

Background

Approximately 40.3% of U.S. adults and 16% of adults globally live with obesity. GLP-1 receptor agonists improve glycemic control, promote weight loss, and reduce cardiovascular risk, but many patients experience treatment interruptions or discontinue therapy before achieving their full potential benefit.

- GLP-1 therapies require gradual dose escalation to balance efficacy with tolerability, particularly gastrointestinal adverse effects.
- Standard schedules generally recommend dose increases every four weeks and are based largely on clinical-trial protocols.
- These protocols may not reflect differences in clinical response, adverse effects, medication access, and adherence in routine care.

Real-world patterns of GLP-1 titration, persistence, switching, and discontinuation therefore remain poorly understood.

Objectives

- Characterize real-world GLP-1 treatment trajectories, including dose titration, persistence, medication switching, treatment gaps, and discontinuation.
- Examine differences in progression to maintenance across patient and treatment groups.
- Evaluate the associations of titration and persistence with changes in weight, BMI, and A1c.

Methods

- We conducted a retrospective analysis of 75,237 patients prescribed GLP-1–based therapy. Clinical outcomes were compared across four groups: titrated and persistent, titrated and nonpersistent, nontitrated and persistent, and nontitrated and nonpersistent.
- Kruskal-Wallis tests and Bonferroni-corrected pairwise Mann-Whitney U tests were used to evaluate group differences.

Key Definitions

- **Titration:** Gradual dose escalation toward maintenance.
- **Maintenance:** Reaching maximum dose or remained at a lower dose after achieving prespecified clinical goals.
- **Persistence:** Continued GLP-1 therapy without a treatment gap of ≥ 60 days.

