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Predictors of Successful Prandial Insulin Withdrawal Following the Initiation of Therapy Based on Glucagon-Like Peptide-1 (GLP-1) in Adults With Type 2 Diabetes (T2D): A Systematic Review of Clinical, Biochemical, and Treatment-Related Factors

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Abstract

Glucagon-like peptide-1 (GLP-1)-based therapy may permit withdrawal of scheduled prandial insulin in adults with type 2 diabetes. The clinical and biochemical factors associated with successful withdrawal remain less clearly established than the feasibility of treatment simplification.

PubMed, Embase, Scopus, and Web of Science were searched for publications from January 1, 2021 through September 16, 2026. The authors' final study selection comprised peer-reviewed primary research evaluating prandial insulin withdrawal, replacement, or related prognostic factors, with follow-up of at least 12 weeks. Prognostic studies, randomized trials, and other nonrandomized studies were assessed using design-specific tools. Clinical and methodological heterogeneity was addressed through narrative synthesis.

Of 467 records identified, 243 duplicates were removed and 224 records were screened. Sixty-one reports underwent full-text assessment, and 15 studies were included: three randomized comparisons and 12 nonrandomized studies. Four included reports examined candidate predictors, of which two provided prandial-specific analyses. Lower baseline insulin requirements and preserved endogenous secretion were the principal signals. Other associations involved diabetes duration, baseline glycemia, microvascular complications, and supervised fasting-test glycemia, although several concerned indirect endpoints. Reported discontinuation proportions varied substantially across selected populations and follow-up periods.

Prandial insulin withdrawal is feasible in selected adults receiving GLP-1-based therapy. Lower insulin requirements and preserved endogenous secretion may help identify candidates, but neither establishes a universally reliable cutoff. Broader prospective validation and consistent definitions of durable glycemic success are needed.

Categories: Cardiology
Keywords: c-peptide, de-intensification, glucagon-like peptide-1 receptor agonist, prandial insulin, prognostic factors, type 2 diabetes

Introduction And Background

For adults with type 2 diabetes mellitus (T2DM), a basal-bolus insulin regimen, which combines a long-acting (basal) insulin that provides background coverage with rapid-acting prandial (mealtime, or bolus) injections given before meals, can control both fasting and meal-related hyperglycemia, but requires repeated injections, dose adjustment, and attention to hypoglycemia. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), used with basal insulin either separately or as a fixed-ratio combination (FRC), in which basal insulin and a GLP-1 RA are co-formulated in a single daily injection, offer an alternative approach to injectable treatment. In DUAL VII (Dual Action of Liraglutide and Insulin Degludec in Type 2 Diabetes) study, insulin degludec/liraglutide (IDegLira) achieved glycemic control comparable to basal-bolus intensification, with advantages in weight and hypoglycemia [1]. SURPASS-6 (A Study of Tirzepatide Versus

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Insulin Lispro in Participants With Type 2 Diabetes) also demonstrated the efficacy of the dual glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonist tirzepatide when added to basal insulin instead of initiating prandial insulin [2]. These trials support the therapeutic rationale for reducing treatment burden; however, avoiding the introduction of mealtime insulin is a different clinical question from withdrawing established mealtime insulin. Evidence for the latter must therefore be evaluated in patients already receiving scheduled prandial injections.

The likelihood of withdrawal may depend on residual insulin secretion, the severity of dysglycemia, and the insulin requirement before treatment change. Jones et al. associated markers of β-cell failure with a weaker glycemic response to GLP-1 RAs, indicating that treatment response is not uniform across insulin-treated T2DM [3]. In a small Japanese investigation, stimulated C-peptide was associated with successful substitution of liraglutide for complex insulin therapy [4]. These findings establish biological plausibility, but the prediction of glycated hemoglobin (HbA1c) improvement, withdrawal of all insulin, and withdrawal of the prandial component are distinct outcomes. A patient may benefit metabolically from a GLP-1 RA while still requiring mealtime insulin; conversely, a prescription may be discontinued without confirming adequate postprandial control. An assessment of predictors must retain these distinctions and examine the timing, measurement, and validation of each proposed factor.

Earlier direct evidence included a randomized albiglutide replacement trial and a routine-care cohort examining prandial insulin discontinuation after GLP-1 RA initiation [5,6]. More recent observational work has specifically related baseline insulin requirements to withdrawal [7]. Nevertheless, successful de-intensification is inconsistently defined, follow-up varies, and treatment selection may favor patients whom clinicians already expect to respond. Successful withdrawal is clinically important because each prandial injection adds to daily treatment burden, hypoglycemia risk, glucose-monitoring requirements, and cost; reliable identification of suitable candidates would allow clinicians to simplify treatment with greater confidence while avoiding unsuccessful attempts. To our knowledge, the factors associated with successful withdrawal of established prandial insulin have not been synthesized separately from the broader evidence on GLP-1-based intensification, and this is the knowledge gap addressed here. The present review evaluates recent original research on clinical, biochemical, and treatment-related factors associated with successful prandial insulin withdrawal. Direct prognostic associations are distinguished from indirect findings in mixed insulin-treated populations and from eligibility criteria used in simplification studies. The objective is to identify credible candidate predictors, describe the circumstances in which withdrawal has been studied, and determine whether the available evidence supports a clinically usable prediction rule.

Review

Methodology

Reporting Framework and Registration

The review is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework [8]. The review was not prospectively registered. The formal synthesis follows the final 15-study selection documented by the review authors; related literature is considered separately in the Discussion.

Eligibility Criteria

Eligibility was structured using population, intervention/exposure, comparator, outcomes, and study design (PICOS), consistent with Cochrane guidance on defining review criteria [9]. Adults receiving scheduled prandial insulin before GLP-1-based treatment initiation were the population of interest. Mixed cohorts were eligible when the relevant subgroup was identifiable or a predominantly basal-bolus population reported a relevant transition outcome. Original, peer-reviewed trials and observational studies were eligible; non-original publications were excluded. A minimum follow-up of 12 weeks distinguished sustained treatment changes from acute insulin reduction. Table *1* summarizes the criteria.

Domain	Inclusion	Exclusion or qualification
Population	Adults with T2DM using scheduled prandial insulin; relevant subgroups eligible.	Type 1/gestational diabetes; basal-only or acute inpatient use.
Intervention	GLP-1–based treatment initiation with planned or observed bolus withdrawal.	Dose reduction without withdrawal or replacement.
Comparator	Continued insulin, nonwithdrawers, predictor strata, or baseline.	A control group was not mandatory.
Outcomes	Prandial cessation, replacement, persistence, or related predictors; ≥12 weeks.	Glycemic response without a relevant insulin transition.
Study design	Peer-reviewed trials and observational primary research.	Reviews, abstracts, letters, editorials, protocols, preprints, case reports.
Period	January 1, 2021 to September 16, 2026.	Outside-period studies used only for context.

