Characteristics of New Users of Dapagliflozin and Other Antidiabetic Drugs: United States and United Kingdom

Johannes C[1], Beachler DC[2], Ziemiecki R[3], Yin R[2], McGrath L[4], Jemison J[2], Lanes S[2], Gilsenan A[5]

[1]Pharmacoepidemiology and Risk Management, RTI Health Solutions, Waltham, Massachusetts, United States; [2]HealthCore, Wilmington, Delaware, United States; [3]Biostatistics, RTI Health Solutions, Research Triangle Park, North Carolina, United States; [4]NoviSci, LLC, Durham, North Carolina, United States; [5]Pharmacoepidemiology and Risk Management, RTI Health Solutions, Research Triangle Park, North Carolina, United States

CONFLICTS OF INTEREST

- C. Johannes, R. Ziemiecki, and A. Gilsenan are full-time employees of RTI Health Solutions (RTI-HS), an independent nonprofit research organization that does work for government agencies and pharmaceutical companies. L. McGrath was a full-time employee of RTI-HS at the time this work was performed. RTI-HS received funding from AstraZeneca to conduct this study. The contract provides the research team independent publication rights.
- D.C. Beachler, R. Yin, J. Jemison, and S. Lanes are employees of HealthCore. AstraZeneca provided funding for the conduct of the study.

BACKGROUND

Dapagliflozin is a selective and reversible inhibitor of human renal sodium-glucose cotransporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin was approved in the United Kingdom (UK) in 2012 and the United States (US) in 2014 to improve glycemic control in adults with type 2 diabetes mellitus. A multidatabase, multiyear, postauthorization safety study (PASS) was initiated in February 2016 to monitor the safety of dapagliflozin in routine clinical practice (EU PAS register 11684, 12110, 12113). The first interim analysis, presented here, includes an initial description of the study cohorts. The outcomes of interest in the PASS are hospitalization for acute kidney injury (AKI), hospitalization for acute liver injury (ALI), and hospitalization or emergency department visit for severe complications of urinary tract infection (UTI), in females and males, separately. The PASS will be 5 years in duration with two interim analyses and one final analysis planned by January 2019.

OBJECTIVES

- To evaluate utilization of dapagliflozin after regulatory approval in the UK and the US (e.g., strength, dose, concomitant use of insulin at index date, number of prescriptions).
- To compare, by insulin use at the index date, baseline characteristics of new users of dapagliflozin and other antidiabetic drugs (ADs) (not including other SGLT2 inhibitors or monotherapy with insulin, metformin or sulfonylurea) to provide context for future comparative risk analyses for each outcome cohort examined in the PASS.

METHODS

Data Sources

- Clinical Practice Research Datalink (CPRD), UK, electronic medical record data
- HealthCore Integrated Research Database® (HIRD), US, administrative claims data

Study Period of First Interim Analysis

- CPRD: 13 November 2012 through 31 March 2015
- HIRD: 9 January 2014 through 30 September 2015

Study Design

- Retrospective cohort study
- Study population: all eligible patient episodes of new use of dapagliflozin (with or without concomitant use of any other AD) and a matched sample of patient episodes of new intiation of an eligible comparator AD (with or without concomitant use of any other AD) during the study period
- New use: no use of the index treatment in all available history before the index date
- Ages ≥ 18 years in CPRD; 18-64 years in HIRD
- Continuous enrollment for ≥ 180 days before the index date (date of first prescription or dispensing of dapagliflozin or the selected eligible comparator AD)
- Exclusions:
  - General: type 1 diabetes, other SGLT2 use on or any time before index date
  - To create the three outcome-specific cohorts, the following exclusions were applied:
    - AKI: acute kidney injury, chronic kidney disease
    - UTI: chronic pyelonephritis
    - ALI: acute liver injury; chronic liver disease or disease involving the liver; chronic alcoholism; chronic or acute infectious hepatitis; acute and chronic cholelithiasis or cholecystitis; acute biliary obstruction; acute or chronic pancreatic disease; hepatic, biliary, or pancreatic cancer; congestive heart failure
- Index treatment episode:
  - Start date: date of first new use of dapagliflozin or eligible AD comparator in study period.
  - Duration: consecutive prescriptions/dispensings for the index exposure medication that are separated by no more than 30 days, plus 30 days added to the end of days' supply of the last prescription in the episode.
- A patient could have more than one index treatment episode if episodes were separated by more than 30 days.
- Up to four comparator index AD episodes matched to each dapagliflozin index episode by age, sex, index year, and geographic region.

