

Evaluation of a Weekly Physician-Driven Bolus Titration Algorithm in Patients with Type 2 Diabetes Prescribed V-Go® Wearable Insulin Delivery Device for Basal-Bolus Therapy

Sandip Mehta¹, Mara Vecchio² and Carla Nikkel^{3*}

¹Texas Star Adult Medicine, USA

²Texas Health Research & Education Institute, USA

³Valeritas, Inc., Bridgewater, USA

ARTICLE INFO

Received Date: January 10, 2022

Accepted Date: January 28, 2022

Published Date: January 31, 2022

KEYWORDS

Insulin
A1C
Type 2 diabetes mellitus
Titration
Bolus
Basal
V-Go

ABSTRACT

Aims: Insulin therapy remains the cornerstone for treatment of type 2 diabetes mellitus (T2DM), and basal-bolus administration usually requires multiple daily injections. Non-adherence to the treatment regimen and failure to achieve target A1C levels are common. To overcome this dilemma, a study evaluated V-Go a 24-hour wearable basal-bolus insulin delivery device using a physician-directed insulin bolus titration algorithm over a 4-month period in patients with T2DM.

Methods: Fifteen (15), most of whom were non-insulin naïve, were initiated on V-Go and advised to record blood glucose four times daily (fasting and 2-hour postprandial breakfast, lunch and dinner) for 4 weeks. At weekly intervals, the physician titrated bolus doses of insulin, based on 2-hour postprandial averages, respectively. Basal doses were adjusted after bolus dosing was optimized. Clinical outcomes were evaluated after 4 months.

Results: Following initiation of V-Go, the bolus dose was actively titrated (either up or down) for the first three weeks of therapy after which insulin dosing remained fairly stable. Nearly two-thirds of patients achieved an A1C <7.5% compared to 13% at baseline on prior regimens. A significant decrease ($p < 0.001$) in A1C of 1.6% was found compared to baseline. The prevalence of hypoglycemia decreased from 23% at baseline to 7% at month four. This study supports the view that V-Go can improve glycemic control using an easy to follow physician-directed titration algorithm.

INTRODUCTION

Despite the increase in the availability of new pharmaceutical products to improve glycemic control over the past decade, nearly half of patients with type 2 diabetes mellitus (T2DM) are not achieving the recommended glycated hemoglobin (A1C) goal of <7% and the percentage of patients poorly controlled (A1C >9%) has increased from 12.6% to 15.5% [1]. Given the progressive nature of T2DM, many patients will require insulin therapy over time to maintain or achieve glycemic control [2]. When insulin therapy is warranted in these patients, basal insulin is typically recommended first and has demonstrated to be an effective therapy. However, with disease progression, pancreatic β -cell function declines leading to elevations in both fasting and postprandial blood glucose levels. Under normal physiological conditions, a continuous small amount of insulin secretion from the β -cells of the pancreas suppresses hepatic glucose output by direct and indirect mechanisms, and a larger amount of

Copyright: © 2022 Nikkel C et al., Annals of Diabetes, Metabolic Disorders & Control This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Citation for this article: Sandip Mehta, Mara Vecchio and Carla Nikkel. Evaluation of a Weekly Physician-Driven Bolus Titration Algorithm in Patients with Type 2 Diabetes Prescribed V-Go® Wearable Insulin Delivery Device for Basal-Bolus Therapy. Annals of Diabetes, Metabolic Disorders & Control. 2022; 3(1):120

Corresponding author:

