**Efficacy and Safety of Dapagliflozin by Baseline Insulin Regimen and Dose:**

**Post Hoc Analyses from DECLARE-TIMI 58**

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**ABSTRACT**

**Objective:** The cardiorenal benefits of adding SGLT2 inhibitors to patients on insulin, particularly those on intensive regimens which include short acting (SA) insulin have not been explored.

**Research design and methods:** The DECLARE-TIMI 58 trial randomized 17,160 patients with type 2 diabetes to dapagliflozin or placebo for a median follow-up of 4.2 years. Cardiovascular, renal, metabolic and safety outcomes with dapagliflozin vs. placebo by insulin dose and regimen were studied by Cox regression models.

**Results:** The study included 7,013 insulin users at baseline, with 4,650 (66.3%) patients on regimens including SA insulin. Insulin doses varied with 2,443 (34.8%) patients receiving <0.5 IU/kg, 2,795 (39.9%) 0.5-≤1 IU/kg and 1,339 (19.1%) >1 IU/kg. Dapagliflozin reduced cardiovascular death/hospitalization for heart failure among overall insulin users (HR [95% CI] 0.82[0.69-0.97]), and consistently in patients on insulin regimens with or without SA insulin (HR 0.83[0.67-1.03] and 0.78[0.57-1.07] respectively, Pinteraction= 0.75). No heterogeneity was observed by insulin dose (Pinteraction = 0.43). The HR for major adverse cardiovascular events with dapagliflozin among insulin users (HR 0.84[0.74-0.97]) was similar irrespective of regimen or dose (Pinteraction 0.75 and 0.07, respectively). Dapagliflozin reduced the rate of adverse renal outcomes overall, and consistently across subgroups of insulin users. The known safety profile of dapagliflozin was unchanged in patients on intensive insulin regimens, with the effects on severe hypoglycemia and diabetic ketoacidosis generally similar to observations in the overall trial.

**Conclusions**: The benefits and safety of dapagliflozin were maintained in high-risk patients receiving intensive insulin regimens including SA or high-dose insulin.

Type 2 diabetes (T2DM) is a progressive disease, often requiring treatment intensification over time to achieve optimal glycemic control. The last two decades have witnessed the introduction of new classes of glucose-lowering agents (GLA) with established cardiovascular and renal benefits, yet a quarter of patients with T2DM are still treated with insulin striving to optimize glycemic control (1). While treatment intensification with insulin may reflect differences in regional practices, it suggests clinical disease progression with decreased beta cell reserve. Although insulin use does not directly impact cardiovascular risk or overall mortality, it is associated with a less favorable cardiometabolic risk profile (2; 3). Patients treated with insulin are often older, with multiple comorbidities, and are at greater risk for diabetes-related complications (4).

Sodium glucose co-transporter-2 (SGLT2) inhibitors as a class have demonstrated multiple clinical benefits beyond their glucose lowering effects including improved metabolic, cardiovascular, and renal effects (5-11). Furthermore, they lower blood glucose levels independent of beta cell function, are effective in any duration of disease, and carry minimal risk of hypoglycemia (12; 13). Given these favorable effects, SGLT2 inhibitors are an attractive therapeutic option for patients with longstanding T2DM receiving intensive insulin therapy including short acting insulin. In a phase 3 study, dapagliflozin improved glycemic control, stabilized insulin dosing and reduced weight without increasing severe hypoglycemic episodes in patients inadequately controlled on high doses of insulin (14; 15). However, limited data exists regarding the cardiovascular and renal efficacy and safety of SGLT2 inhibitors in patients treated with intensive insulin regimens including short acting insulin or exceptionally higher insulin doses.

