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Real-World Use of Once-Weekly Semaglutide in Thai Patients With Type 2 Diabetes Mellitus in a Private Hospital Setting

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Abstract

Objective. To evaluate the real-world use of once-weekly semaglutide among Thai patients with type 2 diabetes (T2DM) in a private hospital setting.

Methodology. A retrospective review of Thai patients with T2DM who have initiated semaglutide for at least 1 month between June 2020 and March 2022 at Theptarin Hospital, Bangkok, Thailand.

Results. A total of 58 patients (50% female, mean age 55.6 ± 15.9 years, with duration of diabetes 12.6 ± 10.3 years, BMI 31.5 ± 4.4 kg/m^2, baseline HbA_{1c} 7.9 ± 1.9%, with prior GLP-1 RA use 24.1%, and concomitant SGLT2i intake (41.4%) were included. During a median follow-up of 6 months, the mean serum HbA_{1c} level reduction was 1.3 ± 1.7% with weight loss of 4.7 ± 4.1 kg. The proportion of patients who achieved optimal and sustainable glycemic control (HbA_{1c} < 7.0%) increased from 43.1% to 55.8% at the last follow-up. The proportion of patients reaching both HbA_{1c} targets of <7.0% and 5% weight loss was 27.8%. No cases of pancreatitis, cancer, or progressive retinopathy were observed.

Conclusions. In this single center undertaking, it was shown that in among persons with T2DM and obesity in Thailand, semaglutide was associated with short-term glycemic control and weight loss comparable with what has been observed in randomized clinical trials and other RWE.

Key words: semaglutide, once-weekly, real-world, Thai

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) have been demonstrated by many randomized controlled trials (RCT) to improve glycemic control, and reduce body weight. It is advocated as a first-line injectable therapy in patients with type 2 diabetes mellitus (T2DM) with established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD in the United States.[1,2] However, the clinical characteristics of people with T2DM in Asia differ from those in Western countries. Asians have a lower BMI, higher risk of developing comorbidities, and younger age at onset of type 2 diabetes mellitus.[3,4] Therefore, real-world evidence (RWE) are required to translate the efficacy of interventions in trials to effectiveness in clinical practice across a broader spectrum of patient populations. Moreover, the cost of most of these newer agents remains prohibitive and inaccessible in low- and middle-income countries (LMICs). The RWE results might also be used for healthcare policy formation to prioritize novel treatments.[5]

Once-weekly semaglutide is a subcutaneous GLP-1 RA with the strongest effect on glycated hemoglobin (HbA_{1c}) and body weight (BW), first approved in the United States in December 2017, and became available in Thailand in June 2020. Various phase III RCTs known as the Semaglutide Unabated Sustainability in Treatment of T2DM (SUSTAIN) demonstrated superiority in its efficacy over comparators and SUSTAIN-6 trial showed a 26% lower risk of the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke than those receiving placebo.[6,7] Recently, the Semaglutide Real-world Evidence (SURE) program comprised of nine observational real-world studies investigating semaglutide initiation in routine clinical practice among European countries and Canada, also confirmed clinically significant improvements in glycemic control and reduction in BW.[8-12] Results from other RWE conducted in other countries also yielded comparable findings.[13-18]

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The unique physicochemical properties of semaglutide may contribute to the greater weight loss observed with semaglutide use compared to other GLP-1 RAs and this benefit is mostly unaffected by gastrointestinal (GI) adverse events.[19,20] Nevertheless, despite the known benefits of GLP-1 RA, long-term adherence rates are suboptimal in routine practice, potentially due to injection-related concerns and high costs.[21]

To date, there are no published real-word data on semaglutide among South-East Asians with T2DM. Therefore, this study aimed to evaluate the real-world use of once-weekly semaglutide among Thai people with T2DM in a private setting.

METHODOLOGY

This retrospective observational cohort study included all Thai people with T2DM who were given once-weekly semaglutide for at least 1 month between June 2020 and March 2022 at Theptarin Hospital, a specialized diabetes center in Bangkok, Thailand. Exclusion criteria included non-Thai patients, patients without T2DM, and duration of semaglutide usage less than 1 month. The first prescription date was the index date and all patients were followed up from then until the end of June 2022 or the last medication usage. Data were collected at baseline and at follow-up visits (3, 6 months, and at the last visit after treatment). Primary endpoints (change in serum HbA_{1c} level and BW) were assessed at baseline and at the last follow-up visit.