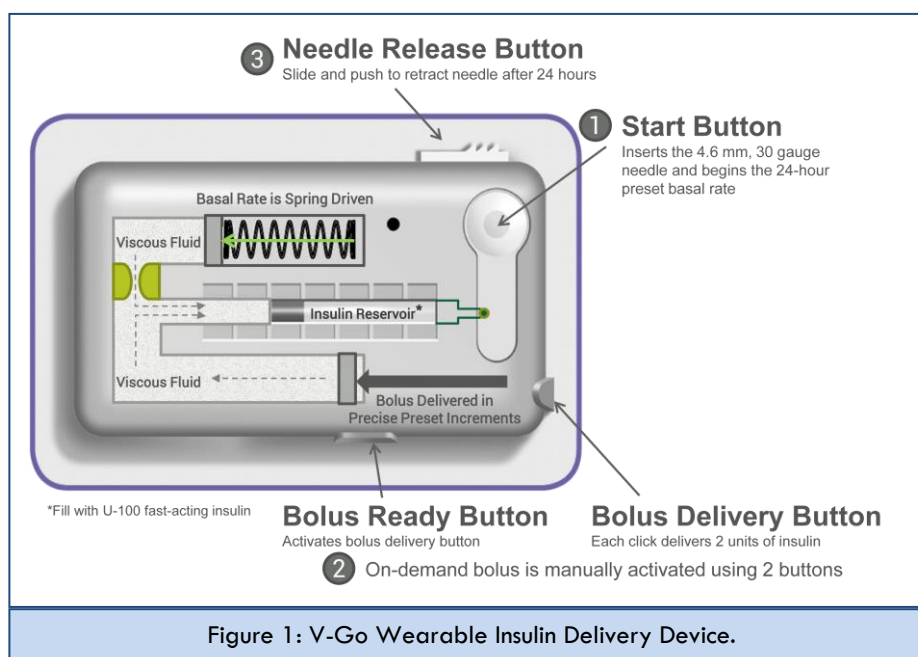
Carla Nikkel,
Valeritas, Inc. 750 Route 202 South,
Suite 600, Bridgewater, NJ 08807,
USA,
Email: cnikkel@valeritas.com

insulin is secreted when food is ingested to maintain euglycemia [3,4]. Exogenous basal insulin administered in the fasting state for the treatment of diabetes is not designed or sufficient to target postprandial hyperglycemia despite ongoing upward titration. Intensification to basal-bolus therapy by incorporation of a prandial insulin also known as bolus or mealtime insulin to address postprandial glucose excursions provides a more physiological way to control glycemia and has proven effective [5].

The initiation and titration of basal-bolus therapy is often viewed as complex and time-consuming. Further, a traditional basal-bolus insulin regimen requires multiple daily injections (MDI) and the need for two types of insulin (a basal insulin for fasting and pre-prandial control and prandial insulin for postprandial control). MDI can interfere with daily living, increase injection discomfort and increase anxiety when injecting in public [6-8]. Unfortunately, evidence supports over

50% of patients prescribed MDI report missing injections [8]. Patients as well as physicians report the two most common difficulties that impact adherence are the number of daily injections required and taking insulin at the prescribed time or with meals on a daily basis⁸. Non-adherence to prescribed regimens can negatively impact efficacy and insulin can only be effective if administered and optimized, therefore, addressing challenges that limit insulin adherence and intensification should be explored.

Advancements in insulin delivery have demonstrated improvements in adherence and glycemic control [9]. One novel device which simplifies basal-bolus therapy is the V-Go[®] Wearable Insulin Delivery device (Valeritas, Inc., Bridgewater, NJ) shown in Figure 1.



This disposable, mechanical device is applied once every 24 hours and provides basal-bolus insulin therapy with the use of one insulin (U-100 fast-acting) and without the need for multiple daily injections. V-Go is available in basal rates of 20, 30, or 40 units/24 h and can administer up to an additional 36 units of insulin for mealtime bolus dosing. V-Go is worn like a patch, and insulin delivery is initiated when the patient presses

a button to insert a small 4.6 mm, 30-gauge needle subcutaneously. Once the needle is inserted, a continuous preset basal rate (0.83 U/hour, 1.25 U/hour or 1.67 U/hour) of insulin is delivered for 24 hours, and on-demand bolus dosing can be administered in 2-unit increments to meet prandial (bolus) insulin needs by pressing two buttons consecutively. Patients report a self-perception of good adherence with V-Go

and report missing only one mealtime dose on average during a 30-day period [10]. V-Go has proven effective across multiple studies [10-13], however, to our knowledge no data exists, evaluating the safety and efficacy of optimizing V-Go bolus dosing using a simple bolus titration algorithm. This proof-of-concept study was designed to evaluate the impact to glycemic control and hypoglycemia when patients were titrated on a weekly basis using a physician-directed bolus titration algorithm and to provide information on the design of a larger prospective study to evaluate a patient-driven insulin titration trial in a similar population.