TABLE 1: Eligibility criteria based on PICOS

PICOS: population, intervention/exposure, comparator, outcomes, and study design; T2DM: type 2 diabetes mellitus; GLP-1: glucagon-like peptide-1.

Information Sources

The authors searched PubMed (MEDLINE), Embase (Embase.com, Elsevier), Scopus (Elsevier), and Web of Science Core Collection (Clarivate). The publication period was January 1, 2021, to September 16, 2026, and the final search date was September 16, 2026, for all four databases. The first peer-reviewed online publication dates determined temporal eligibility; journal issue years are used in the references. No country restriction was applied.

Search Strategy

The PubMed search used the following string, with a publication-date filter for studies published from 2021 onward and an upper cutoff of September 16, 2026: (GLP-1[tiab] OR "glucagon-like peptide"[tiab] OR exenatide[tiab] OR liraglutide[tiab] OR dulaglutide[tiab] OR semaglutide[tiab]) AND (insulin[tiab]) AND (discontinu*[tiab] OR withdraw*[tiab] OR "de-intensification"[tiab] OR "deintensification"[tiab]). The same search terms and Boolean structure were applied to Embase, Scopus, and Web of Science, using the corresponding database field syntax and publication-date limits. In PubMed, [tiab] restricts searching to titles and abstracts, and the asterisk denotes truncation. The complete database-specific search strings, including field codes, filters, limits, and the number of records retrieved from each source, are reported in the Appendices (Table *5*).

The publication window was restricted to 2021 onward because the review aimed to characterize withdrawal in the context of currently used GLP-1-based regimens, including once-weekly semaglutide and the two basal insulin/GLP-1 RA FRCs, whose use in people previously receiving basal-bolus therapy has expanded in recent routine practice. Earlier direct evidence was limited, involved an agent that is no longer marketed (albiglutide) [5], or addressed adding a GLP-1-based agent to basal insulin rather than withdrawing established prandial insulin [1]. Searching titles and abstracts, rather than all fields, was chosen to improve specificity, because insulin, GLP-1 drug names, and withdrawal terms appear incidentally in the full text and indexing of a large volume of intensification literature. Both restrictions may reduce sensitivity. To limit their impact, earlier predictor studies [3,4] and potentially relevant cohorts outside the formal selection [6] are considered explicitly in the Discussion, and the possible effect of these restrictions on completeness is addressed in the Limitations.

Selection Process

Duplicate records were removed before title and abstract screening. Two reviewers independently screened titles and abstracts and then independently assessed potentially relevant full-text reports against the eligibility criteria; disagreements at either stage were resolved by discussion and, when necessary, by consultation with a third reviewer. The review authors completed screening and supplied the final selection record. Records that clearly did not meet the population, intervention, comparator, outcome, follow-up, or design criteria were excluded at title and abstract screening. All primary research reports that reached full-text assessment met the eligibility criteria; consequently, the 46 full-text exclusions were attributable solely to publication type (editorials, letters, short communications, review articles, and meta-analyses), and no report was excluded at full text for population, intervention, outcome, or follow-up reasons. The list of excluded full-text reports, with the reason for each exclusion, is available from the corresponding author on

request. Linked publications were considered together, with the retained extension or final analysis used to avoid counting the same cohort twice.

Data Collection Process and Data Items

Data extraction covered author, publication year, country, design, sample and subgroup sizes, baseline insulin regimen, intervention, comparator, follow-up, outcome definition, glycemic and weight outcomes, and prognostic analyses. For each prognostic association, the effect measure, 95% confidence interval (CI), p-value, predictor scale or category, number of participants analyzed, and whether the estimate was adjusted were extracted where reported. Data were extracted by one reviewer using a standardized form and checked against the full-text publication by a second reviewer; discrepancies were resolved by consensus. Relevant subgroup denominators were retained rather than substituting the total cohort size. Missing information was not imputed, and effect estimates were not assigned an unreported predictor scale. Aggregate published data were used.

Outcomes and Effect Measures

The principal outcome was withdrawal of scheduled prandial insulin, preferably with maintained or improved glycemia. Study-specific definitions were retained. Complete insulin cessation, drug persistence, temporary correction insulin, and glycemic response after replacement were treated as distinct outcomes. Extracted measures included discontinuation proportions, odds ratios and their confidence intervals, model discrimination, changes in glycated hemoglobin (HbA1c), and body weight. HbA1c changes are expressed as percentage points.

Study Risk-of-Bias Assessment

The authors assessed prognostic analyses with the Quality In Prognosis Studies (QUIPS) tool [10] and randomized comparisons with the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [11]. Other nonrandomized studies were evaluated using an adapted nine-domain assessment based on the Joanna Briggs Institute (JBI) cohort checklist [12]. This adaptation covers the first nine cohort-checklist items; it is distinct from the nine-item JBI quasi-experimental checklist. Items 10 (strategies to address incomplete follow-up) and 11 (appropriateness of the statistical analysis) were not rated as separate domains because most of these studies were single-arm before-after cohorts: item 10 overlapped substantially with item 9 (completeness of follow-up and description of losses), and item 11 applies primarily to comparative analyses that most of these studies did not undertake. Attrition and analytical concerns were therefore considered within domain 9 and in the narrative interpretation, and a sensitivity assessment of the two omitted items is reported in the Results. Two reviewers independently performed all risk-of-bias assessments, resolving disagreements by discussion. The authors visualized their ratings with the Risk-of-bias VISualization (robvis) tool [13]. Domain and overall judgments are presented without numerical quality scores. Overall judgments followed the same rule for all three tools: low risk when every domain was rated low, high risk when at least one domain was rated high, and some concerns (RoB 2) or unclear (JBI) when no domain was high but at least one was rated some concerns or unclear. Domain-level judgments for every study are also tabulated in the Appendices (Table *6*).

Synthesis Methods

A structured narrative synthesis separated direct prandial-specific prognostic associations, indirect associations involving mixed populations or complete insulin cessation, and study enrollment criteria. Trial comparisons were interpreted within each study. A meta-analysis was not performed because outcome definitions, selection criteria, follow-up, denominators, and predictor scales differed materially. Quantitative pooling would have been considered if at least two studies had reported the same predictor, measured on the same scale, for the same prandial-specific outcome with comparable follow-up; this condition was not met for any candidate predictor. Heterogeneity was therefore assessed qualitatively by tabulating differences in population, intervention, outcome definition, follow-up, and predictor measurement, and statistical heterogeneity (e.g., I^2) was not estimated. Unreported estimates, scales, or denominators were recorded as not reported rather than derived, and whether each prognostic estimate was adjusted for confounders was considered in its interpretation. Descriptive withdrawal proportions were not pooled or used to rank treatments.

Reporting Bias and Certainty of Evidence

No statistical assessment of small-study effects was performed because the studies did not provide a sufficiently comparable set of effect estimates. Confidence in the findings was considered in relation to design, risk of bias, precision, directness, and validation; no formal certainty rating was assigned.