Secondary endpoints including change in glycemic and weight-loss targets achievement were also assessed. The subgroup analyses were conducted post-hoc. Baseline serum HbA_{1c} level (≤ 8.0%, >8.0–≤ 9.0%, and >9.0 %) and baseline body mass index (BMI) (< 30 kg/m^2, ≥30–<35 kg/m^2, and ≥35 kg/m^2), and background medication use (sulfonylurea; SU, thiazolidinedione; TZD, sodium–glucose co-transporter 2 inhibitor; SGLT2i, or insulin as background glucose-lowering medication) were chosen as basis for the subgroups. Since both GLP-1 RA and SGLT2i are newer classes of anti-diabetic medications that have shown additional cardiovascular and renal benefits, our present study also dealt with the real-world effectiveness of the combination of GLP-1 RA and SGLT2i compared with SGLT2i alone in Thai people with T2DM. Safety data included self-reported GI side effects, abdominal discomfort, documented pancreatitis, cancer, or progressive diabetic retinopathy. Severe hypoglycemic events requiring assistance of another person to actively administer carbohydrates or other resuscitative actions were also collected from medical records.

This study was approved by the Institutional Review Board committee of Theptarin Hospital (EC No.05-2020).

Statistical analysis

Demographics data were presented using descriptive statistics (mean ± standard deviation (SD) or median (interquartile range - IQR Q1, Q3) while categorical variables were summarized using counts and percentages. Baseline data and outcomes were compared between SGLT2i-treated patients and non-SGLT2i-treated patients to determine the real-world effectiveness of the combination of GLP-1 RA and SGLT2i. Normality of data was assessed using the Kolmogorov-Smirnov test. A repeated-measures Analysis of Variance (ANOVA) with a post-hoc Dunnett test comparing the follow-up time points with baseline data was performed and differences between the paired-sample proportions of those who achieved various target HbA_{1c} levels between baseline and last-visit were analyzed by McNemar test. For the subgroup analysis of background medications, the change of HbA_{1c} and BW from baseline to the last visit in each class of anti-diabetic medication compared with other background medications (mean of two independent groups) were analyzed using an unpaired *t-test* if data were normally distributed or a Mann–Whitney U test if data were not normally distributed. A $p<0.05$ was considered statistically significant. All analyses were conducted using SPSS Statistical Package, version 20 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics of the patients

During the study period, a total of 102 patients were prescribed once-weekly semaglutide injection but 44 patients were excluded for various reasons as shown in Figure 1. Treatment discontinuations within 1 month due to GI adverse events were found only in 2 patients (2.0%). Full analysis was done in the remaining 58 patients (50% female, mean age 55.6 ± 15.9 years, duration of diabetes 12.6 ± 10.3 years, baseline BW 86.7 ± 14.5 kg, BMI 31.5 ± 4.4 kg/m^2, baseline serum HbA_{1c} level 7.9 ± 1.9%, prior GLP1-RA use 24.1%, concomitant SGLT2i intake 41.4%, were included in the study with a median follow-up of 6 months (3-12 months). The clinical characteristics of the patients stratified by SGLT2i use are shown in Table 1.

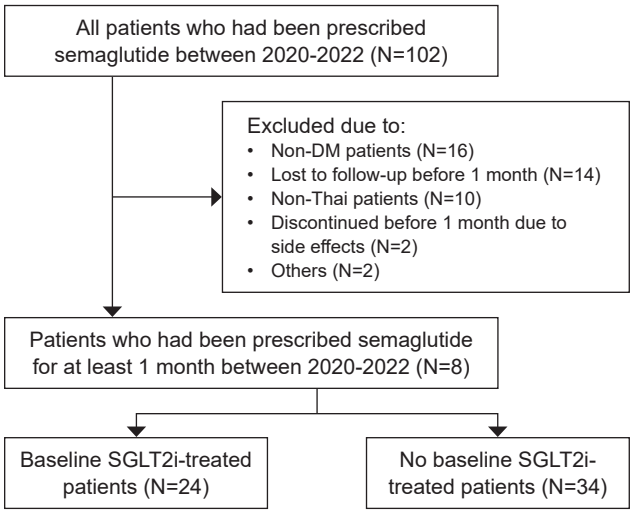

Figure 1. Flow diagram of studied patients (N=58).

