RESEARCH LETTER

Discontinuation of Semaglutide Among Older Adults With Diabetes in the US and Japan

Semaglutide improves cardiovascular, kidney, and metabolic outcomes, but its benefit may be limited if patients discontinue therapy.[1] Prior studies have shown high discontinuation rates of glucagon-like peptide-1 receptor agonists (GLP-1RAs) as a drug class,[2] but few studies have specifically studied frequencies and predictors of injectable semaglutide discontinuation.[3,4] Assessing discontinuation patterns across countries with marked differences in population-level cardiometabolic risk as well as structural differences in health care systems may elucidate important predictors of semaglutide discontinuation and inform strategies to support persistence. Therefore, we used national health care databases in the US and Japan to evaluate frequencies and predictors of discontinuation of injectable semaglutide in older adults with diabetes.

Supplemental content

Methods | We included US adults from a 100% sample of Medicare claims (traditional fee-for-service and Medicare Advantage) between January 1, 2018, and December 31, 2022, and Japanese adults from the DeSC database between January 1, 2018, and October 31, 2023. We included adults aged 65 years or older with diabetes who initiated injectable semaglutide prescriptions. Details of data sources, study population, outcome, and covariates are described in the eMethods in Supplement 1. Institutional review board approval was exempted by the Beth Israel Deaconess Medical Center because this study involved secondary use of data (category 4); informed con-

Table. Demographic and Clinical Characteristics of Patients Who Initiated Injectable Semaglutide Among Adults Aged 65 Years or Older in the US and Japan

Patient characteristic	Cohort		Absolute standardized difference
	United States (n = 318 543)	Japan (n = 8531)	
Age, mean (SD), y	71.7 (5.3)	77.3 (7.3)	0.88
Sex, No. (%)			
Female	175 191 (55.0)	4247 (49.8)	0.10
Male	143 352 (45.0)	4284 (50.2)	
Self-reported race and ethnicity, No. (%)[a]			
American Indian or Alaska Native	2741 (0.9)	NA	NA
Hispanic	11 988 (3.8)	NA	
Non-Hispanic Asian	7117 (2.2)	NA	
Non-Hispanic Black	38 638 (12.1)	NA	
Non-Hispanic White	244 651 (76.8)	NA	
Other	6192 (1.9)	NA	
Unknown	7216 (2.3)	NA	
Insurance type, No. (%)[b]			
Dual enrollment in Medicare Advantage and Medicaid	74 363 (23.3)	NA	NA
Medicare Advantage	187 154 (58.8)	NA	
Comorbidity, No. (%)			
Hypertension	187 154 (58.8)	7374 (86.4)	0.62
Obesity	134 461 (42.2)	316 (3.7)	0.92
Chronic kidney disease	156 923 (49.3)	3813 (44.7)	0.09
Heart failure	63 573 (20.0)	3378 (39.6)	0.43
Ischemic heart disease	110 999 (34.8)	3311 (38.8)	0.08
Stroke or transient ischemic attack	27 077 (8.5)	1739 (20.4)	0.34
Peripheral vascular disease	65 657 (20.6)	314 (3.7)	0.52
Cancer	29 899 (9.4)	1088 (12.8)	0.11
Depression	85 928 (27.0)	921 (10.8)	0.41
Dementia	20 716 (6.5)	1124 (13.2)	0.22
Prior use of any other GLP-1RAs[c]	68 952 (21.6)	1373 (16.1)	0.14

Abbreviations: GLP-1RAs, glucagon-like peptide-1 receptor agonists; NA, not applicable.

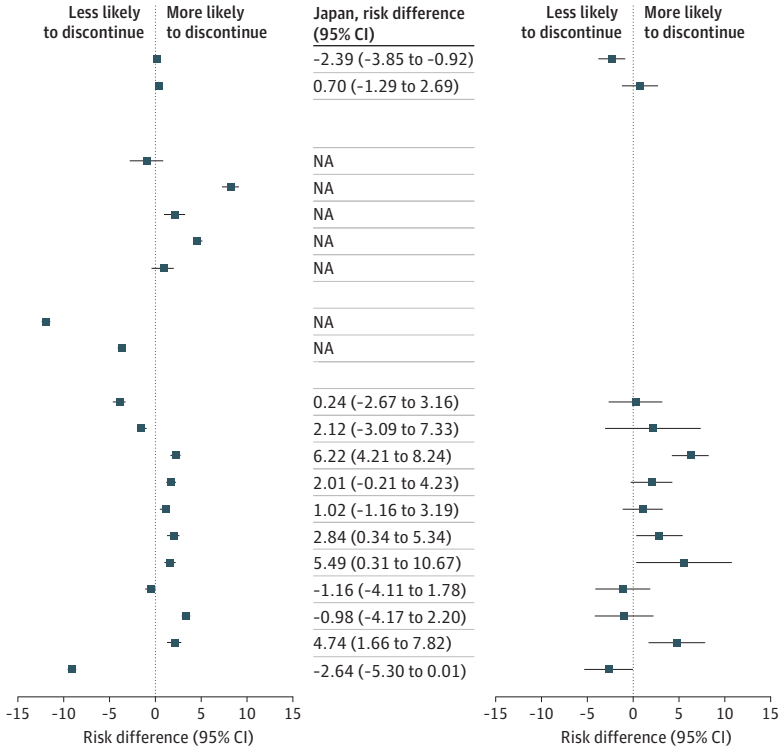
[a] Race and ethnicity are a social construct not used in Japan. For US individuals, Medicare determines race primarily by using self-reported data from the Social Security Administration, enhanced using an algorithm that identifies additional individuals as Asian and Hispanic based on their first or last names. The "other" category includes individuals who self-identify as Native Hawaiian or Other Pacific Islander or other race and ethnicity; these groups were collapsed into a single category due to their small sample size.

