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

Richard Ofori-Asenso[1,2] | Berhe W. Sahle[3] | Ken Lee Chin[2,4] | Mohsen Mazidi[5] | Zanfina Ademi[2] | Marie Louise De Bruin[1] | Danny Liew[2]

[1]Copenhagen Centre for Regulatory Science (CORS), Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[2]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

[3]Melbourne School of Population and Global Health, University of Melbourne, Parkville, Victoria, Australia

[4]Melbourne Medical School, University of Melbourne, Parkville, Victoria, Australia

[5]Department of Twin Research and Genetic Epidemiology, Kings College London, London, UK

Correspondence
Richard Ofori-Asenso, Copenhagen Centre for Regulatory Science (CORS), Department of Pharmacy, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2 Copenhagen, Denmark.
Email: richard.ofori-asenso@sund.ku.dk

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 analysed via random-effects meta-analysis.

Results: A total of 22 studies (31 cohorts) comprising 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 the 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). Adherence and persistence appeared to vary across different SGLT2 inhibitors.

Conclusions: 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

adherence, persistence, discontinuation, SGLT2, sodium glucose cotransporter 2 inhibitors

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major public health issue, which is estimated to affect more than 400 million people worldwide.[1]

Berhe W. Sahle and Ken Lee Chin contributed equally.

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 haemoglobin (HbA_{1c}) 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 (ie, the extent to which patients act in accordance with the prescribed interval, and dose of a dosing regimen[20]) and persistence (ie, 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 patients with T2DM. 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.

2 | 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]

2.1 | Search strategy and study selection

Electronic searches were performed in Medline, Embase, and Web of Science for observational (cohort) 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" (Table S1). The search was initially performed on August 1, 2019 and last updated on October 24, 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,[28,29] 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).

2.2 | 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).

2.3 | 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 = SD/ √sample size, where SD = standard deviation. 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 I^2 statistic. 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) and a *P*-value <.05 was considered statistically significant.

3 | 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 United States (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) (Table S2).

3.1 | 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%) (Figure S1). Four studies (seven cohorts) involving 34 667 individuals reported that 41.0% to 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%) (Figure S2). Across five studies (10 cohorts) involving 28 939 individuals, the reported mean PDC at one year was within the range 0.58 to 0.81. The pooled mean PDC at one year was 0.72 (95% CI 0.66-0.77; I^2 = 99.2%) (-Figure S3). In five studies (10 cohorts), 29.9% to 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) (Figure S4).

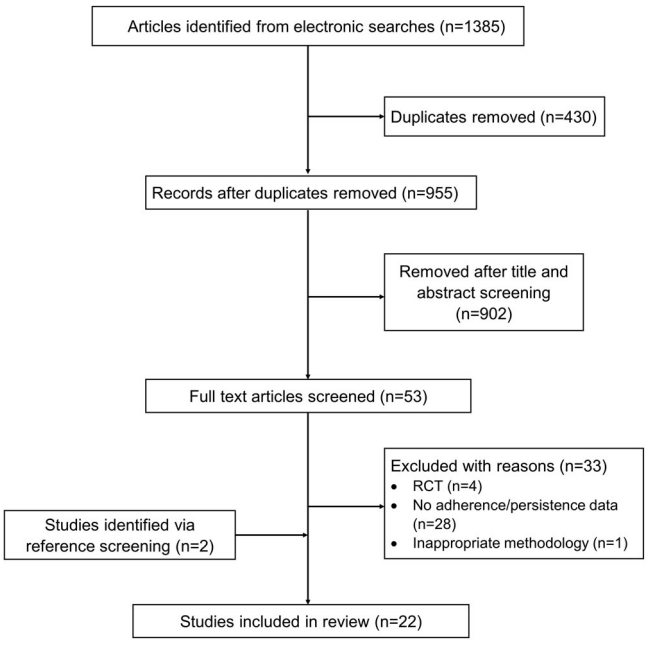

FIGURE 1 Flow chart of studies' selection process

3.2 | 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% to 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%) (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%) (Table 2). Ten studies (16 cohorts) involving 79 181 individuals reported that 40.0% to 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%) (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% to 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%) (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%).

