Lessons From a Diabetes Clinic: Achieving Glycemic Goals and Clinical Use of Antidiabetic Agents in Patients With Type 2 Diabetes

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The proportion of patients with type 2 diabetes who achieve their glycemic goals remains low. We examined medical records and A1C results from patient visits to our referral diabetes center between 21 March to 20 July 2018. After stratifying patients into four groups—monotherapy, dual therapy, triple therapy, or insulin therapy—we found that the target A1C of ≤7.0% was achieved by 86% of patients and that A1C was uniformly low across the treatment categories. Our individualized approach, which included high use of glucagon-like peptide-1 receptor agonists and low use of sulfonylureas, may have contributed to these results.

KEY POINTS

- Globally, about half of patients with diabetes do not hit their glycemic targets.
- Poor glycemic control is directly related to chronic diabetes complications.
- In this Greek clinic, 86% of patients achieved glycemic goals, including 76% of those treated with insulin.
- An individualized approach and the use of newer cardioprotective agents such as glucagon-like peptide 1 receptor agonists can help patients improve their glycemic control while avoiding hypoglycemia.

Achieving glycemic goals is essential for patients with type 2 diabetes. More than 422 million adults suffer from type 2 diabetes worldwide (1), but the proportion of patients who achieve their glycemic goals has remained stable since 2000 and disproportionally low given the advent of novel and sophisticated medications. The implications of this situation cannot be overlooked. Patients who fail to reach their glycemic targets are likely to experience life-threatening complications (2), including cardiovascular disease (CVD), chronic renal failure, blindness, and amputations (1,3) and significant decline in their quality of life.

The percentage of adult patients with type 2 diabetes who achieve an A1C goal of ≤7.0%, as recommended by the American Diabetes Association for most adults, ranges from about 45% to 60%, whereas, in insulin-treated patients it is 34% to 40% (4–8). The results are similar in the Greek population, as documented in a recent multicenter observational study designed by the Hellenic Diabetes Association and the Hellenic Endocrinology Association (9). Reported in 2018, this trial that included 59 diabetes centers and multiple other outpatient clinics from the Greek National Health System found that 53% of patients were achieving an A1C ≤7.0%, whereas the proportion among insulin-treated patients was 35.4%. Also, a 2009 study by Liatis et al. (4) examined this issue among patients who were regularly followed in three major diabetes centers located in Athens and Piraeus, Greece, and found that 61% of patients overall and 34% of those who were taking insulin attained an A1C ≤7.0%. A similar study in the United States found percentages of patients with type 2 diabetes achieving this goal A1C ranging from 44 to 51% for the years from 1999 through 2014 (5), and other sources have reported even lower percentages (10). Somewhat better results were found in primary care units in Germany, where A1C ≤7.0% was

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achieved by 61% of all patients with type 2 diabetes and 40% of those treated with insulin (6). In a 2016 study with 10,000 Japanese patients with type 2 diabetes and mean BMI of 25.9 kg/m^2, the target A1C of ≤7.0% was achieved by 52.9% of patients (7). Moreover, a 2018 meta-analysis of 24 observational studies from 20 countries, involving 369,251 patients with type 2 diabetes, showed that only 42.8% of patients achieved their A1C goal (8).

Although it has been demonstrated that attainment of glycemic goals has remained low among people with type 2 diabetes for many years, studies have also demonstrated limited use of newer antidiabetic agents such as glucagon-like peptide 1 (GLP-1) receptor agonists, and generally poor application of current clinical practice guidelines for diabetes management. Indeed, in some countries, high costs and limited insurance coverage have served to discourage doctors from prescribing the newer medications. Prescription rates are similar in the United States and Europe, including Greece, and are mostly in single-digit percentages (11–14). For these reasons, possibly attributable to the combination of financial issues and conservatism within the medical community, there continues to be widespread use of very old medications such as sulfonylureas. Sulfonylureas used to be considered second-line agents after metformin; however, hypoglycemia was a major concern. Today, aside from cost concerns, there is no need to use sulfonylureas as often because newer medications offer equal efficacy, much lower risks for hypoglycemia, and greater cardioprotective benefit (15).

