REPUBLIC OF AZERBAIJAN

On the rights of the manuscript

ABSTRACT
of the dissertation for the degree of Doctor of Philosophy

EFFICACY, SAFETY AND OUTCOME PREDICTION OF TYPE 2 DIABETES MANAGEMENT WITH GLICLAZIDE MR AND METFORMIN IN THE EDIAZER STUDY

Specialty: 3216.01 – Endocrinology

Field of science: Medicine

Applicant: **Ramila Alimardan Huseynova**

BAKU – 2025

The work was performed at the of Azerbaijan State Advanced Training İnstitute for Doctors named after A. Aliyev

Scientific supervisor: doctor of medical sciences
Valeh Agasafa Mirzazade

Official opponents: doctor of medical sciences, associate professor
Sain Sattar Safarova

philosophy doctor of medicine
Narmina Faiq Huseynova

philosophy doctor of medicine
Leyla Qasım Abbasova

Dissertation council: FD 2.11 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at Azerbaijan State Advanced Training İnstitute for Doctors named after A. Aliyev

Chairman of the dissertation council: doctor of the medical sciences, professor
Nazim Akif Gasimov

Academic Secretary of the Dissertation Council: philosophy doctor of medicine, associate professor
Ilaha Kamal Akbarova

Chairman of the scientific seminar: doctor of the medical sciences, professor
Ziba Bayim Qulam Akhmadova

INTRODUCTION

Relevance and development of the topic. In recent decades, a sharp increase has been observed in the prevalence of diabetes mellitus (DM), particularly type 2 diabetes mellitus[1] (DM2). According to the International Diabetes Federation (IDF) Atlas published in 2021, while 151 million people worldwide were living with diabetes in the year 2000, by 2021 this number had already risen to 537 million[2]. By 2025, the number of patients had reached 589 million[3].

The IDF projects that from 2021 to 2045, the number of people with diabetes will rise to approximately 700 million[2]. In the IDF Atlas published in 2025, the number of patients is expected to increase to 783 million by 2045[4].

In Azerbaijan, 715,300 individuals aged 20–79 years, or 10.2% of the population in this age group, are living with DM[4]. Of these, 33.9% remain undiagnosed and are unaware of their condition[4].

For comparison, data from the US in 2021 indicate that 38.4 million people, representing 11.6% of the population, were living with DM.

Among the different types of DM, DM2 is the most prevalent, accounting for approximately 90% of all cases[5]. Living with DM2

---

[1]Azərbaycan Respublikası Endokrinologiya, Diabetologiya və Terapevnik Təlimat assosiasiyası / Şəkərli diabetin diaqnostikası, profilaktikası və tibbi yardım üzrə standartları – Bakı: Azərdiab nəşriyatı, - 2015. -134 s.

[2]Endokrin Xəstəlikləri /V.A.Mirzəzadə, Y.Z.Qurbanov, V.Ə.Əzizov [və b.] - Bakı: Azərdiab nəşriyyati, - 2022. - 512 s.

[3]American Diabetes Association. 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes - 2025// Diabetes Care, - 2025. 48 (1), - p. S86-S127.

[4] International Diabetes Federation: [Electronic resource] / IDF Diabetes Atlas. 11th Edition. 2025, 125 p., URL:https://diabetesatlas.org/media/uploads/sites/3/2025/ 04/IDF_ Atlas_11th_Edition_2025.pdf

[5] International Diabetes Federation. IDF Diabetes Atlas. 10th Edition. – Brussels, 2021. – 135 p.

for 10 years on average reduces life expectancy by 3–4 years. In 1921, an estimated 6.7 million people worldwide died from DM and its complications[5].

The key to preventing both acute and chronic complications of diabetes is comprehensive disease management. This includes maintaining blood glucose, blood pressure, and low-density lipoprotein cholesterol within target ranges, as well as protecting the cardiovascular system and kidneys[3].

Nevertheless, even in the US, where the annual cost of treatment per patient with DM is 11,779 USD (slightly lower than the record 12,828 USD in Switzerland)[5], adequate control of all three mandatory parameters is achieved in only 21% of patients[6].

One of the most important components of comprehensive DM therapy is glucose-lowering treatment[3]. It has been demonstrated that in a person with DM (regardless of type), maintaining glycated hemoglobin (HbA1c) levels at 7.5% or higher for one-year results in a reduction in life expectancy by approximately 100 days[7].

The relationship between hyperglycemia and the complications of DM has been well established since the landmark DCCT[8] and UKPDS[9] studies. In recent years, sodium–glucose cotransporter-2

---

[6] Wang, L. Trends in prevalence of diabetes and control of risk factors in diabetes among US adults, 1999–2018 / L. Wang, X. Li, Z. Wang [et al.] // JAMA, – 2021. 326, No. 8. – p. 1–13.

[7]Мустафаева,С.А. Применение длительного мониторирования глюкозы аппаратом «DEXCOM» для оценки эффективности комбинированной терапии «метформин-гликлазид» у больного с первые выявленным сахарным диабетом типа 2/ С.А.Мустафаева, В.А Мирзазаде //- Bakı: Azərbaycan Metabolizm Jurnalı, - 2018. 1 (15) , - s.15-20.

[7]Мустафаева,С.А. Применение длительного мониторирования глюкозы аппаратом «DEXCOM» для оценки эффективности комбинированной терапии «метформин-гликлазид» у больного с первые выявленным сахарным диабетом типа 2/ С.А.Мустафаева, В.А Мирзазаде //- Bakı: Azərbaycan Metabolizm Jurnalı, - 2018. 1 (15) , - s.15-20.

[8] Мустафаева С.А. Аппараты длительного мониторирования глюкозы //-Bakı: Azərbaycan Metabolizm Jurnalı, - 2019. 2 (16), - s. 9-22.

inhibitors (SGLT2-Is) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been increasingly employed as glucose-lowering therapies. Beyond their antihyperglycemic effects, both drug classes provide cardioprotective and nephroprotective benefits[10].

Accordingly, the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) in 2019[11], the ESC again in 2023[10], and the American Diabetes Association (ADA) in its "Standards of Care" [7] have recommended SGLT2-Is and GLP-1 RAs as first-line glucose-lowering agents.