Overall, 77.3% of patients were initiated on a 0.25 mg dose of semaglutide. The majority of GLP-1 RA-naïve patients were prescribed a starting semaglutide dose of 0.25 mg, whereas approximately half of the patients in the group with prior GLP-1RA use were started on a 0.5 mg or 1.0 mg dose. At the last follow-up, the majority of patients (87.9%) were taking the 1.0 mg dose of semaglutide. When compared with non-SGLT2i-treated patients, no differences in baseline characteristics were found between groups.

Outcomes

During a median follow-up of 6 months, the overall mean serum HbA_{1c} level reduction was 1.3 ± 1.7% with weight loss of 4.7 ± 4.1 kg. The mean percentage weight loss was 5.4% in the study population. Changes in serum HbA_{1c} levels and BW reductions from baseline to 6 months are shown in Figure 2. The proportion of patients who achieved a sustained optimal glycemic control (serum HbA_{1c} level <7.0%) increased from 43.1% to 55.8% (p=0.022) at the last follow-up as shown in Figure 3A. The proportion of

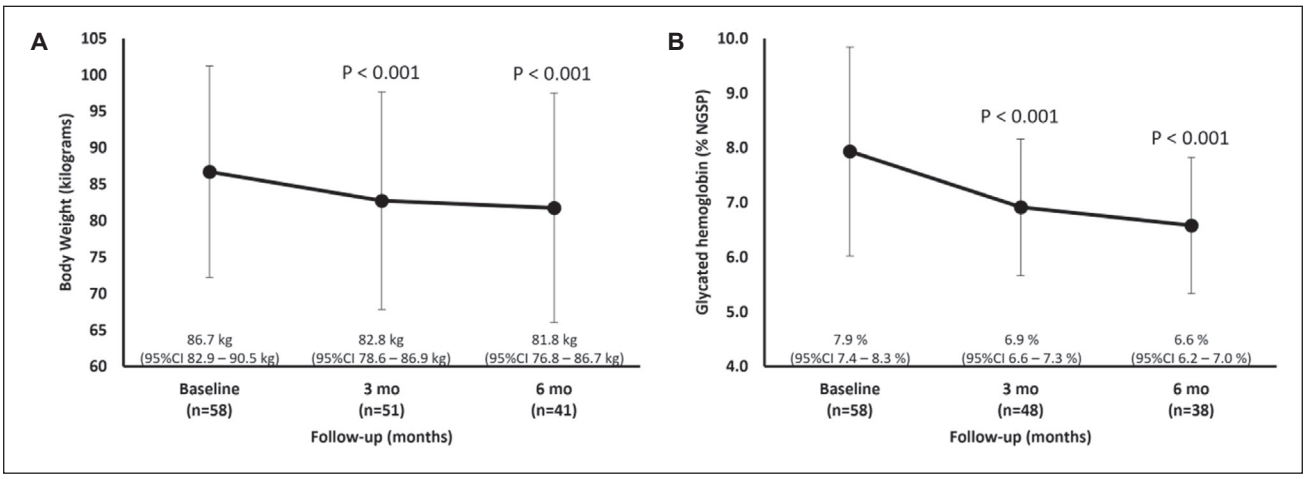

Figure 2. Changes in clinical effectiveness every 3 months after initiation of semaglutide. **(A)** Change in serum HbA_{1c} level from baseline to 6 months. **(B)** BW reduction from baseline to 6 months (Bar graph indicates mean values with standard deviation and numbers in parenthesis indicates 95% Confidence Interval).