MATERIALS AND METHODS

This study was conducted as a retrospective review of Electronic Medical Records (EMR) from an adult internal medicine clinic in Bedford, Texas, United States. Patients were prescribed V-Go as part of their standard clinical practice with the goal of improving A1C levels. A systematic search using keywords to identify potential patients switched to V-Go was conducted and patient charts were then reviewed against predetermined criteria.

Eligibility criteria required (1) a diagnosis of type 2 diabetes; (2) age equal to or > 21 years; (3) a documented baseline A1C prior to switching to V-Go; (4) documented baseline insulin dosing (in patients switched to V-Go for insulin delivery from prior insulin regimens); and (5) a follow-up A1C on V-Go within 6 months of V-Go initiation. Patients were excluded for (1) no baseline A1C; (2) undeterminable insulin dosing due to insufficient medical record information; or (3) discontinuation of V-Go prior to a follow-up A1C measurement.

The primary objective was to evaluate the percentage of patients achieving an A1C target (<7.5%) and the prevalence of hypoglycemia after 4 months of V-Go use. Change in A1C, insulin doses and body weight, compared to baseline were evaluated as secondary objectives.

At baseline, patient age, A1C, BMI, weight, and presence of hypoglycemia were extracted using the EMR system. In addition, prescribed Oral Anti-Hyperglycemic Drugs (OAD) and insulin type and dose were collected. A1C and weight were extracted after 4 months of V-Go use and adjustments to

insulin were captured for the first 4 weeks post V-Go initiation and after 4 months of V-Go use.

Means and Standard Deviations (SD) were reported for continuous measures and percentages were reported for categorical measures. Statistical significance between baseline and month four for changes in A1C, insulin dosing and weight was assessed using the paired t-test for continuous measures. All statistical analyses were performed using SPSS v. 25.0 (Armonk, NY) with a $p < 0.05$ denoting a statistically significant difference.

The study protocol was reviewed by the Texas Health Research and Education Institute institutional review board, and a waiver of patient informed consent was approved as it was determined that the risk that patients could be identified was minimal as only de-identified data was utilized in the analyses and stored in the research database.

BOLUS INSULIN TITRATION APPROACH

The physician-driven titration approach evaluated in this study utilized daily 4-point (fasting and 2-hour postprandial breakfast, lunch and dinner) self-monitored blood glucose (SMBG) profiles for weekly titration decisions. Based on the algorithm, V-Go bolus up-titration was recommended when 2-hour postprandial averages exceeded 170 mg/dL and V-Go bolus down-titration when 2-hour postprandial averages were below 100 mg/dL. The magnitude of the titration was dependent on the SMBG profiles provided by the patients. The pre-set V-Go basal rate of insulin was also adjusted by the physician, if needed, following the optimization of bolus dosing for all meals.

