Ofori-Asenso Richard (Orcid ID: 0000-0002-6643-3269)

Manuscript ID: DMRR-19-RES-574

Poor adherence and persistence to sodium glucose co-transporter 2 inhibitors in real world settings: evidence from a systematic review and meta-analysis

Running title: Real world use of SGLT2 inhibitors

Richard Ofori-Asenso, PhD;1,2* Berhe W. Sahle, PhD;3+ Ken Lee Chin, PhD;2,4+ Mohsen Mazidi, PhD5; Zanfina Ademi, PhD;2 Marie Louise De Bruin, PhD;1 Danny Liew, PhD2

†These authors contributed equally

1Copenhagen Centre for Regulatory Science (CORS), Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, Denmark
2Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
3Melbourne School of Population and Global Health, University of Melbourne, Parkville, Victoria, Australia
4Melbourne Medical School, University of Melbourne, Parkville, Victoria, Australia
5Department of Twin Research and Genetic Epidemiology, Kings College London, United Kingdom

*Address correspondence to:
Richard Ofori-Asenso, PhD
Department of Pharmacy
Faculty of Health and Medical Sciences,
University of Copenhagen, Universitetsparken 2
Copenhagen, Denmark
Email: richard.ofori-asenso@sund.ku.dk
Tel: +4535332395

Abstract word count: 250
Word count (main text): 3075

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/dmrr.3350

This article is protected by copyright. All rights reserved.
DECLARATIONS

Acknowledgments
None

Conflict of Interest Statement
DL reports past participation in advisory boards and/or receiving honoraria from Abbvie, Astellas, AstraZeneca, Bristol-Myers Squibb, Novartis, Pfizer, Sanofi, and Shire for work unrelated to this study. RO and MLDB are employees of The Copenhagen Centre for Regulatory Sciences (CORS). CORS is a cross-faculty university anchored institution involving various public (Danish Medicines Agency, Copenhagen University) and private stakeholders (Novo Nordisk, Lundbeck, Ferring pharmaceuticals, LEO pharma) as well as patient organisations (Rare Diseases Denmark). The center is purely devoted to the scientific aspects of the regulatory field and with a patient-oriented focus and the research is not company-specific product or directly company related and has received funding from Novo Nordisk, Ferring Pharmaceuticals, LEO pharma and Lundbeck for projects not related to this study. All others declare no relevant conflicts of interest.

Authors’ Contribution Statement
RO conceived and designed the study. RO, BSW, and KLC performed data extraction and analysis. RO, BSW, KLC, MM, ZA, MLDB, and DL contributed to manuscript preparation and revision for intellectual content. All authors approved the final version before submission.

Funding
No funding or sponsorship was received for this study or publication of this article.
ABSTRACT

Aims: Despite increasing prescription of sodium glucose co-transporter 2 (SGLT2) inhibitors, there is limited insight of the patterns of use among patients with diabetes prescribed these drugs. This study aimed to summarize available real-world data on the adherence and persistence to SGLT2 inhibitors.

Materials and Methods: A systematic review for observational studies reporting the adherence and persistence to SGLT2 inhibitors was performed in Medline, Embase, and Web of Science from their inception to October 2019. Data were analyzed via random-effects meta-analysis.

Results: A total of 22 studies (31 cohorts) comprising of 123,854 individuals prescribed SGLT2 inhibitors from eight countries were included. The pooled mean proportions of days covered [PDC] at six months and one year were 0.77 (95% confidence interval [CI] 0.72-0.82) and 0.72 (95% CI 0.66-0.77), respectively. The pooled proportions adherent (PDC ≥0.80) at six months and one year were 59.5% (95% CI 52.9-65.9) and 49.0% (95% CI 42.3-55.8), respectively. The pooled proportions of people persistent at six months, one year, and two years were 80.1% (95% CI 75.8-84.0), 61.8% (95% CI 57.8-65.7), and 45.9% (95% CI 35.5-56.5), respectively. When persistence was defined as absence of ≥90-days gap, the equivalent pooled proportions persistent were 81.5% (95% CI 73.1-88.6), 58.9% (95% CI 53.1-64.6), and 34.7% (95% CI 33.6-35.8). Data from the United States suggested higher adherence and persistence with canagliflozin compared to dapagliflozin.
Conclusion: Real world adherence and persistence to SGLT2 inhibitors is poor. Hence, targets for improving treatment adherence and persistence need to be identified and appropriate interventions implemented.

Keywords: sodium glucose cotransporter 2 inhibitors; SGLT2; adherence, persistence, discontinuation

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major public health issue which is estimated to affect more than 400 million people worldwide (1). Chronic hyperglycemia is a key characteristic of T2DM and is associated with increased risk of micro- and macrovascular complications (2, 3).