Table 1. Baseline demographic and clinical characteristics of studied patients

	Total (N = 58)	SGLT2i-treated group (N = 24)	Non-SGLT2i group (N = 34)	*p*
Current age (years)	55.6 ± 15.9	57.4 ± 12.7	54.4 ± 18.0	0.476
<40 years	10.3	4.2	14.7	
40-64 years	62.1	75.0	52.9	
65-74 years	13.8	12.5	14.7	
≥75 years	13.8	8.3	17.7	
Female (%)	29 (50.0)	13 (54.2)	16 (47.1)	0.594
Duration of DM (years)	10.5 (4.0,20.3)	11.5 (7.0,21.8)	8.0 (2.5,20.3)	0.183
Previous GLP-1 RA (%)	14 (24.1)	7 (29.2)	7 (20.6)	0.452
Established ASCVD (%)	4 (6.9)	3 (12.5)	1 (2.9)	0.157
Diabetic Retinopathy (%)*	13 (27.1)	7 (35.0)	6 (21.4)	0.297
Diabetic Nephropathy (%)	24 (41.4)	12 (50)	12 (35.3)	0.263
Baseline HbA_{1c} (%)	7.9 ± 1.9	7.8 ± 1.5	8.1 ± 2.1	0.570
<7.0%	43.1	37.5	47.1	
7.0-7.9%	12.1	25.0	2.9	
8.0-8.9%	15.5	25.0	8.8	
≥9.0%	29.3	12.5	41.2	
Baseline BW (kgs)	86.7 ± 14.5	85.9 ± 12.8	87.3 ± 15.8	0.716
Baseline BMI (kg/m^2)	31.5 ± 4.4	31.7 ± 4.4	31.4 ± 4.5	0.841
23.0-24.9 kg/m^2	3.4	4.2	2.9	
25.0-29.9 kg/m^2	31.0	29.1	32.4	
30.0-34.9 kg/m^2	46.6	50.0	44.1	
≥35.0 kg/m^2	19.0	16.7	20.6	
Concomitant anti-DM medications (%)				
Sulfonylurea	17.2	20.8	14.7	0.543
Metformin	72.4	79.2	67.6	0.334
Thiazolidinedione	32.8	37.5	29.4	0.518
Insulin	19.0	16.7	20.6	0.708
Duration of usage (months)	6.0 (3.0,12.0)	5.0 (3.0,14.3)	6.0 (3.0,12.0)	0.916
Final dose of semaglutide (%)				
≤0.5 mg per week	12.1	16.7	8.8	0.360
1.0 mg per week	87.9	83.3	91.2	

*Available data = 48 patients

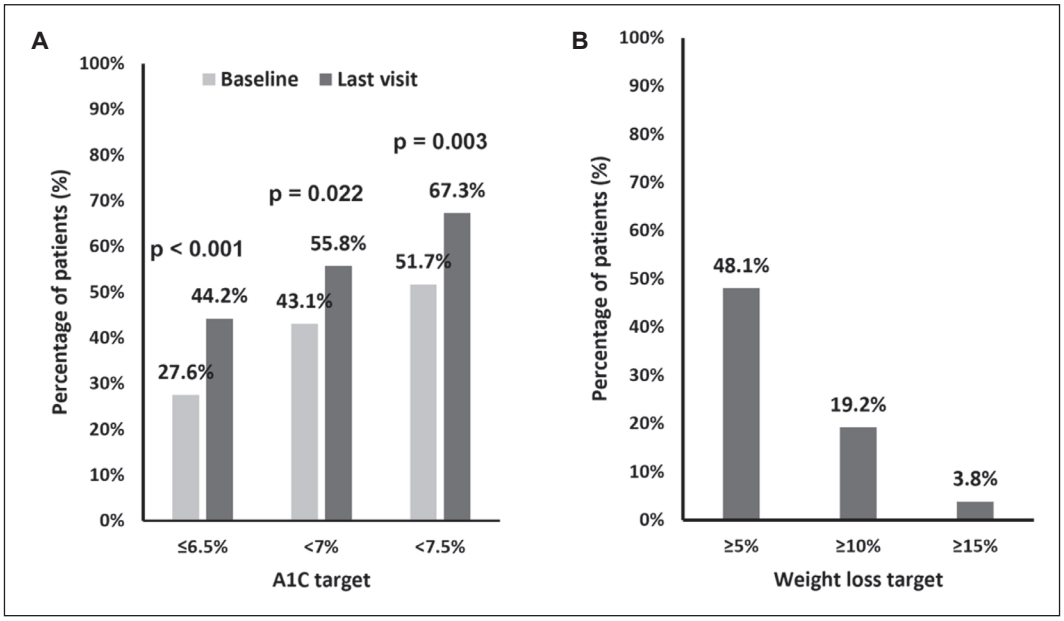

Figure 3. (A) Changes in the proportion of patients who achieved various HbA_{1c} targets from baseline compared to the last follow-up. **(B)** The proportion of patients who achieved various weight loss targets at the last follow-up.