3.3 | Comparisons of different SGLT2 inhibitors

Only one study conducted among Australians compared adherence and persistence between people prescribed empagliflozin and

TABLE 1 Descriptive characteristics of the included studies

Study reference	Country	Population characteristics	Data source(s)	Sample size	Outcomes definition	Outcomes data
Bell et al. (2017)[36]	United States	Adults aged ≥18 years with ≥1 outpatient pharmacy claim between January 1, 2015, and December 31, 2015	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	17 724	Adherence assessed via PDC Adherent: PDC ≥0.80 Non-persistent: gap >60 days	Mean PDC at 6 months: 0.76 ± 0.28% adherent at 6 months: 61.8% % persistent at 6 months: 76.4%
Blonde et al. (2018)[37]	USA	Patients with pharmacy claim from January 1, 2014 to September 30, 2016	Optum Clinformatics database	1116 (Canagliflozin = 558; Dapagliflozin = 558)	Adherence assessed via PDC Adherent: PDC ≥0.80	Mean PDC at 6 months: canagliflozin: 0.74 ± 0.26 dapagliflozin: 0.65 ± 0.28% adherent at 6 months: canagliflozin: 58.1% dapagliflozin: 41.0%
Bowen and Gleason (2018)[38]	United States	Patients with first claim of diabetes medication between January 1, 2016 and March 31, 2018, and who did not have a preceding claim for any other antihyperglyemic agent other than metformin.	Integrated medical and pharmacy claims for 15 million commercially insured members	17 019	Non-persistent: gap >60 days	% persistent at 6mo[a]: 69.4% % persistent at 1y: 56.9% % persistent at 2y[a]: 42.7%
Buysman et al. (2015)[39]	United States	Adult patients (≥18 years) who had filled at least one canagliflozin prescription between April and October 2013	Optum research database	4017 (Canagliflozin 100 mg = 2625; Canagliflozin 300 mg = 1392)	Adherence assessed via PDC	Mean PDC at 6 months: 74.0
Buysman et al. (2017)[40]	United States	Patients with a pharmacy claim for canagliflozin between April 1, 2013 and August 31, 2014	U.S. administrative claims data from commercial and Medicare Advantage healthcare enrollees	2261	Adherence assessed via PDC Adherent: PDC ≥0.80	Mean PDC at 1y: 0.68 ± 0.29% adherent at 1y: 53.7%
Cai et al. (2016)[41]	United States	Patients with medical and pharmacy claims data from February 1, 2013 to July 31, 2015	Truven Health Analytics Marketscan Commercial Claims and Encounters and Medicare Supplemental Databases	4183 (Canagliflozin 100 mg = 1659; Canagliflozin 300 mg = 1266; Dapagliflozin 5 mg = 846; Dapagliflozin 10 mg = 412)	Adherence assessed via PDC Adherent: PDC ≥0.80 Non-persistent: gap ≥90 days	Mean PDC at 1y canagliflozin 100 mg: 0.67 canagliflozin 300 mg: 0.68 dapagliflozin 5 mg: 0.55 dapagliflozin 10 mg: 00.57% Adherent at 1y canagliflozin 100 mg: 49.0% canagliflozin 300 mg: 51.5% dapagliflozin 5 mg: 29.9% dapagliflozin 10 mg: 31.3%

TABLE 1 (Continued)