Effective blood glucose control is central to the management of T2DM. The American Diabetes Association/European Association for the Study of Diabetes (4) and the American Association of Clinical Endocrinologists (AACE) (5) recommend glycated hemoglobin (HbA1c) levels of <7.0% and ≤6.5%, respectively, while also emphasizing the need to individualize treatment goals. Although dietary and lifestyle changes are recommended for patients with T2DM, the majority require pharmacological treatment to achieve the desired glycemic targets (4, 6).
Despite the availability of several antihyperglycemic agents (6, 7), about half of the patients with T2DM do not achieve glycemic targets (8, 9). Thus, there is increasing interest in novel therapeutic options to improve glycemic control in patients with T2DM. Recently, sodium glucose cotransporter 2 (SGLT2) inhibitors have been touted as a ‘game changer’ for the management of T2DM (10). Randomized clinical trials (RCTs) have shown SGLT2 inhibitors to significantly improve glycemic control as well as exert additional pleotropic effects such as reduction in blood pressure and weight in patients with T2DM (11-15). Consequently, increased prescription of SGLT2 inhibitors has been reported in many countries (16-19). However, patients enrolled in RCTs are often highly motivated and usually exhibit higher adherence (i.e., the extent to which patients act in accordance with the prescribed interval, and dose of a dosing regimen (20)) and persistence (i.e., the duration of time from initiation to discontinuation of therapy (20)) to treatment than that observed in routine clinical practice (21, 22). These disparities potentially contribute to poor drug effectiveness observed in real-world settings (22-24).

At present, there is limited insight of the patterns of use of SGLT2 inhibitors among T2DM patients. In particular, McGovern et al recently reported a systematic review of the adherence and persistence to different classes of antidiabetic medications (25). However, data on SGLT2 inhibitors were conspicuously missing. Thus, we conducted a systematic review and meta-analysis to summarize the class-level adherence and persistence to SGLT2 inhibitors and to determine if any differences exist across various SGLT2 inhibitors in real-world settings.
METHODS

The study was performed according to the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (26), the Meta-analysis of Observational Studies in Epidemiology (27) and the Cochrane Collaboration Handbook (28).

Search strategy and study selection

Electronic searches were performed in Medline, Embase, and Web of Science for observational studies published in English that reported the adherence and persistence to SGLT2 inhibitors. The keywords used included “sodium glucose co-transporter 2 inhibitors OR SGLT2 inhibitors OR individual generic and propriety names” AND “adherence OR persistence OR compliance OR discontinuation” (Supplemental Table S1). The search was initially performed on 1 August 2019 and last updated on 24 October 2019. Bibliographic searches of the included studies were also performed. All original research articles reporting on adherence and/or persistence among people dispensed SGLT2 inhibitors were eligible for inclusion. Although the definition of persistence is often variable in the literature (20), similar to other reviews (28), we did not restrict our inclusion to any specific definition. Moreover, studies utilizing any of a variety of methods including pill count, prescription refill records or patient’s self-reports/recalls assessed via validated scales to measure adherence were eligible for inclusion. Two reviewers (RO and BSW) independently performed the searches and reviewed the titles and abstracts of all the articles identified. Any disagreements were resolved with a third reviewer (KLC).

Data extraction and quality assessment
Data were extracted independently by two reviewers (KLC and BWS). For each study, we collected the author details, year, country, participant characteristics, data sources, definition of adherence and persistence, as well as outcome data. If studies assessed adherence using multiple measures, the proportion of days covered (PDC) was preferred as the more robust metric (30). For some studies, persistence at different time points was extracted from Kaplan Meier curves using an online graph digitizer (31). Similar to other drug utilization reviews (25), study quality was assessed using the Newcastle-Ottawa scale for observational studies (NOS) (32). Quality assessments were performed independently by two reviewers (BSW and KLC) and any disagreements were resolved with a third reviewer (RO).

**Data Analysis**

Where data were available, we estimated the adherence and persistence to SGLT2 inhibitors at specific time points. Overall adherence and persistence estimates were obtained through meta-analysis using the Freeman-Tukey double arcsine transformed proportions to stabilize the variance. We also pooled data on the mean PDC at six months and one year of SGLT2 inhibitors use. For this, the standard error (SE) was calculated as: SE=standard deviation (SD)/\(\sqrt{\text{sample size}}\). We pooled persistence data across all studies regardless of definition used. However, we also performed a subgroup analysis by pooling data across studies that defined non-persistence as having a gap of ≥90 days, as this has been a commonly used metric (20,33,34). Furthermore, if data existed from at least two studies that compared adherence or persistence to individual SGLT2 inhibitors, data were pooled with the effect measure expressed as odds ratio (OR). All meta-analyses were performed using the random-effects model due to the anticipated between-study heterogeneity (34). Statistical heterogeneity was quantified with Cochran’s Q test and the
Publication bias was assessed by funnel plot visualization and statistically evaluated with Egger’s test in the event that 10 or more effect sizes were available (28). The robustness of pooled estimates was tested via leave-one-out sensitivity analyses where more than two data points were available (28). A study was considered to be dominant if the pooled effect without it was outside the 95% confidence interval of the overall pooled estimate. Analyses were performed using Stata 16/SE (StataCorp, Texas, USA) and a $p$-value $<0.05$ was considered statistically significant.