In this study, we aimed to record the percentage of patients with type 2 diabetes in our clinic who achieved their glycemic goals and had follow-up during the past 4 months and to identify any potential associations of the results with the way glycemic targets were set and our clinical approach and pharmacological therapy choices.

Research Design and Methods

The Diabetes Clinic of George Papanikolaou Hospital has been operating for the past 30 years and has an electronic database of 5,000 adult patients, of whom 1,500 are currently active. We used the electronic database of the Diabetes Clinic and recorded the latest visit of established patients examined from 21 March to 20 July 2018. Patients examined for the first time during this period were excluded, as were patients who were actively participating in randomized controlled trials and pregnant women. A1C was measured via a fifth-generation ion exchange high-performance liquid chromatography system (the Menarini/ARKRAY ADAMS A1c HA-8180 V analyzer). Analyses were performed with R and SPSS v. 23 statistical software. Quantitative variables included A1C, sex, BMI, diabetes duration, and medications uses and were recorded as percentage or mean ± SD.

Results

We recorded the latest visits of 949 patients, of whom 455 were women (47.8%) and 494 were men (52.2%). The mean age of patients was 69.3 ± 10.3 years, and the mean BMI was 31.3 ± 5.4 kg/m^2.

The stratified distribution of A1C based on specific glycemic targets across all patients is shown in Figure 1. Only three patients (0.3%) had an A1C ≥9.0%. The target A1C of ≤7.0% was achieved by 85.8% of patients, without any sex differences. In addition, 56.9% of patients achieved an A1C ≤6.5%. Among older adults >75 years of age (n = 268), mean A1C was 6.6 ± 0.7%, and the goal A1C of ≤7.0% was met by 82.5%, and 53.7% had an A1C ≤6.5%.

Next, patients were stratified in four groups according to the number of prescribed medications, as indicated by the steps of the therapeutic algorithm. Mean A1C in all groups was 6.5 ± 0.7%. In the Step 1: Monotherapy group, patients who were on diet and lifestyle modifications and/or one oral antidiabetic agent (20.6%) had a mean A1C of 6.3 ± 0.5%. In the Step 2: Dual Therapy group, patients who were treated with two antidiabetic agents (27.3%) had a mean A1C of 6.5 ± 0.7%. In the Step 3: Triple Therapy group, patients treated with three antidiabetic agents (30.1%) had a mean A1C of 6.6 ± 0.5%. In the Step 4: Insulin Therapy group, patients on insulin therapy in combination with other medications (39.7%) had a mean A1C of 6.7 ± 0.7%.

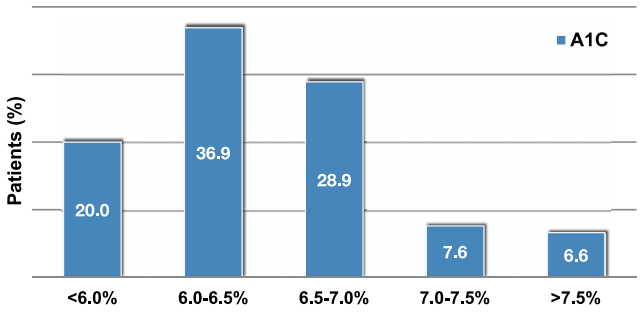

FIGURE 1 Stratified distribution of A1C across all patients based on their achieved glycemic goals.