RESULTS

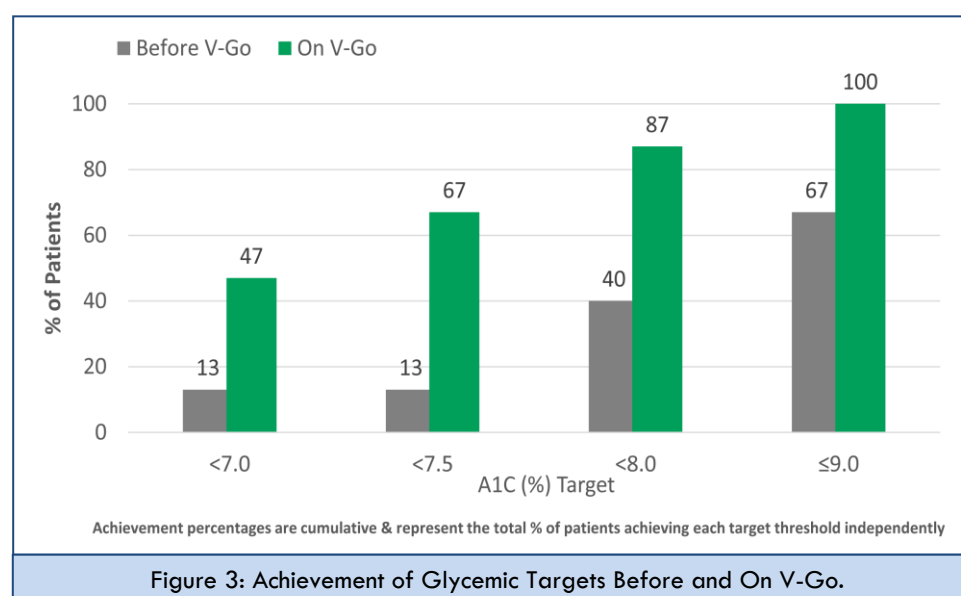
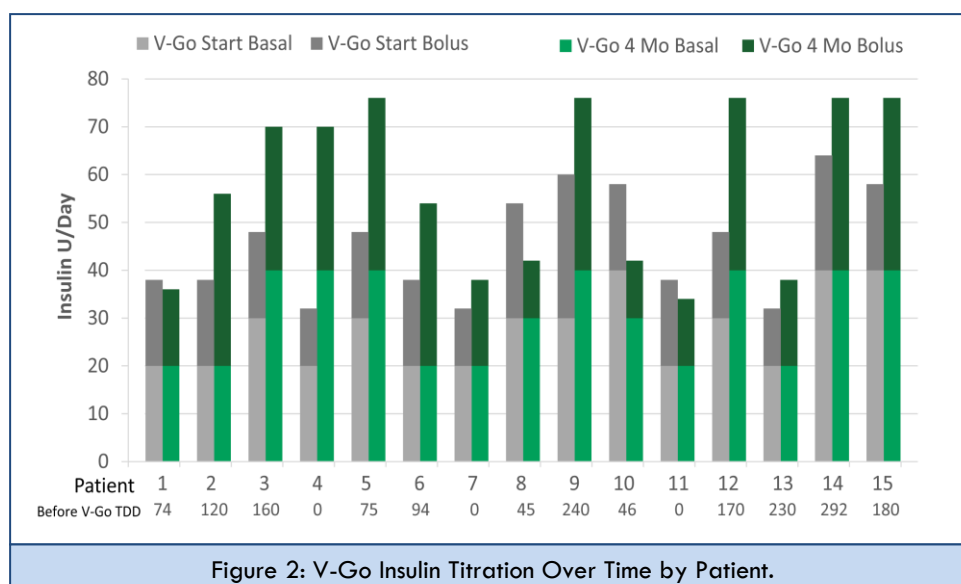
A total of 24 patients with T2DM were screened and 15 of them met eligibility requirements. Reasons for ineligibility included, no follow-up A1C value within 6 months of V-Go initiation ($n=4$), discontinuation of V-Go prior to follow-up A1C ($n=3$), and missing baseline data ($n=2$). In the 15 patients analyzed, baseline characteristics (mean \pm SD) were age 60 ± 9 years, weight 258 ± 76 pounds, BMI 39.4 ± 10.4 kg/m² and A1C $8.7 \pm 1.4\%$ (range 6.7 to 10.8%). Twelve of the 15 patients had been prescribed insulin therapy (3.5 ± 1.4 injections/day) delivered via insulin pen devices or insulin

syringes with a total daily dose (TDD) 144 ± 81 U/day (range 45 to 292 U/day) prior to the initiation of V-Go. Of these 12 patients, 8 had baseline A1C values $> 7.5\%$ despite being prescribed ≥ 75 U/day of insulin. Due to expected non-adherence to prior insulin therapy, conservative dosing was used to initiate V-Go with mean \pm SD basal and bolus doses of 27 ± 8 and 18 ± 5 U/day, respectively.

Following initiation of V-Go, active bolus titration based on SMBG occurred following weeks 1, 2 and 3 post V-Go initiation with 73, 26 and 20% of patients advised to up-titrate and 27, 26 and 20% of patients advised to down-titrate at each time point, respectively. The largest mean adjustment to insulin occurred following the first week of V-Go use when bolus dosing was increased by 10 U/day (18 to 28 U/day)

across the patient population. Basal rates increased in 5 patients and decreased in 1 patient during the first month. Basal and bolus dosing prescribed at V-Go initiation and after 4 months of V-Go, by patient, are shown in Figure 2.

