



Research Article

Adherence, Persistence and Clinical Outcomes with Newer Glucose-Lowering Medications: A Systematic Review

Devang J. Barad¹, Yisha Chandrakar Sharma² and Krishan Datt Upadhyay^{3*}

¹Senior Resident, Department of General Medicine, GMERS Medical College and Hospital, Sola, Ahmedabad, Gujarat, India

²Senior Resident, Department of Biochemistry, Government Medical College, Datia, Madhya Pradesh, India

³Senior Resident, Department of Pharmacology, Gajra Raja Medical College, Gwalior, Madhya Pradesh, India

***Corresponding Author**

Krishan Datt Upadhyay
(drkdupadhyay085@gmail.com)

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Abstract: **Background:** Newer glucose-lowering therapies, particularly sodium-glucose cotransporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonists, provide substantial glycaemic, weight, cardiovascular and renal benefits. Their real-world effectiveness, however, depends on sustained treatment exposure. **Methods:** A systematic review was conducted according to PRISMA 2020 principles. MEDLINE/PubMed, Embase, Scopus, Web of Science and the Cochrane Library were searched from January 2015 through 30 June 2026. Adults with type 2 diabetes receiving SGLT2i, GLP-1 RA or dual GIP/GLP-1 RA therapy were eligible when studies reported persistence, adherence, discontinuation or related clinical outcomes. DPP-4 inhibitors were retained when used as active comparators. Because of substantial methodological heterogeneity, results were synthesized narratively. **Results:** A total of 2,177 records were identified. After removal of 521 duplicates, 1,656 records were screened and 1,458 were excluded. Of 198 reports sought for retrieval, 14 were unavailable; 184 full texts were assessed and 166 were excluded, leaving 18 studies for qualitative synthesis. One-year persistence commonly ranged from approximately 35% to 70%, with estimates influenced by medication class, dosing frequency, healthcare setting and permissible refill gap. Persistent/adherent patients generally achieved greater HbA1c reductions. Recent observational evidence also associated higher adherence with lower risks of hospitalization, cardiovascular or renal events and mortality. Once-weekly GLP-1 RA regimens generally demonstrated better persistence than daily injectable regimens, while comparative persistence between GLP-1 RAs and SGLT2i varied across healthcare systems. **Conclusions:** Treatment persistence with newer glucose-lowering therapies is suboptimal in routine practice and is clinically important. Greater persistence and adherence are consistently associated with improved glycaemic outcomes and increasingly with better cardiorenal outcomes. Treatment selection should integrate efficacy with tolerability, dosing frequency, treatment burden, affordability, access and patient preference.

Keywords: Type 2 Diabetes Mellitus, Treatment Persistence, Medication Adherence, GLP-1 Receptor Agonist, SGLT2 Inhibitor, Semaglutide, Tirzepatide, Real-World Evidence

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic progressive metabolic disorder requiring sustained pharmacological management to prevent microvascular and macrovascular complications. Contemporary treatment has moved beyond a glucose-centred approach toward simultaneous reduction of cardiovascular, renal, metabolic and weight-related risk [1,2].

SGLT2 inhibitors and GLP-1 receptor agonists now occupy central positions in treatment algorithms because their benefits extend beyond glycaemic control. More recently, dual GIP/GLP-1 receptor agonism has further expanded the therapeutic landscape. Nevertheless, the efficacy observed in randomized clinical trials may not be fully realized in routine practice when treatment is interrupted, discontinued, poorly tolerated, inaccessible or taken inconsistently [1-3].

Medication adherence describes the extent to which a patient takes medication according to the prescribed schedule, whereas persistence describes the duration from initiation until discontinuation. Claims-based studies frequently define adherence using a proportion of days covered (PDC) of at least 80%, while persistence is commonly defined by the absence of a treatment gap exceeding 30, 45, 60 or 90 days [4]. These differences materially affect reported persistence estimates.

