ORIGINAL RESEARCH

Impact of Liraglutide to Semaglutide Conversion on Glycemic Control and Cost Savings at a Veterans Affairs Medical Center

Maiah Hardin, PharmD, BCPS[a]; Fiona Adanse, PharmD, BCPS[b,c]; Chandler Schexnayder, PharmD, BCPS, BCACP, CDCES[b,c]; Janeca Malveaux, PharmD, BCPS, CDCES[b,c]; Sylvester Agbahiwe, PharmD, BCACP[b,c]

Background: Semaglutide and liraglutide are glucagon-like peptide 1 receptor agonists (GLP-1 RAs) approved by the US Food and Drug Administration for patients with type II diabetes mellitus (T2DM). Patients with T2DM treated with liraglutide at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) were converted to semaglutide. The primary objective was to assess changes in glycemic control and cost savings that resulted from this conversion.

Methods: We conducted a retrospective chart review of veterans without retinopathy treated at MEDVAMC between March 1, 2021, and November 30, 2021, who were converted from liraglutide 0.6 mg and 1.2 mg daily to semaglutide 0.25 mg weekly (titrated to 0.5 mg weekly after 4 weeks). We compared hemoglobin A_{1c} (HbA_{1c}) values at baseline and 3 to 12 months following conversion to assess glycemic control. Cost savings were evaluated using outpatient pharmacy data.

Results: During the study, 411 patients were converted from liraglutide to semaglutide; 49 additional patients met the criteria for clinician education, and 14 were converted as a result. In total, 304 patients met the criteria for inclusion. At baseline, patients' mean (SD) levels included: HbA_{1c}, 8.1% (1.5); blood glucose, 187.4 (44.2) mg/dL; and body weight, 112.9 (23.0) kg. Three to 12 months postconversion, patients' mean (SD) HbA_{1c} significantly decreased to 7.6% (1.4) ($P < .001$), blood glucose decreased to 172.6 (39.0) mg/dL ($P < .001$), and body weight decreased to 105.2 (32.3) kg ($P < .001$). Cost savings exceeding $400,000 resulted from liraglutide to semaglutide conversion.

Conclusions: Conversion of liraglutide to semaglutide led to significant HbA_{1c} decrease and weight loss and resulted in minimal changes to patients' antihyperglycemic regimen. Common adverse effects included hypoglycemia and gastrointestinal intolerance. Due to the low conversion rate of liraglutide to semaglutide following education, a more effective method of education for clinicians to promote teleretinal imaging before conversion is warranted. Lastly, although the semaglutide cost savings initiative at MEDVAMC resulted in significant savings for the institution, a full cost-effective analysis is needed for further conclusion.

Author affiliations can be found at the end of this article.
Correspondence: Maiah Hardin (maiah.hardin@va.gov)

Fed Pract. 2023;40(suppl 6). Published online September 22. doi:10.12788/fp.0413

Semaglutide and liraglutide are glucagon-like peptide 1 receptor agonists (GLP-1 RAs) that are approved by the US Food and Drug Administration as subcutaneous injections for patients with type 2 diabetes mellitus (T2DM). Both are recommended by the American Diabetes Association (ADA) as first-line options for patients with concomitant atherosclerotic cardiovascular (CV) disease and exert therapeutic effect via incretin-like mechanisms.[1] These agents lower blood glucose levels by stimulating insulin release, increasing the body's sensitivity to insulin, and inhibiting inappropriate glucagon secretion.[2,3] They also slow gastric emptying, resulting in decreased appetite and potential weight loss.[4]