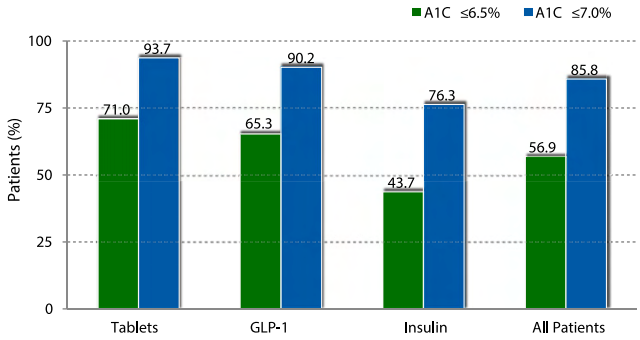

FIGURE 2 Percentage of patients who reached an A1C goal of ≤6.5% (green bars) or ≤7.0% (blue bars) depending on their specific type of treatment and for all patients. Tablets, treatment with tablets only; GLP-1, treatment with tablets + a GLP-1 receptor agonist; Insulin, treatment with tablets + insulin ± a GLP-1 receptor agonist.

We also stratified patients into three groups based on the type of treatments they received (either tablets alone or tablets in combination with injectables) as follows: tablets, tablets + GLP-1 receptor agonist, or tablets + insulin ± GLP-1 receptor agonist. The percentages of patients achieving specific A1C targets in these groups are shown in Figure 2.

The stratification of patients by treatment group and diabetes duration is shown in Figure 3. Mean duration of diabetes in the four treatment groups was as follows: Monotherapy group 8.5 ± 6.2 years, Dual Therapy group 12.4 ± 7.7 years, Triple Therapy group 14.7 ± 8.1 years, and Insulin Therapy group 16.9 ± 8.7 years. Mean A1C did not differ based on longer or shorter duration of diabetes. In patients with a diabetes duration <5 years, mean A1C was 6.3 ± 0.6%; in those with a diabetes duration of 5–10 years, it was 6.5 ± 0.6%; and in those with a diabetes duration >10 years, it was 6.6 ± 0.7%.

Mean A1C with respect to BMI was also not statistically different. In patients with a BMI <27 kg/m^2, mean A1C was 6.4 ± 0.6%; in those with a BMI of 27–30 kg/m^2, it was 6.4 ± 0.6%; and in those with a BMI >30 kg/m^2, it was 6.5 ± 0.7%.

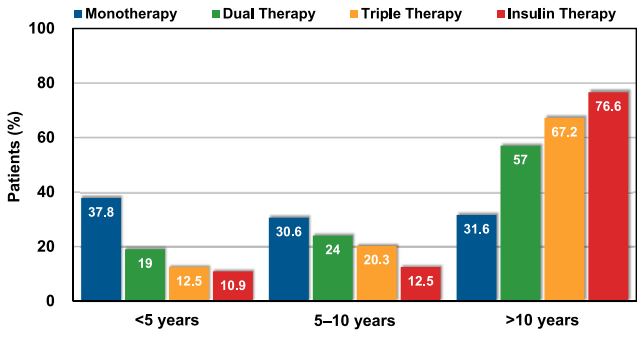

FIGURE 3 Stratification of patients from each treatment group by diabetes duration.

Minor hypoglycemic events were not recorded but were generally taken into consideration for treatment decisions during patients' visits. During the 4 months of the study, we recorded only one serious hypoglycemic event in a patient receiving prandial insulin who did not require admission to a hospital.

Antidiabetic medications used across all patients with type 2 diabetes, either as monotherapy or in combinations, from the most to the least commonly used, were metformin, GLP-1 receptor agonists, basal insulin, sodium–glucose cotransporter 2 (SGLT2) inhibitors, dipeptidyl peptidase 4 (DPP-4) inhibitors, prandial insulin, pioglitazone, and sulfonylureas; their respective percentages are shown in Figure 4. GLP-1 receptor agonists included dulaglutide weekly (59%), liraglutide daily (36%), and weekly exenatide (5%). Semaglutide has not yet been approved in Greece. Among patients receiving liraglutide, 85% used a fixed-ratio combination of liraglutide and basal insulin.

The use of antidiabetic medications within each therapeutic group is as shown in Figure 5.

Discussion

Achieving glycemic goals is an important factor in preventing chronic complications in patients with type 2 diabetes (2,16–18). Doing so requires the setting of strict and individualized glycemic goals based on international clinical practice guidelines, patient adherence to treatments and lifestyle modifications, and prompt appropriate readjustment of the therapeutic regimen according to the course of each patient's disease. In our diabetes center, the adoption of these practices yielded high rates of success in meeting glycemic goals. This success is specifically attributable to our extensive use of injectable drugs, especially GLP-1 receptor agonists, in all steps of the therapeutic algorithm, including with insulin therapy.

