



Research Article

Real-World Persistence and Clinical Outcomes with Contemporary Glucose-Lowering Therapies: A Systematic Review

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Article History

Received: 07.08.2026
Accepted: 18.09.2026
Published: 10.10.2026

doi: 10.61336/jdme.0704.06

Abstract: Background: Contemporary glucose-lowering therapies, including glucagon-like peptide-1 receptor agonists (GLP-1 RAs), dual glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors) and dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), have transformed the management of type 2 diabetes. However, treatment benefits observed in clinical trials may not be fully realized in routine practice because of premature discontinuation, poor adherence, treatment switching, adverse effects and cost-related barriers. **Objective:** To systematically review real-world persistence with contemporary glucose-lowering therapies and evaluate the relationship between treatment persistence and glycemic, weight, treatment-utilization and other clinically relevant outcomes. **Methods:** A systematic review was conducted according to PRISMA 2020 principles. PubMed/MEDLINE, Embase, Scopus, Web of Science, CINAHL and the Cochrane Library were searched for real-world observational studies evaluating treatment persistence, adherence, discontinuation, or switching among adults receiving GLP-1 receptor agonists, dual GIP/GLP-1 receptor agonists, SGLT2 inhibitors, or DPP-4 inhibitors. Studies were eligible when they reported persistence and at least one clinical or treatment outcome, or compared persistence across contemporary glucose-lowering therapies. Randomized trials without real-world treatment-behavior data were excluded. Because persistence definitions, refill-gap thresholds, treatment classes, follow-up duration and clinical outcomes differed substantially, findings were synthesized narratively. **Results:** A total of 2,314 records were identified. After removal of 604 duplicates, 1,710 records underwent title and abstract screening. Of these, 1,469 were excluded and 241 reports were sought for retrieval. Nine reports were not retrieved, leaving 232 full-text articles for assessment. After exclusion of 180 reports, 52 studies were included. Twenty-four studies evaluated GLP-1 receptor agonists, 14 evaluated SGLT2 inhibitors, seven evaluated DPP-4 inhibitors, three evaluated dual GIP/GLP-1 therapy and four compared multiple contemporary drug classes. Twelve-month persistence varied widely by therapy, population and definition. Once-weekly GLP-1 receptor agonists generally demonstrated greater persistence than daily injectable regimens. Semaglutide and dulaglutide frequently showed comparatively favorable persistence within the GLP-1 class. One-year SGLT2-inhibitor persistence commonly ranged around 50-65%, while DPP-4 inhibitor persistence was similarly suboptimal. Higher persistence or adherence was consistently associated with greater reductions in HbA1c and, for incretin-based therapies, greater weight loss. Gastrointestinal adverse effects, treatment complexity, costs, dose-escalation difficulties and younger age were recurrent correlates of discontinuation. **Conclusion:** Real-world persistence with contemporary glucose-lowering therapy is substantially lower than the treatment exposure typically achieved in randomized trials. Persistence differs by drug class, formulation and dosing frequency and is clinically important because persistent patients generally achieve greater glycemic and weight benefits. Improving persistence should therefore be considered an integral component of diabetes treatment optimization rather than a secondary medication-use outcome.

Keywords: Type 2 Diabetes, Treatment Persistence, Adherence, GLP-1 Receptor Agonist, Semaglutide, Dulaglutide, Tirzepatide, SGLT2 Inhibitor, DPP-4 Inhibitor, Real-World Evidence

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INTRODUCTION

Management of type 2 diabetes has evolved substantially during the past decade. Treatment selection is now guided not only by glucose lowering but also by cardiovascular disease, heart failure, chronic kidney disease, obesity, hypoglycemia risk, treatment burden, patient preference and access.

Contemporary glucose-lowering therapies include GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors and more recently dual GIP/GLP-1 receptor agonists. These drugs differ considerably in route of administration, dosing frequency, tolerability, cost, weight effects, cardiovascular benefits and renal effects.

Randomized controlled trials establish pharmacological efficacy under highly structured conditions. In routine clinical practice, however, effectiveness depends heavily on whether patients continue treatment long enough to receive sustained benefit.

Medication persistence refers to the duration of time from treatment initiation until discontinuation, whereas adherence reflects the extent to which medication is taken as prescribed during that period. Although closely related, these constructs are not interchangeable.