The SUSTAIN (1-7) trials concluded that semaglutide presented an equivalent safety profile and greater efficacy compared with other GLP-1 RAs, including exenatide and dulaglutide.[2] The SUSTAIN-10 open-label, head-to-head trial evaluating 1 mg semaglutide once weekly vs 1.2 mg liraglutide daily concluded that semaglutide was superior in hemoglobin A_{1c} (HbA_{1c}) and body weight reduction compared with liraglutide, with slightly increased gastrointestinal (GI) adverse effects (AEs).[5] Similar to the LEADER trial assessing liraglutide, SUSTAIN-6 evaluated semaglutide in patients at increased CV risk and found that compared with placebo, semaglutide decreased rates of serious CV events, such as CV death, myocardial infarction, and stroke and were similar to the CV outcomes in the LEADER trial.[2,6] Although initial results of the SUSTAIN-6 trial were thought to be nearly equivalent to the LEADER trial, analyses later published comparing both trials noted that semaglutide had more potent HbA_{1c} lowering and weight loss benefit when compared with liraglutide.[2,6] The cardioprotective outcomes of SUSTAIN-6 qualified semaglutide for inclusion in the current ADA *Standards of Medical Care* recommendations for CV risk reduction.[6,7] However, despite the CV safety profile and efficacy associated with semaglutide, the SUSTAIN-6 trial noted an increased risk of diabetic retinopathy (DR) complications in 50 of 1648 patients (3%) treated with semaglutide compared with 29 of 1649 (1.8%) who received

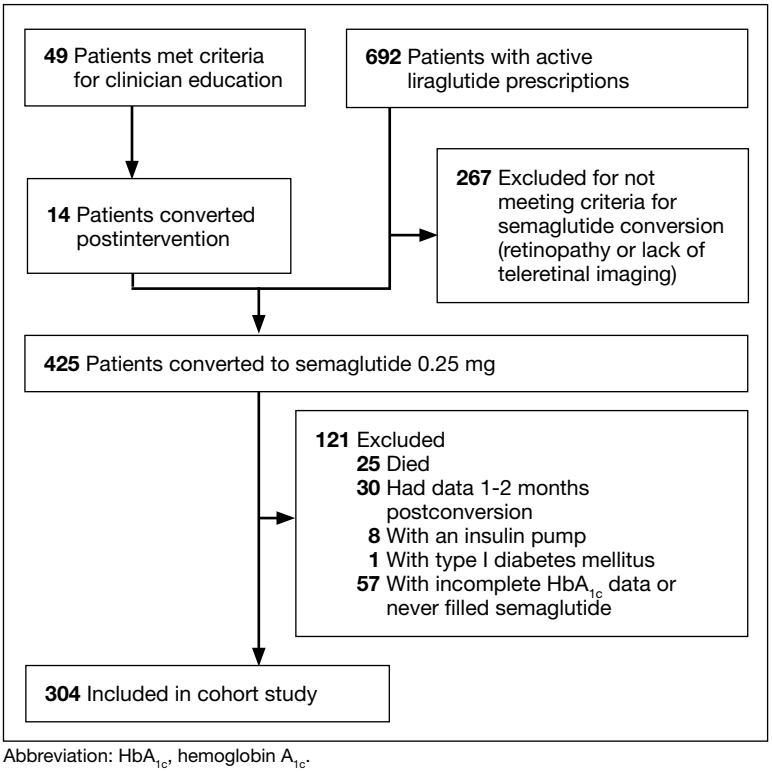
placebo (P = .02; hazard ratio, 1.76; 95% CI, 1.11-2.78).[6] Of the 79 total patients who experienced retinopathy complications, 66 had retinopathy at baseline (42 of 50 [84%]) in the semaglutide group; 24 of 29 [83%] in the placebo group).[6] Worsening of DR became one of the most notable AEs of semaglutide evaluated in clinical trials. This further deemed the effect as a warning in the semaglutide package insert to assist clinicians with treatment decisions.

As part of a US Department of Veterans Affairs (VA) National Lost Opportunity Cost Savings Initiative, which encompasses administrative efforts to promote more cost-effective yet safe and efficacious therapy options for veterans, the Michael E. DeBakey VA Medical Center (MEDVAMC) in Houston, Texas, converted a portion of patients with T2DM established on liraglutide to semaglutide. The 30-day supply cost of the 2-pack liraglutide 6 mg/mL (3 mL) injection pens for the MEDVAMC was $197.64. The 30-day supply cost for the singular multidose semaglutide 0.5 mg/0.375 mL (1.5 mL) injection pen was $115.15. Cost savings for the MEDVAMC facility were initially estimated to reach $642,522.