RESULTS

A total of 1385 articles were retrieved from the database searches, of which 53 were subjected to full-text assessment after removal of duplicates and titles and abstract screening. Subsequently, 20 articles were selected for inclusion. Two additional articles were retrieved via reference screening, resulting in 22 studies (involving 31 cohorts) being included in the review (Figure 1) (36-57). The descriptive characteristics of the studies are presented in Table 1. The included studies, which comprised 123,854 individuals prescribed SGLT2 inhibitors, were published from 2015 to 2019 and were from eight different countries: Australia ($n=1$), Taiwan ($n=1$), Canada ($n=1$), UK ($n=2$), Hungary ($n=1$), Pakistan ($n=1$), Italy ($n=2$) and USA ($n=13$). The median sample size across the included studies was 1981 (interquartile range [IQR] 706-8609). The included studies were of reasonable quality with the median NOS score being 8 (IQR 7-8) (supplemental Table S2).

Adherence to SGLT2 inhibitors
Adherence to SGLT2 inhibitors was reported in 12 studies. Of these, only one did not assess the PDC. In the study which did not assess PDC, participants were followed for only two months and 76.9% were reported to be adherent (48). Among five studies (eight cohorts) involving 38,684 individuals, the mean PDC at six months ranged from 0.65 to 0.86. The pooled six-month mean PDC among people prescribed SGLT2 inhibitors was 0.77 (95% CI 0.72-0.82; $I^2=99.6\%$) (Supplemental Figure S1). Four studies (seven cohorts) involving 34,667 individuals reported that 41.0-76.3% of people were adherent (PDC ≥0.80) to SGLT2 inhibitors at six months. The pooled proportion adherent at six months was 59.5% (95% CI 52.9-65.9; $I^2=99.2\%$) (Supplemental Figure S2). Across five studies (10 cohorts) involving 28,939 individuals, the reported mean PDC at one year was within the range 0.58-0.81. The pooled mean PDC at one year was 0.72 (95% CI 0.66-0.77; $I^2=99.2\%$) (Supplemental Figure S3). In five studies (10 cohorts), 29.9-69.4% of people were reported to be adherent (PDC≥0.80) at one year. The pooled proportion of people adherent to SGLT2 inhibitors at one year was 49.0% (95% CI 42.3-55.8) (Supplemental Figure S4).

Persistence to SGLT2 inhibitors

A total of 16 studies reported data on non-persistence with SGLT2 inhibitors. However, the definition of non-persistence varied across studies. Three studies defined non-persistence as a gap of ≥60 days (34, 36, 41), one study used a gap of ≥180 days (49), seven studies defined non-persistence as a gap of ≥90 days (39, 40, 43, 51-53, 55) and five used other definitions (44-46, 50, 54). Nine studies (10 cohorts) involving 80,894 individuals reported that 72.5-95.7% were persistent to SGLT2 inhibitors at six months. The pooled proportion persistent to SGLT2 inhibitors at six months across these studies was 80.1% (95% CI 75.8-84.0; $I^2=99.4\%$) (Supplemental Figure S5). In three studies (four cohorts) involving 19,163 individuals which defined non-persistence as a gap of ≥90 days, the pooled proportion persistent at six
months was 81.5% (95% CI 73.1-88.6; $I^2=99.5$%). Ten studies (16 cohorts) involving 79,181 individuals reported that 40.0-82.1% were persistent at one year. The pooled proportion persistent to SGLT2 inhibitors at one year across these studies was 61.8% (95% CI 57.8-65.7; $I^2=99.2$%) (Supplemental Figure S6). In six studies (11 cohorts) involving 33,729 individuals which defined non-persistence as a gap of ≥90 days, the pooled proportion persistent at one year was 58.9% (95% CI 53.1-64.6; $I^2=99.1$%).

Four studies (five cohorts) involving 51,510 individuals reported that 29.1-56.8% were persistent to SGLT2 inhibitors at two years. The pooled proportion persistent at two years across these studies was 45.9% (95% CI 35.5-56.5; $I^2=99.8$%) (Supplemental Figure S7). In two studies (two cohorts) involving 7182 individuals which defined non-persistence as a gap of ≥90 days, the pooled proportion persistent at two years was 34.7% (95% CI 33.6-35.8; $I^2=0.0$%).