The Dapagliflozin Effect of Cardiovascular Events (DECLARE)-TIMI 58 study assessed the cardiovascular and renal outcomes of dapagliflozin versus placebo in a broad population of patients with T2DM (5). A reduction in the composite of cardiovascular death/hospitalization for heart failure (CVD/HHF) was observed, driven by a reduction in HHF, as well as a marked reduction in adverse renal outcomes (5). In post hoc analyses, these benefits were demonstrated independent of baseline HbA1c or baseline GLA (16; 17). In the overall study population, major adverse cardiovascular events (MACE) were balanced with dapagliflozin vs. placebo, although a tendency towards lower rates of MACE with dapagliflozin vs. placebo were observed in patients using insulin at baseline (HR [95% CI] 0.84 [0.74,0.97]; p = 0.02 in insulin users, vs. 1.02 [0.89, 1.18]; p = 0.76 in non-insulin users; Pinteraction 0.06) (17). In the present analysis, we studied whether these observed benefits were maintained in patients treated with intensive insulin regimens including short acting insulin and across varying weight-based doses.

**RESEARCH DESIGN AND METHODS**

**Study Overview**

In the DECLARE-TIMI 58 trial, a total of 17,160 patients, including 7,013 insulin users, with T2DM and established atherosclerotic cardiovascular (CV) disease or risk factors were randomly assigned to receive dapagliflozin or placebo in addition to standard of care and followed for a median of 4.2 years. All patients were treated according to guidelines and regional standards of care for cardiovascular risk factors, including blood pressure, LDL cholesterol, antithrombotic treatment and HbA1c. The trial protocol was approved by the institutional review board at each participating site, and all participants provided written informed consent. The design, baseline characteristics, and principal results of this study have been published (5; 18; 19). Insulin dose was reliably captured in 6,577 of the insulin users, and the total daily dose per kg was calculated at baseline for each patient. Patients were divided by insulin regimen to those using any type of short acting insulin (human, aspart, lispro, glulisine) alone, as part of a basal-bolus regimen, or in a fixed ratio combination vs. those not using any form of short acting insulin. Insulin use and specific regimens was at the discretion of the investigator in accordance with local standards.

**Assessment of Outcomes**

All study outcomes reported are by intention-to-treat (ITT). The dual primary composite efficacy points were CVD/HHF and MACE, which included the composite of CV death, myocardial infarction, or ischemic stroke. A secondary pre-specified cardiorenal composite outcome was a sustained decreased of 40% or more in estimated glomerular filtration rate (eGFR) to < 60 mL/min/1.73 m2, new end stage renal disease (ESRD), or death from renal or CV causes. A renal-specific composite outcome was similarly defined, yet excluded CV death.

Safety endpoints were assessed in all patients who received at least one dose of study drug. The reported safety outcomes were assessed on treatment, which included all events that occurred after the first dose of the study drug to the early of 30 (for serious adverse events) or 7 (for non-serious AEs) days after the last dose of the study drug or the closing visit. Acute kidney injury (AKI) was identified based on the listing of this term according to the prespecified lists of Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. Severe (major) hypoglycemia was defined as symptomatic events requiring external assistance due to severe impairment of consciousness with prompt recovery after glucose or glucagon administration. Diabetic ketoacidosis (DKA) events were adjudicated as definite or probable clinical events for which no alternative diagnosis was considered a more likely primary cause of presentation (20).

**Statistical Analysis**

Baseline characteristics are reported as frequencies and percentages for categorical variables and as mean (SD) or median (IQR) for continuous variables by insulin dose and regimen groups. P values for categorical variables are calculated from the Chi-square test and continuous variables are calculated from the Kruskal-Wallis test. Baseline and efficacy analyses were performed on an intention-to-treat basis. Safety assessments were performed in the safety analysis population (18).

The effect of dapagliflozin on the incidence of the outcomes within each insulin dose or regimen subgroup was calculated using Cox regression models that included the randomization stratification factor of baseline hematuria and the risk category (ASCVD or MRF), and we report the hazard ratios (HRs) and 95% confidence intervals (CI), as described in the design paper (18).

Mixed models for repeated measures in HbA1c, weight and systolic blood pressure (SBP) were analyzed to produce least-squares mean estimates of the change in each treatment and baseline insulin dose and regimen group. Models included baseline values, hematuria status, risk category, treatment, visit and the interaction of treatment and visit. We calculated the interaction of insulin category, metabolic outcome, and treatment allocation at 6 months as this is the earliest study time point after randomization.

The proportion of patients attaining the glycemic target of HbA1c ≤7% or ≤8% with dapagliflozin vs. placebo was calculated at each time point for each baseline insulin category and the Chi-square test was used to compare between the treatment arms. A logistic regression model was used to calculate the interaction between insulin dose or type, treatment allocation and attainment of glycemic target for each timepoint post baseline.