Table 2. Comparisons of results from the present study in Thai patients with observed findings from randomized clinical trials and other published real-world cohorts

Study	Sample size (N)	Mean duration of follow-up (months)	Baseline HbA_{1c} (%)	Baseline BW (kgs)	Mean HbA_{1c} reduction	Mean BW reduction
Present study (Thailand)*	58	6.0	7.9 (7.4, 8.4)	86.7 (82.9, 90.5)	-1.3 (-1.8, -0.9)	-4.7 (-5.7, -3.6)
Pooled analysis of SUSTAIN studies at dose of 1.0 mg[6]	994	8.1	8.2	92.4	-1.6	-6.3
Pooled analysis of SURE studies[12]	1,212	7.7	8.1	101.5	-1.1	-4.7
US Commercially insured and Medicare Advantage patients[13]	1,888	6.6	8.2	N/A	-0.9	N/A
Wales, United Kingdom[14]	189	6.0	9.3	101.8	-1.2	-3.0
Copenhagen, Denmark[15]	119	12	7.7	99.0	-0.8	-3.5
Umbria, Italy[16]	216	12.0	8.4	94.6	-0.8	-3.1
Novara, Italy[17]	258	12.0	8.0	92.5	-1.1	-5.3
Spain[18]	166	24.0	7.5	98.5	-0.9	-9.7

*Parenthesis indicated 95% Confidence Interval

patients who attained sustained weight loss at various targets is shown in Figure 3B. The proportion of patients reaching both HbA_{1c} targets of <7.0% and 5% weight loss was 27.8% at the last follow-up.

Larger reductions in serum HbA_{1c} levels but the least BW reduction were observed within the stratum of patients with baseline serum HbA_{1c} level of >9.0% when compared with those with lower baseline serum HbA_{1c} levels as demonstrated in Figure 4. Serum HbA_{1c} level was reduced from baseline to the last follow-up in all subgroups according to background medication use and there was no discernible pattern in serum HbA_{1c} level reductions in these subgroups as shown in Figure 5.

There were no differences between clinical effectiveness of semaglutide in the SGLT2i-treated and non-SGLT2i treated group.

Among SGLT2i-treated patients, overall mean serum HbA_{1c} level reduction when compared with non SGLT2i-treated patients was 1.1 ± 1.7% and 1.4 ± 0.4%, respectively (p=0.342). Body weight reductions in SGLT2i group: 4.4 ± 3.9 kg and non-SGLT2i group: 4.9 ± 4.2 kg did not show statistical significance (p=0.548). Among patients in the SU subgroup, a larger reduction in serum HbA_{1c} level was observed when compared with patients without SU as a background medication (1.8 ± 1.0% and 1.2 ± 1.8%, respectively (p=0.023). Smaller reductions in BW were observed in patients on background insulin treatment compared with non-insulin subgroups but these did not show statistical significance (2.8 ± 2.3 kg vs 5.1 ± 4.3 kg, p=0.139).

When accounting for previous use of other types of GLP-1 RA, the GLP-1 RA-naive stratum had more BW reduction when compared with the stratum with prior GLP-1 RA use (-5.5 ± 4.3 kg vs -2.0 ± 1.8 kg, p<0.001).

The most common adverse events were GI side effects with mild to moderate severity, occurring primarily during dose escalation. Gastrointestinal side effects included