The most significant limitation of these two drug classes, however, is their high cost[12]. At present, the number of patients with DM in low- and middle-income countries continues to rise, while in high-income countries the increase is minimal[2] and, in many cases, prevalence is stabilizing[13]. In low and middle-income settings, mass coverage of costly medications whether through direct government support or health insurance systems is not feasible. At the same time, the lack of financing should not compromise the effectiveness and safety of ongoing medical interventions. Therefore, it is necessary to explore viable strategies to address this situation[14].

---

[9] Мустафаева С.А. Показатель «Time in Range» в зависимости от степени нарушения системы контроля глюкозы // -Украина: Высник проблем быологии и медицини, - 2020. 1(155), - с. 167-170.

[10]American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes - 2024// Diabetes Care, - 2024. 47 (1), - p. S111-S125.

[11]American Diabetes Assosiation. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes - 2023// Diabetes Care, - 2023. 46 (1), - p. S49-S67.

[12]American Diabetes Assosiation. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes – 2025. 48 (1), - p. S59-S85.

[13]American Diabetes Association. 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes – 2020 // Diabetes Care, - 2020, 43(1), - p. S48-S65.

[14]American Diabetes Association. 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes - 2021// Diabetes Care, - 2021. 44 (1), - p. S53-S72

Object and Subject of the Study: The object of the EdiAzer study (United States, ClinicalTrials.gov, NCT03164187) comprised patients with T2DM (n = 105) receiving treatment with Gliclazide MR and/or Metformin.

Aim of the Study:

To investigate the efficacy, safety, and predictive factors of pharmacotherapy with Gliclazide MR and Metformin in the management of T2DM within the framework of the EdiAzer study.

Objectives of the Study:

1. To analyze the effectiveness of Gliclazide MR and Metformin on carbohydrate metabolism based on HbA1c and fasting plasma glucose indicators.
2. To evaluate the safety of Gliclazide MR and Metformin therapy according to the frequency of severe hypoglycemic episodes and the dynamics of body weight.
3. To develop approaches for assessing the extent to which the potential of complex pharmacological glucose-lowering therapy can be utilized in the treatment of T2DM.
4. To identify key factors for predicting therapeutic outcomes in patients with T2DM treated with Gliclazide MR and Metformin.
5. To assess the feasibility of predicting the effect of Gliclazide MR and Metformin therapy on HbA1c levels.

Methods of the Study:

Collection of demographic data and medical history (including patient age, duration of diabetes, and ongoing glucose-lowering therapy). Obtaining information from patients and treating physicians regarding DM, arterial hypertension, and cardiovascular disease. Collecting data from treating physicians on the presence and diagnostic findings of diabetes complications. At baseline, measurement of height, body weight, body mass index (BMI), systolic and diastolic blood pressure, and fasting plasma glucose, measurement of HbA1c levels. Information regarding cardiovascular events, hypoglycemia, and possible adverse effects of therapy was collected to assess the patient's overall condition. During the 2nd, 4th, 6th, 8th, and 16th weeks of the study, body weight, BMI,

systolic and diastolic blood pressure, and fasting plasma glucose levels were measured. At W16, HbA1c was reassessed.

Key Provisions Submitted for Defense:

- Evaluation of the efficacy and safety of pharmacotherapy with Gliclazide MR and Metformin in T2DM.
- Development of a formula for assessing the extent to which the potential of complex pharmacological glucose-lowering therapy can be utilized.
- Identification of major factors for predicting the outcomes of glucose-lowering therapy with Gliclazide MR and Metformin in type 2 diabetes mellitus.
- Formulas for predicting either the HbA1c level or the change in HbA1c following 4 months of glucose-lowering therapy with Gliclazide MR and Metformin.

Scientific Novelty of the Study:

- Identification of factors associated with the outcomes of glucose-lowering pharmacotherapy with Gliclazide MR and Metformin in T2DM, which may be used for predictive purposes.
- Development of a model for predicting changes in HbA1c levels after 4 months of treatment with Gliclazide MR and Metformin.
- Proposal of a model to predict the absolute HbA1c value after 4 months of therapy with Gliclazide MR and Metformin.
- Demonstration of the effectiveness of monitoring HbA1c every 4 months in patients with T2DM.
- In complex glucose-lowering therapy, an indicator has been proposed to assess the extent to which the potential of treatment can be utilized.

Practical Significance of the Study:

- The study conducted in the Republic of Azerbaijan confirmed the efficacy and safety of glucose-lowering therapy with Gliclazide MR and Metformin in patients with T2DM. This is of particular importance, as in our country these medications are provided to patients free of charge by the government.

- The recommended frequency of HbA1c testing once every 4 months will reduce costs associated with patient visits and laboratory examinations (currently, HbA1c testing is required once every 3 months).
- The possibility of predicting treatment outcomes as early as 1 month after the initiation of pharmacotherapy will create opportunities to adjust treatment regimens more effectively.

- **Approbation of the study:** Separate parts of the dissertation were presented and discussed at the following scientific-practical conferences:
- Scientific-Practical Conference dedicated to the 90th Anniversary of Professor Zarifa Zeynalova, Azerbaijan Medical University (2023, Baku, Azerbaijan);
- International Scientific-Practical Conference on "Modern Medicine: Innovations and Contemporary Approaches" (2023, Baku, Azerbaijan);
- Cientific Forum: Medicine, Biology, and Chemistry (2024, Moscow, Russia);
- 6th Azerbaijan Diabetes Congress (2023, Baku, Azerbaijan).

The preliminary discussion of the dissertation was conducted at the interdepartmental meeting of the Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev (05 June 2025, protocol No.04). The dissertation was presented and discussed at the scientific seminar of the Dissertation Council FD 2.11 operating under the Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev (10 september 2025, protocol No.7).

Publications: Based on the dissertation materials, 9 works have been published. These include 5 articles (2 of which are international) and 4 abstracts (1 international), published in journals and proceedings recognized by the Higher Attestation Commission (HAC).

Name of the organization where the work was performed: The dissertation was conducted at the Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev, the Endocrinology, Diabetology and Therapeutic Education Association

of the Republic of Azerbaijan, and "Azər Türk Med Clinic".

Application of the research findings: The results obtained from the research have been applied in clinical practice at the Teaching Therapeutic Clinic of Azerbaijan Medical University and "Zəfər Medical Center" LLC, as well as incorporated into the educational program of the Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev.