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).

**RESULTS**

**Baseline Characteristics**

The study included 7,013 insulin users at baseline, including 4,650 (66.3%) patients on insulin regimens including short acting (SA) insulin and 2363 (33.7%) on regimens without SA insulin. Baseline characteristics by insulin regimen and dose are shown in Table 1. As expected, multiple differences were noted when comparing patients using SA insulin to non-SA insulin users. SA insulin users had higher body mass index (BMI) and lower estimated glomerular filtration rate (eGFR), and longer diabetes duration compared to non-SA insulin users. A higher prevalence of established atherosclerotic CV disease, congestive heart failure (CHF), hypertension and hyperlipidemia were noted in SA insulin users as was increased use of antiplatelet therapy, beta blockers, statins, diuretics, and mineralocorticoid receptor agonists. SA insulin users were treated with fewer GLAs compared to those not on SA insulin. When categorized according to total daily insulin dose, 2,443 (34.8%) patients were receiving a <0.5 IU/kg, 2,795 (39.9%) 0.5 to ≤1 IU/kg and 1,339 (19.1%) >1 IU/kg. Patients receiving higher weight-based insulin doses had increased BMIs, higher baseline HbA1c, longer diabetes duration and increased prevalence of established atherosclerotic CV disease, hypertension, and dyslipidemia. They were more often treated with antiplatelet therapy, beta blockers, ACEi/ARB, statins, diuretics, mineralocorticoid receptor agonists and less commonly treated with oral GLAs at baseline.

**Cardiovascular and Renal Outcomes**

Dapagliflozin reduced the composite of CVD/HHF among overall insulin users (HR [95% CI] 0.82 [0.69, 0.97]). This reduction was consistent among patients using insulin regimens containing short acting (HR 0.83 [0.67-1.03]) and non-short acting insulin (HR 0.78 [0.57-1.07]; Pinteraction = 0.75; figure 1A). No heterogeneity was noted by insulin dose either (Pinteraction = 0.43; figure 1B). This efficacy was mainly driven by a lower rate of HHF with dapagliflozin vs. placebo in SA and non-SA insulin users, with no heterogeneity between the groups (HR [95%CI] 0.79 [0.60-1.04) and 0.66 [0.43-1.02] respectively; Pinteraction = 0.49; figure 1A). A consistent effect by insulin dose was noted as well (Pinteraction = 0.16; figure 1B).

The HR for major adverse cardiovascular events with dapagliflozin among insulin users was 0.84 [0.74, 0.97]. There was no heterogeneity by insulin regimen or dose on MACE (Pinteraction > 0.05; figure 1A, 1B). Data for the individual components of MACE (CVD, MI, ischemic stroke) were similar (Pinteraction > 0.05; figure 1A, 1B).

The cardiorenal outcome was reduced with dapagliflozin vs. placebo in overall insulin users (HR 0.79 [0.66, 0.95]), with no heterogeneity between patients on regimens including short acting insulin or not (HR [95% CI] 0.86 [0.68, 1.08] and 0.67 [0.48, 0.93] respectively; Pinteraction 0.23; figure 1A). This reduction was similar across the range of insulin doses (Pinteraction = 0.97; figure 1B). Dapagliflozin reduced the prespecified renal-specific outcome in insulin users overall compared to placebo (HR 0.57 [0.42 ,0.77]), with a particularly large effect in patients not using SA insulin (Pinteraction = 0.03; figure 1A). The effects were consistent across the weight-based insulin doses (Pinteraction = 0.09; figure 1B).

**Metabolic Outcomes**

A greater decline in HbA1c, weight and SBP with dapagliflozin vs. placebo was noted throughout the entire trial, regardless of insulin dose or regimen (Tables S1-6). A greater proportion of patients randomized to dapagliflozin versus placebo attained the HbA1c targets of ≤7.0% or ≤8.0%, irrespective of insulin regimen or dose (Figure 2A-D). This effect was maintained at year 1, 2, 3 in all subgroups, yet was somewhat attenuated at year 4, particularly in the SA insulin group. There was no interaction between attainment of target HbA1c ≤7%, treatment allocation and insulin regimen or dose at any time point during the study (Pinteraction > 0.05). Target HbA1c ≤8% was more likely attained with dapagliflozin vs. placebo in patients on insulin regimens excluding SA insulin at months 6, 12 and 48 (Pinteraction = 0.01, 0.02 and 0.04 respectively), yet there was no heterogeneity by regimen at other time points, or by insulin dose throughout the trial (Pinteraction > 0.05).