The subset of patients converted had to have undergone teleretinal imaging and not have a diagnosis of nonproliferative DR (NPDR), proliferative DR (PDR), or PDR with or without diabetic macular edema. These recommendations excluding various forms of retinopathy were implemented per local institution guidance supporting clinical data from the SUSTAIN trials. Patients diagnosed with these conditions were continued on liraglutide due to an increased risk of DR complications associated with semaglutide.

In the fall of 2021, there was also a standing list of patients on liraglutide who were not converted due to a lack of teleretinal imaging. As a result, there was potential for a quality improvement (QI) intervention to target this patient population, which could result in further cost savings for MEDVAMC and improved glycemic control because of increased conversion from liraglutide to semaglutide. The purpose of this project was to perform a QI assessment on this subset of patients both initially converted from liraglutide to semaglutide, and those who were yet to be converted due to a lack of teleretinal imaging to determine the impact on glycemic control and cost savings.

FIGURE Inclusion/Exclusion Criteria



Abbreviation: HbA_{1c}, hemoglobin A_{1c}.

METHODS

This QI project was a single-center, prospective cohort study with a retrospective chart review of veterans with T2DM converted from liraglutide to semaglutide at the MEDVAMC. Patient data were collected from the Computerized Patient Record System (CPRS) between March 1, 2021, and November 30, 2021. An initial subset of patients was converted to semaglutide in March and April 2021. Patients initially excluded underwent a second chart review to determine whether they truly met exclusion criteria. Patients who did not have a definitive diagnosis of NPDR or PDR, those due for updated teleretinal imaging, as well as those with updated teleretinal imaging that excluded NPDR or PDR were targeted for clinician education interventions.

Following this intervention, a subset of patients with negative DR findings were converted from liraglutide to semaglutide. Primary care and endocrinology clinicians were notified that patients who met the criteria should be referred for teleretinal imaging if no updated results were present or that patients were eligible for semaglutide conversion based on negative findings. Both patients who

TABLE 1 Baseline Characteristics (N = 304)

Criteria	Results
Sex, No. (%)	
Male	273 (89.8)
Female	31 (10.2)
Age, mean (SD), y	65.9 (9.6)
Race and ethnicity, No. (%)	
African American	93 (30.6)
Hispanic	24 (7.9)
White	180 (59.2)
Hemoglobin A_{1c}, mean (SD), %	8.1 (1.5)
Blood glucose, mean (SD), mg/dL	187.4 (44.2)
Body weight, mean (SD), kg	112.9 (23.0)
Antihyperglycemic agent, No. (%)	
Insulin	236 (77.6)
Metformin	185 (60.9)
Empagliflozin	104 (34.2)
Glipizide	50 (16.4)
Pioglitazone	23 (7.6)
Alogliptin	17 (5.6)

were initially converted as well as those converted following education were included for data collection/analysis of glycemic control via HbA_{1c} and blood glucose levels.

Cost savings were evaluated using outpatient pharmacy procurement pricing data. This project was approved by the MEDVAMC Quality Assurance and Regulatory Affairs Office.

Participants

Patients included in the study were adults aged ≥ 18 years with T2DM, converted from liraglutide 0.6 and 1.2 mg daily to semaglutide 0.25 mg weekly (titrated to 0.5 mg weekly after 4 weeks), and had an active prescription for semaglutide, with or without insulin or other oral antihyperglycemics. Patients with NPDR or PDR, type 1 DM, no HbA_{1c} data, no filled semaglutide prescriptions, insulin pumps, and those without teleretinal imaging within the postintervention period or who died during the study period were excluded.

Patient baseline characteristics collected included demographic data, CV comorbidities, antihyperglycemic medications, and changes in insulin doses. Parameters analyzed at baseline and 3 to 12 months postconversion included body weight, HbA_{1c}, and blood glucose levels.