In our clinic, glycemic targets are set according to the guidelines of the Hellenic (19) and the American Diabetes Association (20). Specifically, glycemic targets are individualized for each patient based on the following rules:

- For patients with long life expectancy, without current CVD, and without risk of serious hypoglycemic events, the A1C target is ≤6.5%.
- For patients with shorter life expectancy or CVD and without risk of serious hypoglycemic events, the A1C target is ≤7.0%.

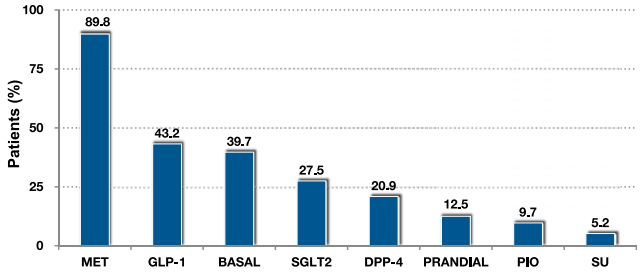

FIGURE 4 Use of antidiabetic medications across all patients with type 2 diabetes. BASAL, basal insulin; DPP-4, DPP-4 inhibitors; GLP-1, GLP-1 receptor agonists; MET, metformin, PRANDIAL, prandial insulin; PIO, pioglitazone; SGLT2, SGLT2 inhibitors; SU, sulfonylureas.

- For patients with short life expectancy or CVD or other serious comorbidities and high risk of hypoglycemic episodes, the A1C target is 7.0–8.0%.

In identifying the optimal antidiabetic treatments, our main concept is to use medications that minimize the risk of hypoglycemia, reduce body weight, confer cardiovascular safety, and maintain an adequate level of quality of life and to avoid polypharmacy and the need for frequent self-monitoring of blood glucose. For more severe cases, our guiding principle is "one injection with one pill," using a long-acting GLP-1 receptor agonist or basal insulin analog, or fixed-ratio combination of the two, accompanied by metformin or a premade combination of metformin and an SGLT2 inhibitor. This approach significantly increases patient adherence to treatment. The fact that optimal glycemic targets were achieved irrespective of diabetes duration, age, or BMI demonstrates the effectiveness of these therapeutic strategies.

Sulfonylureas are used very rarely in our clinic (5.2%), and the same is true of prandial insulin, which is only used when absolutely necessary. The reason for this strategy is that sulfonylureas cause frequent hypoglycemic events, especially in older adults and patients with kidney disease,

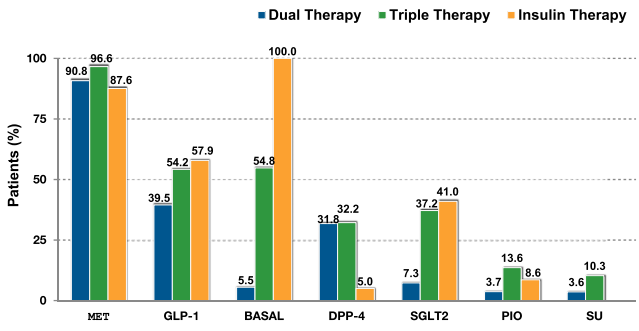

FIGURE 5 Use of antidiabetic medications across the therapeutic steps. BASAL, basal insulin; DPP-4, DPP-4 inhibitors; GLP-1, GLP-1 receptor agonists; MET, metformin, PRANDIAL, prandial insulin; PIO, pioglitazone; SGLT2, SGLT2 inhibitors; SU, sulfonylureas.

and they also increase body weight. Until recently, data on the cardiovascular safety of sulfonylureas were contradictory (21). However, the publication of two recent trials on the cardiovascular safety of linagliptin showed that glimepiride is noninferior to linagliptin in cardiovascular safety (22), while linagliptin has a neutral cardiovascular profile compared with placebo (23). Nonetheless, it should be factored into treatment selection that cardiovascular outcomes trials have shown that GLP-1 receptor agonists and SGLT2 inhibitors are not only safe, but also confer cardiovascular and renal protection (24–29).