Structure and volume of the dissertation: The dissertation consists of 195 computer-typed pages. It includes the Introduction (8,326 characters), Literature Review (51,325 characters), Materials and Methods (12,080 characters), and five chapters presenting the results of personal observations (Chapter III – 11,658 characters; Chapter IV – 9,704 characters; Chapter V – 5,223 characters; Chapter VI – 10,459 characters; Chapter VII – 11,033 characters; Chapter VIII – 47,413 characters), followed by the Conclusion (2,260 characters), Study Results (2,330 characters), Practical Recommendations (1,504 characters), and a list of references. The total volume of the dissertation includes 11 tables, 30 figures and graphs, and a reference list covering 266 sources published in Azerbaijani, Russian, English, and other foreign languages.

MATERIALS AND METHODS OF THE STUDY

The study discussed in this work, "Evaluation of Type 2 Diabetes Treatment with Gliclazide Modified Release in Azerbaijan" (EdiAzer), was a multicenter, non-comparative, observational investigation. The study was conducted in accordance with the standards and principles of the Declaration of Helsinki.

All patients participating in the study were duly informed and signed written informed consent forms prior to enrollment. The study was approved by the Ethics Committee of the Endocrinology, Diabetology and Therapeutic Education Association of the Republic of Azerbaijan.

The study was registered on ClinicalTrials.gov under the identifier NCT03164187.

The research consisted of a 2-month enrollment phase and a 4-

month observation phase. It began on September 1, 2016, and concluded on June 10, 2017. Patient enrollment and monitoring were carried out by 13 physicians across 9 clinics in Baku, Azerbaijan. The number of patients seen by each physician ranged from 1 to 21, with a mean proportion of 8.1% (95% CI 5.11; 11.04).

This scientific study was conducted by the Endocrinology, Diabetology and Therapeutic Education Association of the Republic of Azerbaijan, with financial and organizational support from Servier
Inclusion Criteria:

- Established diagnosis of T2DM.
- Age ≥ 25 years.

  Exclusion Criteria:

  Exclusion criteria were developed taking into account both the aims and objectives of the study as well as contraindications to the pharmacological agents under investigation. Patients were excluded in the following cases:
- Refusal to participate.
- Inability to attend medical examinations at W0 or W16 to monitor general health status.
- Known hypersensitivity to any excipients in Metformin or Gliclazide MR tablets.
- Pregnancy or lactation.
- HbA1c level ≤ 7.0%.
- Presence of life-threatening, uncontrolled, or clinically significant conditions, including:
- Malignant tumors.
- Renal insufficiency with GFR < 45 ml/min/1.73 m².
- Impaired liver function with ALT and AST levels elevated to ≥2 times the upper limit of normal.

At the initial stage, the presence of comorbid conditions was determined based on patient complaints, objective examination data, medical records, and laboratory test results.

At baseline, the height of each patient was measured and recorded in centimeters. At the initial and each subsequent visit, body weight was measured in kilograms, and BMI was calculated using the standard formula:

$$BMI = Weight/Height^2$$

where weight (body mass) is expressed in kilograms and height in meters squared.

Blood pressure was measured according to standard procedures consistent with current requirements. During the preparatory phase of the EdiAzer study, additional instructions on blood pressure measurement techniques were provided to participating physicians.

During the study, at each patient visit fasting plasma glucose levels were measured in the laboratories of the participating medical institutions by the treating physicians.

Initially, 121 patients were enrolled in the study. Subsequently, 11 patients were excluded: 7 patients due to HbA1c levels ≤ 7.0%, 1 patient due to GFR < 45 ml/min/1.73 m², and 3 patients withdrew consent. Among the 110 patients who began participation, 5 were later excluded for failing to attend follow-up visits.

Thus, results were analyzed for 105 patients who completed the EdiAzer study from baseline to final follow-up.

According to the study design, patients were evaluated at weeks 0, 2, 4, 6, 8, and 16 (denoted as W0, W2, W4, W6, W8, and W16 in the discussion of results). HbA1c was measured at W0 and W16. At all visits, plasma glucose, body weight, BMI, and blood pressure were measured. At W0, patient height was also recorded.

Eligible patients received Gliclazide MR either as first-line therapy replacing prior Metformin treatment or as second-line therapy in combination with Metformin.

In both newly diagnosed patients and those with uncontrolled glycemia on Metformin monotherapy, treatment with Gliclazide MR was initiated at 30 mg/day. At each subsequent physician visit, if fasting plasma glucose remained above 6 mmol/L, the dose of Gliclazide MR was increased by 30 mg, up to a maximum daily dose of 120 mg.

Exceptions to the treatment regimen with Gliclazide MR occurred when the physician, based on available patient information, decided to initiate therapy with a higher starting dose of Gliclazide MR.

In cases where fasting plasma glucose levels remained above 6 mmol/L despite the maximum dose of Gliclazide MR, additional Metformin was prescribed (or, in patients already on combination therapy, the dose of Metformin was increased). The maximum dose of Metformin was 3,000 mg per day, with a single dose not exceeding 1,000 mg.

Primary endpoints of the study were as follows:

- Changes in mean HbA1c levels between W0 and W16.
- The proportion of participants achieving HbA1c < 7.0%.
- The proportion of participants with ≥1.0% reduction in HbA1c between weeks W0 and W16.

Secondary endpoints included changes in the following parameters: mean fasting plasma glucose levels, body weight, BMI, and blood pressure.

Throughout the study, patients were monitored for serious adverse events, including severe hypoglycemia. Severe hypoglycemia was defined, in accordance with ADA recommendations, as an episode in which the patient was unable to self-treat and required assistance from another person.

In this dissertation, changes in blood pressure are not considered, as they fall outside the scope of the research questions under discussion.

The study enrolled patients with newly diagnosed T2DM. Of these, 60 patients (57.1%; 95% CI 47.68–66.61) had not previously received pharmacotherapy, while 45 patients (42.9%; 95% CI 33.39–52.32) had been on Metformin therapy. Prior to the start of the study, the difference in frequency between patients with and without prior pharmacotherapy was not statistically significant: p=0.0401 (p> 0.05).