Results

Study Selection

The authors' screening record identified 467 records: 255 from PubMed, 82 from Embase, 47 from Scopus, and 83 from Web of Science. After removing 243 duplicates, 224 records underwent title and abstract screening, and 163 were excluded. All 61 reports sought for retrieval were obtained and assessed for eligibility. Forty-six reports were excluded as editorials, letters, short communications, review articles, or meta-analyses, leaving 15 studies in the final synthesis. No primary research report was excluded at the full-text stage. Figure *1* presents the authors' PRISMA flow diagram.

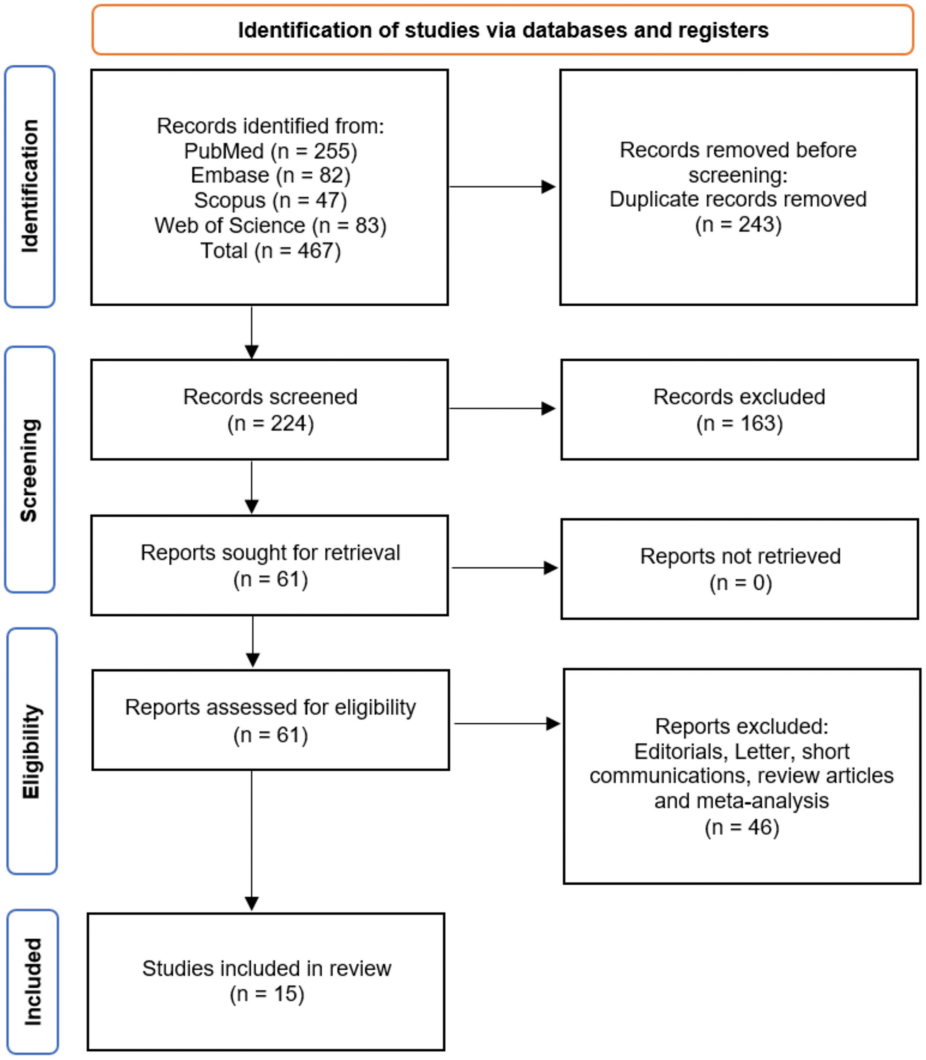


FIGURE 1: PRISMA flow diagram of study selection

Screening counts and exclusion categories are reproduced from the authors' selection record. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses [8].

Study Characteristics

The 15 studies comprised three randomized comparisons and 12 nonrandomized studies. The cohort of Falcetta et al. [7] was followed by EASY (Efficacy and Safety of Insulin Glargine and Lixisenatide in Type 2 Diabetes), the Gavigan cohort, the one-year Taybani cohort, and SIMPLIFY (Simplifying Treatment With Insulin in Type 2 Diabetes) [14-17]. Further reports comprised the BEYOND (Beyond Basal Insulin in Type 2 Diabetes) extension, REX (Real-World Experience), the fasting-test cohort, and the Di Loreto follow-up [18-21]. TRANSITION-T2D (Transitioning From Insulin to GLP-1 Receptor Agonists in Type 2 Diabetes;), GLIMPLES (GLP-1 Receptor Agonist Initiation and Insulin Simplification), the Fejes comparative cohort, soli de-escalation, IDEAL (Insulin Degludec and Liraglutide), and the Chinese transition-pathway study completed the evidence set [22-27]. Table *2* summarizes their populations, treatment strategies, and principal outcomes.

Study / country	Design / follow-up	Population / sample	Treatment	Comparator	Main findings
Falcetta et al. 2023 [7] Italy	Retrospective 24 months	156; basal-bolus	GLP-1 RA	Withdrawers vs nonwithdrawers	Bolus cessation 81%; lower initial insulin need predicted withdrawal.
Tramunt et al. 2022 [14] France	Retrospective ~6 months	629 total; 94 relevant MDI; 53 effectiveness	IDegLira	Before-after	Bolus cessation 41.5%; HbA1c -0.8 pp in relevant subgroup.
Gavigan and Donner 2023 [15] USA	Retrospective 3-12 months	81 total; 38 basal-bolus	GLP-1 RAs	Predictor strata	C-peptide ≥0.8 ng/mL associated with cessation at 3 months only.
Taybani et al. 2023 [16] Hungary	Prospective 12 months	93 enrolled; 72 completers; 62 basal-bolus	IDegLira	Before-after	HbA1c 6.4%→6.2%; weight -3.89 kg; mixed-regimen cohort.
Martinka et al. 2023 [17] Slovakia	Prospective 28 weeks	241 enrolled; 234 completed	IDegLira	Before-after	HbA1c 8.6%→7.6%; weight -3.8 kg; 7 withdrawals.
Giugliano et al. 2024 [18] Italy	RCT extension 24 months	305 total; 102 FRC; 101 basal-bolus	IDegLira / iGlarLixi	Basal-bolus	58/102 retained; HbA1c -0.8 vs -1.3 pp.
Fadini et al. 2024 [19] Italy	Prospective 18 months	358 enrolled; 334 evaluable; 76 basal-bolus	IDegLira	Before-after	Relevant subgroup HbA1c -0.60 pp; broad simplification endpoint.
Pavlikova et al. 2024 [20] Czech Republic	Retrospective 12 months	62 treated; 59 analyzed; 78% basal-bolus	Liraglutide ± basal insulin	Responders vs nonresponders	42/59 persisted; lower dose/HbA1c/fasting glycemia favored success.
Di Loreto et al. 2024 [21] Italy	Retrospective Up to 48 months	156 total; 68 basal-bolus	IDegLira	Before-after	Relevant subgroup HbA1c -1.07 pp; weight -7.7 kg at 48 months.
Rodriguez et al. 2025 [22] USA	RCT 26 weeks	60; 40 semaglutide, 20 MDI	Semaglutide + degludec	Continued MDI	39/40 stopped bolus; HbA1c ≤7.5%: 90% vs 75%.
Bonora et al. 2025 [23] Italy	Retrospective Median 18 months	674 total; 248 bolus-treated	Semaglutide	Before-after / predictor strata	186/248 stopped bolus; model predicts complete insulin cessation.
Fejes et al. 2025 [24] Hungary	Comparative cohort 24 months	162; 104 simplified, 58 controls	IDegLira / iGlarLixi	Intensified insulin	HbA1c -1.3 vs -0.9 pp; weight -5 vs -1 kg.
Giorgino et al. 2025 [25] USA	Database cohort 6 months	372; prior basal-bolus	iGlarLixi	Before-after	HbA1c -0.9 pp; HbA1c <7%: 7.0%→14.8%.
Novodvorský et al. 2026 [26] Czech Republic	RCT 24 weeks	91 randomized; 90 analyzed	iGlarLixi	Continued MDI	Between-arm HbA1c −0.12 pp; weight -4.19 kg.
Zhang et al. 2026 [27] China	Retrospective ≥3 months exposure	1,499 total; 301 prior MDI	IDegLira	Prior-treatment strata	269/301 recorded bolus cessation among continuous users.