Comparisons of different SGLT2 inhibitors

Only one study conducted among Australians compared adherence and persistence between people prescribed empagliflozin and dapagliflozin (52). In this study, empagliflozin was associated with a greater likelihood of being adherent (PDC ≥0.80) (adjusted OR 1.39, 95% CI 1.29-1.51) or persistent (no gap of ≥90-days) (adjusted hazard ratio [HR] 1.14, 95% CI 1.06–1.22) compared to dapagliflozin. Three US-based studies involving a total of 14,932 individuals compared adherence between canagliflozin and dapagliflozin (35, 39, 40). Pooled data from these studies suggested that canagliflozin was associated with higher likelihood of being adherent (PDC ≥0.80) (OR 2.00, 95% CI 1.68–2.40; $I^2=78.0$%) compared to dapagliflozin (Supplemental Table S12). Moreover, in two US studies involving 13,816 individuals, pooled data suggested higher persistence (no-gap of ≥90 days) with canagliflozin compared to dapagliflozin (OR 1.94, 95% CI 1.24-3.04; $I^2=96.8$%). One study found no significant difference in
adherence between canagliflozin 100mg and 300mg (one-year adherence [PDC ≥0.80] rate; canagliflozin 100mg = 49.0%, canagliflozin 300mg, 51.5%; p-value for difference = 0.065) (39).

Similarly, pooled data from two studies involving 14,856 individuals showed that canagliflozin 100mg was not associated with higher persistence (no-gap of ≥90 days) compared to canagliflozin 300mg (OR 0.94, 95% CI 0.88-1.01; I² = 0.0%).

**Sensitivity analyses and assessment of publications bias**

In all the estimates involving three or more effect sizes, a leave-one-out sensitivity analysis did not significantly change the pooled results. We also visually inspected funnel plot asymmetry and quantified with Egger’s test to detect publication bias for pooled estimates based on 10 or more effect sizes. For all of these analyses, Egger’s tests were not statistically significant (proportion adherent at one year, p = 0.120; proportion persistent at six months [all definitions], p = 0.216; proportion persistent at one year [all definitions], p = 0.184; proportion persistent at one year [≥90-days gap], p = 0.09). These results suggested no evidence of publication bias.

**DISCUSSION**

In this systematic review and meta-analysis, we summarized the available real-world data on the adherence and persistence to SGLT2 inhibitors. We found that about 60% and <50% of the patients prescribed SGLT2 inhibitors were adherent at six months and one year, respectively. Moreover, 80%, 62%, and 46% of SGLT2 inhibitors users were persistent at six months, one year, and two years, respectively. Adherence and persistence rates varied across different SGLT2 inhibitors.
The insulin-independent effect of SGLT2 inhibitors is associated with a low risk of hypoglycemia, which makes them attractive for the management of patients with T2DM (58, 59). Data from several RCTs have shown SGLT2 inhibitors to improve glycemic control among patients with T2DM (58, 60, 61).

Furthermore, SGLT2 inhibitors have also been shown to significantly reduce the risk of cardiovascular disease (CVD) and mortality. In the Canagliflozin cardiovascular assessment study (CANVAS), canagliflozin was associated with a 14% risk reduction (HR 0.86, 95% CI 0.75-0.97) in the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke compared to placebo over a median duration of 2.4 years (62). Similarly, the results of the EMPA-REG Outcome trial suggested that empagliflozin led to a 12–15% increase in life expectancy regardless of age, representing a prolongation of life span by, on average, 2.5 years (13). Furthermore, the DECLARE-TIMI 58 showed that dapagliflozin reduced hospitalization for heart failure and appeared to slow the loss of kidney function (63). Similar renal benefits of SGLT2 inhibitors have also been demonstrated in the CREDENCE (Evaluation of the effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy) and EMPAG-REG Renal studies (64, 65). These positive outcomes associated with SGLT2 inhibitors in RCTs have resulted in their increased use in many countries (17, 18). For example, in Australia, the number of patients dispensed SGLT2 inhibitors increased about eight-fold between June 2014 and June 2016 (19). In the United States, the uptake of SGLT2 inhibitors increased more than five-fold (from 0.8% to 4.4%) between 2014 and 2015 (16).

