Preoperative Semaglutide Therapy and New Persistent Opioid Use After Total Knee or Hip Arthroplasty: A Target Trial Emulation

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Background

New persistent opioid use (NPOU) follows 5.9–6.5% of operations in opioid-naive adults; 8.2% after TKA and 4.3% after THA remain on opioids at 6 months.[1,2]

GLP-1 receptor agonists modulate mesolimbic reward pathways, and semaglutide has been associated with lower opioid overdose risk in patients with type 2 diabetes and opioid use disorder.[3]

Preclinical evidence is not uniform, and semaglutide delays first-hour gastric emptying, which could alter absorption of oral analgesics.[4,5]

We hypothesized that preoperative semaglutide therapy would be associated with LOWER NPOU.

Methods

Design. Target trial emulation,[6] reported in accordance with the TARGET statement[7] and STROBE. MarketScan Commercial and Medicare claims, July 2018 – June 2023. IRB HUM00134333.

Population. Opioid-naive adults 45 years or older with osteoarthritis undergoing TKA (CPT 27447) or THA (CPT 27130), enrolled 180 days before through 180 days after surgery.

Exposure. 2 or more semaglutide fills during days −180 to −5 with supply covering the day of surgery; non-users had none. Patients with one fill were excluded.

Outcomes. Primary, NPOU: at least one opioid fill during days 4–90 AND at least one during days 91–180. Secondary: monthly opioid fill, total OME, number of opioid fills, emergency department visit, and time to opioid cessation. Additional: hospital admission, surgical complication, and opioid overdose or related diagnosis.

Analysis. Stabilized selection and censoring weights with propensity-score matching with replacement (1:≤5, caliper 0.2 SD of the logit); weighted logistic regression with robust variance, adjusted rates as marginal effects. The NPOU model also adjusted for an opioid fill by day 3 after surgery.

Sensitivity. Excluding additional surgery within 180 days (a descriptive check, because that surgery follows time zero); excluding non-users on other GLP-1 receptor agonists; multiple imputation of urban/rural. These models omitted the day-3 covariate.

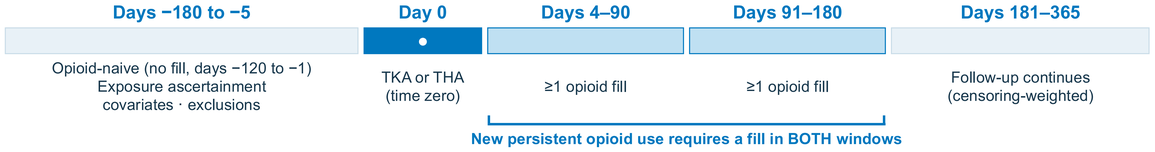


Figure 1. Target trial design. Eligibility, treatment assignment, and the start of follow-up are aligned at day 0. Secondary and additional outcomes were assessed through day 365.

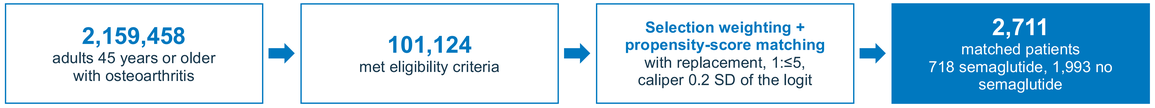


Figure 2. Derivation of the analytic cohort.

Table 1. Selected patient characteristics after matching.

Characteristic	Semaglutide (n = 777)	No semaglutide (n = 3,018)	Characteristic	Semaglutide (n = 777)	No semaglutide (n = 3,018)
Age 45–54 yr	178 (23.0)	736 (24.4)	Medicare payer	117 (15.1)	561 (18.6)
Age 55–64 yr	475 (61.1)	1,719 (56.9)	Total knee arthroplasty	632 (81.4)	2,462 (81.6)
Age 65–74 yr	91 (11.7)	396 (13.1)	Outpatient setting	654 (84.2)	2,530 (83.8)
Age ≥75 yr	33 (4.2)	167 (5.5)	Obesity	465 (60.0)	1,786 (59.2)
Female	512 (65.9)	1,947 (64.5)	Type 2 diabetes mellitus	638 (82.1)	2,306 (76.4)
Midwest region	187 (24.1)	918 (30.4)	Tobacco use disorder	29 (3.8)	61 (2.0)
Southern region	374 (48.1)	1,251 (41.4)	Opioid fill by postoperative day 3*	583 (75.0)	2,211 (73.3)
Rural residence	117 (15.0)	574 (19.0)			

No. (%), selection-weighted counts. Cells of 10 or fewer are not shown per data-use policy. *Measured after surgery; adjusted for in the NPOU model only.