Study reference	Country	Population characteristics	Data source(s)	Sample size	Outcomes definition	Outcomes data
						% Persistent at 1y canagliflozin 100 mg: 61.0% canagliflozin 300 mg: 64.0% dapagliflozin 5 mg: 40.0% dapagliflozin 10 mg: 41.0%
Cai et al. (2017)[42]	United States	Patients with medical and pharmacy claims data from February 1, 2013 to June 31, 2015	QuintilesIMS PharMetrics and Health Plan Claims Database	9633 (Canagliflozin 6546; Dapagliflozin = 3087)	Adherence assessed via PDC Adherent: PDC ≥0.80 Non-persistent: gap ≥90 days	Mean PDC at 1y: Canagliflozin: 0.71 ± 0.31 Dapagliflozin: 0.64 ± 0.31% adherent at 1y: Canagliflozin: 56.2% Dapagliflozin: 41.8% % persistent at 1y: Canagliflozin: 67.6% Dapagliflozin: 57.4%
Coleman et al. (2019)[43]	United States	Patients with at least one dispensation of canagliflozin from January 1, 2013 to March 31, 2015	Optum integrated database	201	Adherence assessed via PDC Adherent: PDC ≥0.80 Non-persistent: gap>60 days	% adherent at 9 months: 60.1% % persistent at 6 mo[a]: 73.6% % persistent at 9 months: 72.1%
Chow et al. (2016)[44]	United States	Patients who filled at least one prescription between April 1, 2013 and October 31, 2013	Optum research database	3846 (Hispanic/Latino cohort = 438; non-Hispanic/Latino cohort = 3408)	Adherence assessed via PDC Adherent: PDC ≥0.80	Mean PDC at 6 months: Hispanic/latino cohort: 0.70 Non-Hispanic/latino: 0.74% adherent at 6 months: Hispanic/latino cohort: 50.0% Non-Hispanic/latino: 58.0%
Diels and Neslusan (2015)[45]	United States	Patients dispensed canagliflozin in 2013	Optum and Truven databases	11 931 (canagliflozin 100 mg = 7445; canagliflozin 300 mg = 4486)	Non-persistent: ≥90 days	% persistent at 1y: Canagliflozin 100 mg: 64.0% Canagliflozin 300 mg: 65.0%
Fadini et al. (2019)[46]	Italy	Patients who were initiated on dapagliflozin in 2015-2016	The DARWIN-T2D multicenter retrospective study conducted at diabetes specialist outpatient clinics	1701	N.S	% persistent at 3-12 months: 48.9%
Gutiérrez Lorenzo et al. (2018)[47]	Italy	Patients with record of SGLT2 prescription for at least 6 monthsnths	Local hospital record	691	Non-persistent: patients who interrupted treatment	% Persistent at 6 months: 95.7%
Htike et al (2015)[48]	UK	Patients treated with dapagliflozin at a university hospital	Hospital electronic and paper records	44	N.S	% persistent at 6 mo: 73.0%
Jain et al. (2016)[49]	United States	Adult patients who received the first canagliflozin claim between April 1, 2013 and April 30, 2014	HealthCore Integrated Research Database	881	Adherence assessed via PDC	Mean PDC at 1y: 0.71

(Continues)

TABLE 1 (Continued)

Study reference	Country	Population characteristics	Data source(s)	Sample size	Outcomes definition	Outcomes data
Jamaluddin et al (2019)[50]	Pakistan	Patients treated from August 2018 to January 2019 at a department of internal medicine	Hospital-based data	260	N.S	% adherent at 2 months: 76.9%
Jermendy et al. (2018)[51]	Hungary	Patients starting with antidiabetic therapy from January 1, 2014 was followed until October 31, 2016	Database of the National Institute of Health Insurance Fund Management	27 309 (treatment intensification cohort = 26 052; initial treatment cohort = 1257)	Non-persistent: gap ≥180 days	% persistent at 6 mo[a]: Intensification cohort: 77.2% % persistent at 1y: intensification cohort: 67.8% initial cohort: 59.6% % persistent at 2y: intensification cohort: 56.8% initial cohort: 47.0%
Lin et al. (2018)[52]	Taiwan	Patients prescribed medication from May 2016 to April	Data from three hospitals	597	N.S	% persistent at 1y: 72.1%
McGovern et al. (2018)[53]	UK	Patients dispensed diabetes medication between January 1, 2004 and January 1, 2015	Royal College of General Practitioners Research and Surveillance Centre (RCGP-RSC) database	1642	Non-persistent: gap ≥90 days	% persistent at 6 months: 79.5% % persistent at 1y: 69.5% % persistent at 2y: 54.8%
Ofori-Asenso et al. (2019)[54]	Australia	Adults aged 18 years and older with diabetes who initiated SGLT2 inhibitors between September 2015 and August 2017	Pharmaceutical benefits scheme (PBS)	11 981 (Dapagliflozin = 5993; Empagliflozin = 5988)	Adherence assessed via PDC Adherent: PDC ≥0.80 Non-persistent: gap ≥90 days	Mean PDC at 6 months: Dapagliflozin: 0.82 ± 0.23 Empagliflozin: 0.86 ± 0.22% adherent at 6mo: Dapagliflozin:68.0% Empagliflozin: 76.3% % persistent at 6mo: Dapagliflozin: 82.9% Empagliflozin: 89.4% Mean PDC at 1y: Dapagliflozin: 0.75 ± 0.28 Empagliflozin: 0.81 ± 0.26% Adherent at 1y: Dapagliflozin: 59.3% Empagliflozin: 69.4% % persistent at 1y: Dapagliflozin: 68.6% Empagliflozin: 73.3%
Singhal et al. (2018)[55]	United States	Patients dispensed canagliflozin between April 2013 and February 2016	HealthCore Integrated Research Database	750	Adherence assessed via PDC Adherent: PDC ≥0.80 Non-Persistent (gap≥90 days)	% adherent at 1y: 47.5% % persistent at 1y: 50.4%
Woo et al. (2018)[56]	Canada	Patients enrolled in the Canadian multicenter, prospective cohort study	CANadian CAnagliflozin REgistry (CanCARE)	527	N.S	% persistent at 1y: 82.1%