Treatment Trajectories

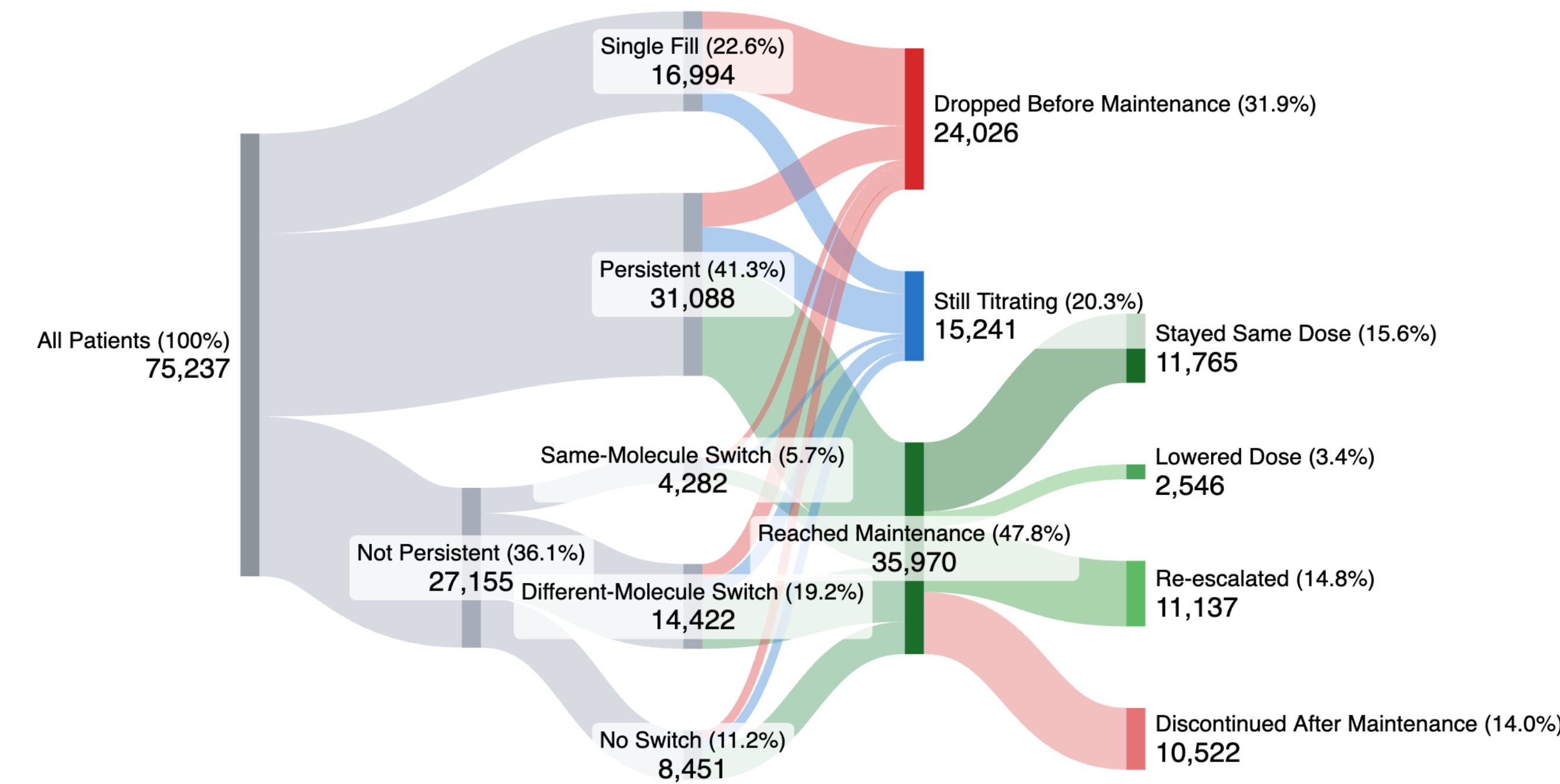


Figure 1. Real-World GLP-1 Treatment Trajectories

Treatment Trajectory

- 47.8% reached maintenance.
- 31.9% discontinued before maintenance.
- Among patients reaching maintenance, 29.3% later discontinued.