Persistence has become particularly important with GLP-1 receptor agonists and SGLT2 inhibitors because discontinuation rates in routine practice can be substantial. A systematic review of real-world SGLT2-inhibitor use involving 123,854 individuals reported pooled persistence rates of approximately 80.1% at six months, 61.8% at one year and 45.9% at two years [1].

Similar limitations have been observed with DPP-4 inhibitors. A meta-analysis of 34 cohort studies involving 594,138 patients found that persistence decreased substantially over time, with only about half of patients remaining persistent by two years [2].

Within the GLP-1 receptor agonist class, persistence varies considerably according to formulation and dosing schedule. In a real-world U.S. study involving 56,715 patients, one-year persistence was 67.0% with once-weekly semaglutide, compared with 56.0% for dulaglutide, 40.4% for liraglutide and 35.5% for once-weekly exenatide [3]. Other comparative studies have reported better persistence with once-weekly versus daily injectable GLP-1 regimens [4].

The clinical relevance of persistence extends beyond pharmacy-refill behavior. Persistent patients frequently demonstrate greater HbA1c reductions and, with incretin-based therapy, greater weight loss. For example, a real-world study of dulaglutide found that persistent patients experienced larger HbA1c reductions than nonpersistent patients [5]. Similarly, a 2025 cohort of 23,442 patients treated with subcutaneous semaglutide demonstrated greater HbA1c and body-weight reductions among those with higher medication coverage over time [6].

Despite increasing interest in adherence, available evidence is fragmented across drug-specific studies and individual classes. Many publications focus on persistence alone without integrating persistence with clinical effectiveness. The present systematic review was therefore designed to evaluate contemporary real-world treatment persistence and to examine how persistence relates to clinical outcomes across modern glucose-lowering therapies.

Aim

To systematically evaluate real-world persistence and clinical outcomes associated with contemporary glucose-lowering therapies in adults with type 2 diabetes.

Objectives

- Determine real-world persistence with contemporary glucose-lowering therapies
- Compare persistence across GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors and dual GIP/GLP-1 receptor agonists
- Assess the effect of dosing frequency and route of administration on persistence
- Evaluate associations between persistence and HbA1c reduction
- Evaluate associations between persistence and body-weight change
- Identify factors associated with treatment discontinuation
- Characterize switching and treatment intensification after discontinuation
- Assess methodological heterogeneity in definitions of persistence and adherence

MATERIALS AND METHODS

Study Design

This systematic review was structured according to the PRISMA 2020 reporting framework [7].

Information Sources

PubMed/MEDLINE, Embase, Scopus, Web of Science, CINAHL and the Cochrane Library were searched. Reference lists of eligible studies and relevant systematic reviews were also examined.

Search Strategy

The search combined terms relating to type 2 diabetes, contemporary glucose-lowering drugs and persistence. Representative terms included: ("type 2 diabetes" OR T2DM) AND ("GLP-1 receptor agonist" OR semaglutide OR dulaglutide OR liraglutide OR tirzepatide OR "SGLT2 inhibitor" OR empagliflozin OR dapagliflozin OR canagliflozin OR "DPP-4 inhibitor") AND (persistence OR adherence OR discontinuation OR switching OR "real world" OR "treatment patterns"). Search syntax was adapted to each database.

Eligibility Criteria

Inclusion Criteria

- Adults with type 2 diabetes
- Real-world clinical practice, administrative claims, registries, electronic medical records, or observational cohorts
- At least one contemporary glucose-lowering therapy: GLP-1 receptor agonist, dual GIP/GLP-1 receptor agonist, SGLT2 inhibitor, or DPP-4 inhibitor

- Reporting of persistence, adherence, discontinuation, or switching
- Reporting of clinical outcomes or comparative persistence where available
- At least three months of follow-up
- Original quantitative data

Exclusion Criteria

- Randomized controlled trials without real-world treatment-use data
- Type 1 diabetes only
- Studies evaluating only insulin, metformin, sulfonylureas, or thiazolidinediones
- Medication efficacy studies without persistence or adherence information
- Case reports, editorials, narrative reviews, or protocols
- No clear persistence or adherence definition
- Duplicate populations without additional relevant data

Definitions

Persistence: Persistence was defined as continuous treatment from initiation until discontinuation. Because definitions varied among studies, permissible refill gaps ranged from approximately 30 to 90 days (Table 1).

