Disclosures for Hamlet Gasoyan, DS, PhD, MPH

- Nothing to disclose

Comparative effectiveness of MBS and other obesity therapies after initial treatment with semaglutide or tirzepatide: A target trial emulation

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Background

- Discontinuation rates of semaglutide and tirzepatide at 1 year range from 47-65%
- Patients frequently seek additional obesity treatment after discontinuation
- Comparative data on alternative obesity treatments after initial semaglutide or tirzepatide therapy are lacking

Study Goals

Compare obesity treatment strategies by emulating a pragmatic trial in which patients who continued injectable semaglutide or tirzepatide for at least 3 months were assigned to:

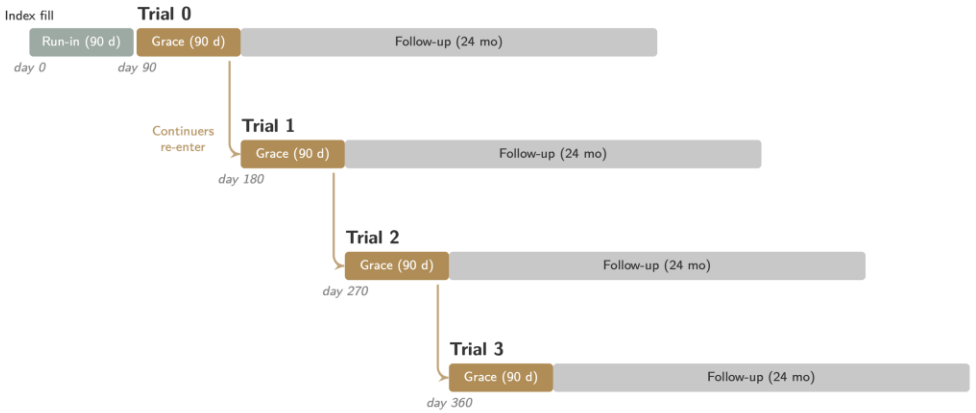
1. continuation of the original medication
2. switching between semaglutide and tirzepatide
3. switching to another obesity medication [OM]
4. undergoing metabolic and bariatric surgery [MBS]
5. discontinuation with no further pharmacological or surgical treatment

Study Design and Participants

- Observational study emulating a target trial
  - Cleveland Clinic EHR data in Ohio and Florida from January 1, 2021, to December 31, 2025

- We used target trial emulation [TTE] to
  - reduce design-related biases, and
  - sharpen the causal question, and then
  - adjusted for a high-dimensional set of clinical covariates to address confounding

Nested sequence of 4 quarterly trials starting from quarter 0



Single trial design (repeated at each quarterly trial)

Eligibility
≥90 days cumulative Index supply, BMI ≥ 27, age 18+

Run-in (90 d)

Treatment classification
90-day grace period

Grace (90 d)

1. Continue index med
2. Switch index med (sema↔tirz)
3. Alternative obesity med
4. Bariatric surgery
5. Stop (no treatment)

Covariates at baseline
Age, sex, race/ethnicity, insurance, ADI, weight, dose tier, index med, prescriber specialty

Measured at trial baseline

Lookback covariates
HbA1c, BP, eGFR, CCI, smoking, alcohol, T2D, HTN, concomitant meds (lipid, antidiabetic, antihypertensive), wt mgmt utilisation

Most recent prior to baseline

Follow-up period
Primary: body weight at 12 months (±60 days)

12-mo weight ±60 d
24-mo weight ±60 d

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Outcomes

Primary outcome was the **percent change in body weight**

- from index date to 1- and 2-years after TTE enrollment

Secondary outcomes included

- **absolute change in HbA1c**, in a subset of patients with T2D, and
- **absolute change in systolic blood pressure**, in a subset of patients with hypertension