Results

10.0% vs 6.1%
adjusted NPOU rate
semaglutide vs. no semaglutide

1.73
adjusted odds ratio for NPOU
95% CI, 1.20 to 2.49 (P = 0.003)

+70 mg
adjusted difference in total OME
95% CI, 3 to 137 (P = 0.041)

2,711 matched patients — 718 semaglutide users and 1,993 non-users (weighted 777 and 3,018), with 193 NPOU events. In the weighted cohort, 64.8% were female, 77.6% had type 2 diabetes, 59.3% had obesity, and 81.5% underwent TKA.

NPOU occurred in 70 of 718 semaglutide users (9.7%) and 123 of 1,993 non-users (6.2%). Standardized mean differences were 0.053 or less after matching; five exceeded 0.10 after selection weighting and were additionally adjusted for.

Compared with the primary model without the day-3 covariate (OR 1.75; 95% CI, 1.22 to 2.51), sensitivity estimates were 1.89 (1.25 to 2.86) excluding additional surgery, 1.85 (1.27 to 2.68) excluding non-users on other GLP-1 receptor agonists, and 1.75 (1.22 to 2.51) with imputation.

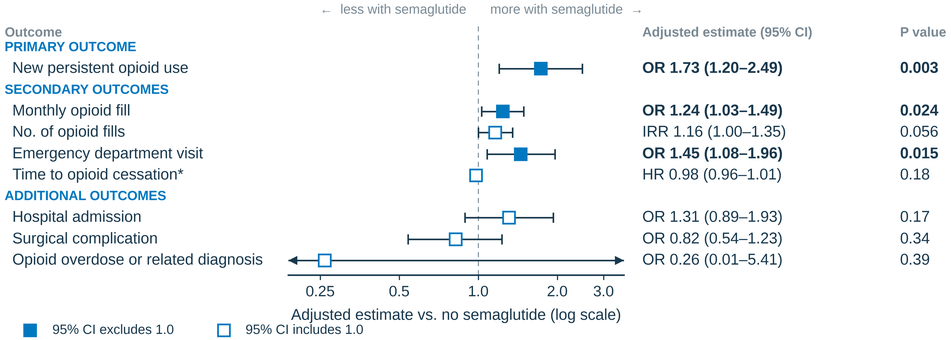


Figure 3. Adjusted associations between preoperative semaglutide therapy and postoperative outcomes. Filled squares denote 95% CIs excluding 1.0; the overdose CI is truncated. *HR below 1.0 means slower cessation; its CI (0.96–1.01) is narrower than the marker. Total oral morphine equivalents, a mean difference, cannot share a ratio axis.

Conclusions

Preoperative semaglutide therapy was NOT associated with lower new persistent opioid use after TKA or THA.

Semaglutide users had higher adjusted odds of NPOU, higher odds of a monthly opioid fill, greater total OME, and more emergency department visits. No outcome significantly favored semaglutide.

Confounding by indication offers one explanation: semaglutide users more often had type 2 diabetes, which is associated with persistent opioid use,[8] and claims lack BMI and HbA1c to capture disease severity. The design cannot establish causation.

These findings do not support a perioperative opioid-sparing effect of semaglutide. Patients taking semaglutide warrant at least the same attention to opioid stewardship as other arthroplasty patients.

References

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Abbreviations: BMI, body mass index; CI, confidence interval; CPT, Current Procedural Terminology; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; HR, hazard ratio; IRR, incidence rate ratio; OME, oral morphine equivalents; OR, odds ratio; SD, standard deviation; THA/TKA, total hip/knee arthroplasty.