Among the study participants, 53.3% (95% CI 43.79–62.88) were women and 46.7% (95% CI 37.12–56.21) were men. The gender distribution differences were not statistically significant (p=0.3400; p>0.05).

The minimum age in the cohort was 25 years, the maximum 79 years, with a mean age of 55.1 years (95% CI 53.06–57.06). Seven patients (6.7%; 95% CI 1.90–11.44) were younger than 40 years. 25

patients (23.8%; 95% CI 15.66–31.96) were in the 40–49 age group. Thirty-nine patients (37.1%; 95% CI 27.90–46.39) were aged 50–59 years. 26 patients (24.8%; 95% CI 16.51–33.02) were aged 60–69 years. 8 patients (7.6%; 95% CI 2.54–12.69) were aged 70 years or older.

For men (n = 49), the age range was 31–79 years, with a mean age of 55.1 years (95% CI 52.25–58.03). For women (n = 56), the age range was 25–79 years, with a mean age of 55.0 years (95% CI 52.16–57.80). Differences in mean age between men and women were not statistically significant ($p > 0.05$).

In the "<40 years" group, the prevalence was 6.1% (95% CI –0.67–12.87) among men and 7.1% (95% CI –0.17–14.36) among women ($p > 0.05$). In the "40–49 years" group, DM was observed in 24.5% of men (95% CI 12.33–36.67) and 23.2% of women (95% CI 11.26–35.14) ($p > 0.05$). In the "50–59 years" group, the prevalence was 38.8% of men (95% CI 25.01–52.59) and 35.7% of women (95% CI 22.15–49.25) ($p > 0.05$). In the "60–69 years" group, 22.4% of men (95% CI –10.61–34.19) and 26.8% of women (95% CI 14.27–39.33) were represented ($p > 0.05$). Among those aged ≥70 years, 8.2% of men (95% CI 0.44–15.96) and 7.1% of women (95% CI –0.17–14.37) were observed ($p > 0.05$). Thus, the age-group distribution between men and women did not differ significantly.

For statistical analysis, the standard Microsoft Excel software package was used to calculate minimum, maximum, and mean values of the analyzed parameters, as well as standard deviations, errors, and Student's *t*-test values. Differences between mean indicators were considered statistically significant at $p < 0.05$. Mean values are presented as mean ± standard deviation (SD).

Comparisons of paired samples were carried out using an online calculator. For comparing two independent samples, the Wilcoxon rank sum test (Wilcoxon–Mann–Whitney test) was also applied using the same online tool.

For statistical indicators of differences between proportions, Fisher's exact test was applied using an online calculator in cases where values approached 0% or 100%. 95 % confidence intervals (95% CI) were also calculated using online software. For differences

between proportions, the χ^2 test was applied, and when relative frequencies approached 0% or 100%, relative error estimation was performed according to the recommendations of L.S. Kaminsky.

To determine the presence or absence of associations between different parameters, correlation analysis was conducted. The correlation coefficient, its standard error, and its statistical significance were calculated in Excel using the appropriate formulas. Regression methods were also employed.

In the EdiAzer study, the mean duration of T2DM (n=105) was 2.3 years (95% CI 1.84–2.83). In 61.0% of patients (95% CI 54.67–73.33), the disease duration was less than 3 years.

Before enrollment in the study, adherence to recommended diet was reported by 52.4% of patients (95% CI 42.83–61.93), and adherence to physical activity recommendations by 35.2% (95% CI 26.10–44.38). The proportion of patients taking Metformin was 42.9% (95% CI 33.39–52.32). Only 11.4% (95% CI 5.34–17.51) adhered to all three approaches (diet, physical activity, and Metformin), while 24.8% (95% CI 16.51–33.02) received no treatment at all.

DM complications were recorded in 40.0% of cases (95% CI 30.63–49.37), with neuropathy being the most common complication, observed in 28.6% (95% CI 19.93–37.21).

The mean BMI was 29.5 kg/m² (95% CI 28.54–30.38). Normal body weight was present in 14.7% (95% CI 8.22–21.19), overweight in 53.9% (95% CI 44.59–63.25), and obesity in 31.4% (95% CI 22.72–40.03) of participants.

The mean systolic blood pressure was 134.0 mmHg (95% CI 130.33–137.67), while mean diastolic blood pressure was 84.3 mmHg (95% CI 82.20–86.38). Arterial hypertension (AH) was identified in 46.7% of patients (95% CI 37.33–56.01).

The mean fasting plasma glucose level was 10.9 mmol/L (95% CI 10.24–11.53), and mean HbA1c was 8.8% (95% CI 8.56–9.09).

Thus, the study group was mainly characterized by patients with relatively short disease duration, high prevalence of overweight and obesity, widespread AH, and inadequate glycemic control.

The effectiveness of combination therapy with Gliclazide MR and Metformin in patients with T2DM was investigated.

At baseline, the mean HbA1c level was 8.8% (95% CI 8.56–9.09). Following treatment, this indicator decreased significantly to 7.6% (95% CI 7.45–7.83) at W16. ($p < 0.001$). Analysis of the distribution of values demonstrated a "leftward shift" of HbA1c frequencies, indicating a reduction in the proportion of high values and an increase in lower values.

The proportion of patients with HbA1c > 8.0% decreased from 65.7% at W0 (95% CI 56.64–74.79) to 32.4% at W16 (95% CI 23.43–41.33) ($p<0.0001$). At the same time, the proportion of patients achieving the "ideal" HbA1c target (< 7.0%) increased from 0.0% at W0 (95% CI –6.92–6.92) to 28.6% at W16 (95% CI 19.93–37.21). The proportion of patients with HbA1c < 7.5% rose from 19.0% at W0 (95% CI –6.92–6.92) to 46.7% at W16 (95% CI 37.12–56.21) ($p < 0.0001$).

Analysis of individual changes demonstrated that in 98.1% of patients, W0 HbA1c was higher than at W16, confirming the effectiveness of therapy. A reduction in HbA1c of ≥1.0% was observed in 58.1% of patients (95% CI 48.66–67.53), a reduction of ≥1.5% in 24.8% (95% CI 16.51–33.02), and a reduction of ≥2.0% in 18.1% (95% CI 10.73–25.46). An increase in HbA1c during the treatment period was recorded in only 1.9% of participants.