Covariates

Baseline covariates included

- Socio-demographic, and
  - age, sex, race and ethnicity, primary insurance type, Area Deprivation Index
- a rich set of anthropometric and clinical variables
  - height, smoking status, alcohol use, specialty of the original therapy's prescriber, presence of T2D, hypertension, age-adjusted Charlson comorbidity index, prior weight management encounters, index medication (semaglutide or tirzepatide), number of antihypertensive medications, number of antidiabetic medications, lipid-lowering medication use, and baseline values of time-varying covariates

Time-varying covariates included

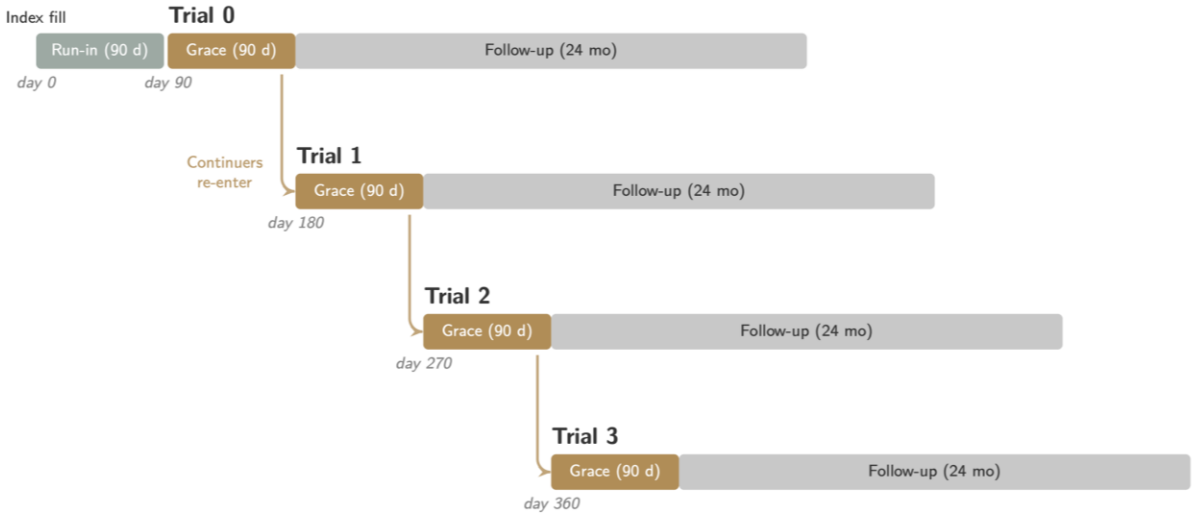
- body weight, eGFR, HbA1C, and SBP, and the attained dose from index date to start of quarterly trial

Analyses

- We assessed baseline and time-varying characteristics of all patients at enrollment as well as those who persisted with each strategy at the conclusion of the grace period
- To account for baseline confounding, we estimated inverse probability of treatment weights (IPTW)
- The primary estimand was the per-protocol effect, estimated with combined IPTW × Inverse probability of censoring weights (IPCW) × Inverse probability of observation weights (IPOW)
- Intention-to-treat estimates (IPTW × IPOW) are reported as secondary analyses
- Treatment effects and marginal mean outcomes were estimated via g-computation from weighted linear outcome model

Descriptive Data

- 20,486 patients were available for first sequential trial
- 74% filled an index Rx for semaglutide, 26% for tirzepatide
- At trial entry, the mean body weight was 109 kg representing a -2.3 kg (-2.1%) reduction from index date
- 51% attained the highest dose during the run-in period
- 68% had hypertension 66% T2D



Sequential trial enrollment

Trial	Total	Continue	Switch	Alt Med	Bariatric	Stop
Period 0	**20,486**	18,203	440	537	441	865
Period 1	**18,043**	14,672	501	512	94	2,264
Period 2	**14,556**	12,107	411	392	38	1,608
Period 3	**12,014**	10,225	384	250	18	1,137
Total	**65,099**	**55,207**	**1,736**	**1,691**	**591**	**5,874**

Arm assignment determined at conclusion of the 90-day grace period. Eligible pool declines as non-continuers permanently exit.