Analysis

- Descriptive analyses were conducted in each database and each outcome cohort separately using a common protocol.
- Frequency distributions of variables of interest were examined. These variables will be assessed for propensity score models in future analyses.
- Results were stratified by concomitant insulin use at the index date.
- For the UTI cohort, results are conducted separately for males and females.

RESULTS

Table 1. Results of the Cohort Selection Process: Counts of New-Use Episodes for the First Interim Analysis in the CPRD and the HIRD for Each Outcome Cohort

	CPRD		HIRD	
Cohort to Assess	Dapagliflozin	Matched Comparator AD	Dapagliflozin	Matched Comparator AD
AKI	3,601	11,530	4,937	19,743
ALI	3,210	10,473	4,080	16,314
UTI female	1,641	5,419	1,608	6,432
UTI male	2,317	7,584	2,559	10,231

- Descriptive results presented are based on the AKI cohort because baseline results were similar among all three outcome cohorts.

Table 2. Baseline Characteristics of Dapagliflozin and Comparator AD Treatment Episodes for Each Data Source, AKI Cohort

	CPRD		HIRD	
Outcome	Dapagliflozin	Matched Comparator AD	Dapagliflozin	Matched Comparator AD
	N = 3,601	N = 11,530	N = 4,937	N = 19,743
Age, years				
Mean (SD)	57.0 (10.3)	57.6 (10.4)	51.4 (8.2)	51.6 (8.2)
Min, max	20, 88	20, 89	18, 64	18, 64
Sex, female, n (%)	1,480 (41.1%)	4,734 (41.1%)	2,227 (45.1%)	8,908 (45.1%)
Mean duration of enrollment before index date, years (SD)	12.0 (6.2)	11.7 (6.6)	4.7 (3.1)	4.0 (3.1)
Concomitant insulin use at index date, n (%)	641 (17.8%)	561 (4.9%)	896 (18.1%)	2,042 (10.3%)
4 or more outpatient visits in 180 days before index date, n (%)	2,462 (68.4%)	7,724 (67.0%)	3,906 (79.1%)	14,143 (71.6%)

SD = standard deviation.

- Concomitant insulin use at the index date was observed more frequently for dapagliflozin than comparator AD index episodes in the CPRD and HIRD.
- In the HIRD, frequent outpatient visits were more common in the 6 months before index episodes of dapagliflozin than comparator medications.

Table 3. Description of Index Use of Dapagliflozin by Data Source, AKI Cohort

	CPRD 2013-2015[a] (N = 3,601)	HIRD 2014-2015[b] (N = 4,937)
Calendar year of index date		
2013	694 (19.3%)	NA
2014	2,162 (60.0%)	2,474 (50.1%)
2015	745 (20.7%)	2,463 (49.9%)
Number of prescriptions over the entire study period for dapagliflozin initiators		
1-5	2,122 (58.9%)	2,759 (55.9%)
6-10	923 (25.6%)	1,423 (28.8%)
More than 10	556 (15.4%)	755 (15.3%)
Dose frequency at the index date		
Once a day	3,209 (89.1%)	4,937 (100%)
Twice a day	6 (0.1%)	—
Unknown	386 (10.7%)	—
Strength at the index date		
5 mg	807 (22.4%)	2,295 (46.5%)
10 mg	2,794 (77.6%)	2,642 (53.5%)
Number of months of continuous exposure to dapagliflozin for the index exposure episode		
Mean (SD)	6.3 (5.1)	5.7 (4.4)
Median (IQR)	4.7 (7.0)	4.5 (6.3)
Min, Max	0, 25.5	0, 20.3
Index medication type		
Monotherapy	27 (0.7%)	545 (11.0%)
Combined therapy	17 (0.5%)	238 (4.8%)
Add-on therapy[c]	2,587 (71.8%)	3,634 (73.6%)
Switched-to index therapy[d]	224 (6.2%)	504 (10.2%)
Not evaluable[e]	746 (20.7%)	8 (0.2%)
Person-years of dapagliflozin exposure	1,884	2,330

