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

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CONFLICT OF INTEREST

- L. Gutierrez, L. McQuay, 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.
- J. Overbeek, J. Kuiper, E. Houben, and R. Herings are employees of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government, health care authorities, and pharmaceutical companies. AstraZeneca provided funding for the conduct of the study.
- DC. 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 Europe in 2012 and in the United States (US) in 2014 to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). 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 12116). The PASS is a 10-year study with four interim analyses and one final analysis planned by January 2024. The first interim analysis, presented here, includes an initial description of the study cohorts. The primary outcomes of interest are in situ and invasive bladder cancer and female invasive breast cancer.

OBJECTIVES

- To evaluate utilization of dapagliflozin after regulatory approval in the US, the United Kingdom (UK), and the Netherlands (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 cancer outcome cohort examined in the PASS.

METHODS

Data Sources

- Clinical Practice Research Datalink (CPRD), UK, electronic medical record data
- PHARMO Database Network (PHARMO), the Netherlands, linked database network of 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
- PHARMO: 1 November 2013 through 31 December 2014
- HIRD: 9 January 2014 through 30 September 2015

Study Design

- Retrospective cohort study.
- Study population: all eligible patients newly initiating dapagliflozin (with or without concomitant use of other eligible AD) and a matched sample of patients newly initiating eligible comparator AD (with or without concomitant use of other eligible AD) during the study period.
- New use: no use of the index treatment in all available history before the index date (minimum 180 days).
- Age ≥ 40 years in CPRD and PHARMO; age 40-64 years in the HIRD.
- Continuous enrollment for ≥ 180 days before the index date (date of first prescription or dispensing of dapagliflozin or the selected eligible comparator AD).
- General exclusions: type 1 diabetes, other SGLT2 use on or before index date, prior diagnosis of any invasive cancer (other than nonmelanoma skin cancer) on or before the index date.
- Exclusions specific to the primary outcomes if recorded within 180 days before and including the index date:
  - Breast cancer cohort: breast biopsy
  - Bladder cancer cohort: hematuria, cystoscopy, and/or urine cytology
- Up to four comparator index dates of new AD use matched to each dapagliflozin index date by age, sex, index year, and geographic region.
- The main outcome cohorts consisted of a female breast cancer cohort and a bladder cancer cohort (females and males).

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 modeling in future analyses.
- Results were stratified by concomitant insulin use at the index date.
- For the bladder cohort, analyses are conducted for males and females combined and separately.

RESULTS

Table 1. Results of the Cohort Selection Process: Counts of Selected New Users by Outcome Cohort in CPRD, PHARMO, and HIRD, 2016 Interim Analyses

	CPRD		PHARMO		HIRD	
Cohorts	Dapagliflozin	Matched Comparator AD	Dapagliflozin	Matched Comparator AD	Dapagliflozin	Matched Comparator AD
Overall cancer cohort (before exclusions applied)	2,711	9,906	402	1,545	4,335	17,352
Female breast cancer cohort	1,117	4,116	181	677	1,823	7,282
Bladder cancer cohort (females and males)	2,693	9,825	402	1,545	3,904	15,632

- Descriptive results are presented for the overall cohort of all patients, before cancer exclusions were applied, because baseline results were similar among all cancer outcome cohorts.

Table 2. Baseline Characteristics of Dapagliflozin and Comparator AD Initiators for Each Data Source

	CPRD		PHARMO		HIRD	
Outcome	Dapagliflozin N = 2,711	Matched Comparator AD N = 9,906	Dapagliflozin N = 402	Matched Comparator AD N = 1,545	Dapagliflozin N = 4,335	Matched Comparator AD N = 17,352
Age, years						
Mean (SD)	58.2 (9.2)	58.5 (9.4)	61.0 (9.4)	62.3 (9.6)	53.2 (6.3)	53.3 (6.4)
Min, max	40, 91	40, 96	40, 85	40, 89	40, 64	40, 64
Sex, female, n (%)	1,117 (41.2%)	4,116 (41.6%)	181 (45.0%)	680 (44.0%)	1,886 (43.5%)	7,536 (43.4%)
Mean length of lookback time before index date, years (SD)	12.1 (6.1)	11.7 (6.6)	12.1 (4.1)	11.0 (4.5)	4.9 (3.1)	4.2 (3.1)
Concomitant insulin use at index date, n (%)	532 (19.6%)	635 (6.4%)	29 (7.2%)	341 (22.1%)	824 (19.0%)	1,889 (10.9%)
Mean duration since first recorded diagnosis of T2DM, years (SD)	9.3 (5.7)	7.1 (5.4)	6.3 (4.4)	4.7 (4.1)	3.9 (2.8)	3.1 (2.6)
≥ 3 AD classes used within 12 months before index date, n (%)	1,327 (49.0%)	1,545 (15.6%)	88 (21.9%)	116 (7.5%)	1,177 (27.2%)	1,393 (8.0%)

SD = standard deviation.

- Concomitant insulin use at the index date was observed more frequently for dapagliflozin than comparator AD initiators in the CPRD and HIRD but not in PHARMO, where it was more frequently observed in comparator AD initiators.
- On average, dapagliflozin initiators had a longer time since first recorded diagnosis of T2DM at the index date than AD comparator patients.
- Use of ≥ 3 antidiabetic drug classes in the year before the index date was more common in dapagliflozin than comparator AD initiators. This did not change by insulin use (data not shown).