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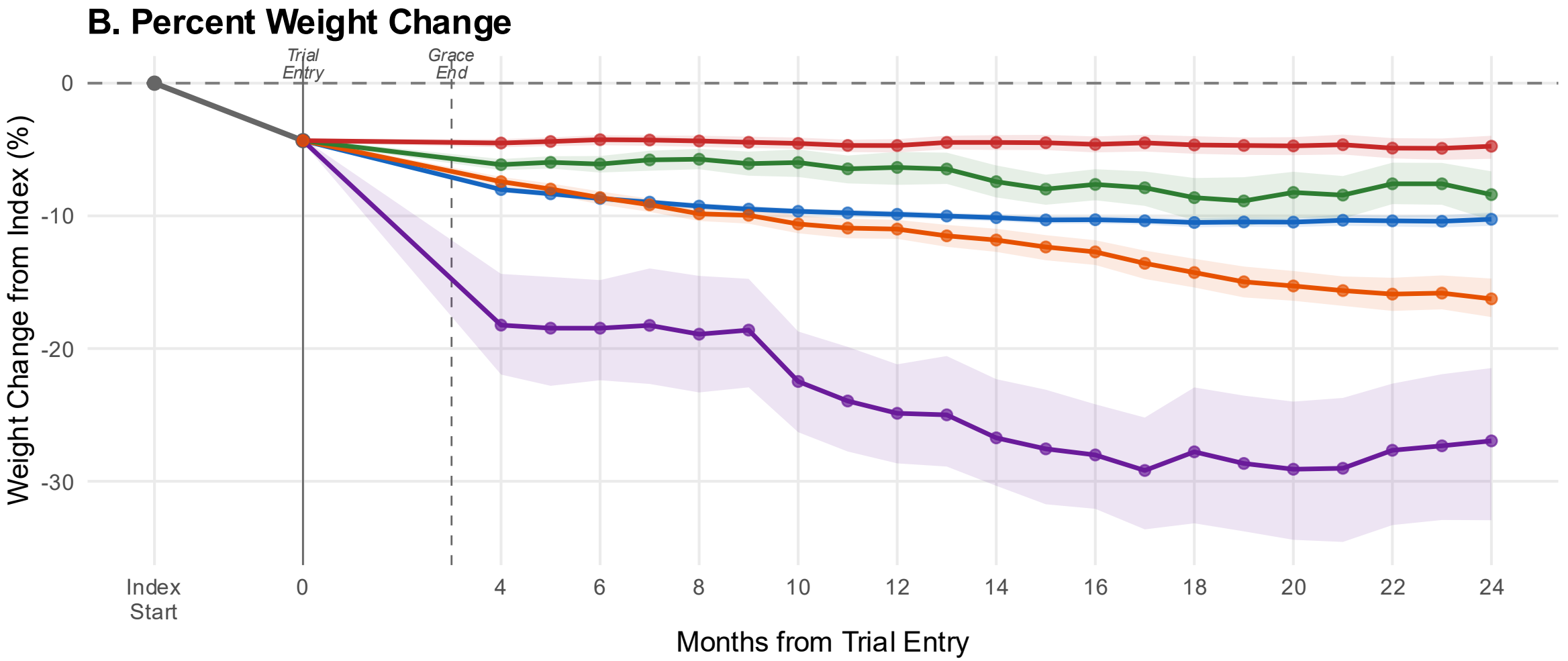
Weight change from index date to 1-year and 2-years after TTE enrollment (per-protocol analysis)