Earlier evidence indicates that adherence and persistence to glucose-lowering therapies are frequently suboptimal. A systematic review of SGLT2 inhibitors reported pooled persistence of 80.1% at 6 months, 61.8% at 1 year and 45.9% at 2 years, while only 49.0% of patients were adherent at 1 year using PDC $\geq$ 80% [4]. The present review therefore evaluated real-world persistence and adherence with newer glucose-lowering therapies and examined their associations with glycaemic, weight, cardiovascular, renal, mortality, healthcare-utilization and economic outcomes.

MATERIALS AND METHODS

Study Design and Reporting

This systematic review was prepared in accordance with the PRISMA 2020 framework. The review question, eligibility criteria, information sources, outcomes and synthesis plan were defined before evidence synthesis. The review was not prospectively registered.

Eligibility Criteria

Domain	Criteria
Population	Adults aged ≥ 18 years with T2DM.
Interventions	SGLT2 inhibitors, GLP-1 receptor agonists, oral or injectable semaglutide and dual GIP/GLP-1 receptor agonists such as tirzepatide.
Comparators	Another newer glucose-lowering therapy, DPP-4 inhibitor, alternative GLP-1 RA or persistent/adherent versus non-persistent/non-adherent treatment.
Outcomes	Persistence, adherence, discontinuation, PDC/MPR, HbA1c, weight, cardiovascular events, heart-failure hospitalization, kidney outcomes, mortality, healthcare utilization or costs.
Study designs	Real-world cohort, claims-database, registry, electronic health-record or other observational studies.
Exclusions	Type 1 diabetes-only populations; obesity-only cohorts without T2DM; RCT efficacy reports without real-world persistence/adherence outcomes; case reports; editorials; narrative reviews; insufficient outcome data.

Information Sources and Search Strategy

MEDLINE/PubMed, Embase, Scopus, Web of Science and the Cochrane Library were searched from January 2015 through 30 June 2026. Citation and reference-list searching was also performed.

Representative search syntax: ("type 2 diabetes" OR T2DM) AND ("SGLT2 inhibitor" OR empagliflozin OR dapagliflozin OR canagliflozin OR "GLP-1 receptor agonist" OR semaglutide OR dulaglutide OR liraglutide OR exenatide OR tirzepatide OR "GIP GLP-1") AND (persistence OR adherence OR discontinuation OR "proportion of days covered" OR PDC OR "medication possession ratio") AND ("real world" OR observational OR cohort OR claims OR registry).

Study Selection

After deduplication, titles and abstracts were screened against predefined eligibility criteria. Potentially eligible reports underwent full-text assessment. Overlapping reports were examined to avoid double-counting substantially identical populations and outcomes. Reasons for full-text exclusion were recorded.

Data Extraction and Outcomes

Data were extracted on country, data source, population, therapy, sample size, follow-up, persistence/adherence definition, persistence estimates, HbA1c and weight outcomes, cardiorenal events, mortality, healthcare utilization and costs. The principal outcome was treatment persistence at approximately 12 months. Secondary outcomes were adherence (usually PDC $\geq 80\%$), discontinuation, glycaemic and weight outcomes, cardiovascular and kidney events, mortality and resource utilization.

Risk-of-Bias Assessment

Observational studies were assessed using ROBINS-I domains. Particular attention was given to confounding by indication, selection bias, exposure classification, missing data, outcome measurement, selective reporting, healthy-adherer bias and immortal-time bias. Overall judgments were categorized as low, moderate, serious or critical risk of bias.

Data Synthesis

A quantitative meta-analysis was not undertaken because of substantial clinical and methodological heterogeneity in treatment classes, permissible refill gaps, adherence thresholds, follow-up duration, healthcare systems and reported outcomes. A structured narrative synthesis was therefore used.