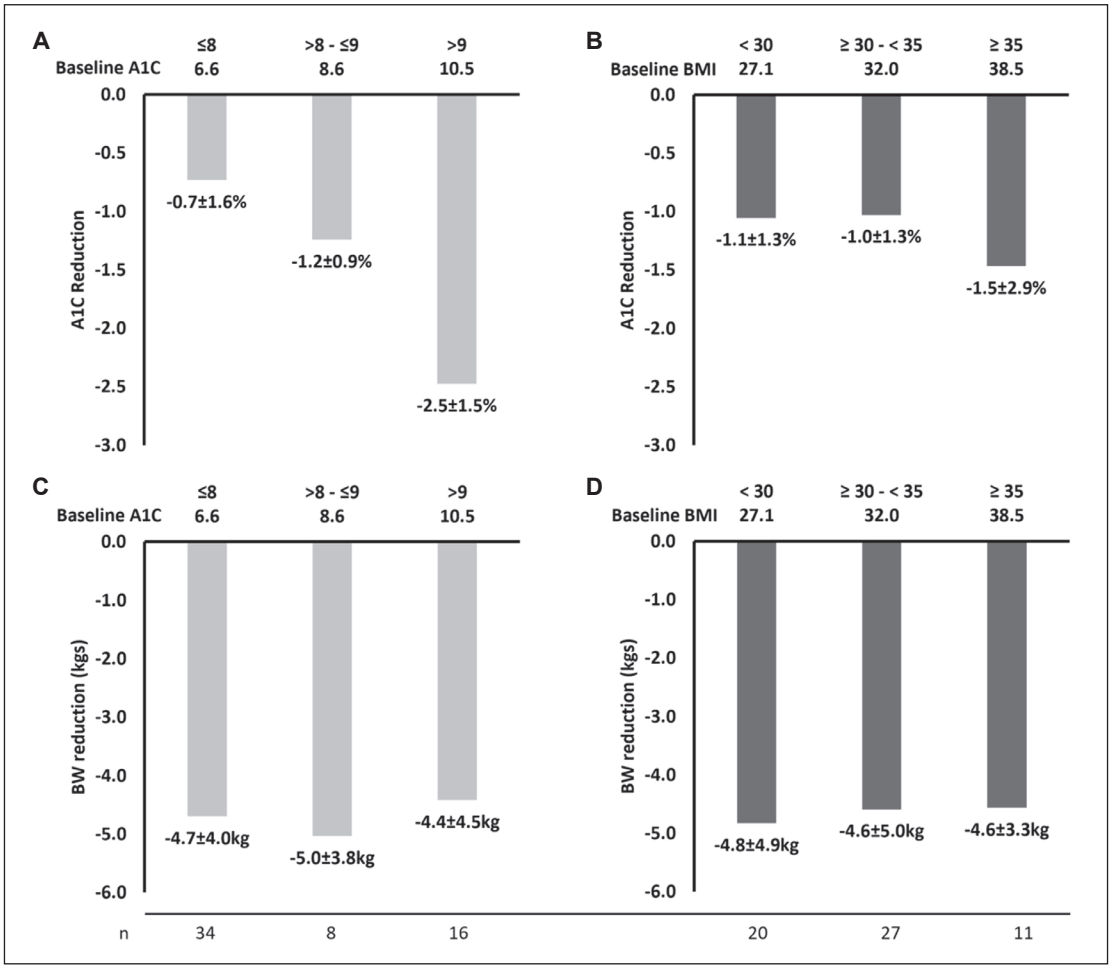

Figure 4. (A) Changes in serum HbA_{1c} level from baseline to the last follow-up according to the stratum of serum HbA_{1c} levels. **(B)** Changes in serum HbA_{1c} level from baseline to the last follow-up according to the stratum of BMI categories. **(C)** Changes in body weight from baseline to the last follow-up according to the stratum of serum HbA_{1c} levels. **(D)** Changes in body weight from baseline to the last follow-up according to the stratum of BMI categories.

nausea and vomiting in 17 patients (29.3%), diarrhea in 3 patients (5.2%), and constipation in 3 patients (5.2%). Treatment was discontinued due to GI side effects only in 3 patients (5.2%) within 3 months after usage. No cases of pancreatitis, cancer, or progressive diabetic retinopathy were observed. No severe hypoglycemia was documented during the study period.

DISCUSSION

In this study, once weekly semaglutide injection was associated with short-term sustained glycemic control and weight loss among persons with T2DM and obesity in Thailand comparable with what has been observed in RCT and other RWE as summarized in Table 2.

Our data suggested that these findings were consistent across subgroups based on background medication despite more frequent use of TZD in our cohort. The result of this study can be used to inform the decisions of healthcare service users to prioritize novel treatments for universal coverage. Although RCTs are important for demonstrating treatment efficacy and safety, it is also important to collect additional evidence in a real-world setting to validate results from the RCT setting because many factors like ethnicity, demography, healthcare infrastructure, service delivery and reimbursement system may affect the outcome. The result of this study represented the RWE of semaglutide in a private setting in Thailand, but the data may be used for policy formation to prioritize novel treatments in resource-limited LIMC's.