IQR = interquartile range; NA = not available.

[a] Contains prescriptions that were initiated beginning in November 2012 and were added to 2013 prescriptions. The study period in 2015 ended March 31.

[b] The study period in 2015 ended September 30.

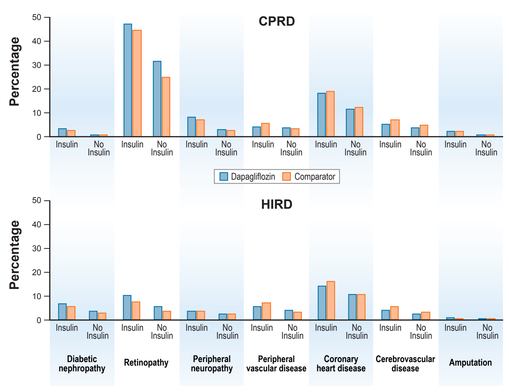
[c] Add-on therapy: Prescription or dispensing of an AD other than index therapy is recorded within the 90 days before and after the index date. This category also includes add-on and switched-to index therapy. (Index therapy meets definition of add-on therapy to some drug[s] and switched-to therapy for other drug[s].)

[d] Prescription or dispensing other than index AD medication is recorded within the 90 days before the index date, and there are no prescriptions/dispensings for that medication from the index date to 90 days after the index date.

[e] Patients in this category did not have sufficient follow-up time in the study to assess the 90-day add-on/switch requirement.

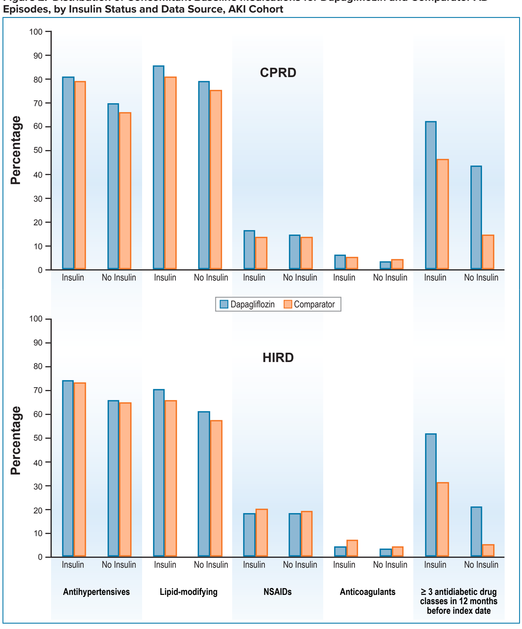
- Dapagliflozin was initiated most commonly as add-on therapy in the CPRD and the HIRD.
- The length of the index exposure episode was similar in both data sources.

Figure 1. Distribution of Baseline Indicators of Diabetes Severity for Dapagliflozin and Comparator AD Episodes, by Insulin Status and Data Source, AKI Cohort



- In general, in the CPRD and the HIRD, the prevalence of medical conditions that are considered indicators of diabetes severity was higher among index treatment episodes with concomitant insulin use at the index date.
- Retinopathy was more common among dapagliflozin episodes than comparator AD episodes and was more prevalent in the CPRD than in the HIRD.
- All other conditions were somewhat more frequent among episodes with concomitant insulin use but similar between dapagliflozin and comparator AD.

Figure 2. Distribution of Concomitant Baseline Medications for Dapagliflozin and Comparator AD Episodes, by Insulin Status and Data Source, AKI Cohort



NSAID = nonsteroidal anti-inflammatory drug.