Sulfonylureas should not be prescribed for older adults who live alone, have unreliable food intake, or lack an adequate social or family support system. An exception could be made for patients with inadequate health insurance who cannot afford the cost of alternative treatments. Moreover, the use of glibenclamide specifically should be seriously examined for possible exclusion from the therapeutic armamentarium for safety issues (15).

With regard to prandial insulin, it significantly increases body weight, causes frequent hypoglycemic episodes, and requires frequent glucose monitoring, which hampers the quality of life of patients with diabetes. Therefore, it is not used unless absolutely necessary.

The results of our study show that achievement of glycemic goals is extremely high for patients with type 2 diabetes at our center. This success is mainly attributable to our use of newer antidiabetic medications, especially GLP-1 receptor agonists, which surpassed 40%, compared with reports in similar studies in which these agents were used in one-digit percentages of patients (11–13). Of note, a study of data from the Greek national registry on antihyperglycemic medications excluding insulin showed that GLP-1 receptor agonists, along with SGLT2 inhibitors and glinides, were the least prescribed (4.6%), whereas the majority of patients (77.4%) received metformin, followed by DPP-4 inhibitors (44.8%), and sulfonylureas (34.5%) (13).

We are particularly focusing on GLP-1 receptor agonists because, as part of the overall approach we employed, they played a decisive role in enabling patients to achieve their glycemic goals, especially those who needed intensive insulin therapy. Our clinic has a wealth of experience in using GLP-1 receptor agonists combined with insulin and presented in 2011 and 2013 a study involving patients on intensive insulin therapy who had their prandial insulin fully replaced by exenatide twice daily, with remarkable results (i.e., A1C reduction of 1%,

weight loss of 6 kg, and reduction in hypoglycemic events) (30–32).

Furthermore, we routinely add GLP-1 receptor agonists to basal insulin for patients with poor glycemic control despite optimal insulin titration. We also add basal insulin for patients not achieving their A1C goal while taking a GLP-1 receptor agonist. In patients on oral medications who still have a very high A1C, we add both a GLP-1 receptor agonist and a basal insulin analog. GLP-1 receptor agonists minimize hypoglycemia risk, facilitate weight loss, and are easy to use, especially when given once weekly. As has been shown, GLP-1 receptor agonists have a high degree of efficacy similar to that of basal insulin (33) in all steps of the therapeutic algorithm. Even in patients on intensive insulin therapy, their efficacy is similar to that of prandial insulin, while their use is much simpler, does not require as frequent glucose self-monitoring, does not lead to weight gain, and reduces the risk of hypoglycemia (34). These features can significantly improve the quality of life for patients.

The effectiveness of antidiabetic medications varies significantly when comparing results from clinical trials to data on real-world experience, mainly because of lower patient adherence to treatment in real-world settings (35). In real-world clinical experience, fewer than 50% of patients adhere to their oral medication regimen (36,37), and best adherence was generally observed with DPP-4 inhibitors (38). In a meta-analysis examining initiation of GLP-1 receptor agonists in patients with type 2 diabetes in United States between 2010 and 2016, adherence to treatment during the first year was also low, at 50% (39).

It is evident, however, that once-weekly GLP-1 receptor agonists are associated with significantly greater patient adherence compared with those administered daily (40,41). In that regard, once-weekly dulaglutide, with its novel, single-use delivery device, can help patients attain better clinical results (42,43).