Use of V-Go improved achievement of A1C targets after 4 months with nearly two-thirds of patients achieving an A1C $< 7.5\%$ compared to 13% at baseline (Figure 3). A significant decrease in mean A1C of 1.6% (8.7 to 7.1%; $p < 0.001$) was observed with V-Go despite a significant decrease in insulin 84 U/day (144 to 60 U/day; $p = 0.002$). Mean \pm SD body weight was unchanged from baseline to month four (258 ± 76 to 258 ± 72 pounds) and hypoglycemia prevalence decreased from 23% of patients at baseline to 7% after 4 months.



Individual data for A1C, insulin dosing and concomitant OADs at both baseline and during V-Go use are shown in Table 1. Use of OADs remained unchanged after 4 months of V-Go use in 11 of 15 patients prescribed OADs at baseline.

Table 1: Comparison of Treatment Regimen by Patient before and On V-Go.										
Patient	Diabetes Treatments Before V-Go					Diabetes Treatments On V-Go (4 months)				
	A1C (%)	Basal Insulin U/day	Prandial Insulin U/day	TDD Insulin U/day	OAD	A1C (%)	V-Go Basal U/day	V-Go Bolus U/day	V-Go TDD U/day	OAD
1	6.7	26	48	74	D	6.4	20	16	36	D
2	6.8	60	60	120	-	6.2	20	36	56	-
3	7.6	70	90	160	-	7.5	40	30	70	-
4	7.6				A, B	5.9	40	30	70	A, B
5	7.6	75		75	-	7.1	40	36	76	A
6	7.8	40	54	94	A	6.7	20	34	54	A
7	8.5				B	6.7	20	18	38	B
8	8.7	11*	34*	45	-	7.7	30	12	42	-
9	8.8	120	120	240	A, C	7.5	40	36	76	A, C, E
10	9.0	46		46	A	6.9	30	12	42	A
11	9.3				B	6.1	20	14	34	-
12	10.2	80	90	170	A	9.0	40	36	76	A
13	10.5	120	110	230	-	7.3	20	18	38	-
14	10.7	160	132	292	C	7.4	40	36	76	C
15	10.8	180		180	D	8.8	40	26	76	D, E
Mean	8.7	82**	82**	144		7.1	31	26	57 [†]	

OAD: Oral Anti-hyperglycemic Drug; TDD: Total Daily Dose of Insulin

*Patient prescribed 15 u/day 70/30 premix insulin (calculated 11 basal, 4 prandial) + 30 u/day prandial insulin.

**Mean calculated from patients prescribed insulin at baseline

[†]Mean calculated from all patients on V-Go

A: Metformin; B: Sulfonylurea; C: DPP-4 Inhibitor; D: Metformin/DPP-4 Inhibitor Combination, E: SGLT-2 Inhibitor

DISCUSSION

Insulin is the most consistently effective and potent way to improve blood glucose control and with disease progression, basal-bolus insulin therapy is required by many patients with T2DM. However, as is the case for all therapeutics, to achieve ultimate effectiveness, appropriate titration and adherence to insulin dosing are necessary to maximize benefit [14]. Optimizing basal-bolus titration reduces the incidence of both hypoglycemia and hyperglycemia and can be an important component in maintaining optimal glucose ranges for individuals who have previously been unable to achieve. When persistent hyperglycemia exists, it is important to evaluate if the prescribed insulin regimen provides adequate coverage to match glycemic fluctuations and to explore potential therapy challenges which may hinder adherence by the patient.