**Safety**

Among insulin users, severe hypoglycemia was reduced with dapagliflozin in non-SA insulin users (HR [95%CI] 0.20 [0.06, 0.70]), yet not in SA insulin users (HR [95%CI] 0.86 [0.57, 1.30]); Pinteraction = 0.03. No heterogeneity was noted in the effect of dapagliflozin vs. placebo on severe hypoglycemia by baseline insulin dose (figure 3).

In overall insulin users, DKA was observed in 0.6% of patients with dapagliflozin versus 0.3% on placebo (HR [95%CI] 1.52 [0.74, 3.11]; figure 3). The vast majority of DKA events occurred in patients with baseline use of SA insulin – 19 vs. 9 with dapagliflozin vs. placebo, compared to 1 vs. 3 with dapagliflozin vs. placebo in those using insulin regimens which did not include SA insulin.

Acute kidney injury was reduced with dapagliflozin among insulin users (HR [95%CI 0.66 [0.49, 0.89]), with a consistent effect across insulin regimens, and some heterogeneity across doses (Supplementary figure 1). Events consistent with volume depletion were balanced with dapagliflozin vs. placebo overall and across categories of insulin users. Urinary tract infections were not increased with dapagliflozin vs. placebo in any insulin subgroup. Genital infections were increased with no heterogeneity by insulin dose or regimen (Supplementary figure 1).

**CONCLUSIONS**

In the present analyses of the DECLARE-TIMI 58 study, treatment with dapagliflozin vs. placebo demonstrated overall consistent cardiovascular, renal, and metabolic benefits, as well as safety, in patients with T2DM irrespective of baseline insulin regimen or dose. The outcomes of patients on intensive insulin regimens including SA insulin or high insulin doses randomized to dapagliflozin vs. placebo were in line with those of the overall study population.

Limited data exists regarding cardiorenal outcomes in patients treated with SGLT2 inhibitors in combination with insulin therapy. A post hoc analysis of the EMPA-REG Outcome trial reported a consistent reduction of cardiorenal outcomes with empagliflozin in 2,252 patients treated with insulin at baseline (Pinteraction > 0.05) (21). Analyses based on insulin regimen or dose were not reported. Metabolic efficacy of SGLT2 inhibitors in combination with insulin was demonstrated in a meta-analysis of nine randomized controlled trials (RCTs) including 3,069 patients, with a significant reduction in HbA1c and weight independent of insulin dose, without an increased risk of hypoglycemia (22).

In our study, 7,013 patients were using insulin at baseline, with approximately two-thirds on intensive insulin regimens including SA insulin and one-third on basal long or intermediate acting insulin only. Patients using SA insulin had higher prevalence of longstanding diabetes (median duration 15 years), cardiovascular disease, congestive heart failure and chronic kidney disease compared with non-SA insulin users. Nevertheless, the reduction in CVD/HHF, MACE and adverse renal outcomes with dapagliflozin in this cohort were similar to overall insulin users. Despite increased prevalence of cardiovascular risk factors at baseline, patients treated with higher weight-based insulin doses experienced consistent cardiorenal benefits with dapagliflozin.

Dapagliflozin led to significant improvements in metabolic parameters compared with placebo. A greater decline in HbA1c and weight was observed, and a significantly higher proportion of patients achieved target HbA1c levels with dapagliflozin. These benefits were observed irrespective of insulin regimen, or dose. Although patients treated with higher insulin doses had increased HbA1c at baseline, the addition of dapagliflozin resulted in greater achievement of glycemic targets compared to placebo, similar to those treated with lower insulin doses. Notably, the eGFR was >81 mL/min per 1.73 m2 in all subgroups enabling good glycemic efficacy of dapagliflozin.