RESULTS

PRISMA Study Selection

The search identified 2,177 records: 2,146 from electronic databases and 31 through citation/reference searching. Database records comprised 612 from MEDLINE/PubMed, 548 from Embase, 436 from Scopus, 384 from Web of Science and 166 from the Cochrane Library. After removal of 521 duplicates, 1,656 records underwent title/abstract screening, of which 1,458 were excluded. Full text was sought for 198 reports; 14 reports could not be retrieved. Of 184 full-text reports assessed, 166 were excluded: wrong population ($n = 42$), absence of a persistence/adherence outcome ($n = 51$), randomized efficacy-only design ($n = 31$), review/editorial publication ($n = 22$), overlapping cohort ($n = 11$) or insufficient outcome data ($n = 9$). Eighteen studies were included in the qualitative synthesis (Figure 1).

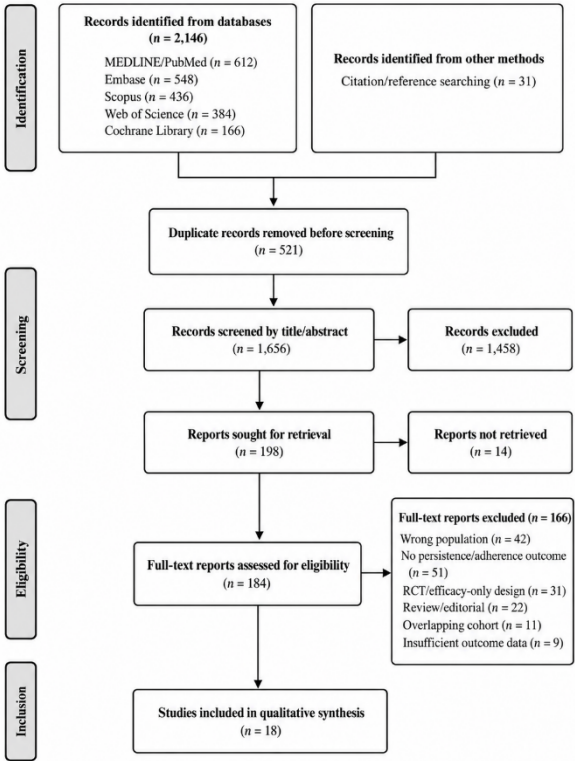


Figure 1: PRISMA 2020 Flow Diagram of Study Identification, Screening, Eligibility and Inclusion