In this study, the majority of patients were prescribed insulin at baseline and despite a baseline mean TDD of 144 U/day, glycemic targets were not achieved in most cases. Insulin doses of this magnitude should provide better glycemic control

suggesting non-adherence was likely prevalent in those previously prescribed insulin. Adherence can be improved by providing straightforward solutions to ease the complexities of insulin therapy and minimize the impact to daily living. As suggested by the improvement in glycemic control in this proof of concept study, insulin adherence improved by initiating a novel way to deliver insulin delivery. The treatment burden of a basal-bolus insulin regimen was lessened by removing the need for multiple daily injections and allowing for discrete, on-demand dosing with the incorporation of a 24-hour wearable V-Go insulin delivery device. Further, implementation of a simple weekly physician-directed bolus titration algorithm based on 2-hour postprandial SMBG levels maximized the benefit of V-Go. Patient follow-up is a critical component to successful treatment outcomes. Following the initiation of insulin therapy, insulin dosing should be evaluated and titrated (up or down) every 3 to 7 days if blood glucose levels are not within set targets. Due to suspected non-adherence to prior insulin

therapy, conservative dosing was prescribed when initiating V-Go, making the need for patient follow-up even more crucial. After 1 week of V-Go use, all patients required a dose adjustment, resulting in a mean bolus dose increase of 10 U/day. This bolus titration was necessary to achieve the level of glycemic improvement observed and without it, the patient experience and satisfaction may have been diminished. In most patients, insulin dosing remained stable after 3 weeks of titration without the need for further active titration. Hypoglycemia decreased over time, which we attribute to lower prescribed doses of insulin, appropriate matching of insulin dosing and timing to glycemic needs due to the ability of patients to bolus dose on-demand with meals or snacks as insulin is readily available at the push of a button with V-Go. Simplifying both the initiation and intensification of insulin therapy can lessen the treatment burden for both health care providers and patients. However, intensification of insulin by health care providers is often delayed due to a lack of time and resources. The majority of patients with diabetes receive diabetes care from their primary care physician [15], yet primary care teams often report a lack of confidence in newer therapies and insulin initiation [16]. Often a “wait until next visit” approach is employed. This puts the patient at unnecessary risk for an extended glycemic burden and the potential for related complications. Partnering with patients to empower self-management of their disease and insulin regimen has been shown to be beneficial [17]. Recent studies [18,19], have shown that titration is equally effective whether it is guided by the healthcare professional or a patient who has been instructed on a simple titration approach based on SMBG readings. Based on the findings in this proof-of-concept study, it is our opinion, that patients prescribed V-Go could simply and safely titrate bolus dosing with physician oversight which would lessen the burden on healthcare providers and empower the patient to manage their own diabetes. A randomized trial to assess V-Go with a similar patient-driven bolus titration algorithm based on weekly SMBG for the first 4 weeks would be of interest to evaluate the impact to glycemic control and treatment satisfaction. As is the case with all studies, this study is not without limitations. First and foremost, the sample size

was small, and the study was retrospective, non-randomized and did not include a comparator. It is possible that the threshold levels for adjusting the insulin dose or the frequency of glucose measurements per week could be modified to improve control, but the results shown here clearly demonstrate that this method is feasible and robust over a 4-month period. It should be noted that prescribed insulin dosing and perceived adherence were based on information obtained from EMR; actual insulin dosing and adherence may have differed. Finally, the prevalence of hypoglycemia, recorded by the patient may have differed as patient self-reports were evaluated in the study.

CONCLUSION

With appropriate titration and management, insulin therapy is the most effective option to treat hyperglycemia. Practical and straight forward guidance to manage insulin therapy can positively impact outcomes. The adoption of a physician-directed bolus titration algorithm to optimize insulin dosing when prescribed V-Go in this proof-of-concept study proved safe and resulted in clinically relevant glycemic improvement. These findings support the view that many patients could safely and effectively self-manage their insulin treatment with physician oversight. Applying these findings to a patient-directed approach needs further investigation.

ACKNOWLEDGEMENT/FUNDING

We thank Kenneth Duchin, PhD for assistance in writing the manuscript.

CONFLICTS OF INTEREST

SM serves on the speaker's bureau for Valeritas, Inc. MV has no conflicts of interest. CN is an employee and stockholder of Valeritas, Inc.

