Clinical Study Report Synopsis

Study code	D1690R00004
ClinicalTrials.gov Identifier:	NCT02695082
Date	09 November 2020

Comparison of the Risk of Acute Kidney Inury Between Patients With Type 2 Diabetes Exposed to Dapafliglozin and Those Exposed to Other Antidiabetic Treatments

POST-AUTHORISATION SAFETY STUDY INFORMATION

Title	Post-authorisation Observational Study: Comparison of the Risk of Acute Kidney Injury Between Patients With Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatments
Version identifier of the final study report	Version 1.0
Date of last version of study report	09 November 2020
European Union Post-Authorisation Studies Register number	Acute kidney injury: ENCEPP/SDPP/11684
Active substance	A10BX09 (dapagliflozin) A10BD15 (metformin and dapagliflozin) A10BD21 (saxagliptin and dapagliflozin)
Medicinal product	Dapagliflozin (Edistride, Forxiga [EU]; Farxiga [US]) Dapagliflozin + metformin (Ebymect, Xigduo) Dapagliflozin + saxagliptin (Qtern)
Product reference	Forxiga EU/1/12/795/001-010 Edistride: EU/1/15/1052/001-010 Xigduo: EU/1/13/900/001-012 Ebymect: EU/1/15/1051/001-012 Qtern: EU/1/16/1108/001-004
Procedure number	Forxiga: EMEA/H/C/002322 Edistride: EMEA/H/C/004161 Xigduo: EMEA/H/C/002672 Ebymect: EMEA/H/C/004162 Qtern: EMEA/H/C/004057
Marketing authorisation holder(s)	AstraZeneca AB

Is this a joint post-authorisation safety study (PASS)?	No
Research question and objectives	This study was a multinational cohort study to estimate the risk of acute kidney injury in patients with type 2 diabetes mellitus (T2DM) who are new users of dapagliflozin compared with those who are new users of antidiabetic drugs (ADs) other than SGLT2 (sodium-glucose cotransporter 2) inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy. The main study objective was to compare, by insulin use at the date of the index episode, the incidence of hospitalisation for acute kidney injury among patients with T2DM who are new users of dapagliflozin with those who are new users of ADs other than SGLT2 inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy.
Country/countries of study	United Kingdom (UK) United States of America (US)
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ABSTRACT

Title: Post-authorisation Observational Study: Comparison of the Risk of Acute Kidney Injury Between Patients With Type 2 Diabetes Exposed to Dapagliflozin and Those Exposed to Other Antidiabetic Treatments

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Date: 09 November 2020

Keywords: diabetes mellitus type 2, dapagliflozin, acute kidney injury

Rationale and background: Post-authorisation safety study (PASS) evaluating risk of acute kidney injury in real-world use of dapagliflozin.

Research question and objectives: The primary objective was to compare, by insulin use at the date of the index episode, the incidence of "hospitalisation for acute kidney injury" (hereafter, "AKI") among patients with type 2 diabetes mellitus (T2DM) who were new users of dapagliflozin compared with that of patients with T2DM who were new users of antidiabetic drugs (ADs) other than sodium-glucose cotransporter 2 (SGLT2) inhibitors, insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy. Additional analyses were also conducted on the overall exposure cohorts without stratification by insulin use at the date of the index episode.

Secondary objectives were to (1) compare baseline characteristics of both exposure groups and (2) examine potential risk factors for AKI if an increased risk was found with dapagliflozin new use compared with new use of other ADs.

Study design: Non-interventional cohort study using data from three longitudinal, population-based data sources. The study cohorts were defined by new use of an eligible study medication (ie, new use of dapagliflozin or comparator AD). The date of prescription or dispensing of this medication was considered the date of the index episode if all study eligibility criteria were met. The unit of analysis was the index episode. A single patient could have multiple index episodes if a different comparator AD was initiated on a different date, the eligibility criteria were met at the time of the new index episode, and the episodes did not overlap. Comparator AD index episodes were randomly matched—by calendar year of the index episode, age, sex, and geographic region—to each dapagliflozin index episode in the following ratios of comparator AD to dapagliflozin: up to 6 to 1 in the Clinical Practice Research Datalink (CPRD) and up to 15 to 1 in the HealthCore Integrated Research Database (HIRD®) and Medicare.

Propensity score trimming and stratification were used to adjust for multiple possible confounding variables. Descriptive analyses were conducted before and after propensity score trimming on the overall sample (with insulin use groups combined) and were stratified by

concomitant insulin use at the date of the index episode. Incidence and comparative analyses were conducted on the sample after propensity score trimming.

Crude and propensity score–adjusted incidence rates of AKI were calculated separately for dapagliflozin-exposed and comparator AD–exposed person-time for each insulin use group and for the overall sample not stratified by insulin use. Incidence rate ratios (IRRs) compared the incidence of AKI in dapagliflozin index episodes with that of comparator AD index episodes. Adjusted IRRs were calculated using Mantel-Haenszel methods from propensity score–stratified IRRs for each insulin use group and for the overall sample.

Due to very small numbers for the analyses stratified by insulin use at the index episode, particularly in the insulin use group in all data sources, and a lack of meaningful results in the stratified analyses, the text of this report focuses on the analyses performed overall without stratification by insulin use at the index episode.

Setting: The study used data from CPRD in the United Kingdom and the HIRD and Medicare in the United States of America. The study period began the day after regulatory approval of dapagliflozin in each country and ended at the last date of observation available at the time of data extraction in each data source.