[b] These insurance categories are defined for Medicare Advantage beneficiaries and are not used in Japan.

[c] Any other GLP-1RAs include albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide.

Figure. Association of Patient Characteristics With Discontinuation of Injectable Semaglutide in the US and Japan

Characteristic	US, risk difference (95% CI)	Japan, risk difference (95% CI)
Age (per 10 y)	0.21 (-0.12 to 0.54)	-2.39 (-3.85 to -0.92)
Female (reference: male)	0.43 (0.08 to 0.78)	0.70 (-1.29 to 2.69)
Self-reported race and ethnicity (reference: non-Hispanic White)		
American Indian or Alaska Native	-0.91 (-2.72 to 0.90)	NA
Hispanic	8.28 (7.37 to 9.19)	NA
Non-Hispanic Asian	2.17 (1.02 to 3.31)	NA
Non-Hispanic Black	4.65 (4.12 to 5.18)	NA
Other	0.88 (-0.33 to 2.09)	NA
Insurance type		
Dual Medicare and Medicaid	-11.89 (-12.32 to -11.46)	NA
MA vs FFS	-3.60 (-4.05 to -3.15)	NA
Comorbidities		
Hypertension	-3.91 (-4.60 to -3.22)	0.24 (-2.67 to 3.16)
Obesity	-1.42 (-1.90 to -0.94)	2.12 (-3.09 to 7.33)
CKD	2.27 (1.73 to 2.82)	6.22 (4.21 to 8.24)
Heart failure	1.76 (1.24 to 2.28)	2.01 (-0.21 to 4.23)
Ischemic heart disease	1.10 (0.61 to 1.59)	1.02 (-1.16 to 3.19)
Stroke	1.94 (1.29 to 2.59)	2.84 (0.34 to 5.34)
Peripheral vascular disease	1.57 (1.08 to 2.07)	5.49 (0.31 to 10.67)
Cancer	-0.44 (-1.04 to 0.02)	-1.16 (-4.11 to 1.78)
Depression	3.36 (2.90 to 3.82)	-0.98 (-4.17 to 2.20)
Dementia	2.12 (1.38 to 2.85)	4.74 (1.66 to 7.82)
Prior use of GLP-1RA	-9.04 (-9.44 to -8.63)	-2.64 (-5.30 to 0.01)



We used multivariable linear regression models to evaluate the association of baseline characteristics with discontinuation of all glucagon-like peptide-1 receptor agonists (GLP-1RAs) within 12 months of injectable semaglutide initiation, separately for the US and Japanese cohorts. The models included the covariates shown in the figure as well as an indicator variable for the calendar year in which semaglutide was initiated. Note that race and ethnicity are a social construct that is not used in Japan; for US individuals, Medicare determines race primarily by using self-reported data from the Social Security Administration, enhanced using an algorithm that identifies additional individuals as Asian and Hispanic based on their first or last names. The "other" category includes individuals who self-identify as Native Hawaiian or Other Pacific Islander or other race and ethnicity; these groups were collapsed into a single category due to their small sample size. The US model accounted for type of Medicare (fee-for-service [FFS] or Medicare Advantage [MA]) and whether or not the individual was dually enrolled in Medicare and Medicaid; these categories are not applicable to the Japanese cohort and were therefore excluded from the Japan model. CKD indicates chronic kidney disease.

sent was waived. Data analysis was performed from July 1, 2024, to June 30, 2025.

First, we described the sociodemographic and clinical characteristics of adults who initiated semaglutide. Second, we calculated the frequency of discontinuation at 12 months after initiating semaglutide, defined as having a gap in any GLP-1RAs (semaglutide or other) of 60 days or greater. Last, we assessed the associations of patient characteristics among those who discontinued at 12 months using multivariable linear regression models.

All analyses were complete-case analyses conducted using SAS version 9.4 (SAS Institute Inc) and R version 4.2.3 (R Project for Statistical Computing).