REFERENCES

1. Carls G, Huynh J, Tuttle E, Yee J, Edelman SV. (2017). Diabetes Therap. Achievement of Glycated Hemoglobin Goals in the US Remains Unchanged Through 8: 863-873.
2. LaSalle JR, Berria R. (2013). Insulin Therapy in Type 2 Diabetes Mellitus: A Practical Approach for Primary Care Physicians and Other Health Care Professionals. J Am Osteopath Assoc. 113: 152-162.

3. Edgerton DS, Kraft G, Smith M, Farmer B, Williams PE, et al. (2017). Insulin's direct hepatic effect explains the inhibition of glucose production caused by insulin secretion. *JCI Insight*. 2: e91863.
4. Polonsky KS, Given BD, Hirsch L, Shapiro ET, Tillil H, et al. (1988). Quantitative study of insulin secretion and clearance in normal and obese subjects. *J Clin Invest*. 81: 435–441.
5. Holman RR, Farmer AJ, Davies MJ, Levy JC, Darbyshire JL, et al. (2009). Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med*. 361: 1736–1747.
6. García-Pérez LE, Álvarez M, Dilla T, Gil-Guillén V, Orozco-Beltrán D. (2013). Adherence to Therapies in Patients with Type 2 Diabetes. *Diabetes Therap*. 4: 175–194.
7. Peyrot M, Rubin RR, Kruger DF, Travis LB. (2010). Correlates of Insulin Injection Omission. *Diabetes Care*. 33: 240–245.
8. Peyrot M, Barnett AH, Meneghini LF, Schumm-Draeger PM. (2012). Factors associated with injection omission/non-adherence in the Global Attitudes of Patients and Physicians in Insulin Therapy study. *Diabetes, ObesMetab*. 14: 1081–1087.
9. Ayyagari R, Wei W, Cheng D, Pan C, Signorovitch J, et al. (2015). Effect of adherence and insulin delivery system on clinical and economic outcomes among patients with type 2 diabetes initiating insulin treatment. *Value Health* 18: 198–205.
10. Rosenfeld CR, Bohannon NJ, Bode B, Kelman AS, Mintz SN, et al. (2012). The V-Go insulin delivery device used in clinical practice: patient perception and retrospective analysis of glycemic control. *Endocrine Practice*. 18: 660–667.
11. Lajara R, Davidson JA, Nikkel C, Morris TL. (2016). Clinical and cost effectiveness of insulin delivery with V-Go disposable insulin delivery device versus multiple daily injections in patients with type 2 diabetes inadequately controlled on basal insulin. *Endocrine Practice*. 22: 726–735.
12. Lajara R, Fetchick DA, Morris TL, Nikkel C. (2015). Use of V-Go insulin delivery device in patients with sub-optimally controlled diabetes mellitus: a retrospective analysis from a large specialized diabetes system. *Diabetes Therapy*. 6: 531–545.
13. Sutton D, Higdon C, Nikkel C, Hilsinger KA. (2018). Clinical benefits over time associated with use of V-Go Wearable Insulin Delivery Device in adult patients with diabetes: a retrospective analysis. *Advances in Therapy*. 35: 631–643.
14. Garber AJ, Abrahamson MJ, Barzilay JL, Blonde L, Bloomgarden ZT, et al. (2018). Consensus Statement by The American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2018 Executive Summary. *EndocrPract*. 24: 91–120.
15. Mosenzon O, Raz I. (2013). Intensification of Insulin Therapy for Type 2 Diabetic Patients in Primary Care: Basal-Bolus Regimen Versus Premix Insulin Analogs. *Diabetes Care*. 36: S212–S218.
16. Strain WD, Blüher M, Paldanius P. (2014). Clinical inertia in individualizing care for diabetes: is there time to do more in type 2 diabetes? *Diabetes Therap*. 5: 347–354.
17. Khunti K, Davies MJ, Kalra S. (2013). Self-titration of insulin in the management of people with type 2 diabetes: a practical solution to improve management in primary care. *Diabetes Obes Metab*. 15: 690–700.
18. Riddle MC, Rosenstock J, Gerich J. (2003). Insulin Glargine Study 4002 Study Investigators. The treat-to-target trial: Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care*. 26: 3080–3086.
19. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, et al. (2006). A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetes Care*. 29: 1269–1274.