TABLE 2: Characteristics and principal findings of included studies

GLP-1 RA: glucagon-like peptide-1 receptor agonist; MDI: multiple daily insulin injections; IDegLira: insulin degludec/liraglutide; iGlarLixi: insulin glargine/lixisenatide; FRC: fixed-ratio combination; RCT: randomized controlled trial; HbA1c: glycated hemoglobin; pp: percentage points; USA: United States of America. Sample sizes distinguish total cohorts from relevant subgroups and completers. BEYOND also randomized 102 participants to a sodium-glucose cotransporter-2 inhibitor strategy.

Predictors of Withdrawal

Four included reports examined candidate predictors. Falcetta et al. associated lower baseline insulin requirements with prandial cessation [7]. Gavigan and Donner found an association with preserved random C-peptide at three months, but not at six or 12 months [15]. Pavlikova et al. examined clinical variables and

supervised fasting-test glycemia against treatment persistence in a mixed population [20]. GLIMPLES reported bolus withdrawal, but its prognostic model concerned complete insulin cessation [23]. Table *3* distinguishes these endpoints and separates prognostic findings from trial entry criteria.

Factor	Study	Endpoint	Finding	Interpretation
Insulin requirement	Falcetta et al. [7]	Prandial cessation	aOR 0.144; 95% CI 0.046–0.456 (n=156)	Lower dose favored withdrawal; scale not specified.
Random C-peptide	Gavigan and Donner [15]	Prandial cessation	≥0.8 vs <0.8 ng/mL: 11/23 vs 0/7 (n=30 at 3 months)	3-month association; not sustained at later visits.
Dose and HbA1c	Pavlikova et al. [20]	Regimen persistence	Lower baseline values in responders (n=59)	Mixed population; indirect endpoint.
Fasting-test glycemia	Pavlikova et al. [20]	Regimen failure	>8.1 mmol/L: OR 5.24; 95% CI 1.55–17.65 (n=59)	Exploratory 72-hour test; no external validation.
Duration, HbA1c, dose, microangiopathy	Bonora et al. 2025 [23]	Complete insulin cessation	Shorter duration; lower HbA1c/dose; no microangiopathy (cohort n=674)	C-statistic 0.74; not a bolus-specific model.
C-peptide/dose thresholds	Selected trials [16,17,22,26]	Eligibility	Preserved secretion and/or capped insulin dose	Enrollment restrictions, not validated predictors.

TABLE 3: Candidate predictors and their clinical interpretation

aOR: adjusted odds ratio; OR: odds ratio; CI: confidence interval; HbA1c: glycated hemoglobin. Falcetta: p=0.001, with predictor scale unavailable; Gavigan: p=0.029 at three months. Bonora model discrimination concerns complete insulin cessation, not bolus withdrawal. Enrollment thresholds are not validated prognostic cutoffs. n: number of participants contributing to the analysis, as reported.

Effect estimates are reported as published. Falcetta et al. reported an adjusted odds ratio (aOR) of 0.144 (95% CI 0.046-0.456; p=0.001) among 156 participants; because the scale of the insulin-requirement variable was not reported, this estimate conveys the direction and statistical significance of the association but not a clinically interpretable magnitude per unit of dose [7]. Gavigan and Donner reported cessation in 11 of 23 participants with random C-peptide ⩾0.8 ng/mL versus 0 of 7 below this value at three months (p=0.029), without an adjusted estimate [15]. Pavlikova et al. reported an odds ratio of 5.24 (95% CI 1.55-17.65) for regimen failure when mean fasting-test glycemia exceeded 8.1 mmol/L among 59 analyzed participants [20]. The GLIMPLES model reported a C-statistic of 0.74 for complete insulin cessation [23]. Where a CI or p-value is absent from Table *3*, it was not reported in the source publication.

Withdrawal Outcomes and Durability

Reported prandial discontinuation proportions varied across populations and follow-up periods (Figure *2*). EASY separated participants newly receiving a GLP-1 RA from those already using one; the former subgroup directly informs initiation [14]. In TRANSITION-T2D, 39 of 40 participants stopped scheduled bolus insulin, although correction insulin was permitted during early titration [22]. In GLIMPLES, 186 of 248 bolus-treated participants discontinued prandial insulin [23]. Zhang et al. recorded cessation in 269 of 301 prior multiple daily insulin injection (MDI) users selected for continued treatment [27]. These proportions do not measure an identical composite of withdrawal and sustained glycemic control.