Table 1: Characteristics and Key Findings of Studies

Study	Setting	N	Therapy	Follow-up	Key finding
Cai <i>et al.</i> [5]	USA	11,961	SGLT2i, GLP-1 RA, DPP-4i	12 mo	Canagliflozin 61-64%; liraglutide 47%; exenatide 23%
Mody <i>et al.</i> [6]	USA	308	Dulaglutide	~6 mo	61% adherent; 37% discontinued
Mody <i>et al.</i> [7]	USA	Claims cohort	Dulaglutide vs. liraglutide/exenatide QW	12 mo	Dulaglutide persistence ~55%; comparators lower
Mody <i>et al.</i> [8]	USA	Claims cohort	Dulaglutide vs. semaglutide/exenatide BCise	6 mo	Early claims-based adherence favored dulaglutide
Uzoigwe <i>et al.</i> [9]	USA	56,715	GLP-1 RAs	360 d	Semaglutide QW 67%; dulaglutide 56%; liraglutide 40.4%; exenatide QW 35.5%
Rea <i>et al.</i> [10]	Italy	1,276 matched pairs	GLP-1 RA vs. SGLT2i	Follow-up	Discontinuation ~24% vs. ~29%
Polonsky <i>et al.</i> [11]	USA	784 matched pairs	Weekly vs. daily GLP-1 RA	~12 mo	Median persistence 333 vs. 269 days
Jung <i>et al.</i> [12]	Germany/Austria	15,111	GLP-1 RAs	Registry	Median persistence ~11 months
Palanca <i>et al.</i> [13]	Spain	7,392	GLP-1 RA vs. other agents	2 y	GLP-1 RA persistence 48.4%
Ciardullo <i>et al.</i> [14]	Italy	Matched cohorts	GLP-1 RA/SGLT2i	Longitudinal	Adherence associated with fewer clinical events
Lv <i>et al.</i> [15]	USA	10,465	Oral semaglutide vs. DPP-4i	12 mo	PDC≥80%: 41.6% vs. 42.9%
Conti <i>et al.</i> [16]	Italy	242	Oral vs. SC semaglutide	18 mo	12-mo persistence 72.3% vs. 92.4%
Ali <i>et al.</i> [17]	Saudi Arabia	5,087	Semaglutide vs. empagliflozin	12 mo	Adherence 57.7% vs. 60%; persistence 40% vs. 45%
Bowe <i>et al.</i> [18]	USA	44,434 matched	GLP-1 RA vs. SGLT2i	12 mo	37.6% vs. 47.0% persistence
Ulrich <i>et al.</i> [19]	UK	8,200	GLP-1 RAs	12 mo	1-year discontinuation risk 41.1%
Baldassarre <i>et al.</i> [20]	Italy	232	Oral semaglutide	24 mo	Persistence 68.5%
Li <i>et al.</i> [21]	USA	>45,000	SGLT2i	Longitudinal	Objective exposure marker associated with better cardiorenal outcomes
Maruyama <i>et al.</i> [22]	Japan	828	Tirzepatide	Real-world	Discontinuation due to adverse events, preference or clinical reasons

Characteristics of Included Studies

The 18 included studies were published between 2016 and 2026 and included claims databases, electronic health records, population-based cohorts, registries and specialist clinical cohorts. Sample sizes ranged from several hundred participants to more than 50,000. Evidence was strongest for GLP-1 RAs and SGLT2 inhibitors; long-term persistence data for tirzepatide remained comparatively limited (Table 1).

Treatment Persistence Across Drug Classes

Persistence varied substantially across therapies and healthcare settings. In early US claims data, 12-month persistence was 61-64% for canagliflozin, 47% for liraglutide and 23% for exenatide, with several DPP-4 inhibitors ranging from approximately 42-52% [5].

Comparative class rankings were not uniform. In an Italian matched analysis, discontinuation occurred in approximately 24% of GLP-1 RA users and 29% of SGLT2i users [10]. In contrast, a large Medicare Advantage analysis reported 1-year persistence of 37.6% for GLP-1 RA initiators and 47.0% for SGLT2i initiators using a 45-day permissible gap; GLP-1 RA users were more likely to discontinue (HR 1.39) [18]. Increasing the permissible gap to 90 days increased persistence to 50.1 and 59.1%, respectively, demonstrating the sensitivity of persistence estimates to operational definitions.

Within GLP-1 RAs, once-weekly administration generally favored persistence. In a 56,715-patient US analysis, 360-day persistence was 67.0% with once-weekly semaglutide, 56.0% with dulaglutide, 40.4% with liraglutide and 35.5% with once-weekly exenatide [9]. In the STAY study, median persistence was 333 days with once-weekly versus 269 days with daily injectable GLP-1 RAs [11].

Persistence and Glycaemic Outcomes

Persistent and adherent patients consistently achieved better glycaemic outcomes. In a dulaglutide cohort, mean HbA1c fell by 0.90 percentage points overall but reductions were approximately 1.14 percentage points among adherent patients and 1.12 percentage points among persistent patients [6].

In the STAY study, once-weekly GLP-1 RA users achieved a greater 6-month HbA1c reduction than daily-regimen users (-1.1 vs. -0.9%), with the largest reductions among adherent patients [11]. In the DPV Registry, longer persistence was similarly associated with greater improvement in HbA1c [12].