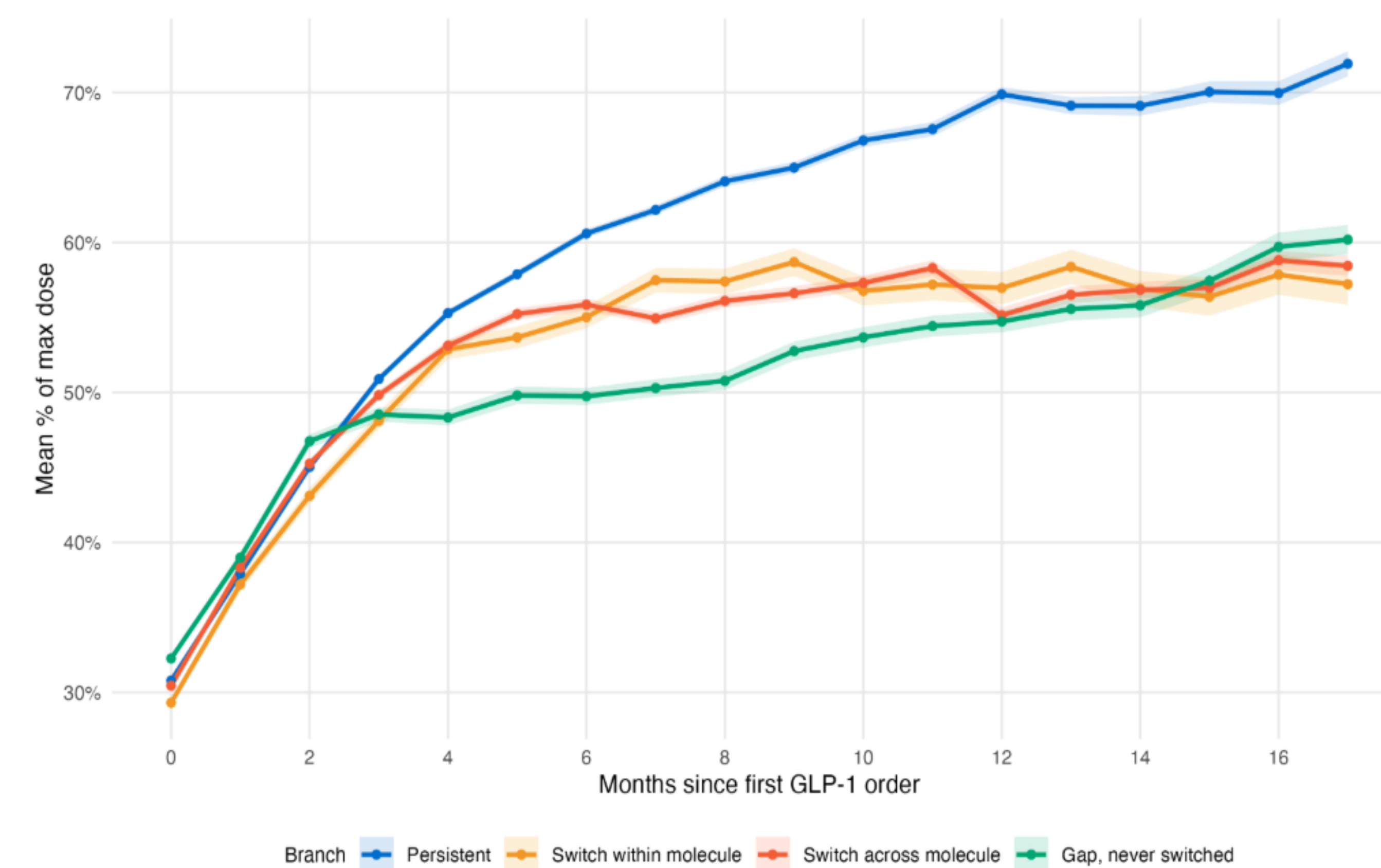


Figure 2. Titration progression by patient trajectory. Mean percentage of the medication-specific maximum dose is shown by month after the first GLP-1 order.

Switching Patterns

- Wegovy $\leftrightarrow$ Zepbound accounted for approximately 53% of observed switching pathways.
- Among within-molecule switchers, 73% switched at the first dose level.
- The median interval was 22 days for tirzepatide $\rightarrow$ semaglutide switches and 69 days for semaglutide $\rightarrow$ tirzepatide switches.
- These differences may reflect medication access, indication, tolerability, or clinical response.

Clinical Implications

Treatment group	Weight Change (%)	BMI Change (%)	A1c Change (%)
Titrated + persistent	−5.1%	−4.9%	−0.57
Titrated + nonpersistent	−4.6%	−4.4%	−0.51
Nontitrated + persistent	−1.8%	−1.7%	−0.18
Nontitrated + nonpersistent	−1.0%	−0.9%	−0.09

Table 1. Mean Changes in Clinical Outcomes by Titration and Persistence

Titrated and persistent patients experienced the largest mean reductions in weight, BMI, and A1c. Treatment duration and follow-up differed across groups, so these findings should be interpreted as associations.