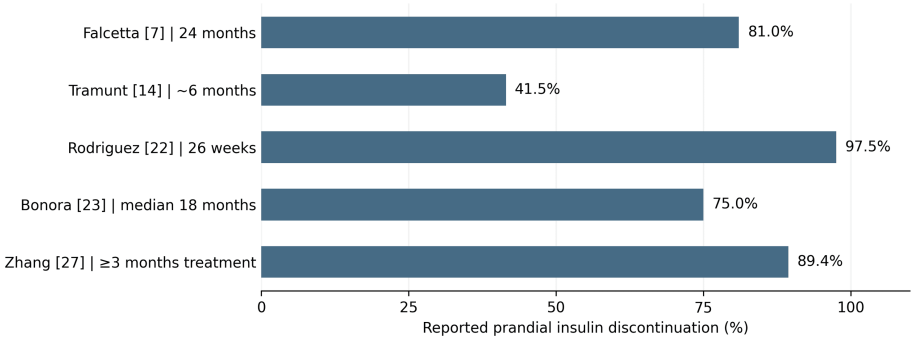


FIGURE 2: Reported prandial insulin discontinuation proportions

Descriptive comparison without pooling. Falcetta et al.: n=156; Tramunt et al.: effectiveness subgroup n=53; Rodriguez et al.: 39/40; Bonora et al.: 186/248; Zhang et al.: 269/301 [7,14,22,23,27]. Follow-up, selection, correction insulin, and outcome ascertainment differ; treatment superiority cannot be inferred.

Treatment persistence also differed from glycemic success. In the BEYOND extension, 58 of 102 participants assigned to FRC treatment completed 24 months [18]. This is a retention measure, not a stand-alone withdrawal success rate. Table *4* summarizes the endpoint distinctions relevant to interpretation.

Outcome	Study examples	Meaning	Main qualification
Scheduled bolus cessation	Falcetta et al. [7], Tramunt et al. [14], Rodriguez et al. [22], Bonora et al. [23], Zhang et al. [27]	Stopping prescribed bolus	Does not establish durable glycemic success.
Regimen persistence	Taybani et al. [16], Martinka et al. [17], Giugliano et al. [18], Pavlikova et al. [20]	Remaining on simplified treatment	Includes tolerability and follow-up selection.
Glycemic response	Fadini et al. [19], Di Loreto et al. [21]; Fejes et al. [24], Giorgino et al. [25], Novodvorský et al. [26]	Mean HbA1c change	Does not identify individual withdrawal success.
Complete insulin cessation	Bonora et al. 2025 [23]	Stopping basal and bolus insulin	More extensive than bolus withdrawal.
Correction insulin	Rodriguez et al. [22]	Temporary rescue during titration	Allowed during the first 12 weeks.

TABLE 4: Interpretation of the principal outcome definitions

HbA1c: Glycated hemoglobin.

Glycemic and Treatment-related Outcomes

Most simplification studies reported improved or maintained mean glycemia alongside lower insulin exposure or weight. SIMPLIFY also reported continuous glucose monitoring in a subgroup [17]. REX and Di Loreto provided longer-term observations, although mixed populations and changing denominators limit inference [19,21]. Fejes included a nonrandomly selected comparison group [24], and soli de-escalation examined patients with high baseline HbA1c [25]. In IDEAL, the between-arm HbA1c difference was −0.12 percentage points (95% confidence interval −0.48 to 0.23), with lower weight in the iGlarLixi group [26]. Uncontrolled changes and nonsignificant comparisons do not establish equivalence or identify individual withdrawal predictors.

Risk of Bias in Prognostic Studies

The authors' QUIPS assessment classified Falcetta et al., Gavigan et al., and Bonora et al. studies as low risk across the six domains [7,15,23]. Pavlikova et al. was classified as high overall risk because of attrition and statistical analysis/reporting, with low ratings in the remaining domains [20]. Figure *3* presents these judgments. These classifications do not remove concerns about small predictor subsets, indirect endpoints, or limited external validation.

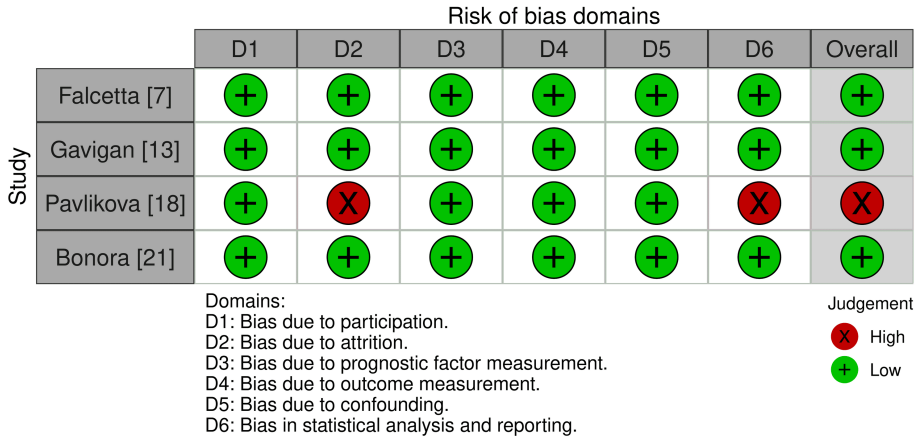


FIGURE 3: QUIPS risk-of-bias assessment

Author-supplied judgments, with citation labels aligned to this manuscript [7,15,20,23]. QUIPS: Quality In Prognosis Studies. D1: participation; D2: attrition; D3: prognostic factor measurement; D4: outcome measurement; D5: confounding; D6: statistical analysis and reporting. Overall categories are qualitative summaries [10].

Risk of Bias in Randomized Trials

The RoB 2 assessment classified the BEYOND extension as high overall risk because of missing outcome data, with some concerns for randomization, deviations from intended interventions, and selective reporting [18]. TRANSITION-T2D and IDEAL were rated low risk across all five domains [22,26]. Figure *4* presents the randomized-trial assessment.

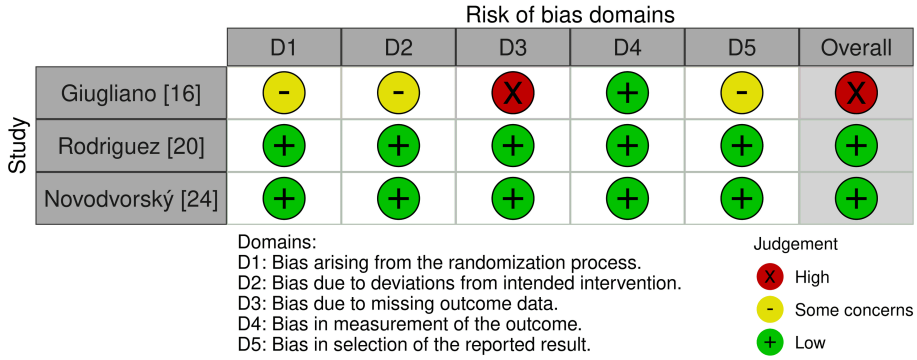


FIGURE 4: RoB 2 assessment of randomized comparisons

Author-supplied judgments [18,22,26]. RoB 2: revised Cochrane risk-of-bias tool for randomized trials. D1: randomization; D2: deviations from intended interventions; D3: missing outcome data; D4: outcome measurement; D5: selection of the reported result [11].