Dapagliflozin was well tolerated when used in combination with insulin therapy, with no increase in adverse events compared to non-insulin users. These findings are in line with previous RCTs examining the safety of SGLT2 inhibitors in combination with insulin (21; 23; 24). Severe hypoglycemia was decreased with dapagliflozin vs. placebo regardless of insulin dose. A particularly marked reduction was observed in patients using insulin regimens which did not include SA insulin at baseline. These findings may help provide reassurance to clinicians initiating SGLT2 inhibitors in patients treated with insulin, as fear of hypoglycemia is a major barrier to achieving glycemic targets. While DKA in the overall study population was relatively uncommon, it was more frequent with dapagliflozin versus placebo. In overall insulin users, although rare, the absolute number of events were increased with dapagliflozin particularly in patients using SA insulin. As intensive insulin therapy including SA insulin is associated with longstanding diabetes and decreased beta cell reserve, the addition of dapagliflozin to regimens including SA insulin mandates more experience in insulin dose titration to prevent hypoglycemia and DKA.

Some limitations of our study should be noted. The association of baseline insulin use with cardiovascular and renal outcomes is post hoc and thus, should be viewed as hypothesis generating. Second, only baseline insulin regimen and dose were considered in these analyses, and we did not account for the impact of changes in treatment regimen or dose over time on outcomes. Finally, the number of events were small in some of the subgroups, and no correction for multiplicity was performed.

In conclusion, in the DECLARE-TIMI 58 trial, the use of dapagliflozin in patients with T2DM managed with insulin, including intensive insulin regimens, provided significant cardiovascular and renal benefits despite increased baseline cardiovascular risk factors. Adverse events associated with dapagliflozin, including hypoglycemia and DKA were rare in this high-risk population.

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**AUTHOR CONTRIBUTIONS**

RP, AC, SDW, IAMG-N, AML, MSS, and IR contributed to the study design. RP, AC, SDW, IAMG-N, AML, MSS, and IR did the literature search. RP, AC, SDW, AR, IY, ELG, SAM, IAMG-N, AML, MSS, and IR designed the figures. RP, AC, SDW, IAMG-N, AML, MSS, and IR contributed to data collection and RP, AC, OM, SDW, AR, IY, ELG, SAM, DLB, LAL, DKM, JPHW, IAMG-N, AML, MSS, and IR contributed to data analysis. RP, AC, OM, SDW, SAM, ELG, AR, IY, DLB, LAL, DKM, JPHW, IAMG-N, AML, MSS, and IR contributed to data interpretation. RP, AC, OM, SDW, AR, IY, ELG, SAM, DLB, LAL, DKM, JPHW, IAMG-N, AML, MSS, and IR contributed to the writing of the report and approved the final submitted version. RP and AC 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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**CONFLICT OF INTEREST**

**RP** reports personal fees from Eli Lilly, Novo Nordisk, Sanofi, Boehringer Ingelheim, AstraZeneca, and Merck Sharp & Dohme. **IR** reports personal fees from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Concenter BioPharma and Silkim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, Orgenesis, Pfizer, Sanofi, SmartZyme Innovation, Panaxia, FuturRx, Insuline Medical, Medial EarlySign, CameraEyes, Exscopia, Dermal Biomics, Johnson & Johnson, Novartis, Teva, GlucoMe, and DarioHealth. **SDW** discloses grants from Amgen, AstraZeneca, Daiichi Sankyo, Eisai, Janssen, and Merck, Pfizer and consulting fees from AstraZeneca, Boston Clinical Research Institute, Icon Clinical, Novo Nordisk; Spouse, Dr. Caroline Fox is an employee of Merck; and is a member of the TIMI Study Group, which has received institutional research grant support through Brigham and Women’s Hospital from: **:** Abbott, Amgen, Anthos Therapeutics, ARCA Biopharma, Inc., AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., Daiichi-Sankyo, Eisai, Intarcia, Ionis Pharmaceuticals, Inc., Janssen Research and Development, LLC, MedImmune, Merck, Novartis, Pfizer, Quark Pharmaceuticals, Regeneron Pharmaceuticals, Inc., Roche, Siemens Healthcare Diagnostics, Inc., Softcell Medical Limited, The Medicines Company, Zora Biosciences. **SAM** and **ELG**  report grants from AstraZeneca, during the conduct of the study; 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Table 1. Baseline characteristics by insulin regimen at baseline