Outcomes

The primary objectives of this QI project were to assess glycemic control (via changes in HbA_{1c} levels) and cost savings following patient conversion from liraglutide to semaglutide. A second objective was to educate clinicians for referral of T2DM patients without teleretinal imaging in the past 2 years.

The purpose of the latter objective was to encourage conversion from liraglutide to semaglutide in the absence of DR. We predicted that 50% of patients with clinician education would be converted. Secondary objectives included assessing body weight differences, evaluating modifications in diabetes regimen, and documenting AEs. We predicted that glycemic control would either remain stable or improve with conversion to semaglutide.

TABLE 2 Comorbid Cardiovascular Characteristics (N = 304)

Conditions	No. (%)
Hypertension	300 (98.7)
Hyperlipidemia	298 (98.0)
Coronary artery disease	114 (37.5)
Peripheral vascular disease	34 (11.1)
Heart failure	32 (10.5)
Prior stroke or transient ischemic attack	28 (9.2)
Prior myocardial infarction	19 (6.3)

Statistical Analysis

Patient demographic data were analyzed using descriptive statistics. Quantitative data (HbA_{1c}, blood glucose, and body weight differences as continuous variables) were analyzed using a paired *t* test, and categorical variables were analyzed using the χ^2 test.

RESULTS

During the study period, 692 patients were identified with active liraglutide prescriptions (Figure). Of these, 49 patients who were initially excluded due to outdated teleretinal imaging or negative findings met the criteria for clinician education, and 14 of those 49 patients (28.6%) were converted from liraglutide to semaglutide. Thirty-three patients (67.3%) did not schedule teleretinal imaging or did not convert to semaglutide following negative teleretinal findings. Two patients (4.1%) either scheduled or proceeded with teleretinal imaging, without any further action from the clinician.

TABLE 3 Change in Outcomes From Baseline to 3 to 12 Months Postconversion

Parameters	Baseline, mean (SD)	Postconversion, mean (SD)	Δ (95% CI)	*P* value
Hemoglobin A_{1c}, %	8.1 (1.5)	7.6 (1.4)	-0.5 (-0.7 to -0.3)	< .001
Blood glucose, mg/dL	187.4 (44.2)	172.6 (39.0)	-14.8 (-19.3 to -10.2)	< .001
Body weight, kg	112.9 (23.0)	105.2 (32.3)	-7.7 (-10.6 to -4.8)	< .001

Including the 14 patients converted post-educational intervention, 425 patients were converted to semaglutide. Excluded from analysis were 121 patients: 57 for incomplete HbA_{1c} data or no filled semaglutide prescription; 30 for HbA_{1c} and weight data outside of the study timeframe; 25 died of causes unrelated to the project; 8 had insulin pumps; and 1 was diagnosed with late-onset type 1 DM. The final sample was 304 patients who underwent analysis.

Two hundred seventy-three patients (89.8%) were male, and 180 (59.2%) were White (Table 1). The mean (SD) age of patients was 65.9 (9.6) years, and 236 (77.6%) were established on insulin therapy (either basal, bolus, or a combination). The most common antihyperglycemic agents (other than insulin) that patients used included 185 metformin (60.9%), 104 empagliflozin (34.2%), and 50 glipizide (16.4%) prescriptions.

Most patients had CV disease. Three hundred patients (98.7%) had comorbid hypertension, 298 (98.0%) had hyperlipidemia, and 114 (37.5%) had coronary artery disease (Table 2). Other diseases that patients were concomitantly diagnosed with included peripheral vascular disease, heart failure, history of stroke or transient ischemic attack, and history of myocardial infarction.

Documented AEs included 83 patients (27.3%) with hypoglycemia at any point within 3 to 12 months of conversion and 25 patients (8.2%) with mainly GI-related events, including nausea, vomiting, diarrhea, decreased appetite, and abdominal pain. Six patients (2.0%) had a new diagnosis of DR 3 to 12 months postconversion.