Risk of Bias in Other Nonrandomized Studies

In the adapted JBI assessment, six studies received low overall ratings [14,16,19,24,25,27]. Martinka et al. and Di Loreto et al. were rated high risk because confounding factors and strategies to address confounding were inadequately covered; exposure measurement and outcome-free status at baseline were unclear [17,21]. Figure *5* presents the nine assessed domains. The adaptation and qualitative overall classification limit direct comparison with complete standard JBI appraisals. In a sensitivity assessment of the two omitted JBI items, the most conservative assumption (rating items 10 and 11 as high risk for every JBI-assessed study) would change the overall rating of the six low-risk studies to high risk. However, none of these eight studies contributed a prognostic estimate to the predictor synthesis, which rests on the four QUIPS-assessed studies

(Figure 3). The candidate-predictor conclusions would therefore be unchanged; the assumption would lower confidence only in the descriptive withdrawal and glycemic outcomes from these cohorts, which are already presented without pooling or ranking.

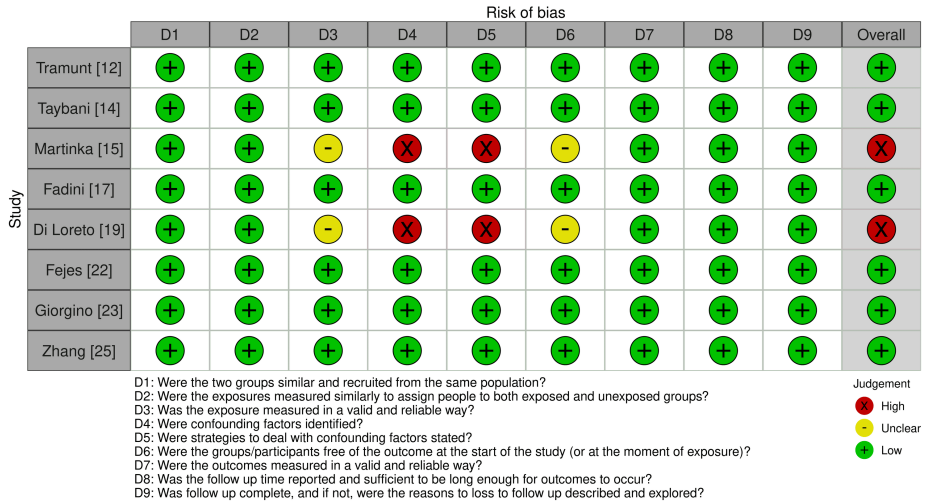


FIGURE 5: Adapted JBI cohort-based assessment

Author-supplied judgments [14,16,17,19,21,24,25,27]. JBI: Joanna Briggs Institute. D1: group comparability and source population; D2: comparable exposure ascertainment; D3: valid/reliable exposure measurement; D4: identification of confounders; D5: strategies addressing confounding; D6: outcome-free status at baseline; D7: valid/reliable outcome measurement; D8: sufficient follow-up; D9: completeness of follow-up. This nine-domain adaptation displays the first nine items of the 11-item cohort checklist; strategies for incomplete follow-up and appropriate statistical analysis are not separate displayed domains. Overall labels are author-defined qualitative judgments [12].

Discussion

Principal Findings

The principal finding is that the evidence supporting the feasibility of prandial insulin withdrawal is substantially broader than the evidence supporting prediction of an individual patient's success. The identified studies encompass multiple drugs, baseline glycemic states, and clinical settings. Nevertheless, only a small subset formally compared baseline characteristics between people who did and did not sustain a simplified regimen. Lower insulin requirements and preserved endogenous secretion emerge as plausible candidate factors, but the included studies do not establish a broadly transportable, prospectively validated rule for prandial insulin withdrawal. Consequently, the observed success of a treatment strategy in a selected group should not be interpreted as proof that its enrollment criteria accurately identify responders in routine practice. The following subsections interpret each candidate factor in turn; limitations of the review itself are presented separately.

Baseline Insulin Requirement

Baseline insulin dose is clinically attractive because it is readily available and may summarize several aspects of disease severity. Falcetta et al. report an adjusted association with the specific outcome of prandial discontinuation [7]. The direction is consistent with the earlier cohort of Bonora et al., which related successful de-intensification to lower insulin requirements, shorter diabetes duration, and better glycemic control [6]. However, dose is partly a prescribing variable. It reflects prior titration, adherence, dietary intake, concurrent therapy, and clinicians' willingness to accept different glucose targets. A low prescribed dose may indicate modest physiological need, but it may also indicate undertreatment. Because the scale of the dose variable was not reported, the magnitude of the association cannot be translated into a clinical threshold [7]. Bonora et al.'s 2021 study also reported validation of a probability estimate in a separate cohort of 40 patients [6]. The relevant gap is larger-scale validation with transparent calibration, standardized follow-up, and evaluation of clinical decision benefit.

A future analysis should record basal and prandial components separately, express dose both in absolute units and relative to body weight, and document whether prescriptions reflect actual administration. Dose reduction occurring after the GLP-1-based treatment begins should not be incorporated into a model

advertised as predicting success before initiation. Such a model would use information unavailable at the intended decision point and could appear more accurate than it would be in practice. If early dose changes are useful, they should instead form a clearly defined dynamic prediction model that updates the probability of success after several weeks of monitored treatment.

Endogenous Secretion and C-peptide

C-peptide is closer to the hypothesized biological mechanism because it reflects endogenous insulin secretion. The short-term association reported by Gavigan and Donner is encouraging, but the small number with low C-peptide and the absence of a persisting statistically significant association at later visits limit confidence [15]. Jones et al. provide external support for a relationship between β-cell failure and reduced glycemic response, although that study did not establish a prandial withdrawal rule [3]. Iwao et al. found predictive value in a meal-stimulated measurement when examining substitution of liraglutide for insulin therapy [4]. The differing test conditions and endpoints mean that these thresholds cannot be combined into a single clinical cutoff.

Biomarker validation should therefore begin with a specified sampling protocol and a prespecified decision threshold. Fasting, random, and meal-stimulated values represent different physiological conditions. Any clinical model should also record glucose at sampling and relevant renal function, rather than interpreting a C-peptide value in isolation. The useful question is not simply whether the biomarker differs between responders and nonresponders, but whether it improves discrimination and calibration beyond routinely collected clinical information. A test that adds little to insulin dose and baseline glycemia may have limited value even when its association is statistically significant.

Supervised Fasting Test

The fasting-test study illustrates the distinction between an interesting physiological observation and a validated clinical procedure. Pavlikova et al. reported associations between glycemia during supervised fasting and persistence with liraglutide-based treatment, but their cohort included different baseline insulin regimens and used a treatment-persistence endpoint [20]. The proposed cutoffs were derived within the same small dataset in which performance was examined. These findings are hypothesis-generating. They do not establish that a prolonged fast improves decisions over simpler assessments, and they do not justify unsupervised insulin withdrawal or fasting. Independent replication would need to show incremental predictive benefit, reproducibility, acceptable resource use, and safety before such an approach could be considered part of routine assessment.