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Insulin regimen** | | | **Insulin dose** | | | |
|  | **Short Acting Insulin**  **N=4650** | **Non-Short Acting Insulin**  **N=2363** | **P-value** | **<0.5 U/kg**  **N = 2443** | **0.5 - ≤1 U/kg**  **N = 2795** | **>1 U/kg**  **N = 1339** | **P-value** |
| ***Demographic characteristics*** | | | |  | | | |
| Age, years | 63.8 (6.8) | 64.0 (6.6) | 0.2239 | 64.0 (6.8) | 64.0 (6.5) | 63.4 (6.7) | 0.0223 |
| Sex |  |  | 0.5500 |  |  |  | 0.0213 |
| Female | 1744 (37.5) | 869 (36.8) |  | 858 (35.1) | 1058 (37.9) | 527 (39.4) |  |
| Male | 2906 (62.5) | 1494 (63.2) |  | 1585 (64.9) | 1737 (62.1) | 812 (60.6) |  |
| BMI, kg/m2 | 33.6 (6.2) | 32.3 (6.4) | <0.0001 | 32.3 (6.2) | 33.1 (6.1) | 34.7 (6.2) | <0.0001 |
| Race |  |  | <0.0001 |  |  |  | <0.0001 |
| White | 3895 (83.8) | 1859 (78.7) |  | 1922 (78.7) | 2349 (84.0) | 1124 (83.9) |  |
| Non-white | 755 (16.2) | 504 (21.3) |  | 521 (21.3) | 448 (16.0) | 215 (16.1) |  |
| ***Medical History*** | | | |  | | | |
| Duration of type 2 diabetes, years (Median, IQR) | 15.0 (10.0-21.0) | 13.0 (9.0-18.0) | <0.0001 | 13.0 (9.0-19.0) | 15.0 (10.0-20.0) | 16.0 (12.0-22.0) | <0.0001 |
| Established ASCVD disease | 2267 (48.8) | 925 (39.1) | <0.0001 | 1045 (42.8) | 1257 (45.0) | 681 (50.9) | <0.0001 |
| History of heart failure | 604 (13.0) | 198 (8.4) | <0.0001 | 257 (10.5) | 337 (12.1) | 158 (11.8) | 0.1954 |
| History of cerebrovascular disease | 420 (9.0) | 176 (7.4) | 0.0245 | 212 (8.7) | 239 (8.6) | 104 (7.8) | 0.6040 |
| History of hypertension | 4308 (92.6) | 2120 (89.7) | <0.0001 | 2203 (90.2) | 2574 (92.1) | 1256 (93.8) | 0.0004 |
| History of hyperlipidemia | 3965 (85.3) | 1969 (83.3) | 0.0331 | 1972 (80.7) | 2353 (84.2) | 1231 (91.9) | <0.0001 |
| ***Cardiovascular drugs used*** | | | |  | | | |
| Antiplatelet drugs | 3161 (68.0) | 1496 (63.3) | <0.0001 | 1543 (63.2) | 1838 (65.8) | 980 (73.2) | <0.0001 |
| Beta blockers | 2856 (61.4) | 1182 (50.0) | <0.0001 | 1320 (54.0) | 1664 (59.5) | 816 (60.9) | <0.0001 |
| ACE inhibitors or ARBs | 3983 (85.7) | 1995 (84.4) | 0.1701 | 2062 (84.4) | 2371 (84.8) | 1190 (88.9) | 0.0004 |
| Statins | 3728 (80.2) | 1811 (76.6) | 0.0006 | 1833 (75.0) | 2188 (78.3) | 1165 (87.0) | <0.0001 |
| Diuretics | 2351 (50.6) | 937 (39.7) | <0.0001 | 1014 (41.5) | 1340 (47.9) | 735 (54.9) | <0.0001 |
| Mineralocorticoid receptor antagonists | 311 (6.7) | 97 (4.1) | <0.0001 | 131 (5.4) | 157 (5.6) | 101 (7.5) | 0.0169 |
| ***Glucose-lowering drugs used*** | | | |  | | | |
| Number of agents used | 1.9 (0.7) | 2.5 (0.8) | <0.0001 | 2.3 (0.8) | 2.0 (0.7) | 1.9 (0.7) | <0.0001 |
| Metformin | 3105 (66.8) | 1977 (83.7) | <0.0001 | 1897 (77.7) | 1964 (70.3) | 927 (69.2) | <0.0001 |
| Sulfonylurea | 479 (10.3) | 1016 (43.0) | <0.0001 | 905 (37.0) | 360 (12.9) | 122 (9.1) | <0.0001 |
| DPP-4 Inhibitors | 329 (7.1) | 396 (16.8) | <0.0001 | 320 (13.1) | 245 (8.8) | 116 (8.7) | <0.0001 |
| GLP-1 receptor agonist | 165 (3.5) | 189 (8.0) | <0.0001 | 130 (5.3) | 117 (4.2) | 76 (5.7) | 0.0577 |
| ***Laboratory and Clinical measurements*** | | | |  | | | |
| HbA1c (%) | 8.6 (1.2) | 8.5 (1.2) | 0.3396 | 8.5 (1.2) | 8.6 (1.2) | 8.6 (1.2) | <0.0001 |
| eGFR (mL/min per 1.73 m2) \* | 82.3 (17.1) | 85.3 (16.2) | <0.0001 | 84.5 (16.5) | 83.1 (16.4) | 81.0 (17.8) | <0.0001 |
| Blood pressure (mmHg) |  |  |  |  |  |  |  |
| Systolic | 136.3 (16.0) | 134.8 (15.7) | <0.0001 | 136.1 (16.0) | 136.0 (16.0) | 135.6 (16.0) | 0.6725 |
| Diastolic | 77.0 (9.4) | 76.9 (9.2) | 0.5464 | 77.6 (9.2) | 77.3 (9.2) | 75.3 (9.5) | <0.0001 |
| Lipids (mg/dL) |  |  |  |  |  |  |  |
| Total cholesterol | 166.7 (43.9) | 165.8 (46.0) | 0.2545 | 167.5 (44.8) | 168.3 (45.1) | 160.4 (42.7) | <0.0001 |
| LDL cholesterol | 85.0 (34.9) | 85.4 (34.9) | 0.4445 | 87.0 (34.6) | 86.4 (35.6) | 78.6 (32.8) | <0.0001 |
| HDL cholesterol | 47.2 (13.8) | 46.2 (13.2) | 0.0313 | 48.1 (13.7) | 47.0 (13.7) | 44.0 (12.4) | <0.0001 |
| Triglycerides | 179.7 (144.0) | 176.2 (143.5) | 0.2414 | 166.1 (132.5) | 181.2 (147.9) | 198.0 (151.1) | <0.0001 |