The RCT-demonstrated benefits of SGLT2 inhibitors have been observed against a background of high treatment adherence and persistence. In trials of SGLT2 inhibitors, about 70-80% of patients were persistent with treatment for more than two years of follow-up (13, 62, 63). However, our meta-analysis
based on data from real world settings suggests significantly lower persistence, with <50% of patients being persistent with treatment at two years. The lower persistence in real world settings could contribute to poor drug effectiveness and hamper the realization of the effects of SGLT2 inhibitors demonstrated within trial settings. For example, a US study involving adult commercial and Medicare Advantage health plan enrollees found that those adherent to SGLT2 inhibitors experienced larger reductions in glycated hemoglobin (HbA1c) than non-adherent individuals (1.17% versus 0.73%, \( p < 0.001 \)) (38). Moreover, non-adherent individuals increased insulin use by 5.4% in the follow-up period whereas there was no change in insulin use among people adherent to SGLT2 inhibitors.

To optimize the clinical use of SGLT2 inhibitors, Vardeny and Vaduganathan recently published a practical guide for clinicians in which they emphasized key areas including pre-initiation safety screening, selecting an appropriate drug and starting dose, patient counselling, tracking of adherence, and monitoring for adverse effects (66). For adverse effects of SGLT2 inhibitors, the most common one appears to be genital infections, the risk of which was increased up to four-fold in RCTs (67). Recently, Gutiérrez Lorenzo et al reported that of the patients who discontinued SGLT2 inhibitors in their Italian cohort, 57% were due to genital and urinary tract infections, whereas 30% were due to other medication-related adverse events (47). Thus, educating patients on measures to minimize these risks could improve adherence and treatment persistence. For example, to reduce the risk of genital infections, counseling about maintenance of perineal hygiene should be included in all diabetes education sessions (68).

Moreover, because SGLT2 inhibitors create an osmosis diuresis, they may cause intravascular volume depletion and hypotension (59). Thus, patients need to be advised to maintain adequate fluid and
electrolyte intake while at the same time clinicians should be cautious when co-prescribing SGLT2 inhibitors with loop diuretics (66, 68).

Overall, the results of our meta-analysis concur with previous studies which have shown poor adherence and persistence to different T2DM medications in real world settings (25, 67, 70). Thus, greater efforts to identify the determinants and modifiable drivers of poor adherence and persistence are important. Different interventions including real-time medication monitoring combined with short message service (SMS) (71), those aimed at reducing regimen complexity (72, 73), as well as interventions seeking to improve patient knowledge (e.g., through pharmacist-led integrated management and education programmes) (74) or those providing extended supervisory health services (75) have shown positive effects on treatment adherence and persistence. However, available evidence suggests that multi-factorial interventions that are tailored to patient-specific needs are more likely to provide greater improvements in adherence and persistence compared to unifactorial interventions (72, 76, 77). Our meta-analysis showed a temporal continuous decline in adherence and persistence to SGLT2 inhibitors from six months to two years. Thus, adherence monitoring may need to be implemented as soon as patients commence treatment and should also be an ongoing process and incorporated into patients’ routine management plans.

Our systematic review and meta-analysis has limitations that warrant mention. In particular, most studies relied on indirect measures of adherence and it was impossible to ascertain whether the patients prescribed SGLT2 inhibitors actually took the medication. Studies also did not report detailed information as to why patients were non-adherent or non-persistent to SGLT2 inhibitors. For example, adverse events or poor drug effectiveness may contribute to patient- or clinician-initiated treatment discontinuations (78).
More than half of the included studies were also from the United States. While this reflects market entry of SGLT2 inhibitors, the generalizability of our findings could be limited and further studies evaluating the adherence and persistence to SGLT2 inhibitors in other regions are needed. Furthermore, the heterogeneity across the included studies was high, although, potential sources of heterogeneity could not be fully explored through statistical approaches such as meta-regression due to the small number of studies included in individual analysis (28). Also, it is possible that the timing of the publication of the results of the cardiovascular outcome trials of the different SGLT2 inhibitors could potentially influence adherence and persistence patterns, although, the extent of the influence if present could not be quantified. Furthermore, while in some instances patients who may be persistent may not be necessarily adherent (20), we were unable to thoroughly investigate this pattern due to limited data. Lastly, further bias may have arisen from our limitation of component studies to English, although the extent of this bias, if present, would likely have been small. Despite the above limitations, the available real-world data generally suggest sub-optimal adherence and persistence to SGLT2 inhibitors which warrant attention. Large real-world studies have confirmed substantial cardiovascular benefit with the use of SGLT2 inhibitors (79). Hence, addressing issues of poor adherence and persistence could lead to greater benefits for many patients with T2D.

CONCLUSION

This systematic review and meta-analysis identified poor adherence and persistence to SGLT2 inhibitors in real world settings. Thus, potential targets for improving treatment adherence and persistence need to be identified and appropriate interventions implemented.
REFERENCES


21. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet. 2005;365(9453):82-93.


This article is protected by copyright. All rights reserved.