Likewise, the use of a fixed-ratio combination of lir-aglutide plus insulin degludec (IDegLira) induced significantly fewer gastrointestinal adverse events compared with the use of its components given alone, mainly because of the gradual dose titration recommended with the combination product (44). The effectiveness of, patient satisfaction with, and adherence to treatment with IDegLira have also been demonstrated in real-world settings (45,46). Because more complex therapeutic regimens have been linked to lower adherence rates (47), simplifying the treatment regimen by initiating a combination product can improve adherence. Concerns about hypoglycemia and weight gain have also been evaluated as important factors in poor adherence rates (48). All of these issues were considered in the paradigm we applied in our practice, as shown by the high percentage of our patients who are treated with a once-weekly GLP-1 receptor agonist or a fixed-ratio combination product, which contributes to the high rate of A1C target attainment among our patients.

Treatment adherence does not depend solely on the types of medications used, but rather is a multifactorial issue, described by the World Health Organization as encompassing patient-related, socioeconomic, condition-related, health system, and therapy-related factors (49). With regard to patient-provider relationships, health care professionals need to thoroughly discuss the potential benefits and possible side effects of medication options, engage patients in discussions about drug selection, and take their point of view fully into account in clinical decision-making (50,51). In our center, in addition to adopting a personalized therapeutic approach, we provide long-term follow-up by the same doctor to facilitate the development of a strong doctor-patient relationship. Outpatient visits to the clinic occur every 4 months on average, although some patients have shorter or longer follow-up intervals depending on the nature and side effects of their treatments and their level of glycemic control. Patients are also offered the opportunity to contact the clinic via telephone for queries on medication intolerances and insulin titration, which also contributes to their good adherence and improved glycemic control.

The high costs of certain medications can negatively affect adherence, as seen in countries where a public health system does not provide benefits to uninsured or low-income patients (48). Thus, we consider important the support offered by the Hellenic National Health System to all patients, even those who are uninsured, which allows patients access to newer, more expensive medications. The National Organization for Health Care Services Provision reimburses 90% of the cost of all diabetes medications without any prescription limitations and does not require a patient to demonstrate inability to attain glycemic goals before trying newer, more expensive, but perhaps more suitable treatments. The generalizability of our therapeutic approach may thus be hampered in countries where socioeconomic factors shape guidelines on diabetes management that discourage the use of novel medications such as GLP-1 receptor agonists as primary agents in the therapeutic algorithm.

With regard to making treatment adjustments for patients who are far from meeting their glycemic goals, our intervention is to act strict and immediately to achieve "zero

therapeutic inertia." The therapeutic algorithms dictate the appropriate time to move on to the next therapeutic step to achieve optimal glucose control. The notion of "zero inertia" thus means that we strive to always implement adjustments within the recommended timeframes between therapeutic steps of the recommended algorithm and to not procrastinate because of a lack of vigilance, time pressures, conservatism, resistance to implement newer drugs, or patients' fears.

The strength of our study is the ubiquitous use of a standardized A1C measurement based on international criteria across all patients and visits. Although we did not record minor, sporadic hypoglycemic episodes, which poses a limitation to the study, continual or severe hypoglycemic episodes were taken into consideration when implementing and adjusting therapy, and only one severe hypoglycemic episode was recorded throughout the study, reinforcing the efficacy of our treatment strategies. Of note, this was a cross-sectional study reflective of the practices of a single referral center for diabetes, but these practices have potential for implementation on a larger scale with given appropriate consideration.

Conclusion

Despite our study involving a relatively homogenous population in Greece, we strongly believe that our strategies and subsequent high rates of glycemic goal attainment can be generalizable to all countries in which health system policies support the widespread use of novel medications. Clinicians should always strive for zero inertia, set strict but individualized glycemic targets, and opt for antidiabetic medications that reduce hypoglycemia, improve weight, and optimize quality of life and adherence. The extensive use of GLP-1 receptor agonists at all steps of the therapeutic algorithm, including during intensive insulin therapy, can facilitate the attainment of glycemic goals in patients with type 2 diabetes.

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DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

I.A. designed and conducted the study and wrote the manuscript. A.A., E.T., and G.K. recorded data and performed all statistical analyses. A.Z.L. contributed to revision and editing of the manuscript. N.P. and G.P. contributed to clinical management and acquisition of data. I.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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