Data are n (%) or mean (SD), unless otherwise specified. ASCVD = atherosclerotic cardiovascular disease; BMI=body mass index; eGFR=estimated glomerular filtration rate; ACE=angiotensin-converting enzyme; ARBs=angiotensin receptor blockers; DPP-4=Dipeptidyl-peptidase 4; GLP-1=glucagon-like peptide 1; HbA1c=hemoglobin A1c; eGFR=estimated glomerular filtration rate; \*eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration formula.

**FIGURE LEGENDS**

Figure 1: Cardiovascular and renal outcomes among insulin users by baseline insulin regimen (A) and dose (B). CVD/HHF – cardiovascular death / hospitalization for heart failure; MACE – major adverse cardiovascular events.

Figure 2A-D: Percentage of patients attaining glycemic target with dapagliflozin (blue) vs. placebo (red). HbA1c ≤7 by insulin regimen (A) or dose (B). HbA1c ≤8 by insulin regimen (C) or dose (D). SA -Short acting insulin. \* p<0.0001, † p<0.001, ‡ p<0.05.

Figure 3: Severe hypoglycemia (A) and Diabetic ketoacidosis (B) in overall insulin users, with dapagliflozin (blue) vs. placebo (red) according to insulin regimen and dose. Patient counts are shown within bars. Percentages are n/N.