The dynamics of fasting plasma glucose also demonstrated a pronounced positive treatment effect. At W0, mean fasting glucose was 10.9 mmol/L (95% CI 10.24–11.53). By W16, this value had decreased significantly to 7.1 mmol/L (95% CI 6.77–7.38) ($p < 0.001$).

The most substantial reductions occurred during the initial weeks of therapy. By W2, fasting glucose had already declined to 8.7 mmol/L (95% CI 8.33–9.04), representing a 2.1 mmol/L decrease (95% CI 1.58–2.55) compared to baseline ($p<0.001$). At W4, fasting glucose was 7.9 mmol/L (95% CI 7.58–8.24), and by we W6 it had dropped to 7.3 mmol/L (95% CI 7.05–7.62). After W6, the rate of decline slowed considerably: at W8 the level was 7.1 mmol/L (95% CI 6.84–7.43), and at W16 it remained stable at 7.1 mmol/L (95% CI

6.78–7.37). The difference between W8 and W16 values was not statistically significant ($p > 0.05$), indicating stabilization of glycemic control.

Individual analysis further revealed that at W16, fasting glucose was lower than W0 in 94.3% of patients, increased in 4.8%, and unchanged in 1.0%.

Thus, W16 of combination therapy with Gliclazide MR and Metformin resulted in significant improvements in carbohydrate metabolism control. The greatest effects were observed during the first W6, when both HbA1c and fasting plasma glucose decreased rapidly. By the end of the study, approximately half of the patients (46.7%) had achieved HbA1c < 7.5%, while the proportion of patients with HbA1c > 8.0% had been reduced by more than twofold. These results confirm the high efficacy of the Gliclazide MR and Metformin combination in achieving and maintaining target outcomes in patients with T2DM.

The second objective of the study was to evaluate the safety of glucose-lowering therapy with Gliclazide MR and Metformin, taking into account the frequency of major cardiovascular events, severe hypoglycemia, adverse effects, and body weight dynamics. Major cardiovascular events were defined as: acute myocardial infarction, stroke, cardiovascular death, hospitalization due to unstable angina, revascularization procedures, or hospitalization for heart failure. During the study, no cardiovascular events were recorded; the frequency was 0% (95% CI –6.92 to 6.92).

The most common adverse effects of Metformin are gastrointestinal disorders which occur in approximately 25% of patients. Less frequently reported are headache, upper respiratory tract infections, and metallic taste in the mouth. A very rare but serious complication is lactic acidosis, which develops mainly in the presence of renal or hepatic disease, severe congestive heart failure, dehydration, or alcohol use.

Gliclazide MR may cause hypoglycemia, rare cutaneous and allergic reactions hematological abnormalities, transient visual disturbances, dyspepsia, as well as rare liver function disorders.

According to the Standards of Care of the ADA**,** hypoglycemia is classified into three levels. A plasma glucose concentration of 55–69 mg/dL (3.0–3.8 mmol/L) corresponds to "level 1 hypoglycemia"**.** Severe hypoglycemia is categorized as "level 2" or "level 3 hypoglycemia"**,** defined as plasma glucose ≤54 mg/dL (≤3.0 mmol/L). These episodes are characterized by the patient's inability to self-manage and the need for assistance from another person.

During the study, only one patient experienced a level 1 hypoglycemic episode, which was associated with a delayed lunch. No severe hypoglycemia (level 2 or level 3) was recorded. The overall frequency of adverse events was 1.0% (95% CI –5.97 to 7.87).

Overweight was observed in 41.1% of women and 65.3% of men, while obesity was present in 39.3% of women and 20.4% of men. The maximum recorded weight loss was 5 kg, while the maximum weight gain was 4 kg. The mean weight difference between W0 and W16 was 0.5 kg (95% CI –1.06 to 0.06).

Obesity is recognized as a major risk factor not only for cardiovascular disease but also for oncological, hepatic, and other chronic conditions.

Across the entire cohort, body weight remained unchanged in 16.7% of patients, decreased in 45.1%, and increased in 38.2%. The proportion of patients who did not gain weight was statistically significantly higher compared with those who gained weight (61.8% vs 38.2%, $p < 0.001$). Similar results were obtained in men (61.2% vs 38.8%, $p < 0.05$) and in women (62.3% vs 37.7%, $p<0.05$).

In conclusion, in patients with T2DM, treatment with Gliclazide MR and/or Metformin was associated with an absence of major cardiovascular events, no occurrence of severe hypoglycemia, and no significant increase in body weight, thereby confirming the favorable safety profile of these agents.

The third objective of the study was to develop approaches for assessing the extent to which the potential of complex pharmacological glucose-lowering therapy could be utilized in patients with T2DM. At the initial stage, analysis was performed of the dose dynamics of Gliclazide MR and Metformin and of the distribution of

patients according to stable dosing regimens, across the study control points (W0–W16).

At W0, no patients were taking Gliclazide MR, and the mean dose was 0 mg. By W2, the mean dose had increased to 52.0 mg (95% CI 47.82–56.18), at W4 to 67.7 mg, at W6 to 78.9 mg, at W8 to 83.7 mg, and at W16 to 84.2 mg. In most comparisons between early and subsequent stages (W2 vs W4, W2 vs W6, W4 vs W6, W2 vs W8, etc.), the differences were statistically significant ($p<0.001$). However, no statistically significant differences were observed between later stages (e.g., W6 vs W8, W6 vs W16).

Dose Distribution in the Groups-at the W2 stage, 38.1% of patients were receiving 30 mg of Gliclazide MR, 55.2% were receiving 60 mg, 1.9% were receiving 90 mg, and 4.8% were receiving 120 mg. The proportion of patients on higher doses increased toward the middle of the study, reaching a maximum at H8 (90 mg – 22.9%, 120 mg – 31.4%). At W16, the distribution was as follows: 7.6% on 30 mg, 39.0% on 60 mg, 19.0% on 90 mg, and 34.3% on 120 mg. Thus, the maximum dose was prescribed to approximately one in three patients, indicating that the full therapeutic potential of the regimen was not fully utilized.

At W0, the mean Metformin dose was 519.5 mg (95% CI 388.09–650.96), and the drug was prescribed to 42.9% of patients. The mean dose changed over time as follows: W2 – 508.1 mg, W4 – 556.2 mg, W6 – 593.3 mg, W8 – 650.5 mg, W16 – 675.7 mg. A statistically significant difference was observed only between W0/W2 and the end of the study (723.6 mg; 95% CI not specified, $p<0.05$).

