
	NO	7.85±0.02*	8.09±0.02	86.39±0.07*	88.36±0.07	132.54±0.19*	134.90±0.20	76.83±0.17*	75.22±0.17	138.63±13.84¶	181.79±13.92
Insulin	YES	8.07±0.03*	8.35±0.03	90.89±0.13*	92.85±0.14	133.10±0.31*	135.50±0.32	74.44±0.26*	72.81±0.27	162.97±31.28	232.56±32.04
	NO	7.70±0.02*	7.92±0.02	84.33±0.08*	86.25±0.08	132.04±0.24*	134.41±0.24	78.54±0.21*	76.88±0.21	111.37±6.93+	145.17±6.97

Values are mean ± SE. *p<0.0001, +p<0.01, ¶p<0.05 for dapagliflozin vs. placebo. eGFR – estimated glomerular filtration rate; SBP – Systolic blood pressure; SUR – sulfonylureas; UACR – urinary albumin creatinine ratio

Figure 1A – CVD/HHF with dapagliflozin vs. placebo by baseline glucose lowering agents

Subgroups	Dapagliflozin n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	p-value	p-interaction
Overall	417/8582 (4.9%)	496/8578 (5.8%)	0.83 (0.73, 0.95)	0.0027	
Baseline Metformin					
Yes	293/7020 (4.2%)	362/7048 (5.1%)	0.81 (0.69, 0.94)	0.0063	0.5603
No	124/1562 (7.9%)	134/1530 (8.8%)	0.88 (0.69, 1.12)	0.2914	
Baseline Sulfonylureas					
Yes	153/3615 (4.2%)	196/3707 (5.3%)	0.80 (0.65, 0.98)	0.0354	0.6386
No	264/4967 (5.3%)	300/4871 (6.2%)	0.85 (0.72, 1.00)	0.0536	
Baseline DPP-4 inhibitors					
Yes	44/1418 (3.1%)	58/1470 (3.9%)	0.82 (0.55, 1.21)	0.3223	0.9709
No	373/7164 (5.2%)	438/7108 (6.2%)	0.83 (0.72, 0.95)	0.0069	
Baseline GLP-1 receptor agonists					
Yes	10/397 (2.5%)	24/353 (6.8%)	0.37 (0.18, 0.78)	0.0085	0.0257
No	407/8185 (5.0%)	472/8225 (5.7%)	0.86 (0.75, 0.98)	0.0229	
Baseline Insulin					
Yes	237/3567 (6.6%)	274/3446 (8.0%)	0.82 (0.69, 0.97)	0.0224	0.9142
No	180/5015 (3.6%)	222/5132 (4.3%)	0.83 (0.68, 1.01)	0.0599	