Weight Change – Subgroup Analyses

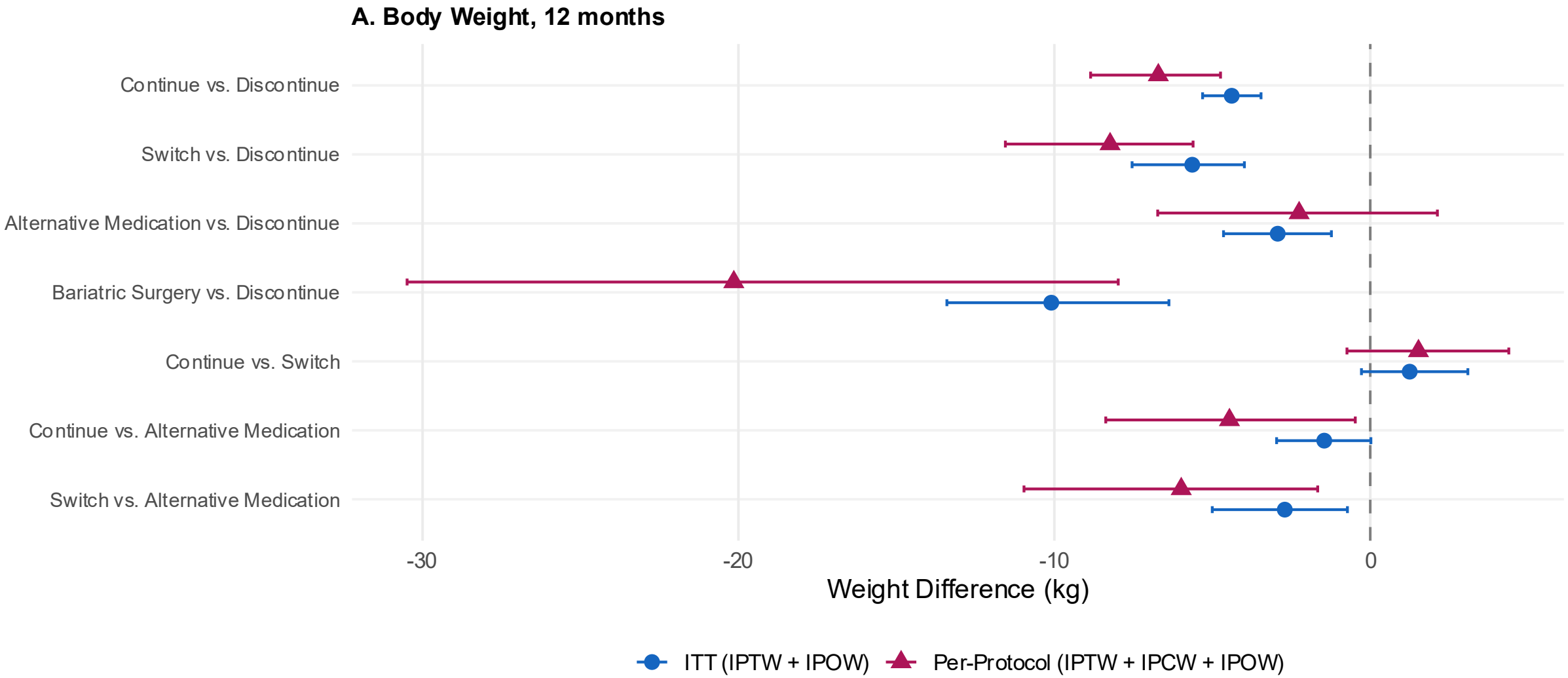
By index medication

- among patients originally on semaglutide, switching to tirzepatide was associated with greater weight loss than continuing semaglutide (difference, −3.0 kg; 95% CI, −4.9 to −1.3)
- among patients on tirzepatide, continuing the original medication was associated with greater weight loss than switching to semaglutide (difference, 4.5 kg; 95% CI, 0.3 to 7.2)