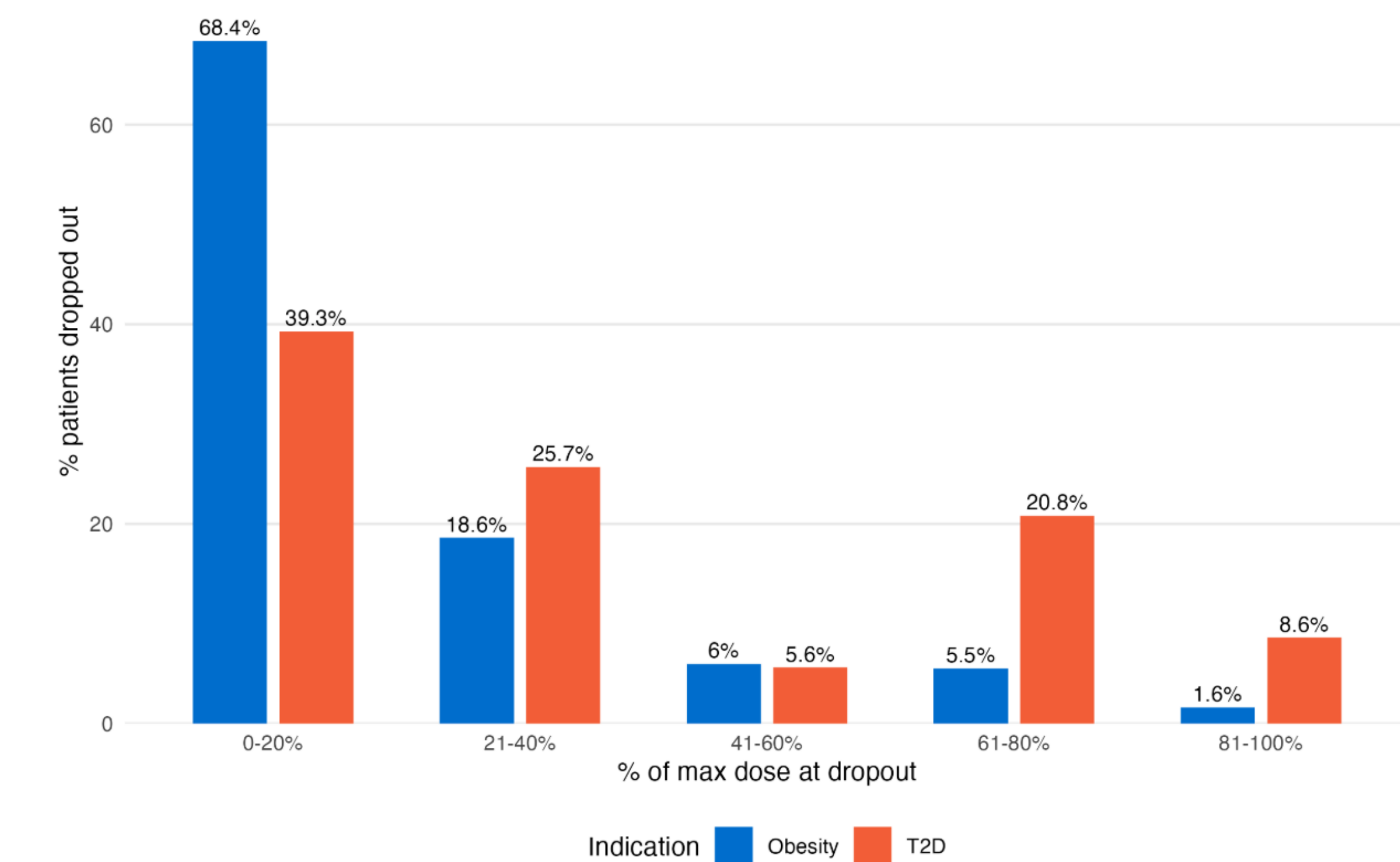


Figure 3. Dose Level at Discontinuation by Insurance.

70.9% of Medicaid patients who discontinued stopped within the lowest 20% of the dose ladder, compared with 40.4% of self-pay patients.

Conclusions

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- GLP-1 treatment frequently followed a nonlinear trajectory involving switching, treatment gaps, and discontinuation.
- Nearly one-third of patients discontinued before maintenance, often during early titration.
- Reaching maintenance did not necessarily indicate sustained treatment.
- Titration and persistence were associated with greater improvements in weight, BMI, and A1c.

Limitations

Medication orders may not indicate actual medication use, and reasons for switching or discontinuation were not directly observed. Clinical outcome comparisons may be confounded by differences in treatment duration and follow-up.