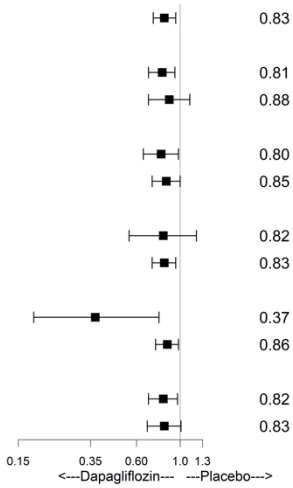


Figure 1B – Hospitalization for heart failure with dapagliflozin vs. placebo

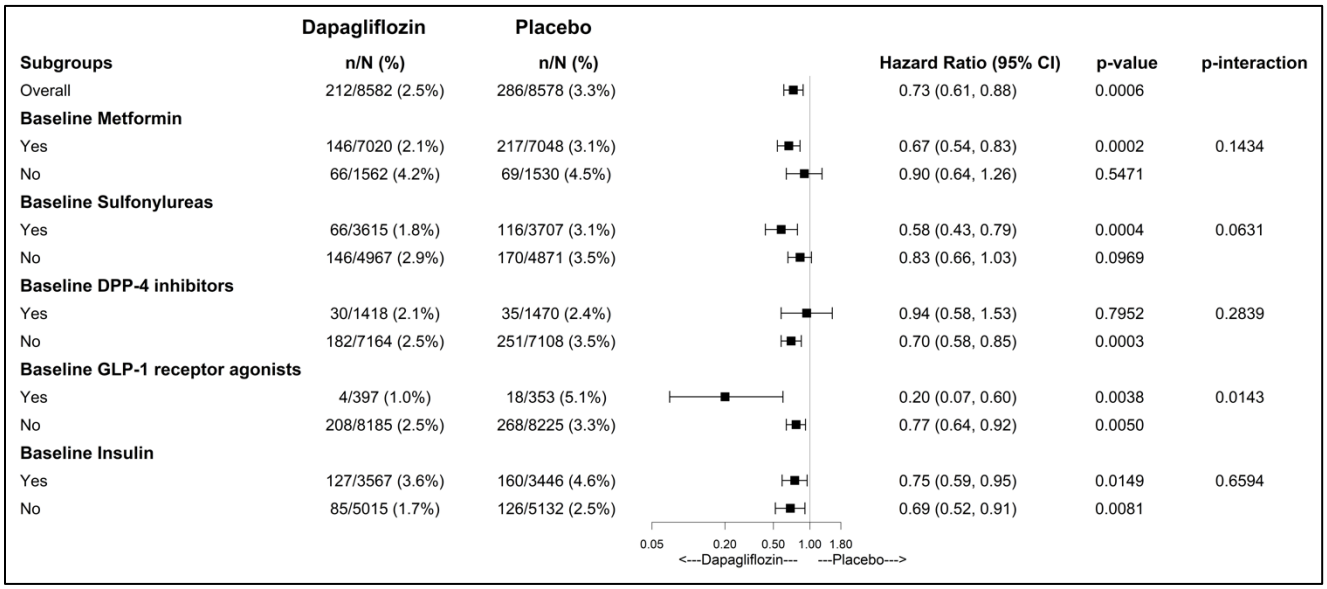


Figure 2 – Major adverse cardiovascular events with dapagliflozin vs. placebo by baseline glucose lowering agents