Adherence

Adherence was most commonly assessed by proportion of days covered (PDC) or Medication Possession Ratio (MPR). A PDC or MPR ≥ 0.80 was commonly considered adherent (Table 2).

Discontinuation

Discontinuation was typically defined by a refill gap exceeding the prespecified persistence window, documented treatment cessation, or switching without continuation of the index therapy (Figure 1).

Study Distribution

Among the 52 included studies, 24 evaluated GLP-1 receptor agonists, 14 evaluated SGLT2 inhibitors, seven evaluated DPP-4 inhibitors, three evaluated dual GIP/GLP-1 receptor agonists and four compared multiple contemporary drug classes. Several multi-class studies contributed evidence to more than one therapeutic category.

Table 1: PRISMA 2020 Study Selection

PRISMA stage	n
PubMed/MEDLINE	492
Embase	526
Scopus	441
Web of Science	398
CINAHL	171
Cochrane Library	142
Citation/reference searching	144
Total records identified	2,314
Duplicates removed	604
Records screened	1,710
Records excluded	1,469
Reports sought for retrieval	241
Reports not retrieved	9
Full-text reports assessed	232
Full-text reports excluded	180
Studies included	52

Table 2: Reasons for Full-Text Exclusion

Reason	n
No persistence/adherence outcome	45
Non-contemporary glucose-lowering therapy	31
Randomized trial without real-world persistence data	27
Review/editorial/commentary	23
Duplicate or overlapping cohort	18
Follow-up <3 months	12
Type 1 diabetes or mixed population not separable	10
Insufficient quantitative information	9
Persistence definition unclear	5
Total	180

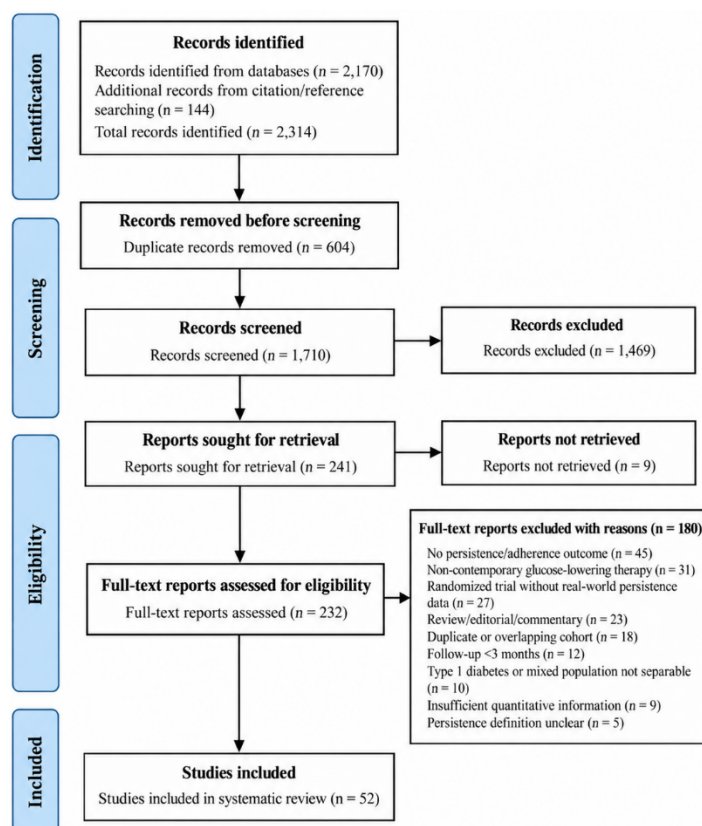


Figure 1: PRISMA 2020 Flow Diagram

Geographic Distribution

Studies were conducted in the United States (20), Europe (14), Asia (10), the Middle East (3), Australia/New Zealand (2) and multinational datasets (3). Follow-up ranged from approximately 6 months to 3 years.