The proportion of patients receiving Metformin increased from 42.9% at W0 to 56.2% at W16. After the study was completed, therapy was recommended for 57.1% of participants. The increase in patient share between W0/W2 and W16 was statistically significant ($p < 0.05$); no differences were recorded in other comparisons.

The distribution of Metformin doses was as follows: <1,000 mg/day – 9.5–13.3% at various stages, with no significant changes; 1,000–<2,000 mg/day – 22.9–33.3%, without significant differences; ≥2,000 mg/day – 8.6–10.5%, also without significant changes.

Thus, during the study, the mean dose of Gliclazide MR increased from zero to approximately 84 mg/day. Significant differences were observed between baseline and intermediate stages, and by the end of treatment one-third of patients were on the maximum dose. The mean Metformin dose increased moderately, with statistical significance observed only between baseline and the final stage; the proportion of patients receiving Metformin rose to 56–57%. In both cases, use of the maximum permitted doses was uncommon: only 34.3% reached the maximum for Gliclazide MR, and the upper dose threshold was not reached for Metformin. Overall, this indicates that the full potential of complex glucose-lowering therapy was not realized and that opportunities remain for optimization of treatment regimens.

In the treatment of patients with T2DM, it becomes necessary to assess the extent to which the potential of pharmacological glucose-lowering agents is fully utilized, as well as to compare the relative strength of glucose-lowering effects among different patients. To date, no indicator has been available for such an analysis.

For general evaluation (using a single indicator), we proposed the **General Pharmacological Glucose-Lowering Effect Index (GLEI)**.

$$GLEI= a1\times X1/Y1 + a2 \times X2/Y2 + an\times Xn/Yn \quad (2)$$

where:

- X1,X2,…,XnX_1, X_2, \dots, X_nX1,X2,…,Xn – the actual daily doses of drug №1, №2, … №n;
- Y1,Y2,…,YnY_1, Y_2, \dots, Y_nY1,Y2,…,Yn – the maximum daily doses of drug №1, №2, … №n;
- a1,a2,…,ana_1, a_2, \dots, a_na1,a2,…,an – the efficacy coefficients of drug №1, №2, … №n, calculated as the ratio of the drug's mean ability to reduce HbA1c within 3 months to the maximum recognized glucose-lowering effect (1.5 percentage points, considered the highest effect among non-insulin glucose-lowering drugs such as sulfonylureas and Metformin).

For example, for Metformin, the coefficient is calculated as 1.5/1.5=1.01.5/1.5 = 1.01.5/1.5=1.0. For Sitagliptin, the coefficient is 0.8/1.5=0.530.8/1.5 = 0.530.8/1.5=0.53.

Since the simultaneous use of more than 3–4 glucose-lowering drugs is uncommon in practice, the maximum theoretical index value can be considered as 4 units.

Example Calculation №1: If a patient receives 120 mg/day of Gliclazide MR:

$$GLEI = 1,5/1,5 \times 120/120 = 1,0 \times 1,0 = 1,0$$

If we are interested in the percentage of glucose-lowering potential utilized, the obtained GLEI value (1.0) is divided by the maximum index value (4.0), resulting in 0.25 or 25%.

Example Calculation №2. The patient is taking two drugs: Gliclazide MR 30 mg/day and Metformin 1,000 mg/day.

GLEI=1,5/1,5 × 30/120 + 1,5/1,5 × 1000/3000 = 0,25 + 0,33 = 0,58. The proportion of glucose-lowering potential utilized is calculated as 0,58/4 = 0,145, or 14.5%. Despite the use of two glucose-lowering drugs, the utilization of therapeutic potential in this patient was lower compared with patient №1.

Example Calculation №3. The patient is taking Gliclazide MR 60 mg/day, Metformin 1,700 mg/day, and Sitagliptin 100 mg/day.

GLEI=1,5/1,5 × 60/120 + 1,5/1,5 × 1700/3000 + 0,8/1,5 × 100/100 = 0,50 + 0,57 + 0,53 = 1,60

The proportion of glucose-lowering potential utilized is calculated as 1,6/4,0 = 0,4, or 40%.

Future studies (not part of the present dissertation) may explore the practical applicability of this indicator, its association with the effectiveness of glucose-lowering therapy, and its potential role as a predictor for the need for insulin therapy.

Based on the EdiAzer study data, an analysis was conducted to evaluate the impact of various clinical and metabolic factors on changes in HbA1c over the W16 treatment period (difference between W0 and W0 HbA1c). Correlation analysis was applied, and appropriate linear regression models were constructed.

The influence of factors such as age, duration of T2DM, and height was examined. The effects of body weight, BMI, and systolic

and diastolic blood pressure at W0 and at the end of the study were also analyzed. In addition, the influence of Gliclazide MR and Metformin dosages at different stages of the study, W0 HbA1c, and fasting plasma glucose levels atW0, W2, W 4, W 6, W 8, and W16 was evaluated. Moreover, the effect of differences in fasting plasma glucose values between paired intervals (W0 vs W2, W2 vs W4, W4 vs W6, W6 vs W8, and W8 vs W12) was also assessed.

Age did not have any significant effect on the effectiveness of glucose-lowering therapy ($r = –0.08$; $p>0.05$). Likewise, the duration of T2DM ($r = –0.01$; $p>0.05$), height ($r = –0.04$; $p>0.05$), body weight at W0 ($r = –0.07$; $p>0.05$) and at W16 ($r = –0.09$; $p>0.05$), and change in body weight from W0 to W16 ($r = –0.11$; $p> 0.05$) were not significant. Similarly, W0 BMI ($r = –0.03$; $p>0.05$), W16 BMI ($r = –0.05$; $p>0.05$), and BMI change ($r =+0.12$; $p>0.05$) showed no significant influence.

For blood pressure, no significant associations were found: baseline systolic blood pressure (SBP) ($r =+0.03$; $p>0.05$), W16 SBP ($r =+0.01$; $p>0.05$), SBP change ($r=+0.06$; $p>0.05$); baseline diastolic blood pressure (DBP) ($r =+0.08$; $p>0.05$), W16 DBP ($r = +0.02$; $p > 0.05$), and DBP change ($r =+0.10$; $p>0.05$).