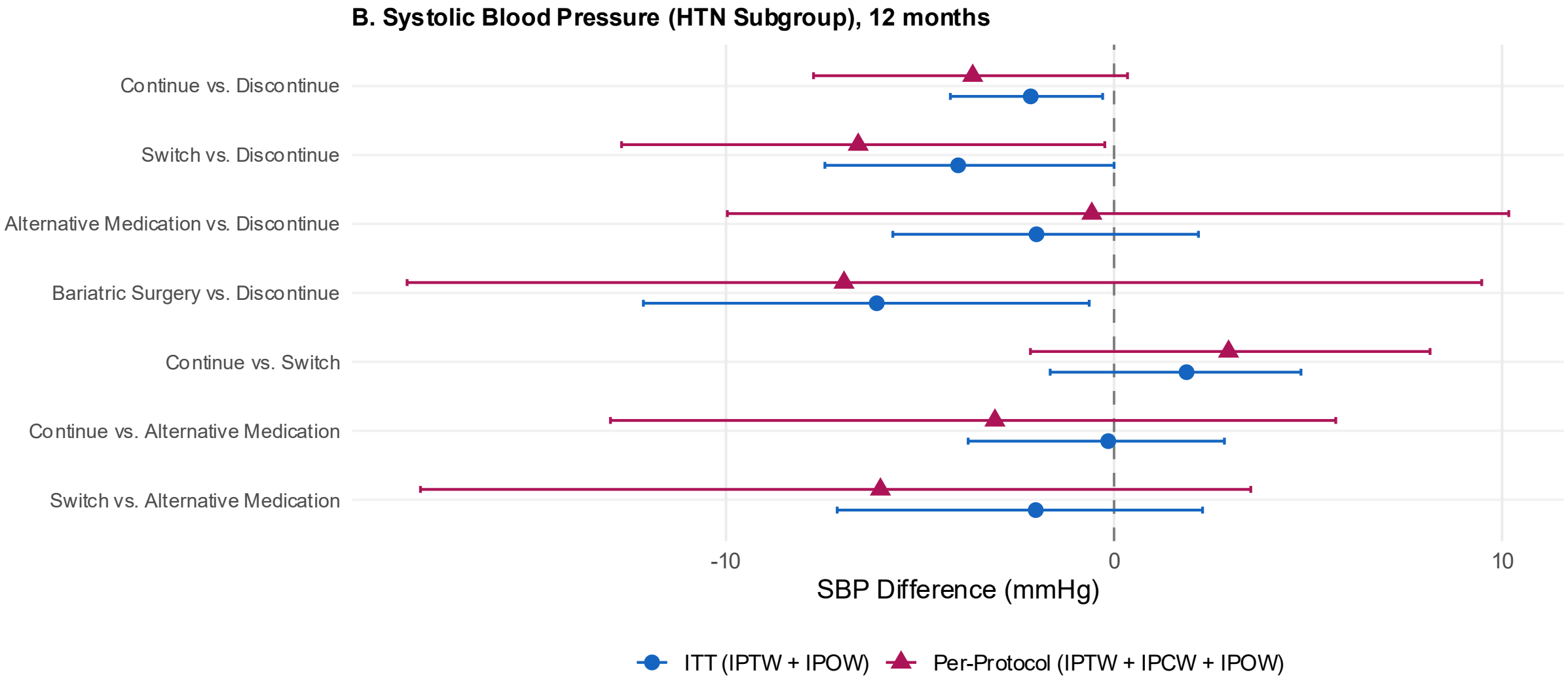
By indication

- in the obesity indication subgroup, all active strategies showed larger weight differences vs. discontinuation compared with the T2D subgroup