Glycemic Control and Weight Changes

At baseline, mean (SD) HbA_{1c} was 8.1% (1.5), blood glucose was 187.4 (44.2) mg/dL, and body weight was 112.9 (23.0) kg (Table 3). In the timeframe evaluated (3 to 12 months postconversion), patients' mean (SD) HbA_{1c} was found to have significantly decreased to 7.6% (1.4) ($P < .001$; 95% CI, -0.7 to -0.3), blood glucose decreased to 172.6 (39.0) mg/dL ($P < .001$; 95% CI, -19.3 to -10.2), and body weight decreased to 105.2 (32.3) kg ($P < .001$; 95% CI, -10.6 to -4.8). All parameters evaluated were deemed statistically significant.

Further analyses evaluating specific changes in HbA_{1c} observed postconversion are as follows: 199 patients (65.5%) experienced a decrease, 92 (30.3%) experienced an increase, and 13 (4.3%) experienced no change in their HbA_{1c}.

As the timeframe was fairly broad to assess HbA_{1c} changes, a prespecified subgroup analysis was conducted to determine specific changes in HbA_{1c} within 3 to 6, 6 to 9, and 9 to 12 months postconversion (Table 4). At 3 to 6 months postconversion, patient mean (SD) HbA_{1c} levels significantly decreased from 8.2% (1.5) at baseline to 7.6% (1.3) postconversion ($P = .002$; 95% CI, -1.0 to -0.2). At 6 to 9 months postconversion, the mean (SD) HbA_{1c} significantly decreased from 8.1% (1.5) at baseline to 7.6% (1.4) postconversion ($P = .002$; 95% CI, -0.8 to -0.2).

Glucose-Lowering Agent Adjustments

One hundred thirteen patients (37.2%) required no changes to their antihyperglycemic regimen with the conversion, 85 (28.0%) required increased insulin doses, and 77 (25.3%) required decreased insulin doses (Table 5). Forty-five (14.8%) patients underwent discontinuation of either insulin or other antihyperglycemic agents; 44 (14.5%) had other antihyperglycemic agents dose increased, 39 (12.8%) required adding other glucose-lowering agents, 28 (9.2%) discontinued semaglutide, and 10 (3.3%) had other glucose-lowering medication doses decreased.

Cost Savings

Cost savings were evaluated with outpatient pharmacy procurement service data.

TABLE 4 Hemoglobin A_{1c} Level Change Subgroup Analysis

Postconversion follow-up timeframe	No.	Hemoglobin A_{1c}, mean (SD), %		Δ (95% CI)	*P* value
		Baseline	Follow-up		
3 to 6 mo	113	8.2 (1.5)	7.6 (1.3)	-0.6 (-1.0 to -0.2)	.002
6 to 9 mo	170	8.1 (1.5)	7.6 (1.4)	-0.5 (-0.8 to -0.2)	.002
9 to 12 mo	107	8.1 (1.4)	7.8 (1.5)	-0.3 (-0.7 to 0.1)	.13

The total cost savings per patient per month was $82.49. For the 411 preclinician education patients converted to semaglutide, this resulted in a prospective annual cost savings of $406,840.68. An additional $13,858.32 was saved due to the intervention/clinician education for 14 patients converted to semaglutide. The total annual cost savings was $420,699.00.

DISCUSSION

Overall, glycemic control significantly improved with veterans' conversion from liraglutide to semaglutide. Not only were significant changes noted with HbA_{1c} levels and weight, but consistencies were noted with mean HbA_{1c} decrease and weight loss expected of GLP-1 RAs noted in clinical trials. The typical range for HbA_{1c} changes expected is -1% to -2% and weight loss of 1 to 6 kg.[4,7] Data from the LEAD-5 and SUSTAIN-4 trials, evaluating glycemic control in liraglutide and semaglutide, respectively, have noted comparable yet slightly more potent HbA_{1c} decreases (-1.33% for liraglutide 1.8 mg daily vs -1.2% and -1.6% for semaglutide 0.5 mg and 1 mg weekly, respectively).[8,9] However, more robust weight loss has been noted with semaglutide vs liraglutide (-4.62 kg for semaglutide 0.5 mg weekly and -6.33 kg for semaglutide 1 mg weekly vs -3.43 kg for liraglutide 1.8 mg daily).[8,9] Results from the SUSTAIN-10 trial also noted mean changes in HbA_{1c} of -1.7% for semaglutide 1 mg weekly vs -1.0% for liraglutide 1.2 mg daily; mean body weight differences were -5.8 kg for semaglutide and -1.9 kg for liraglutide at their respective doses.[5] The mean weight loss noted with this QI project is consistent with prior trials of semaglutide.