<table>
<thead>
<tr>
<th>Study reference</th>
<th>Country</th>
<th>Population characteristics</th>
<th>Data source(s)</th>
<th>Sample size</th>
<th>Outcomes definition</th>
<th>Outcomes data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell et al. (2017)</td>
<td>USA</td>
<td>Adults aged ≥18 years with ≥1 outpatient pharmacy claim between January 1, 2015, and December 31, 2015</td>
<td>Administrative health insurance claims data extracted from the Truven Health MarketScan Commercial Claims and Encounters (Commercial), Medicare Supplemental and Coordination of Benefits (Medicare Supplemental), and Early View databases</td>
<td>17724</td>
<td>Adherence assessed via PDC</td>
<td>Adherent: PDC ≥0.80 Non-persistent: gap &gt;60 days</td>
</tr>
<tr>
<td>Blonde et al. (2018)</td>
<td>USA</td>
<td>Patients with pharmacy claim from 1 January 2014 to 30 September 2016</td>
<td>Optum Clinformatics database</td>
<td>1116</td>
<td>Adherence assessed via PDC</td>
<td>Adherent: PDC ≥0.80</td>
</tr>
<tr>
<td>Bowen and Gleason (2018)</td>
<td>USA</td>
<td>Patients with first claim of diabetes medication between Jan. 1, 2016 and March 31, 2018, and who did not have a preceding claim for any other antihyperglycemic agent other than metformin.</td>
<td>Integrated medical and pharmacy claims for 15 million commercially insured members</td>
<td>17019</td>
<td>Non-persistent: gap &gt;60 days</td>
<td></td>
</tr>
<tr>
<td>Buysman et al. (2015)</td>
<td>USA</td>
<td>Adult patients (≥18 years) who had had filled at least one canagliflozin prescription between April and October 2015</td>
<td>Optum Research Database</td>
<td>4017</td>
<td>Adherence assessed via PDC</td>
<td>Adherent: PDC ≥0.80</td>
</tr>
<tr>
<td>Buysman et al. (2017)</td>
<td>USA</td>
<td>Patients with a pharmacy claim for canagliflozin between April 01, 2013 and August 31, 2014</td>
<td>US administrative claims data from commercial and Medicare Advantage healthcare enrollees</td>
<td>2261</td>
<td>Adherence assessed via PDC</td>
<td>Adherent: PDC ≥0.80</td>
</tr>
<tr>
<td>Cai et al. (2016)</td>
<td>USA</td>
<td>Patients with medical and pharmacy claims data from February 1, 2013 to July 31, 2015</td>
<td>Truven Health Analytics Marketscan Commercial Claims and Encounters and Medicare Supplemental Databases</td>
<td>4183</td>
<td>Adherence assessed via PDC</td>
<td>Adherent: PDC ≥0.80 Non-persistent: gap ≥90 days</td>
</tr>
</tbody>
</table>
Manuscript ID: DMRR-19-RES-574