Baseline Glycemia and the Definition of Success

Baseline HbA1c requires similarly careful interpretation. Lower values may indicate that withdrawal can be attempted without needing a large additional glucose-lowering effect. In contrast, a higher value can provide more opportunity for an absolute reduction following any effective intervention. Thus, the factors associated with the largest HbA1c fall need not be the same as those associated with achieving an individualized target without mealtime insulin. Defining success solely by a percentage reduction from baseline risks classifying a person with persistently high glucose as a success. Defining it solely by an absolute target can disadvantage participants who start with more severe hyperglycemia. Both baseline severity and the clinical objective need to be specified when interpreting a predictor.

Randomized and Contextual Evidence

This subsection distinguishes direct evidence from contextual evidence. The included randomized comparisons [18,22,26] address withdrawal or replacement of established prandial insulin, whereas the older add-on trials discussed below [1,2,5,28-31] address how to advance basal insulin and are cited only for therapeutic plausibility, not as evidence of withdrawal predictors. The randomized evidence demonstrates why patient selection and outcome definition matter. TRANSITION-T2D studied people whose diabetes was already reasonably controlled and used structured monitoring during the transition [22]. BEYOND's longer follow-up addresses durability, including failures of the simplified strategy [18]. IDEAL extends randomized evidence to another FRC and a different selected population [26]. These studies should not be ranked by a simple comparison of withdrawal percentages. Differences in starting HbA1c, insulin dose, residual secretion, rescue treatment, and follow-up create different opportunities for success. Randomization protects the comparison of assigned strategies within a trial, but does not by itself validate a baseline prognostic factor or demonstrate that a subgroup characteristic modifies treatment benefit.

The albiglutide trial demonstrated that prandial insulin could be replaced in a substantial proportion of participants while evaluating glycemic outcomes against continued basal-bolus therapy [5]. Its design and population differ from those of the recent semaglutide trial, and a higher percentage in one study cannot establish superiority of one molecule for withdrawal without an appropriate randomized comparison. Similarly, DUAL VII supports the effectiveness of IDegLira as an alternative to adding bolus insulin after basal treatment failure, but it does not directly answer whether longstanding bolus therapy can be stopped

[1]. SURPASS-6 showed that tirzepatide improved glycemia and weight with less hypoglycemia than adding insulin lispro to basal insulin [2]; it supports the plausibility of future withdrawal studies with dual incretin agonists rather than supplying a validated predictor. Separate administration and FRC treatment also differ in dosing flexibility and in the relationship between incretin exposure and basal insulin titration, and future studies should investigate whether these treatment features interact with baseline patient characteristics instead of relying on cross-study comparisons.

The 4B trial provides a useful comparison: exenatide added to optimized basal insulin achieved glycemic control comparable to mealtime lispro, with a different weight and hypoglycemia profile [28]. Harmony 6 similarly compared weekly albiglutide with prandial lispro as an addition to basal insulin [29]. GetGoal Duo-2 extended this therapeutic comparison to lixisenatide versus once-daily or three-times-daily glulisine [30]. SUSTAIN 5 (Semaglutide Added to Basal Insulin in Type 2 Diabetes) adds placebo-controlled evidence that semaglutide improves glycemia and weight in people receiving basal insulin [31]. Together, these trials support the premise that incretin-based treatment can address meal-related hyperglycemia while limiting the burden of insulin intensification, but their randomized question concerned how to advance basal treatment, not which established basal-bolus users can successfully stop bolus insulin.

Relevant Studies Outside the Formal Synthesis

Evidence in older adults also deserves attention. The STOP (Simplifying Treatment in Older People) study evaluated 96 insulin-treated people with a mean age of 77 years; three-quarters had previously used basal-bolus therapy [32]. This contemporaneous cohort broadens the clinical context beyond relatively selected trial participants and emphasizes treatment burden, hypoglycemia, and functional ability when interpreting simplification. As with other observational studies, favorable outcomes following a clinician-selected switch cannot establish that age itself predicts success. The contribution of frailty, cognitive impairment, support with medication administration, and individualized glycemic targets needs to be separated from chronological age. Bonora et al. 2021 and STOP are discussed here as contextual evidence outside the authors' formal 15-study synthesis; their relevance limits any claim that this selected corpus exhausts all applicable research. Neither report was retained in the authors' final selection record, and they were not added post hoc so that the documented selection process remains reproducible. As an informal sensitivity check, their inclusion would be unlikely to alter the conclusions: Bonora 2021 associated lower insulin requirements, shorter diabetes duration, and better glycemic control with successful de-intensification [6], which is directionally concordant with the formal synthesis, and STOP informs the clinical context of simplification in older adults rather than the identification of individual predictors [32].

Observational Evidence and Estimands

Observational cohorts broaden the picture of routine practice but introduce several interpretive problems. Clinicians choose whom to switch, patients decide whether they can afford and tolerate treatment, and subsequent follow-up often depends on continued engagement with care. Excluding people who discontinue early can remove clinically important failures from the denominator. For the patient considering treatment, gastrointestinal intolerance, financial barriers, and inability to sustain monitoring are part of the probability of a successful strategy. Analyses restricted to persistent users answer a narrower question about effectiveness among those who remain treated. Both estimands are useful, but they should be named explicitly and should not be presented as interchangeable. The GLIMPLES (GLp-1 for therapeutic sIMPLification in type 2 diabetES) model of complete insulin discontinuation can suggest candidate variables for future prandial-specific research, but its performance cannot be transferred automatically to that outcome [23]. A model also needs evaluation of absolute predicted risks, not only a measure of discrimination; external validation should retain the original model specification, report calibration across risk groups, and examine whether clinically important subpopulations are systematically overestimated or underestimated.

Outcome Standardization and Future Research

Outcome standardization is a priority. A useful core outcome would document discontinuation of all scheduled mealtime injections, absence of recurrent rescue insulin after a defined transition period, maintenance of an individualized glycemic target, and acceptable hypoglycemia burden. These components should also be reported separately so readers can understand why a strategy failed. Continuous glucose monitoring could complement HbA1c through time in range, time below range, and post-meal glucose patterns. Durability deserves distinct analysis because early withdrawal and sustained withdrawal are not the same event. Studies should report time to bolus reintroduction, the clinical reason for restarting, and what happens after discontinuation of the GLP-1-based drug, and death, loss to follow-up, and treatment cessation should be accounted for transparently rather than silently excluded.

The next research step should be a multicenter prospective cohort embedded within a standardized withdrawal pathway, followed by independent validation in another setting. Candidate variables should be specified before analysis, with sufficient outcome events for the intended model complexity and transparent handling of missing data. A pragmatic randomized study could then test whether using the prediction model

improves decisions compared with usual clinical assessment. Such work should measure clinical benefit, failed withdrawal, treatment burden, and resource use, rather than discrimination alone.