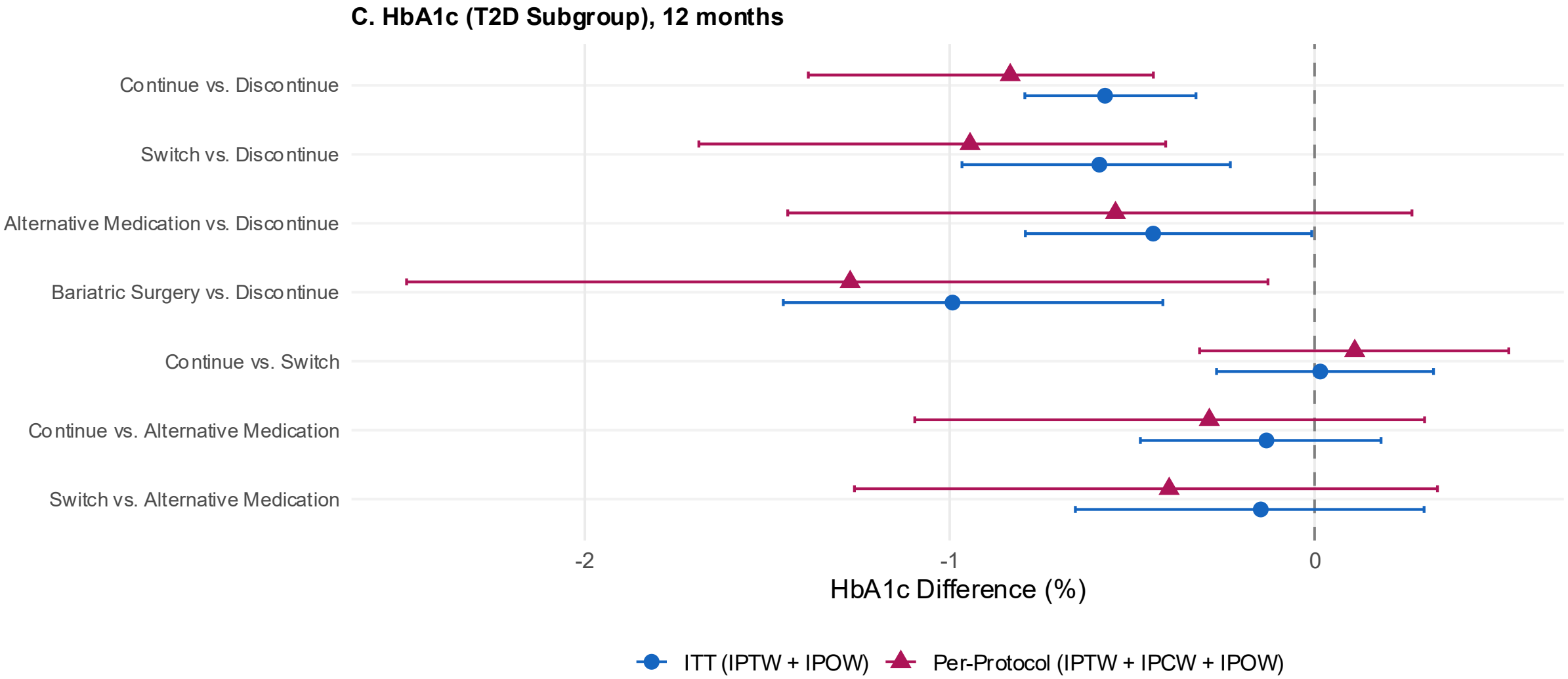
Forest plots of pairwise treatment arm comparisons



Forest plots of pairwise treatment arm comparisons



Forest plots of pairwise treatment arm comparisons



Discussion

- The average weight loss from initial semaglutide or tirzepatide fill to 2-years after target trial emulation enrollment:
  - Underwent MBS (-28.2%)
  - Switched between semaglutide and tirzepatide (-16.0%)
  - Continued original medication (-10.9%)
  - Switched to another OM (-8.2%)
  - Discontinued the treatment (-4.0%)
- Among patients originally on semaglutide, switching to tirzepatide was associated with greater weight reduction than continuing semaglutide
- Changes in HbA1c (in patients with T2D) and SBP (in those with hypertension) followed a similar pattern

Limitations

- Generalizability, although our study population was diverse (including 17% non-Hispanic Black, 7% Hispanic), and obesity treatment discontinuation and reinitiation patters from this cohort were largely comparable to those from other US settings
- Unmeasured residual confounding
- Some of the observed weight reduction may be associated with unstructured lifestyle or dietary interventions, or compounded medications that we were unable to capture

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