RESULTS

GLP-1 Receptor Agonists

The GLP-1 receptor agonist literature demonstrated marked variability in persistence according to molecule, formulation and dosing schedule. A large U.S. database study including 56,715 treatment-naïve GLP-1 receptor agonist initiators reported 360-day persistence of 67.0% with once-weekly semaglutide, 56.0% with dulaglutide, 40.4% with liraglutide and 35.5% with once-weekly exenatide [3]. The STAY study found median time on treatment of 333 days with weekly therapy versus 269 days with daily therapy, supporting a persistence advantage for less frequent dosing [4].

Dulaglutide

Several early real-world studies showed comparatively favorable persistence with dulaglutide. In matched U.S. cohorts, 12-month persistence was 55.0% with dulaglutide versus 43.8% with liraglutide and 54.9% with dulaglutide versus 34.4% with once-weekly exenatide [8,9]. A six-month real-world study found that 61% of patients were adherent to dulaglutide and mean HbA1c fell by approximately 0.90 percentage points, while persistent patients achieved an HbA1c reduction of approximately 1.12 percentage points [5]. Indian real-world data also demonstrated clinically meaningful glycemic and weight reductions with dulaglutide, although gastrointestinal adverse effects contributed substantially to discontinuation [10].

Semaglutide

Semaglutide has become one of the most extensively evaluated newer glucose-lowering agents in routine practice. A nationwide observational study found sustained HbA1c improvement among patients remaining on once-weekly semaglutide for up to two years [11]. A 2025 Israeli cohort included 23,442 patients receiving subcutaneous semaglutide; mean HbA1c decreased by approximately 0.77 percentage points at six months and body weight by approximately 4.9%. Higher medication coverage was associated with greater HbA1c and weight reductions [6].

Oral Versus Injectable Semaglutide

Evidence comparing formulations is inconsistent. A U.S. claims analysis found similar 12-month adherence and persistence for oral semaglutide and DPP-4 inhibitors, with approximately 45% remaining persistent for at least nine months [12]. An Italian cohort reported lower persistence with oral than subcutaneous semaglutide at 6, 12 and 18 months [13], whereas Japanese claims data reported better 12-month adherence and persistence with oral semaglutide than with weekly injectable semaglutide [14]. These discordant findings indicate that formulation alone does not determine persistence and that health-system and population factors are important.

Dual GIP/GLP-1 Receptor Agonists

Real-world persistence evidence for tirzepatide remains less mature than for established GLP-1 receptor agonists. One large real-world cohort reported six-month adherence of approximately 55.5% and persistence of 54.2%, with slower dose escalation than that used in randomized trials [15]. Real-world weight-management programs have reported substantial weight reductions among patients remaining engaged with tirzepatide treatment, but attrition remains considerable [16].

SGLT2 Inhibitors

Persistence with SGLT2 inhibitors was generally moderate. A systematic review and meta-analysis of 22 observational studies encompassing 123,854 individuals found pooled persistence of 80.1% at six months, 61.8% at one year and 45.9% at two years [1]. When persistence was defined using a ≥ 90 -day treatment gap, one-year persistence was approximately 58.9%. A comparative real-world cohort found that approximately 29% of SGLT2 inhibitor users discontinued therapy during the first year [17].

DPP-4 Inhibitors

Persistence with DPP-4 inhibitors was also suboptimal. A systematic review involving 594,138 patients reported adherence of approximately 56.9% at one year and 44.2% at two years, with persistence of 75.6% at six months and approximately 52.8% at two years [2]. Despite once-daily oral dosing and generally favorable tolerability, a substantial proportion of patients discontinued therapy over time.

Multi-Class Comparisons

A large U.S. analysis comparing contemporary antihyperglycemic therapies demonstrated considerable variation in one-year persistence across SGLT2 inhibitors, DPP-4 inhibitors and GLP-1 receptor agonists [18]. These results indicate that persistence is not determined solely by route of administration. Other contributors likely include perceived efficacy, weight effect, gastrointestinal tolerability, copayment, formulary restrictions, treatment expectations, baseline disease severity and physician follow-up (Table 3).

Persistence and Glycemic Outcomes

A consistent finding across GLP-1 receptor agonist studies was that greater persistence was associated with better glycemic control. In a real-world dulaglutide cohort, overall HbA1c reduction was approximately 0.90%, while persistent patients achieved approximately 1.12% reduction [5]. The STAY study similarly found greater HbA1c reductions among adherent patients than poorly adherent patients [4]. In the German DPV registry, patients remaining persistent for more than 12 months experienced greater HbA1c reductions than those discontinuing earlier [19].