Figure presents the overall scheme of the influence of glycemia and HbA1c-related factors on changes in HbA1c after W16 of therapy.

As seen in Figure 1, the principal factors affecting the change in HbA1c after W16 of therapy were: W0 HbA1c ($r = +0.70$; $p < 0.001$), W0 fasting plasma glucose ($r = +0.38$; $p < 0.001$), Change in fasting plasma glucose during the first W2 ($r =+0.44$; $p < 0.001$), Change in fasting plasma glucose during W2–W4 ($r =+0.28$; $p < 0.001$).

The next stage of the study involved assessing the possibility of predicting changes in HbA1c levels during W16 of treatment with Gliclazide MR and/or Metformin in patients with T2DM. For this purpose, actual observed values (Yreal) were compared with calculated values obtained from six mathematical models (Y1he–Y6he). The aim was to identify the model with the highest predictive accuracy and the greatest practical clinical value.

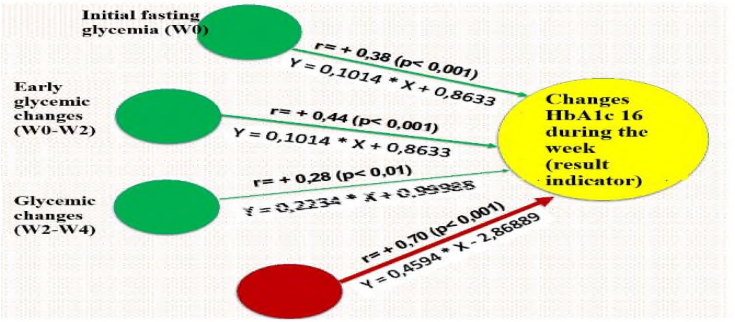

Figure. General scheme of the influence of glycemia and HbA1c-related factors on changes in HbA1c after 16 weeks of treatment

In the study, six mathematical models were applied to predict the change in HbA1c between W0 and W16.

Y — the calculated difference in HbA1c level between W0 and W16.

The first four models were based on a single variable:

- **Model 1:** Y1he= Y1he = 0,1014·X + 0,08633
  X — W0 fasting plasma glucose, mmol/L.
- **Model 2:** Y2he=0,1713·X + 0,82531
  X — the difference between W0 and W2 fasting plasma glucose (W0 – W2), mmol/L.
- **Model 3:** Y3he=0,2234·X + 0,99988
  X — the difference between W 2 and W4 fasting plasma glucose (W2 – W4), mmol/L.
- **Model 4:** Y4he=0,4594·X – 2,86889
  X — W0 HbA1c level, %.

  The subsequent models included multiple variables:
- **Model 5:** Y5he=1,02552– 0,0355·X1 + 0,1926·X2 + 0,1691·X3
  X1— W0 fasting plasma glucose, mmol/L;
  X2 — the difference between W0 and W 2 fasting plasma glucose (W0 –W), mmol/L;

X3 — the difference between W 2 and W 4 fasting plasma glucose (W2 – W4), mmol/L.

- **Model 6:** Y6he–1,93608– 0,1647·X1 + 0,2414·X2 + 0,2273·X3 + 0,4472·X4
  X1 —W0 fasting plasma glucose, mmol/L;
  X2 — the difference between W0 and W2 fasting plasma glucose (W0 – W2), mmol/L;
  X3 — the difference between W 2 and W 4 fasting plasma glucose (W2 – W4), mmol/L;
  X4 — W0 HbA1c level, %.

Clinical Case No. 1 (code 047-06-06)

Patient: Male, 44 years old, T2DM, disease duration 1 month. At baseline, the patient was not receiving any glucose-lowering therapy. Medical history was negative for AH. The patient adhered to dietary recommendations and reported more than 30 minutes of daily physical activity.

Anthropometric data: Height — 155 cm; body weight at W0 — 58 kg, after W16 — 56 kg; body mass index at W0— 24.1 kg/m², after W16 — 23.3 kg/m².

Blood pressure: At baseline — 140/90 mmHg; after W16 — 120/75 mmHg.

Fasting plasma glucose (mmol/L): W0— 11.2; W 2 — 7.2; W 4 — 6.0; W 6 — 5.9; W 8 — 5.9; W 16 — 5.7.

HbA1c (%): W0— 7.5; after W16 — 6.5.

Therapy: FromW0— Gliclazide MR 30 mg once daily in the morning; from week 2 — 60 mg once daily in the morning, without Metformin. Actual HbA1c change: –1.0%.

Predicted change according to models: Model 1: –1.2%; Model 2: –1.5%; Model 3: –1.3%; Model 4: –0.6%; Model 5: –1.6%; Model 6: –1.0%;

Conclusion: Actual reduction was –1.0%. The prediction from Model 6 fully matched the observed result, whereas other models provided either overestimates or underestimates.

Clinical Case No. 2 (code 002-02-01)

Patient: Female, 45 years old, T2DM, disease duration — 1 year. At baseline, the patient was not receiving continuous glucose-lowering

therapy. She had previously used Metformin, but discontinued due to gastrointestinal side effects. Medical history was negative for arterial hypertension. She adhered to dietary recommendations and reported more than 30 minutes of daily physical activity.

Anthropometric data: Height — 155 cm; body weight at W0 — 95 kg, after W16 — 83 kg; body mass index at W0— 39.5 kg/m², after W16 — 34.5 kg/m².

Blood pressure: At W0— 110/80 mmHg; after W16 — 130/80 mmHg.

Fasting plasma glucose (mmol/L): W0— 17.5; W 2 — 11.9;W 4 — 11.1; W6 — 9.7; W 8 — 9.3; W16 — 8.7.

HbA1c (%): W0— 10.4; after W16 — 8.3.

Therapy: From W0— Gliclazide MR 60 mg once daily in the morning, without Metformin; the dose remained unchanged throughout the study.

Actual HbA1c change: –2.1%.

Predicted change according to models: Model 1: –1.9%; Model 2: –1.8%; Model 3: –1.2%; Model 4: –1.9%; Model 5: –1.6%; Model 6: –1.7%;

Conclusion: Actual reduction was–2.1%. All models underestimated the reduction; the closest predictions (difference <0.4%) were obtained from Models 1, 2, 4, and 6, although none provided a perfect match.