In contrast with observed findings in the SURE program,[8-12] there was no clear relationship between the use of background oral medications with the changes in HbA_{1c} or BW reduction except in patients with SU as a background medication. The different findings between the SURE program and our study might be explained by the different nature of a real-world clinical setting and the relatively lower baseline serum HbA_{1c} level and BMI in our study to begin with. The lower baseline serum HbA_{1c} level of our patients (7.9%) when compared with the SUSTAIN program (8.0%-8.4%) and in the SURE studies (8.1%) may have contributed to the comparatively lower reduction in serum HbA_{1c} level from baseline to the last follow-up visit.

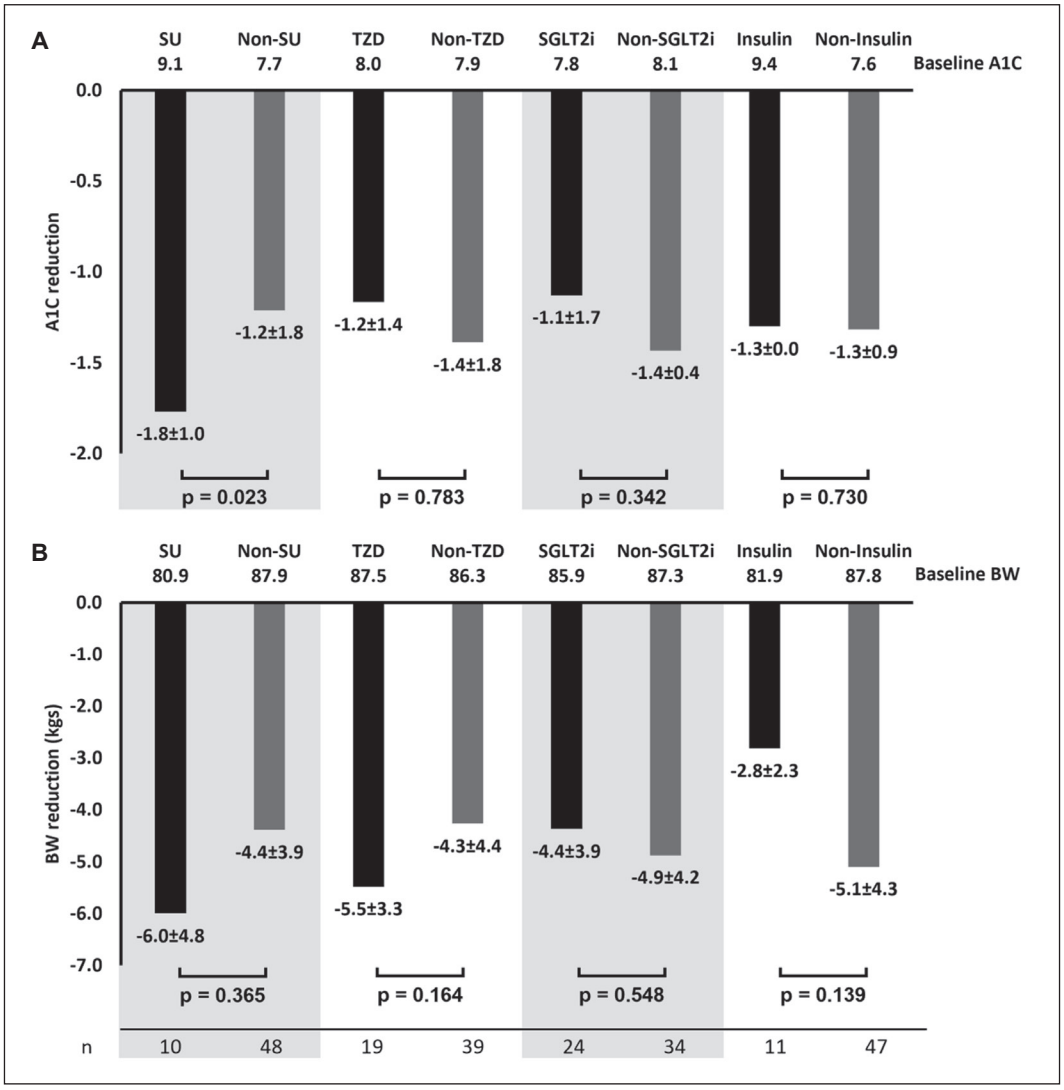

Figure 5. (A) Changes in serum HbA_{1c} level from baseline to the last follow-up according to the background anti-diabetic medication. **(B)** Changes in body weight from baseline to the last follow-up according to the background anti-diabetic medication.