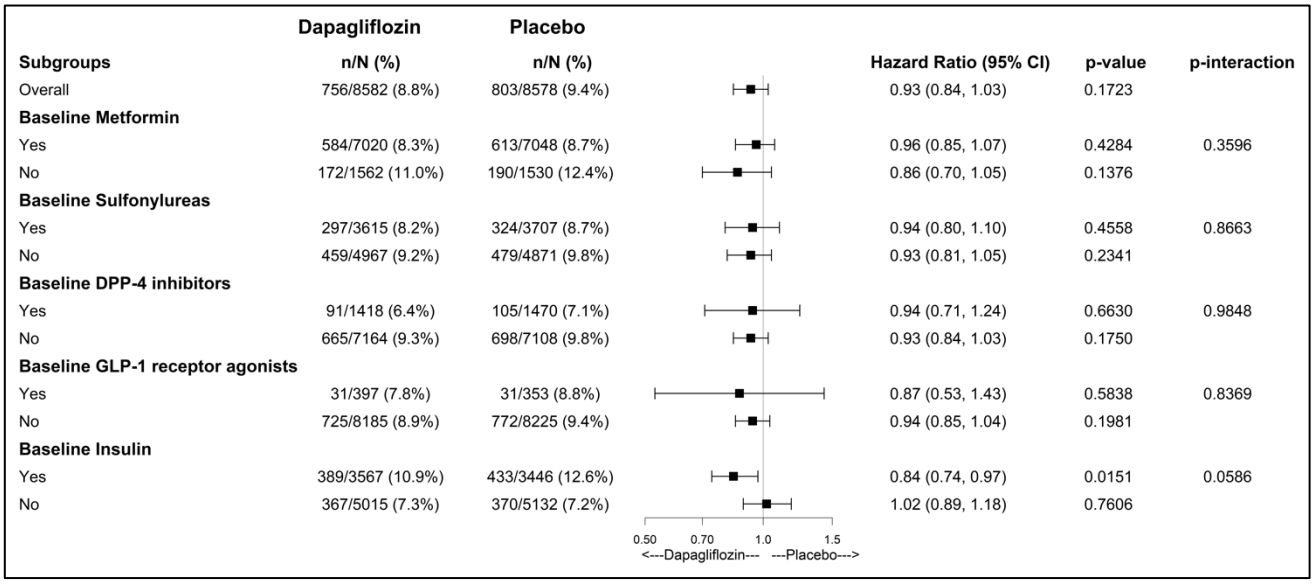
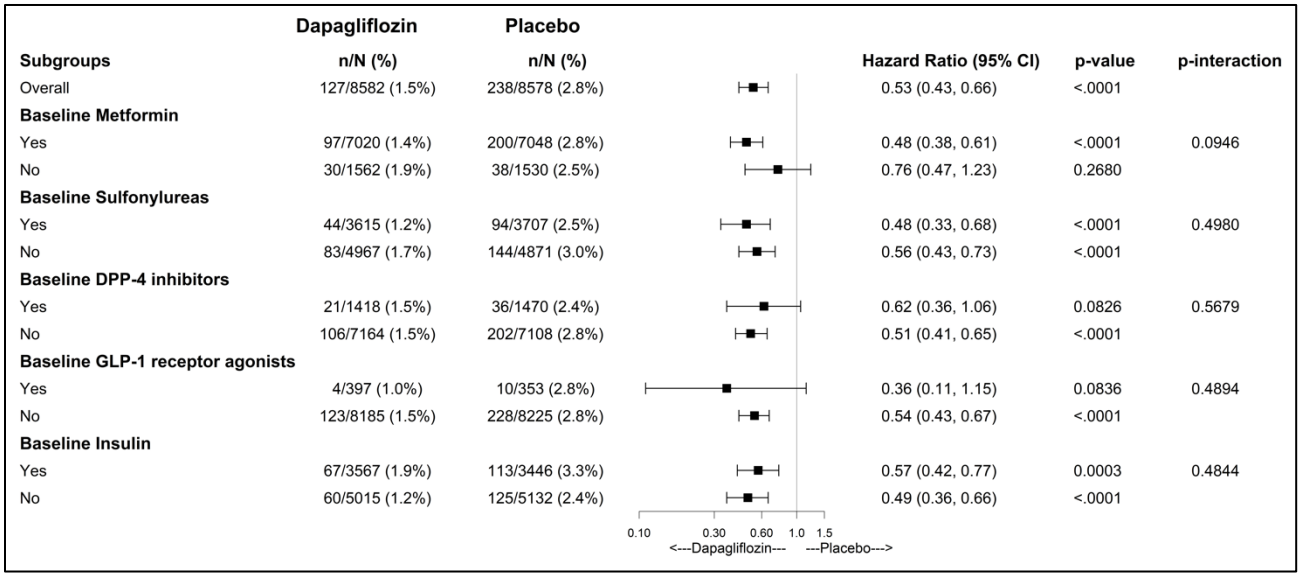
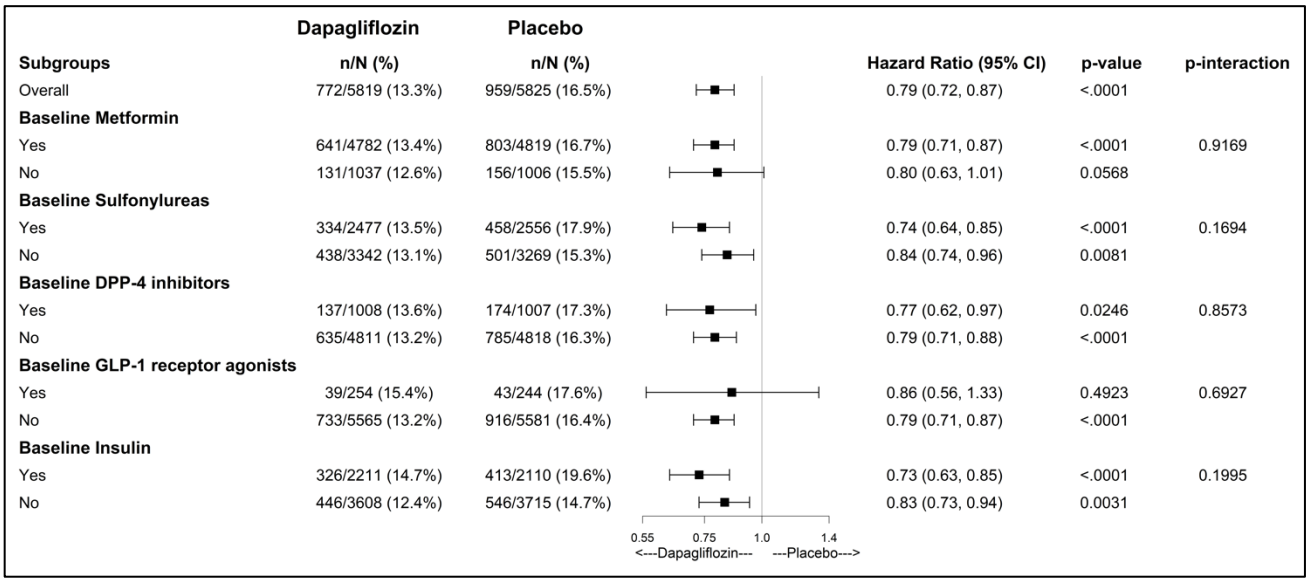


Figure 3 – Renal specific outcome with dapagliflozin vs. placebo by baseline glucose lowering agents



The renal specific outcome was a composite of: sustained decrease of 40% or more in eGFR to less than 60 ml/min/1.73m^2, new end-stage renal disease, or death from renal causes

Figure 4 – New onset albuminuria with dapagliflozin vs. placebo by baseline glucose lowering agents



New onset, sustained, albuminuria (micro or macro) in patients with normoalbuminuria at baseline.