TABLE 1 (Continued)

Study reference	Country	Population characteristics	Data source(s)	Sample size	Outcomes definition	Outcomes data
Wysham et al. (2018)[57]	United States	Patients who with prescription for canagliflozin on or after March 29, 2013	IQVIA Real-World Data Electronic Medical Records-US database	5540	Non-persistence: gap ≥90 days	% persistent at 6 mo: 72.5% % persistent at 1y: 51.4% % persistent at 2y: 29.1%

Abbreviations: NS, not specified; PDC, proportion of days covered; SGLT2, sodium glucose co-transporter 2 inhibitors.
[a]Read from Kaplan meier graph.

TABLE 2 Summary of the meta-analysis results of mean PDC, proportion adherent, and the proportion persistent at different follow-up periods

Outcome	Number of studies	Number of cohorts	Sample size	Pooled results (95% CI)	I^2
Mean PDC					
6 months	3[a]	5	30 821	0.77 (0.72–0.82)	99.6%
1 y	3[a]	5	23 875	0.72 (0.66-0.77)	99.6%
% Adherent (PDC ≥0.80)					
6 months	4	7	34 667	59.5 (52.9–65.9)	99.2%
1 y	5	10	28 808	49.0 (42.3–55.8)	99.2%
% persistent					
6 months					
All definitions	9	10	80 894	80.1 (75.8–84.0)	99.4%
≥90-day gap	3	4	19 163	81.5 (73.1–88.6)	99.5%
1 y					
All definitions	10	16	79 181	61.8 (57.8–65.7)	99.2%
≥90-day gap	6	11	33 729	58.9 (53.1–64.6)	99.1%
2 y					
All definitions	4	5	51 510	45.9 (35.5–56.5)	99.8%
≥90-day gap	2	2	7182	34.7 (33.6–35.8)	0.0%

[a]Some studies did not report SD and therefore could not be included in the meta-analysis.
Abbreviations: CI, confidence interval; PDC, proportion of days covered.

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 (Table S12). Moreover, in two U.S. 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 100 mg and 300 mg (one-year adherence [PDC ≥0.80] rate; canagliflozin 100 mg = 49.0%, canagliflozin 300 mg, 51.5%; *P*-value for difference = .065).[39] Similarly, pooled data from two studies involving 14 856 individuals showed that canagliflozin 100 mg was not associated with higher persistence (no-gap of ≥90 days) compared to canagliflozin 300 mg (OR 0.94, 95% CI 0.88-1.01; I^2 = 0.0%).

3.4 | 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* = .120; proportion persistent at six months [all definitions], *P* = .216; proportion persistent at one year [all definitions], *P* = .184; proportion

persistent at one year [≥90-days gap], P = .209). These results suggested no evidence of publication bias.

4 | 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% to 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.[14] 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.[63,64] 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 8-fold between June 2014 and June 2016.[19] In the United States, the uptake of SGLT2 inhibitors increased more than 5-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% to 80% of patients were persistent with treatment for more than two years of follow-up.[13,14,62] 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 U.S. study involving adult commercial and Medicare Advantage health plan enrollees found that those adherent to SGLT2 inhibitors experienced larger reductions in glycated haemoglobin (HbA1c) than non-adherent individuals (1.17% vs 0.73%, P < .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.[65] For adverse effects of SGLT2 inhibitors, the most common one appears to be genital infections, the risk of which was increased up to 4-fold in RCTs.[66] 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, counselling about maintenance of perineal hygiene should be included in all diabetes education sessions.[67] 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.[65,67]

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.[25,66,68,69] 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),[70] those aimed at reducing regimen complexity,[71,72] as well as interventions seeking to improve patient knowledge (eg, through pharmacist-led integrated management and education programmes)[73] or those providing extended supervisory health services[74] have shown positive effects on treatment adherence and persistence. However, available evidence suggests that multifactorial interventions that are tailored to patient-specific needs are more likely to provide greater improvements in adherence and persistence compared to unifactorial interventions.[71,75,76] 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.[77] 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.[78] Hence, addressing issues of poor adherence and persistence could lead to greater benefits for many patients with T2DM.

5 | CONCLUSIONS

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.

CONFLICT OF INTEREST

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 organizations (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

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.

ORCID

Richard Ofori-Asenso https://orcid.org/0000-0002-6643-3269

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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