However, the BW reduction in our study (-4.7 kg) was comparable to the SUSTAIN trials (-3.5 kg to -6.4 kg) and the SURE studies (-4.7 kg). However, it should be noted that the small sample size of our SU cohort (only 17.2% of all patients) and relatively high baseline serum HbA_{1c} (9.1%) in this cohort could potentially affect the observed larger serum HbA_{1c} reduction in our study.

It is well-known that the concomitant use of other anti-diabetic drugs with a potential weight gain effect may mask the weight benefit of GLP-1-RA. However, pioglitazone has beneficial effects to treat both hyperglycemia and non-alcoholic fatty liver disease (NAFLD).[22] This inexpensive generic medication has been used frequently in our diabetes center at a lower dose of 15 mg/day. Combination therapy with semaglutide and low-dose pioglitazone might attenuate the risk of weight gain associated with pioglitazone as shown in the present study. Our study validated the effectiveness of and limited side effects associated with low-dose pioglitazone as a background medication in patients who have added once-weekly semaglutide.

Both SGLT2i and GLP-1 RA have well-documented cardiovascular and renal benefits and have potential additive benefits for combination usage.[23-25] However, there is limited data in clinical trials that combined the use of both classes of medication. Based on our study, this combination had generally safe profiles but did not demonstrate superior reductions in serum HbA_{1c} level or BW compared with other background medications. Further studies including cost-effectiveness analysis are required to clarify the role and additive benefits of this combination therapy in people with T2DM as a primary preventive strategy for cardiovascular risk reduction. The proportion of patients discontinuing treatment due to adverse events within one month in our study was 2.0% and lower than in the SURE studies (9.5%) and the SUSTAIN clinical trial program (≤15%).[6-12] This highlighted that semaglutide was very well tolerated in real-world practice among South-east Asian patients.

Long-term adherence to GLP-1 RA treatment may be affected by other issues such as lack of affordability or

injection-related burden rather than GI adverse events. In the retrospective SPARE observational study among patients initiating semaglutide in a specialist endocrinology practice in Canada which was publicly reimbursed, the discontinuation rate was found at 17.3%, which was higher than that reported in the RCT setting but lower when compared to other real-world evaluations of GLP-1 RA medications.[26] The affordability of novel anti-diabetic medications has been a major factor impacting medication adherence in LMICs.[27] Therefore, it is necessary to conduct cost-effectiveness studies that could facilitate wider acceptability and usage among patients in various settings with different healthcare policies.

There were several limitations which could have influenced our results. First, the limitations related to the observational nature of this study and a single data source from a specialized diabetes center in Thailand should be acknowledged. Uncontrolled factors such as changes in lifestyle, concomitant medication use, and verification of medication adherence could confound the observed effectiveness of semaglutide in this study.[28] However, to the best of our knowledge, this study is the first RWE of semaglutide injection among Southeast Asian patients. Our study also provided insight on how semaglutide was initiated and used in routine clinical practice. Second, the small number of study participants and relatively short duration of follow-up in our study may limit the generalizability of the results. Third, this study was not powered for subgroup analyses and only reliably identified potential relationships between baseline variables and treatment effects. It should be interpreted with caution because of the small number of patients in each subgroup. Finally, the present study only assessed the clinical effectiveness of GLP-1 RA in terms of glycemic and BW reductions. The hard endpoints of treatments such as cardiovascular disease, progression to end-stage renal disease, and mortality risk reduction need to be further studied in a multi-center setting with a longer follow-up period.

CONCLUSION

Initiation of once weekly semaglutide injection in this single center study was associated with short-term glycemic control and weight loss among persons with T2DM and obesity in Thailand comparable with what have been observed in randomized clinical trials and other RWE.

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Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
YT: Conceptualization, Methodology, Investigation, Data Curation, Writing – original draft preparation; **NY:** Conceptualization, Methodology, Investigation, Data Curation, Writing – original draft preparation; **SB:** Software, Resources, Data Curation, Visualization, Project administration; **SN:** Software, Resources, Data Curation, Visualization, Project administration; **PC:** Validation, Formal analysis; **WC:** Validation, Formal analysis; **EW:** Validation, Writing – review and editing; **SK:** Validation, Writing – review and editing; **TH:** Supervision, Funding acquisition

Author Disclosure
The authors declared no conflict of interest.

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