- Antihypertensive medications and lipid-modifying agents were the two most frequent baseline medications in the CPRD and HIRD.
- Use of ≥ 3 antidiabetic drug classes in the year before the index date was more common with dapagliflozin than comparator AD episodes, and in episodes with concomitant insulin use.

Table 4. Baseline Characteristics in the CPRD by Insulin Use at Index Date, Acute Kidney Injury Cohort

	Insulin Use at the Index Date		No Insulin Use at the Index Date	
Variable	Dapagliflozin N = 641	Matched Comparator AD N = 561	Dapagliflozin N = 2,960	Matched Comparator AD N = 10,969
HbA1c (%), n (%)				
< 7.0	23 (3.6%)	22 (3.9%)	65 (2.2%)	419 (3.8%)
7.0 to 10.0	291 (45.4%)	282 (50.3%)	1,881 (63.5%)	7,011 (63.9%)
> 10.0	245 (38.2%)	172 (30.7%)	856 (28.9%)	2,718 (24.8%)
Unknown	82 (12.8%)	85 (15.2%)	158 (5.3%)	821 (7.5%)
Body mass index (kg/m²), n (%)				
< 20 (underweight)	1 (0.2%)	2 (0.4%)	11 (0.4%)	66 (0.6%)
20 to < 25 (normal)	9 (1.4%)	27 (4.8%)	100 (3.4%)	835 (7.6%)
25 to < 30 (overweight)	78 (12.2%)	97 (17.3%)	576 (19.5%)	2,831 (25.8%)
30 to < 40 (obese)	379 (59.1%)	309 (55.1%)	1,633 (55.2%)	5,489 (50.0%)
40+ (severely obese)	171 (26.7%)	123 (21.9%)	623 (21.0%)	1,656 (15.1%)
Unknown	3 (0.5%)	3 (0.5%)	17 (0.6%)	92 (0.8%)
Smoking history, n (%)				
Current	76 (11.9%)	103 (18.4%)	431 (14.6%)	2,000 (18.2%)
Former	322 (50.2%)	271 (48.3%)	1,419 (47.9%)	4,927 (44.9%)
Nonsmoker	243 (37.9%)	187 (33.3%)	1,109 (37.5%)	4,037 (36.8%)
Unknown	0	0	1 (< 0.1%)	5 (< 0.1%)
Mean duration of diabetes, years (SD)	12.9 (6.7)	12.3 (6.6)	8.1 (5.3)	6.4 (5.0)

Note that the variables in this table are not available in the HIRD.

- In the CPRD, where HbA1c levels, body mass index and smoking history are captured, highest levels of HbA1c, obesity, and longer duration of diabetes were more common in dapagliflozin than in comparator AD episodes, but current smoking was less common.

CONCLUSIONS

- Use of dapagliflozin in both data sources was consistent with the product labeling and diabetes treatment guidelines in each country with respect to dose frequency and the initiation of dapagliflozin as an add-on medication type.
- Within each data source, very few potential confounding variables were distributed differently between dapagliflozin and comparator AD initiators.
- Dapagliflozin was used less often as first-line therapy for type 2 diabetes than medications in the comparator AD group, as indicated by the higher proportion of three or more antidiabetic drug classes in the year before the index date among dapagliflozin episodes than in comparator AD episodes. These results may change in subsequent analyses as the time since approval of dapagliflozin increases.
- These interim results suggest that diabetes severity may be greater in patients starting dapagliflozin therapy than in patients starting comparator AD therapy.
- This analysis illustrates the importance of the planned stratification of results by insulin use at the index date and provides information for construction of propensity score models in future comparative analyses.

CONTACT INFORMATION

Catherine Johannes, PhD
Senior Director, Epidemiology

RTI Health Solutions
307 Waverley Oaks Road, Suite 101
Waltham, MA 02542-8413

Phone: +1.781.434.1784
E-mail: cjohannes@rti.org