Clinical Implications

For current clinical interpretation, the evidence favors individualized consideration of simplification with a planned monitoring and rescue strategy. It does not support a rigid dose, HbA1c, or C-peptide threshold that guarantees success. Patient priorities should be treated as outcomes in their own right: injection burden, fear of hypoglycemia, confidence in self-management, and treatment affordability may influence whether a metabolically successful change is worthwhile. Patients outside tightly selected trial populations should not automatically be assumed to fail; their outcomes are simply less securely characterized. Until prospective validation is available, the present findings are best used to frame candidate predictors and guide careful interpretation of simplification studies, while recognizing that the certainty of individual prediction remains limited.

Limitations

Interpretation is limited by heterogeneous definitions of successful withdrawal, follow-up durations, baseline insulin regimens, and treatment selection. Mixed-cohort outcomes were not always separately available for prandial-treated participants, and aggregate data prevented harmonized adjustment. Exclusion of early discontinuers, missing observations, changing co-therapy, and clinician selection can bias both withdrawal proportions and prognostic associations. Several proposed thresholds were examined in small development datasets, and low risk-of-bias ratings do not establish transportability or clinical utility. The formal synthesis retains the authors' selected 15-study set, while relevant contemporaneous cohorts, including Bonora et al. 2021 and STOP, are considered only as contextual literature; exhaustive coverage of all potentially eligible research is therefore not established [6,32]. The specified title/abstract search may also miss studies using different terminology, and the restriction to publications from 2021 onward excluded earlier studies from the formal synthesis; although the principal earlier predictor studies are concordant in direction [3,4,6], unidentified older or differently indexed studies could add further candidate factors. The adapted JBI assessment does not rate items 10 and 11 of the standard cohort checklist as separate domains, although the sensitivity assessment indicates that this does not affect the predictor conclusions. Full texts were retrieved for all assessed reports and extracted data were checked against the original publications; however, some details could not be verified because they were not reported by the primary studies, notably the scale of the insulin-requirement variable [7], effect estimates for C-peptide beyond three months [15], and outcomes restricted to prandial-treated participants in mixed cohorts [16,19,20]. These gaps limit the interpretation of effect magnitudes rather than the direction of the reported associations. The review was not prospectively registered. These limitations, together with the absence of a pooled analysis or formal certainty grading, warrant cautious interpretation of individual prediction and cross-study differences.

Conclusions

GLP-1-based therapy can support withdrawal of scheduled prandial insulin in selected adults with T2DM. Lower baseline insulin requirements and preserved endogenous secretion are promising candidate predictors, but existing evidence does not define a universally reliable selection threshold. Prandial withdrawal, complete insulin cessation, treatment persistence, and glycemic success should be evaluated separately. Larger prospective studies should validate prediction models and test whether their use improves patient outcomes.

Appendices

Database (platform)	Search string	Limits / filters	Records
PubMed (MEDLINE)	(GLP-1[tiab] OR "glucagon-like peptide"[tiab] OR exenatide[tiab] OR liraglutide[tiab] OR dulaglutide[tiab] OR semaglutide[tiab]) AND (insulin[tiab]) AND (discontinu*[tiab] OR withdraw*[tiab] OR "de-intensification"[tiab] OR "deintensification"[tiab])	Publication date 2021/01/01 to 2026/09/16; no language or country limit	255
Embase (Embase.com, Elsevier)	('glp-1':ti,ab OR 'glucagon-like peptide':ti,ab OR exenatide:ti,ab OR liraglutide:ti,ab OR dulaglutide:ti,ab OR semaglutide:ti,ab) AND insulin:ti,ab AND (discontinu*:ti,ab OR withdraw*:ti,ab OR 'de-intensification':ti,ab OR deintensification:ti,ab)	Publication years 2021–2026; records first published after 16 September 2026 excluded at screening	82
Scopus (Elsevier)	TITLE-ABS("GLP-1" OR "glucagon-like peptide" OR exenatide OR liraglutide OR dulaglutide OR semaglutide) AND TITLE-ABS(insulin) AND TITLE-ABS(discontinu* OR withdraw* OR "de-intensification" OR deintensification)	PUBYEAR > 2020 AND PUBYEAR < 2027; records first published after 16 September 2026 excluded at screening	47
Web of Science Core Collection (Clarivate)	(TI=("GLP-1" OR "glucagon-like peptide" OR exenatide OR liraglutide OR dulaglutide OR semaglutide) OR AB=("GLP-1" OR "glucagon-like peptide" OR exenatide OR liraglutide OR dulaglutide OR semaglutide)) AND (TI=(insulin) OR AB=(insulin)) AND (TI=(discontinu* OR withdraw* OR "de-intensification" OR deintensification) OR AB=(discontinu* OR withdraw* OR "de-intensification" OR deintensification))	Publication years 2021–2026; records first published after 16 September 2026 excluded at screening	83

TABLE 5: Complete database-specific search strategies

All searches were last run on 16 September 2026. Fields were restricted to titles and abstracts in every database; the asterisk denotes truncation.

Study	Tool	D1	D2	D3	D4	D5	D6	D7	D8	D9	Overall
Falcetta [7]	QUIPS	L	L	L	L	L	L	–	–	–	Low
Gavigan [15]	QUIPS	L	L	L	L	L	L	–	–	–	Low
Pavlikova [20]	QUIPS	L	H	L	L	L	H	–	–	–	High
Bonora 2025 [23]	QUIPS	L	L	L	L	L	L	–	–	–	Low
Giugliano [18]	RoB 2	SC	SC	H	L	SC	–	–	–	–	High
Rodriguez [22]	RoB 2	L	L	L	L	L	–	–	–	–	Low
Novodvorský [26]	RoB 2	L	L	L	L	L	–	–	–	–	Low
Tramunt [14]	JBI	L	L	L	L	L	L	L	L	L	Low
Taybani [16]	JBI	L	L	L	L	L	L	L	L	L	Low
Martinka [17]	JBI	L	L	U	H	H	U	L	L	L	High
Fadini [19]	JBI	L	L	L	L	L	L	L	L	L	Low
Di Loreto [21]	JBI	L	L	U	H	H	U	L	L	L	High
Fejes [24]	JBI	L	L	L	L	L	L	L	L	L	Low
Giorgino [25]	JBI	L	L	L	L	L	L	L	L	L	Low
Zhang [27]	JBI	L	L	L	L	L	L	L	L	L	Low

TABLE 6: Domain-level risk-of-bias judgments for all included studies

Judgments are identical to those displayed in Figures 3-5 and are tabulated for reference. L: low; H: high; SC: some concerns; U: unclear; –: domain not applicable to the tool. QUIPS domains D1–D6: participation, attrition, prognostic factor measurement, outcome measurement, confounding, statistical analysis and reporting. RoB 2 domains D1–D5: randomization, deviations from intended interventions, missing outcome data, outcome measurement, selection of the reported result. Adapted JBI domains D1–D9: as defined in Figure 5.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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