<table>
<thead>
<tr>
<th>Study Authors (Year)</th>
<th>Country</th>
<th>Study Population</th>
<th>Data Source</th>
<th>Adherence Assessment</th>
<th>Mean PDC at 1y</th>
<th>% Adherent at 1y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cai et al. (2017) (42)</td>
<td>USA</td>
<td>Patients with medical and pharmacy claims data from February 1, 2013 to June 31, 2015</td>
<td>QuintilesIMS PhaMetrics and Health Plan Claims Database</td>
<td>Adherent: PDC ≥0.80 Non-persistent: gap ≥90 days</td>
<td>0.71±0.31</td>
<td>56.2%</td>
</tr>
<tr>
<td>Coleman et al. (2019) (43)</td>
<td>USA</td>
<td>Patients with at least one dispensation of canagliflozin from 1 January 2013 to 31 March 2015</td>
<td>Optum integrated database</td>
<td>Adherent: PDC ≥0.80 Non-persistent: gap &gt;60 days</td>
<td>60.1%</td>
<td>73.6%</td>
</tr>
<tr>
<td>Chow et al. (2016) (44)</td>
<td>USA</td>
<td>Patients who filled at least one prescription between 1 April 2013 and 31 October 2013</td>
<td>Optum Research Database</td>
<td>Adherent: PDC ≥0.80</td>
<td>0.70</td>
<td>50.0%</td>
</tr>
<tr>
<td>Diels and Neslusan (2015) (45)</td>
<td>USA</td>
<td>Patients dispensed canagliflozin in 2013</td>
<td>Optum and Truven databases</td>
<td>Adherent: PDC ≥0.80 Non-persistent: ≥90 days</td>
<td>Canagliflozin 100mg: 64.0% Canagliflozin 300mg: 65.0%</td>
<td>Non-persistent: ≥90 days</td>
</tr>
<tr>
<td>Fadini et al. (2019) (46)</td>
<td>Italy</td>
<td>Patients who were initiated on dapagliflozin in 2015-2016</td>
<td>The DARWIN-T2D multicenter retrospective study conducted at diabetes specialist outpatient clinics</td>
<td>Adherent: PDC ≥0.80</td>
<td>1701</td>
<td>N.S</td>
</tr>
<tr>
<td>Gutiérrez Lorenzo et al. (2018) (47)</td>
<td>Italy</td>
<td>Patients with record of SGLT2 prescription for at least 6 months</td>
<td>Local hospital record</td>
<td>Non-persistent: patients who interrupted treatment</td>
<td>% Persistent at 6 mo: 95.7%</td>
<td>95.7%</td>
</tr>
<tr>
<td>Htike et al. (2015) (48)</td>
<td>UK</td>
<td>Patients treated with dapagliflozin at a university hospital</td>
<td>Hospital electronic and paper records</td>
<td>% Persistent at 6 mo: 73.0%</td>
<td>44</td>
<td>N.S</td>
</tr>
<tr>
<td>Jain et al. (2016) (49)</td>
<td>USA</td>
<td>Adult patients who received the first canagliflozin claim between 1 April 2013 and 30 April 2014</td>
<td>HealthCore Integrated Research Database</td>
<td>Adherent: PDC ≥0.80</td>
<td>881</td>
<td>N.S</td>
</tr>
<tr>
<td>Jamaluddin et al (2019) (50)</td>
<td>Pakistan</td>
<td>Patients treated from August 2018 to January 2019 at a department of internal medicine</td>
<td>Hospital-based data</td>
<td>% Adherent at 2 mo: 76.9%</td>
<td>260</td>
<td>N.S</td>
</tr>
<tr>
<td>Jermendy et al. (2018) (51)</td>
<td>Hungary</td>
<td>Patients starting with antidiabetic therapy from 1 January 2014 was followed until October 31, 2016</td>
<td>Database of the National Institute of Health Insurance Fund Management</td>
<td>Non-persistent: gap ≥180 days</td>
<td>% Persistent at 6 mo: 77.2% Intensification cohort: 77.2%</td>
<td>77.2%</td>
</tr>
</tbody>
</table>

This article is protected by copyright. All rights reserved.
<table>
<thead>
<tr>
<th>Lin et al. (2018) (52)</th>
<th>Taiwan</th>
<th>Patients prescribed medication from May 2016 to April</th>
<th>Data from 3 hospitals</th>
<th>597</th>
<th>N.S</th>
<th>% persistent at 1y: 72.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGovern et al. (2018) (53)</td>
<td>UK</td>
<td>Patients dispensed diabetes medication between January 1, 2004 to January 1, 2015</td>
<td>Royal College of General Practitioners Research and Surveillance Centre (RCGP-RSC) database</td>
<td>1642</td>
<td>Non-persistent: gap ≥90 days</td>
<td>% persistent at 6 mo: 79.5%</td>
</tr>
<tr>
<td>% persistent at 1y: 69.5%</td>
<td>% persistent at 2y: 54.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ofori-Asenso et al. (2019) (54)</td>
<td>Australia</td>
<td>Adults aged 18 years and older with diabetes who initiated SGLT2 inhibitors between September 2015 and August 2017</td>
<td>Pharmaceutical benefits scheme (PBS)</td>
<td>11,981</td>
<td>Non-persistent: gap ≥90 days</td>
<td>% adherent at 6mo: Dapagliflozin: 0.82±0.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Empagliflozin: 0.86±0.22</td>
<td>% adherent at 6mo: Dapagliflozin: 68.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Empagliflozin: 76.3%</td>
<td>% persistent at 6mo: Dapagliflozin: 82.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Empagliflozin: 89.4%</td>
<td>Mean PDC at 6mo: Dapagliflozin: 0.75±0.28</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Empagliflozin: 0.81±0.26</td>
<td>% Adherent at 1y: Dapagliflozin: 59.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Empagliflozin: 69.4%</td>
<td>% persistent at 1y: Dapagliflozin: 68.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Empagliflozin: 73.3%</td>
<td>Mean PDC at 1y: Dapagliflozin: 0.82±0.23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Empagliflozin: 0.86±0.22</td>
<td>% adherent at 6mo: Dapagliflozin: 68.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Empagliflozin: 76.3%</td>
<td>% persistent at 6mo: Dapagliflozin: 82.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Empagliflozin: 89.4%</td>
<td>Mean PDC at 1y: Dapagliflozin: 0.75±0.28</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Empagliflozin: 0.81±0.26</td>
<td>% Adherent at 1y: Dapagliflozin: 59.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Empagliflozin: 69.4%</td>
<td>% persistent at 1y: Dapagliflozin: 68.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Empagliflozin: 73.3%</td>
<td>Mean PDC at 1y: Empagliflozin: 0.81±0.26</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% adherent at 6mo: Empagliflozin: 68.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% persistent at 6mo: Empagliflozin: 82.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean PDC at 1y: Empagliflozin: 0.81±0.26</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% Adherent at 1y: Empagliflozin: 59.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% persistent at 1y: Empagliflozin: 68.6%</td>
<td>750</td>
</tr>
<tr>
<td>Singh et al. (2018) (55)</td>
<td>USA</td>
<td>Patients dispensed canagliflozin between April 2013 and February 2016</td>
<td>HealthCore Integrated Research Database</td>
<td>750</td>
<td>Adherence assessed via PDC Adherent: PDC ≥0.80</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% Adherent at 1y: 47.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% persistent at 1y: 50.4%</td>
<td></td>
</tr>
<tr>
<td>Woo et al. (2018) (56)</td>
<td>Canada</td>
<td>Patients enrolled in the Canadian multicenter, prospective cohort study</td>
<td>CANadian CANagliflozin REGistry (CanCARE)</td>
<td>527</td>
<td>N.S</td>
<td>% persistent at 1y: 82.1%</td>
</tr>
<tr>
<td>Wysham et al. (2018) (57)</td>
<td>USA</td>
<td>Patients who with prescription for canagliflozin on or after March 29, 2013</td>
<td>IQVIA™ Real-World Data Electronic Medical Records–US database</td>
<td>5540</td>
<td>Non-persistence: gap ≥90 days</td>
<td>% persistent at 6 mo: 72.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% persistent at 1y: 51.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% persistent at 2y: 29.1%</td>
<td></td>
</tr>
</tbody>
</table>