Results | A total of 327 074 individuals were included in the study: 318 543 in the US (mean [SD] age, 71.7 [5.3] years; 175 191 [55.0%] female) and 8531 in Japan (mean [SD] age, 77.3 [7.3] years; 4247 [49.8%] female) (**Table**). At 12 months after initiating injectable semaglutide, 2.8% of US patients and 10.1% of Japanese patients had switched to oral semaglutide or other GLP-1RAs, while 59.5% of US patients and 30.8% of Japanese patients had discontinued all GLP-1RAs. In both countries, preexisting chronic kidney disease (CKD) and cardiovascular disease were associated with greater discontinuation (eg, CKD, +2.27 [95% CI, 1.73 to 2.82] percentage points in the US and +6.22 [95% CI, 4.21 to 8.24] percentage points in Japan; stroke, +1.94 [95% CI, 1.29 to 2.59] percentage points in the US and +2.84 [95% CI, 0.34 to 5.34] percentage points in Japan) (**Figure**). In the US, discontinuation was less frequent in individuals dually enrolled in Medicare and Medicaid compared with those enrolled in Medicare alone (−11.89 [95% CI, −12.32 to −11.46] percentage points).

Discussion | In this binational study of older adults with diabetes, nearly 6 in 10 US adults and 3 in 10 Japanese adults discontinued GLP-1RAs within 12 months of initiating injectable semaglutide. Individuals with cardiovascular disease and CKD were more likely to discontinue GLP-1RAs in both countries. Patients with established cardiovascular disease and CKD had higher discontinuation rates in both countries, which is troublesome given the substantial clinical benefit these high-risk individuals would be expected to derive from GLP-1RA therapy.[1,5]

Our findings suggest that both individual- and structural-level factors likely contribute to GLP-1RA discontinuation. Although our study could not directly assess the reasons for semaglutide discontinuation, potential drivers include medication intolerance, out-of-pocket costs, and drug stockouts. The lower discontinuation rates observed in Japan compared with the US may reflect lower copayments for medications in Japan.[6] This interpretation is supported by the finding that US individuals with dual Medicare and Medicaid enrollment—who generally have lower medication out-of-pocket costs—were less likely to discontinue therapy than patients with Medicare alone. These observations underscore the importance of minimizing cost sharing to improve the affordability of these effective therapies.

Study limitations include lack of information on out-of-pocket costs and characteristics of health care professionals as well as uncertain generalizability to patients without diabetes, younger populations, or individuals initiating oral semaglutide.

In conclusion, the high frequency of discontinuation in 2 countries with structurally different health care systems and differing burdens of cardiometabolic conditions highlights the need for concerted global efforts to support persistence with semaglutide, particularly among populations at high risk.

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Accepted for Publication: July 24, 2025.

Published Online: September 24, 2025. doi:10.1001/jamacardio.2025.3109

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Conflict of Interest Disclosures: Dr Inoue reported consulting fees from Cancerscan, Cykinso, and Mizkan outside the submitted work. Dr Khan reported grants from NHLBI outside the submitted work. No other disclosures were reported.

Funding/Support: This work was supported by institutional funds from the Richard A. and Susan F. Smith Center for Outcomes Research. Dr Inoue receives research support from the Japan Society for the Promotion of Science (23KK0240, 25K02887), the Japan Science and Technology Agency (PRESTO; JPMJPR23R2), and the Program for the Development of Next-Generation Leading Scientists With Global Insight sponsored by the Ministry of Education, Culture, Sports, Science, and Technology. Dr Decker was partially supported by the Program of Academic Excellence (23038.011210/2020-53) Coordination for the Improvement of Higher Education Personnel–Brazil (financial code 001). Dr Kazi is supported by funding from the National Heart, Lung, and Blood Institute of the National Institutes of Health (1R01HL157530 and 1R01HL175300), the American Heart Association, and the Agency for Healthcare Research and Quality.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: Dr Khan is an associate editor of *JAMA Cardiology* but was not involved in any of the decisions regarding review of the manuscript or its acceptance.

Data Sharing Statement: See Supplement 2.

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COMMENT & RESPONSE

High-Risk Areas—The Trees in the Forest

To the Editor Liu et al[1] show that prevalence of cardiometabolic risk factors and coronary heart disease, but not stroke, was higher in rural vs urban areas of the US using the data from the 2022 National Health Interview Survey using county-level assessments of urban vs rural status. We see high prevalence of cardiometabolic risk factors and cardiovascular outcomes in the Bronx, which is the poorest urban county in New York state.[2] We are left to wonder whether relative homogeneity of markers of poverty in rural counties, defined as population less than 50 000, might bias the results in favor of rural counties. Markers of wealth are highly heterogeneous in the urban counties of New York City, New York. For example, we have shown that redlined census tracks (denied access to housing loans from the 1930s to 1960s) currently have higher stroke prevalence than nonredlined census tracks.[3] Such local hot zones, or high-risk geographic places, likely represent the highest risk of cardiovascular disease in the US. The structural driv-