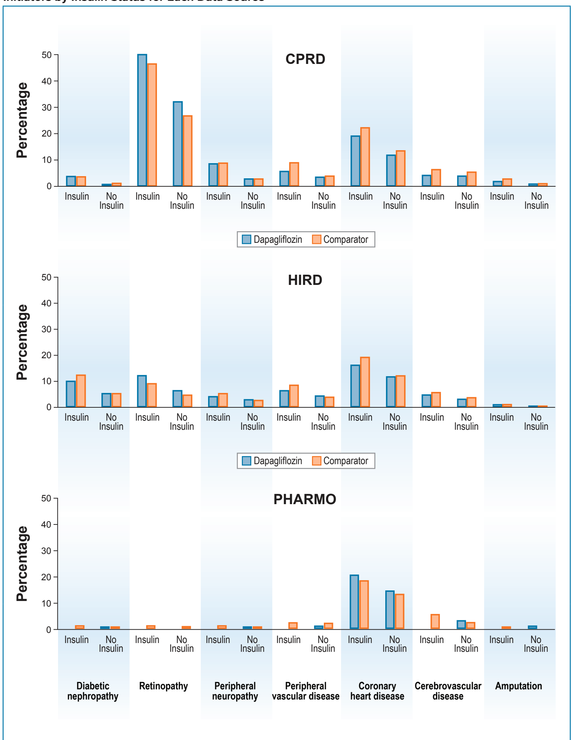
Table 3. Description of Index Use of Dapagliflozin by Data Source

	CPRD 2013-2014[a] (N = 2,711)	PHARMO 2013-2014[a] (N = 402)	HIRD 2014-2015[a] (N = 4,335)
Number of prescriptions over the entire study period for dapagliflozin initiators[b]			
1-5	1,127 (41.6%)	311 (77.4%)	2,396 (55.3%)
6-10[b]	964 (35.6%)	80 (19.9%)	1,261 (29.1%)
More than 10[b]	620 (22.9%)	11 (2.7%)	678 (15.6%)
Strength at index prescription			
5 mg	614 (22.6%)	61 (15.2%)	1,989 (45.9%)
10 mg	2,096 (77.3%)	341 (84.8%)	2,346 (54.1%)
Number of months exposed to dapagliflozin during the analysis period			
Mean (SD)	7.5 (5.1)	5.2 (4.3)	7.9 (5.2)
Min, Max	0.1, 25.4	0, 14.0	< 0.1, 20.3
Index medication type			
Monotherapy	32 (1.2%)	22 (5.5%)	461 (10.6%)
Combined therapy	20 (0.7%)	7 (1.7%)	191 (4.4%)
Add-on therapy	1,497 (55.2%)	167 (41.5%)	3,176 (73.3%)
Switched-to therapy	95 (3.5%)	91 (22.6%)	437 (10.1%)
Add-on plus switched-to therapy	1,067 (39.4%)	NA	63 (1.5%)
Monotherapy plus switch[c]	NA	17 (4.2)	NA
Combined plus switched-to therapy[c]	NA	2 (< 0.5%)	NA
Unknown[c]	NA	96 (23.9%)	NA
Person-years of dapagliflozin exposure	1,681	241	2,511[d]

NA = not applicable.
[a] The first prescription occurred in the CPRD on 1 February 2013, in PHARMO on 1 November 2013, and in the HIRD on 28 January 2014. The latest date of available data was 31 March 2015 in the CPRD, 31 December 2014 in PHARMO, and 30 September 2015 in the HIRD.
[b] In PHARMO, the number of prescriptions were categorized as 6-9 and > 9.
[c] PHARMO defined index prescription based on treatment episodes of uninterrupted use resulting in additional index exposure categories and an unknown category.
[d] The number represents dapagliflozin exposure for the bladder cancer cohort.

- Dapagliflozin was initiated most commonly as add-on therapy at 10 mg daily in all three data sources.

Figure 1. Distribution of Baseline Indicators of Diabetes Severity for Dapagliflozin and Comparator AD Initiators by Insulin Status for Each Data Source



- In the CPRD, diabetic retinopathy was the most frequent comorbidity and was more common among dapagliflozin initiators than comparator AD initiators at index date. Retinopathy was also more prevalent in patients with concomitant insulin use at the index date in the CPRD and HIRD.
- In PHARMO and the HIRD, coronary heart disease was the most frequent comorbidity and was more common among patients with concomitant insulin use. The prevalence was similar for dapagliflozin and comparator AD initiators.
- In PHARMO, comorbidity was assessed based on hospital discharge diagnoses, which resulted in overall low prevalences for other diabetes severity indicators. In future analyses, these will be supplemented with diagnoses from general practitioner data.
- In all three data sources, indicators of diabetes severity were generally more frequent among insulin users than noninsulin users.

CONCLUSIONS

- Use of dapagliflozin in all three data sources was consistent with the product labeling in each country with respect to daily dose and initiation of dapagliflozin as an add-on medication type.
- Use of three or more AD classes in the year before the index date was notably more common in dapagliflozin than in comparator AD initiators. This indicates that during the study period, dapagliflozin was less commonly used as a first-line therapy compared with the comparator AD group.
- In general, the indicators of diabetes severity were more common in patients with concomitant insulin use.
- There was evidence that dapagliflozin initiators may have more severe, longstanding diabetes than comparator AD initiators. All other comorbidities were similar between the exposure groups.
- This first interim analysis highlights 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 analysis to adjust for observed differences between the two exposure cohorts.

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