*read from Kaplan meier graph; PDC=proportion of days covered; SGLT2 = sodium glucose co-transporter 2 inhibitors; N.S= not specified*
Table 2: Summary of the meta-analysis results of mean PDC, proportion adherent, and the proportion persistent at different follow-up periods

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies</th>
<th>Number of cohorts</th>
<th>Sample Size</th>
<th>Pooled results (95% CI)</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean PDC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>3*</td>
<td>5</td>
<td>30821</td>
<td>0.77 (0.72-0.82)</td>
<td>99.6%</td>
</tr>
<tr>
<td>1 y</td>
<td>3*</td>
<td>5</td>
<td>23875</td>
<td>0.72 (0.66-0.77)</td>
<td>99.6%</td>
</tr>
<tr>
<td><strong>% Adherent (PDC ≥0.80)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>4</td>
<td>7</td>
<td>34667</td>
<td>59.5 (52.9-65.9)</td>
<td>99.2%</td>
</tr>
<tr>
<td>1 y</td>
<td>5</td>
<td>10</td>
<td>28808</td>
<td>49.0 (42.3-55.8)</td>
<td>99.2%</td>
</tr>
<tr>
<td><strong>% persistent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All definitions</td>
<td>9</td>
<td>10</td>
<td>80894</td>
<td>80.1 (75.8-84.0)</td>
<td>99.4%</td>
</tr>
<tr>
<td></td>
<td>1 y</td>
<td>2 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥90-day gap</td>
<td>3 4 19163 81.5 (73.1-88.6) 99.5%</td>
<td>6 11 33729 58.9 (53.1-64.6) 99.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All definitions</td>
<td>10 16 79181 61.8 (57.8-65.7) 99.2%</td>
<td>4 5 51510 45.9 (35.5-56.5) 99.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥90-day gap</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All definitions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥90-day gap</td>
<td>2 2 7182 34.7 (33.6-35.8) 0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Some studies did not report standard deviation and therefore couldn’t be included in the meta-analysis; PDC= proportion of days covered; CI= confidence interval*
Figure legends

Figure 1: Flow chart of studies’ selection process
Articles identified from electronic searches (n=1385)

- Duplicates removed (n=430)

Records after duplicates removed (n=955)

- Removed after title and abstract screening (n=902)

Full text articles screened (n=53)

- Excluded with reasons (n=33)
  - RCT (n=4)
  - No adherence/persistence data (n=28)
  - Inappropriate methodology (n=1)

- Studies identified via reference screening (n=2)

Studies included in review (n=22)
Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Ofori-Asenso, R; Sahle, BW; Chin, KL; Mazidi, M; Ademi, Z; De Bruin, ML; Liew, D

Title:
Poor adherence and persistence to sodium glucose co-transporter 2 inhibitors in real-world settings: Evidence from a systematic review and meta-analysis

Date:
2021-01

Citation:

Persistent Link:
http://hdl.handle.net/11343/275937