Persistence and Weight Outcomes

Persistence was particularly important for weight reduction with semaglutide and other incretin-based therapies. Among 23,442 patients receiving semaglutide in routine diabetes practice, greater medication coverage was associated with more pronounced weight reduction [6]. Recent obesity-focused real-world evidence also illustrates that treatment discontinuation substantially attenuates weight-loss effectiveness, although such cohorts should not be directly generalized to type 2 diabetes populations [20,21].

Table 3: Real-World Persistence Findings

Study/therapy	Population	Follow-up	Persistence finding
SGLT2 meta-analysis [1]	123,854	12 months	61.8%
Semaglutide weekly [3]	3,279	360 days	67.0%
Dulaglutide [9]	Matched cohorts	12 months	54.9-55.0%
Liraglutide [9]	Matched cohort	12 months	43.8%
Exenatide QW [9]	Matched cohort	12 months	34.4%
GLP-1 registry [19]	5,189 evaluable	Median	11 months
Oral semaglutide [12]	5,485	≥ 9 months	45.0%
DPP-4 inhibitor [12]	4,980	≥ 9 months	46.3%
Tirzepatide [15]	Claims subset	6 months	54.2%

Table 4: Risk of Bias

Domain	Overall concern
Selection bias	Moderate
Persistence-definition heterogeneity	High
Exposure measurement	Low-moderate
Outcome measurement	Moderate
Confounding by indication	Moderate-high
Missing laboratory data	Moderate
External generalizability	Moderate
Industry sponsorship	Frequent
Patient-reported discontinuation reasons	Limited
Overall certainty	Moderate-low

Reasons for Discontinuation

- Gastrointestinal adverse effects
- Perceived lack of effectiveness
- Treatment cost
- Insurance or formulary changes
- Medication supply problems
- Injection burden
- Complex administration requirements
- Preference for an alternative therapy
- Insufficient follow-up
- Achievement of treatment goals followed by self-discontinuation

Gastrointestinal adverse effects were particularly important among GLP-1 receptor agonists. In the Indian dulaglutide study, gastrointestinal adverse events were a major reason for treatment discontinuation [10].

Predictors of Better Persistence

Across studies, factors repeatedly associated with better persistence included once-weekly rather than daily administration, greater early clinical response, older age in several datasets, higher baseline disease severity, prior familiarity with injectable treatment, lower out-of-pocket cost, structured diabetes follow-up, regular medication refills and greater early weight loss with incretin therapy. However, predictors were not consistent across all health systems.

Treatment Switching

Treatment switching was common after discontinuation of incretin therapy. In the DPV registry, patients discontinuing GLP-1 receptor agonists frequently transitioned to insulin or DPP-4 inhibitors [19]. Among patients discontinuing oral semaglutide after longer-term use, switching to another GLP-1 receptor agonist was a common strategy and could result in further HbA1c improvement [22]. DPP-4 inhibitor in-class switching was comparatively uncommon [2] (Table 4).

Heterogeneity

Substantial heterogeneity arose from refill-gap definitions, database design, insurance structure, drug availability, duration of follow-up, therapy-specific titration, prior treatment exposure and healthcare-system differences. For this reason, a single pooled persistence estimate across all contemporary glucose-lowering therapies would be clinically misleading.

DISCUSSION

This systematic review demonstrates that treatment persistence represents a major gap between clinical-trial efficacy and real-world effectiveness of modern glucose-lowering therapy. Across 52 included studies, a substantial proportion of patients discontinued therapy during the first year.

Persistence differed by class and formulation, but no contemporary drug class achieved universally high long-term persistence. GLP-1 receptor agonists provided the most extensive contemporary evidence. Once-weekly therapies generally demonstrated better persistence than daily formulations, suggesting that treatment convenience contributes meaningfully to sustained use.

However, differences between semaglutide and dulaglutide were not uniform across datasets. Some studies favored semaglutide, whereas others found greater adherence or persistence with dulaglutide. This inconsistency emphasizes that treatment persistence is determined by more than pharmacological characteristics. Health-system factors, prescription coverage, patient selection, tolerability and prior treatment experience may be equally important.