Subjects and study size, including dropouts: After applying exclusion criteria, after matching and before propensity score trimming, the number of dapagliflozin index episodes in each data source in the overall cohort (with both insulin use groups combined) was as follows: CPRD, 12,051; the HIRD, 21,173; and Medicare, 18,079. After propensity score trimming, the number of dapagliflozin index episodes in each data source in the overall cohort was as follows: CPRD, 10,341; the HIRD, 18,777; and Medicare, 15,368. The number of person-years of dapagliflozin and comparator AD exposure, respectively, during the study period in the propensity score–trimmed cohorts was 12,389 and 30,737 in CPRD, 12,575 and 111,919 in the HIRD, and 9,208 and 141,313 in Medicare.

Variables and data sources: The occurrences of AKI were identified with electronic algorithms. Validation of provisional cases identified by the electronic algorithms was performed in the three data sources.

The primary exposure was newly initiated dapagliflozin. Comparator AD exposure was defined as new initiation of an eligible AD, which did not include SGLT2 inhibitors or monotherapy with insulin, metformin, or sulfonylurea.

Potential confounding variables assessed at baseline were medical conditions related to diabetes severity, other medical comorbidities, selected medications, lifestyle factors as available in each data source, and health care resource utilisation.

Results: Before propensity score trimming, there were some relevant differences in baseline characteristics at the index episode when comparing patients presenting with episodes of dapagliflozin to patients presenting with episodes of comparator AD. The following differences were observed in all data sources: patients on dapagliflozin had greater use of concomitant insulin; greater use of previous AD classes; fewer emergency department visits or hospitalisations; higher HbA1c (glycated haemoglobin) levels or higher number of HbA1c tests; and in CPRD, more frequent obesity and longer time since diagnosis of T2DM. After propensity score trimming and stratification, good balance was observed between exposure groups in the overall sample and in the two insulin use groups for most covariates for all data sources, as indicated by absolute standardised difference values less than 0.20.

After propensity score trimming, the mean age at baseline was as follows: CPRD—57 years, dapagliflozin; 59 years, comparator AD; the HIRD—52 years in both exposure groups; and Medicare—71 years in both exposure groups. The percentage of index episodes with concomitant insulin was as follows: CPRD—10.2%, dapagliflozin; 4.7%, comparator AD; the HIRD—13.1%, dapagliflozin; 10.4%, comparator AD; and Medicare—15.0%, dapagliflozin; 12.0%, comparator AD. The prevalence of diabetic nephropathy or renal insufficiency at baseline was 0.8% (dapagliflozin) and 0.7% (comparator AD) in CPRD and was 0.1% across both the dapagliflozin and comparator AD exposure groups in the HIRD and Medicare. The prevalence of retinopathy at baseline was as follows: CPRD—26.7%, dapagliflozin; 24.5%, comparator AD; the HIRD—23.3%, dapagliflozin; 21.0%, comparator AD; and Medicare—34.6%, dapagliflozin; 30.4%, comparator AD.

The estimated positive predictive value of the electronic algorithm to identify cases of AKI was 63.0% (95% confidence interval [CI], 48.7%-75.7%) in CPRD, 55.6% (95% CI, 45.8%-65.3%) in the HIRD, and 56.5% (95% CI, 46.6%-66.0%) in Medicare.

Overall and in both insulin use categories, the incidence rate of AKI was lower in dapagliflozin than in comparator AD index episodes in all data sources. The overall adjusted incidence rate per 1,000 person-years, not stratified by insulin use at the index episode, for dapagliflozin and comparator AD index episodes, respectively, was 1.05 (95% CI, 0.56-1.79) and 2.23 (95% CI, 1.46-3.17) in CPRD; 7.95 (95% CI, 6.47-9.67) and 10.48 (9.84-11.14) in the HIRD, and 20.63 (95% CI, 17.80-23.79) and 30.19 (95% CI, 29.13-31.27) in Medicare. The overall adjusted IRR estimates in CPRD (0.44; 95% CI, 0.22-0.86), the HIRD (0.76; 95% CI, 0.62-0.93), and Medicare (0.69; 95% CI, 0.59-0.79) were all below the null value. This finding was consistent in each insulin use group. The overall pooled estimate across all three data sources for the adjusted IRR for AKI was 0.70 (95% CI, 0.62-0.78). The pooled estimate was 0.68 (95% CI, 0.53-0.87) for the insulin use group and 0.69 (95% CI, 0.61-0.79) for the insulin non-use group. Sensitivity analyses were consistent with the primary analysis findings.

Discussion: The results of this final analysis did not find an increased risk of hospitalisation for acute kidney injury associated with dapagliflozin exposure compared with exposure to other ADs. Instead, the results support the conclusion of a decreased risk of hospitalisation for acute kidney injury associated with dapagliflozin exposure. All observed adjusted IRR estimates for hospitalisation for acute kidney injury comparing dapagliflozin with other ADs were below the null value in all data sources and were consistent, with or without stratification by insulin use at the index episode. Adjusted IRR estimates could be pooled across the three data sources, resulting in a precise pooled estimate. The observed results were robust to various sensitivity analyses and to evaluation of potential bias from a possible unmeasured confounder. The findings from this observational study align with results from randomised controlled trials of dapagliflozin and other SGLT2 inhibitors and with prior observational studies (Menne et al., 2019; Wiviott et al., 2018).

Marketing Authorization Holder(s): AstraZeneca AB

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