Of note, 44 patients (14.5%) required the dosage increase of either one or multiple additional glucose-lowering agents at any time point within the 3- to 12-month period. Of those patients, 38 (86.4%) underwent further semaglutide dose titration to 1 mg weekly. Common reasons for a further dose increase to 1 mg weekly were an indication for more robust HbA_{1c} lowering, a desire to decrease patients' either basal or bolus insulin requirements, or a treatment goal of completely titrating patients off insulin.

It is uncertain why 30.3% of patients experienced an increase in HbA_{1c} and 4.3% experienced no change. However, possibilities for the divergence in HbA_{1c} outcomes in these subsets of patients may include suboptimal adherence to semaglutide or other antihyperglycemic agents as indicated by clinicians or nonadherence to dietary and lifestyle modifications.

Most patients (65.5%) experienced a decrease in HbA_{1c} because of conversion to semaglutide, and AEs appeared as follows: 27.3% experienced hypoglycemia, and 8.2% experienced GI intolerance. The semaglutide discontinuation rate neared 10%, a majority due to intolerable AEs as previously described. Overall, patients seemed to tolerate the medication well as their glycemic control and weight loss improved. Adherence was not objectively assessed for this QI project but could be an area of improvement for future studies.

Liraglutide is a MEDVAMC nonformulary agent and semaglutide is now the formulary-preferred option. For patients with uncontrolled T2DM, if a GLP-1 RA is desired for therapy, clinicians are to place a prior authorization drug request (PADR) consultation for semaglutide for further evaluation and review of VA Criteria for Use (CFU) by clinical pharmacist practitioners. Liraglutide is the alternative option if patients do not meet the CFU for semaglutide (ie, have a diagnosis of DR among other exclusions). However, the semaglutide CFU was updated in April 2022 to exclude those specifically diagnosed with PDR, severe NPDR, and macular edema unless an ophthalmologist deems semaglutide

acceptable. This indicates that patients with mild-to-moderate NPDR (who were originally excluded from this QI project) are now eligible to receive semaglutide. The incidence of new DR diagnoses (2%) observed in this study could indicate an unclear relationship between semaglutide and increased rates of DR; however, no definitive correlation can be established due to the retrospective nature of this project. The implications of the results of this QI project in relation to the updated CFU remain undetermined.

Due to the comparable improvements in HbA_{1c} and more robust weight loss noted with semaglutide vs liraglutide, we deem it appropriate to select semaglutide as the more cost-efficient GLP-1 RA and formulary preferred option. The data of this QI project supports the overall safety and treatment utility of this option. Although significant cost savings were achieved (> $400,000), the long-term benefit of the liraglutide to semaglutide conversion remains unknown.

Strengths and Limitations

Strengths of this project include the large sample size, its setting in a large VA medical center, and the evaluation of multiple outcomes beyond HbA_{1c} for assessment of glycemic control (ie, mean blood glucose, insulin titration, and dose adjustment of other glucose-lowering agents).

Limitations of this study include the retrospective chart review used for data collection, limited accuracy of objective data due to the COVID-19 pandemic, and inconsistencies with documentation in patients' electronic health records. As a protective measure in the height of the pandemic between March 2021 and November 2021, the VA promoted using telephone and virtual-visit clinics to minimize exposure for patients with nonurgent follow-up needs. Patient hesitance to present to the clinic in person due to COVID-19 was also a significant factor in obtaining objective follow-up data. As a result, less accurate and timely baseline and postconversion weight and HbA_{1c} data resulted, leading to our decision to extend the timeframe evaluated postconversion to 3 to 12 months. We also noted inconsistencies with documentation in CPRS. Unless veterans were closely followed by clinical pharmacist practitioners or endocrine consultation service clinicians, it was more difficult to follow and document trends of insulin titration to assess the impact of semaglutide conversion. The number of AEs, including hypoglycemia and GI intolerance, were also not consistently documented within the CPRS, and the frequency of AEs may be underestimated.