At 2 years, Palanca *et al.* [13] found that 40.5% of persistent GLP-1 RA users showed reduced HbA1c compared with 18.6% of non-persistent users. These findings support treatment persistence as an important mediator of real-world glycaemic effectiveness.

Persistence and Weight Outcomes

Longer exposure to GLP-1-based therapies was generally accompanied by sustained weight reduction. In a 24 month real-world oral semaglutide cohort, mean body weight decreased by 5.7 kg, while 44% achieved the combined endpoint of HbA1c $\leq 7\%$ and at least 5% weight loss [20]. Real-world tirzepatide cohorts reported substantial metabolic effectiveness but long-term persistence evidence remained less mature because of its more recent introduction [22].

Adherence and Cardiovascular, Renal and Mortality Outcomes

Evidence increasingly linked adherence with outcomes beyond glycaemic control. Ciardullo *et al.* reported a lower incidence of a composite endpoint of insulin initiation, hospitalization for microvascular or macrovascular complications and all-cause mortality among adherent GLP-1 RA users (HR 0.85, 95% CI 0.72-0.98) and adherent SGLT2i users (HR 0.69, 95% CI 0.55-0.87) compared with non-adherent users [14].

A 2026 analysis using glucosuria as an objective marker of SGLT2i exposure found associations with lower all-cause mortality (HR 0.78, 95% CI 0.73-0.83), heart-failure hospitalization (HR 0.87, 95% CI 0.78-0.98) and end-stage kidney disease (HR 0.73, 95% CI 0.58-0.91) [21]. Although residual confounding remains possible, the use of a negative-control outcome strengthened the interpretation that continued exposure may contribute to realization of established cardiorenal benefits.

Oral Versus Injectable Semaglutide

Conti *et al.* reported lower persistence with oral than subcutaneous semaglutide at 6 months (85.3 vs. 94.8%), 12 months (72.3 vs. 92.4%) and 18 months (46.0% vs 83.8%) [16]. Gastrointestinal adverse effects were the most frequently identified reason for discontinuation. Conversely, a specialist cohort published in 2026 reported 68.5% persistence with oral semaglutide at 24 months [20], suggesting that structured follow-up may mitigate some administration-related barriers.

Factors Associated with Non-Persistence

Recurring determinants included gastrointestinal adverse effects, daily dosing or injection burden, delayed dose escalation, medication cost, insurance authorization, formulary restrictions, drug shortages and patient preference. Once-weekly regimens generally demonstrated better persistence than daily injectable regimens [11]. Among 8,200 UK GLP-1 RA initiators, the 1-year discontinuation risk was 41.1% and a substantial proportion did not reach recommended maintenance doses promptly [19].

Table 2: Summarizes Study-Level Judgments

Study	Confounding	Selection	Classification	Missing data	Outcome measurement	Reporting	Overall
Cai <i>et al.</i> [5]	Moderate	Moderate	Low	Moderate	Low	Low	Moderate
Mody <i>et al.</i> [6]	Moderate	Moderate	Low	Moderate	Moderate	Low	Moderate
Mody <i>et al.</i> [7]	Moderate	Moderate	Low	Moderate	Low	Low	Moderate
Mody <i>et al.</i> [8]	Moderate	Moderate	Low	Moderate	Low	Low	Moderate
Uzoigwe <i>et al.</i> [9]	Moderate	Moderate	Low	Moderate	Low	Low	Moderate
Rea <i>et al.</i> [10]	Moderate	Low	Low	Moderate	Low	Low	Moderate
Polonsky <i>et al.</i> [11]	Moderate	Low	Low	Moderate	Low	Low	Moderate
Jung <i>et al.</i> [12]	Moderate	Moderate	Low	Moderate	Moderate	Low	Moderate
Palanca <i>et al.</i> [13]	Moderate	Low	Low	Moderate	Low	Low	Moderate
Ciardullo <i>et al.</i> [14]	Moderate	Low	Low	Moderate	Low	Low	Moderate
Ly <i>et al.</i> [15]	Moderate	Moderate	Low	Moderate	Low	Low	Moderate
Conti <i>et al.</i> [16]	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Ali <i>et al.</i> [17]	Moderate	Moderate	Low	Moderate	Moderate	Low	Moderate
Bowe <i>et al.</i> [18]	Moderate	Low	Low	Moderate	Low	Low	Moderate
Ulrich <i>et al.</i> [19]	Moderate	Low	Low	Moderate	Low	Low	Moderate
Baldassarre <i>et al.</i> [20]	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Li <i>et al.</i> [21]	Moderate	Low	Low	Low	Low	Low	Moderate
Maruyama <i>et al.</i> [22]	Moderate	Moderate	Low	Low	Moderate	Low	Moderate