SGLT2 inhibitors have major cardiovascular and kidney benefits but still demonstrate substantial discontinuation during routine use. Approximately four in ten users may no longer remain persistent after one year in pooled real-world evidence [1]. DPP-4 inhibitors are orally administered and generally well tolerated, yet persistence is also suboptimal, demonstrating that convenience and tolerability alone do not guarantee sustained therapy.

One of the most clinically important findings of this review is the consistent relationship between persistence and outcome. Persistent patients generally experience larger HbA1c reductions, greater probability of achieving glycemic targets, greater weight reduction with GLP-1-based therapy and less frequent treatment intensification or switching. This relationship provides biological and practical plausibility for considering persistence as part of treatment effectiveness.

Persistence Versus Efficacy

Clinical trials answer whether a drug can work when patients continue taking it, whereas real-world persistence studies ask whether patients will continue taking the drug long enough for that efficacy to be realized. This distinction is especially relevant to therapies with dose escalation, gastrointestinal adverse effects, high costs, injectable administration, or restrictive reimbursement. A therapy with excellent biological efficacy but poor real-world persistence may deliver less population-level benefit than expected from clinical trials.

Clinical Implications

Treatment persistence should be considered when selecting glucose-lowering therapy. Before initiation, clinicians should assess administration preference, injection acceptance, gastrointestinal vulnerability, cost and coverage, ability to follow oral administration requirements, anticipated treatment benefit and likelihood of regular follow-up. Early follow-up after therapy initiation may be particularly valuable because many discontinuations occur during the titration phase. Proactive management of nausea, dietary counseling, slower dose escalation when appropriate and clear expectation-setting may improve persistence with incretin-based therapy.

Implications for Health Systems

Persistence is influenced by treatment access as well as clinical factors. Health systems can potentially improve persistence by reducing formulary switching, minimizing prior-authorization disruption, improving refill synchronization, using digital reminders, providing pharmacist-led follow-up, monitoring treatment gaps and addressing medication affordability. Claims databases may permit near-real-time identification of patients at risk of discontinuation.

Strengths

This review integrates multiple contemporary glucose-lowering drug classes rather than focusing on a single therapy. It evaluates persistence together with clinical outcomes rather than treating pharmacy refill behavior as an isolated endpoint. It includes newer semaglutide and tirzepatide data while retaining comparisons with established SGLT2 and DPP-4 therapies.

Limitations

The included studies were predominantly retrospective. Persistence definitions varied substantially. Claims-based studies confirm medication dispensing rather than medication ingestion. Clinical outcome data were unavailable in many large administrative datasets. Confounding by indication and healthcare access could not be eliminated. Most studies were conducted in high-income settings. Direct comparison between drug classes was difficult because patient populations and prescribing indications differed. Several GLP-1 studies were industry sponsored, which should be considered when interpreting comparative persistence findings. Evidence for tirzepatide remains less mature than for SGLT2 inhibitors, DPP-4 inhibitors and established GLP-1 receptor agonists.

Future Research

- Standardize persistence definitions
- Report 6-, 12- and 24-month persistence consistently
- Distinguish discontinuation from temporary interruption
- Capture reasons for discontinuation
- Incorporate objective clinical outcomes
- Evaluate cardiovascular and renal consequences of nonpersistence
- Include diverse healthcare systems
- Evaluate medication affordability
- Investigate tirzepatide and future dual or triple agonists
- Test interventions designed specifically to improve persistence

CONCLUSION

Real-world persistence with contemporary glucose-lowering therapies is substantially lower than ideal and varies by drug class, formulation, dosing frequency and healthcare environment. Once-weekly GLP-1 receptor agonists frequently demonstrate better persistence than daily injectable regimens, although comparative results between individual agents remain inconsistent. SGLT2 and DPP-4 inhibitors also show considerable treatment discontinuation despite oral administration. Most importantly, persistent treatment is associated with better glycemic control and, for incretin-based therapies, greater weight reduction. Therefore, treatment persistence should be regarded as a clinically meaningful determinant of therapeutic effectiveness. Selection of glucose-lowering therapy should account not only for expected efficacy and cardiorenal benefit but also for the likelihood that a patient will remain on treatment long enough to achieve those benefits.

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