Another possible limitation regarding the interpretation of the results includes the portion of patients titrated up to semaglutide 1 mg weekly. As the focal point of this project was to review changes in glycemic control in the conversion to semaglutide 0.5 mg, this population of patients converted to 1 mg could potentially overestimate the HbA_{1c} and weight changes described, as it is consistent with the SUSTAIN trials that show more robust decreases in those parameters described earlier.

TABLE 5 Changes Made to Glucose-Lowering Agents (N = 304)

Outcomes	No. (%)
No changes made to regimen	113 (37.2)
Insulin dose increased	85 (28.0)
Insulin dose decreased	77 (25.3)
Insulin/other glucose-lowering agents discontinued	45 (14.8)
Other glucose-lowering agents dose increased	44 (14.5)
Additional glucose-lowering agents initiated	39 (12.8)
Semaglutide discontinued	28 (9.2)
Other glucose-lowering agents dose decreased	10 (3.3)

CONCLUSIONS

A subset of patients with T2DM converted from liraglutide to semaglutide experienced significant changes in glycemic control and body weight. Significant differences were noted for a decreased HbA_{1c}, decreased mean blood glucose, and weight loss. A fair portion of patients' antihyperglycemic regimens required no changes on conversion to semaglutide. Although the semaglutide discontinuation rate neared 10%, AEs that may have contributed to this discontinuation rate included hypoglycemia and GI intolerance. Clinician education resulted in a substantial number of patients undergoing teleretinal imaging and further conversion to semaglutide; however, due to the low conversion response rate, a more effective method of educating clinicians

is warranted. Although the semaglutide cost savings initiative at MEDVAMC resulted in significant savings, a full cost-effective analysis is needed to assess more comprehensive institution savings.

Author affiliations

[a]Veterans Affairs Texas Valley Coastal Bend Healthcare System, Corpus Christi
[b]Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas
[c]Baylor College of Medicine, Houston, Texas

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

Disclaimer

The opinions expressed herein are those of the authors and do not necessarily reflect those of *Federal Practitioner*, Frontline Medical Communications Inc., the US Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review the complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.

Ethics and consent

The quality improvement project was approved by the Michael E. DeBakey Veterans Affairs Medical Center Quality Assurance and Regulatory Affairs Office. Approval from the Research and Development Committee and Institutional Review Board is not required.

References

1. ElSayed NA, Aleppo G, Aroda VR, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2023. *Diabetes Care*. 2023;46(suppl 1):S140-S157. doi:10.2337/dc23-S009
2. Aroda VR, Ahmann A, Cariou B, et al. Comparative efficacy, safety, and cardiovascular outcome with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: insights from the SUSTAIN 1-7 trials. *Diabetes Metab*. 2019;45(5):409-418. doi:10.1016/j.diabet.2018.12.001
3. Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an updated review of head-to-head clinical studies. *Ther Adv Endocrinol Metab*. 2021;12:2042018821997320. Published 2021 Mar 9. doi:10.1177/2042018821997320
4. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metab*. 2018;27(4):740-756. doi:10.1016/j.cmet.2018.03.001
5. Capehorn MS, Catarig AM, Furberg JK, et al. Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). *Diabetes Metab*. 2020;46(2):100-109. doi:10.1016/j.diabet.2019.101117
6. Marso SP, Bain SC, Consoli A, et al; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834-1844. doi:10.1056/NEJMoa1607141
7. ElSayed NA, Aleppo G, Aroda VR, et al. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2023. *Diabetes Care*. 2023;46(suppl 1):S158-S190. doi:10.2337/dc23-S010
8. Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia*. 2009;52(10):2046-2055. doi:10.1007/s00125-009-1472-y
9. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5(5):355-366. doi:10.1016/S2213-8587(17)30085-2