Risk of Bias

Most studies were judged to have moderate overall risk of bias, principally because of residual confounding, claims-based exposure measurement and potential healthy-adherer effects. No study was judged to have critical risk of bias (Table 2).

DISCUSSION

This systematic review demonstrates a substantial gap between the efficacy of newer glucose-lowering therapies and their sustained use in routine clinical practice. Across diverse real-world settings, many patients discontinued therapy during the first year and persistence generally declined with longer follow-up.

The first major finding is that persistence should be considered a clinical effectiveness variable rather than merely a medication-use statistic. Persistent and adherent users repeatedly achieved greater HbA1c reductions than patients who discontinued early. The consistency of this relationship across claims databases, electronic medical records, registries and specialist cohorts supports its clinical importance.

Second, emerging evidence links adherence with major clinical outcomes. Lower event rates among adherent GLP-1 RA and SGLT2i users, together with associations between objective SGLT2i exposure and reduced mortality, heart-failure hospitalization and kidney failure, suggest that interruption of therapy may attenuate established cardiorenal benefits [14,21].

Third, there is no universal class hierarchy for persistence. Some populations favored SGLT2i, while others favored GLP-1 RAs. Route, dosing frequency, tolerability, medication access, age, insurance structure and the permissible refill gap all influenced results. Therefore, persistence should be interpreted as an interaction between drug characteristics, patient factors and healthcare-system factors rather than an intrinsic property of a medication class.

Within GLP-1 RAs, dosing frequency appears particularly important. Once-weekly formulations generally outperformed daily injectable regimens [9,11]. Oral administration also did not automatically guarantee greater persistence; in one direct comparison, weekly subcutaneous semaglutide showed markedly higher persistence than daily oral semaglutide [16].

These findings have practical implications. Clinicians should anticipate gastrointestinal adverse effects, use gradual titration, provide early follow-up after initiation, address affordability and supply barriers and consider switching within a therapeutic class rather than abandoning a beneficial mechanism when appropriate. Pharmacy refill gaps may also be used as triggers for proactive outreach.

Strengths and Limitations

This review incorporates contemporary real-world evidence through June 2026 and evaluates both medication-taking behavior and patient-important outcomes. Nevertheless, most included studies were observational and therefore susceptible to residual confounding and healthy-adherer bias. Persistence definitions varied substantially, claims data demonstrated dispensing rather than ingestion, cardiorenal outcomes were not reported in every study and long-term tirzepatide evidence remained limited. The review also did not perform quantitative pooling because heterogeneity in exposure definitions and outcomes would have made a single summary estimate potentially misleading.

CONCLUSION

Newer glucose-lowering therapies provide major glycaemic, cardiovascular, renal and weight-related benefits but real-world persistence is frequently suboptimal. Greater persistence and adherence are consistently associated with better

glycaemic control and increasingly with improved cardiorenal and mortality outcomes. Treatment selection should therefore aim not only for maximal pharmacological efficacy but also for a regimen that the individual patient can realistically tolerate, access and continue. Future studies should standardize persistence definitions, evaluate treatment interruptions prospectively and determine whether structured persistence-support interventions reduce cardiovascular and renal events.

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