Comparative model analysis (generalized sample indicators): In most models, the average predicted HbA1c reduction was 1.2% (exception — Y5he). Minimum values ranged from –0.3% for the actual data to +0.7% for Models 1 and 2; maximum values ranged from 1.9% for Model 3 to 5.7% for the actual data. The standard deviation was highest for the actual values (0.89) and lowest for Model 3 (0.25), reflecting the smoothing of variability when simple single-factor regressions were applied.

Analysis of “real vs. calculated” differences

Across all models, the mean difference was 0.00; however, based on mean absolute deviation, Model 6 performed best: 0.40 ± 0.035%. The next closest was Model 4: 0.46 ± 0.434%. Models 1, 2,

3, and 5 demonstrated higher absolute deviations and were statistically inferior to Model 6 ($p<0.05$ vs. $p<0.001$).

"Correlation analysis: Y vs. models"

A positive correlation was observed in all cases between actual changes in HbA1c and model-predicted values: Model 3: r = +0.2885; Model 1: r = +0.3772; Model 2: r = +0.4500; Model 5: r = +0.4796; Model 4: r = +0.7013; Model 6: r = +0.7961 (highest correlation);

This finding confirms the superiority of a multifactorial approach that incorporates baseline HbA1c.

HbA1c at W16 and clinical-anamnestic indicators

At week 16, HbA1c showed no significant associations ($p>0.05$) with age, duration of T2DM, height, body weight, BMI (W0, W16, or their differences), systolic and diastolic blood pressure (W0, W 16, or their differences), or the doses of Metformin and Gliclazide MR.

HbA1c at W16 and glycemia.

Changes in fasting plasma glucose (differences W0–W2, W2–W4, W4–W6, W6–W8, W8–W16) were not statistically significant. However, the absolute fasting glucose values at each time point consistently showed positive correlations with HbA1c at W16: W0: r = +0.31; W2: r=+0.45; W4: r = +0.53; W6: r = +0.53; W8: r = +0.50; W16: r =+0.58 (all $p<0.001$). From W4 onward, the strength of association reached $r \geq 0.50$.

Practical interpretation

- The most accurate model for predicting changes in HbA1c was Model 6, which incorporated baseline fasting plasma glucose, its early differences (W0–W2 and W2–W4), and W0 HbA1c.
- Most demographic and clinical variables did not show significant influence on HbA1c at W16, whereas the dynamics of fasting plasma glucose remained an informative predictor.
- These findings are consistent with the clinical rationale of HbA1c responding early to changes in glycemia and support the use of a 4-month monitoring interval for therapeutic decision-making.

During the analysis, an integrated model Preform HbA1c was developed to predict the final HbA1c level at W16. This model was based on two principal parameters: baseline HbA1c and the difference between baseline and predicted HbA1c according to Model 6 (Preform DiA1c).

The formula was as follows:

Preform HbA1c = 2.8926 + 0.3948 × HbA1c (W0) + 0.1652 × (HbA1c (W0) – Preform DiA1c)

This approach accounted for both the absolute W0 HbA1c level and the expected treatment-related change. Calculations using this formula produced predictions that were maximally close to actual values: the mean difference between predicted and actual HbA1c was 0.00 ± 0.634%, while the mean absolute deviation was 0.47 ± 0.430%.

The distribution of predictive accuracy showed that in 60.0% of patients, the difference between predicted and actual HbA1c was ≤0.5%; in 32.4%, the difference ranged from 0.5% to 0.9%; and only in 9.5% was the discrepancy ≥1.0%.

Thus, the Preform HbA1c model allows highly accurate prediction of HbA1c at W16, enabling early evaluation of treatment efficacy and timely adjustment of therapy when required.

Analysis of the EdiAzer study results demonstrated that:

- The highest accuracy and best agreement with actual HbA1c changes were achieved with Model 6, which included baseline fasting glucose, early glycemic changes (W0–W2 and W2–W4), and W0 HbA1c.
- Based on this model, the integrated formula Preform HbA1c was constructed, enabling prediction of HbA1c at W16 with minimal error (mean absolute deviation 0.47%).
- This approach allows early assessment of therapeutic efficacy and timely treatment modification.
- The findings support extending the HbA1c monitoring interval to four months without loss of clinical informativeness, which may reduce the burden on laboratory services and optimize healthcare costs.

RESULTS

1. Monotherapy with Gliclazide MR and combined therapy with Gliclazide MR plus Metformin in T2DM allowed: [1]
   - Reduction of mean HbA1c level from 8.8 ± 1.36% at baseline to 7.6±0.97% after 16 weeks (p<0.001); [1]
   - Achievement of lower HbA1c values than baseline in 98.1% of patients; [1,9]
   - Achievement of HbA1c <7% at study end in 28.6% of patients;
   - Reduction of HbA1c by ≥1% in 56.2% of participants;
   - Attainment of the primary study endpoint—HbA1c <7.0% and/or reduction by ≥1%—in 68.6% of participants;
   - Reduction of mean fasting plasma glucose from 10.9±3.3 mmol/L at baseline to 7.1±1.6 mmol/L at week 16 (p<0.001); [1]
   - Achievement of lower fasting glucose values than baseline in 95.2% of patients.
2. Monotherapy with Gliclazide MR and its combined use with Metformin also proved favorable in terms of safety, as no episodes of severe hypoglycemia were recorded; body weight was not significantly affected (80.7±12.1 kg at baseline vs. 80.3±11.9 kg at study end); and no cardiovascular events or serious adverse effects were observed during the study period [1,4,6].
3. The study results indicated that in T2DM, the frequency of physician visits could potentially be reduced from four times per year to three times per year [2].
4. A predictive model was developed to estimate the difference in HbA1c between baseline and study end. Based on fasting glucose at baseline, the difference between weeks 0–2 and 2–4, and baseline HbA1c, the Preform DiA1c index was calculated. The results obtained with this model showed a strong correlation with actual HbA1c outcomes (r =+0.80; p<0.001), with concordance for ≥ or <1.0% HbA1c change achieved in 74.3% of cases [2].
5. A model was developed to predict HbA1c level after 4 months of treatment. This index, termed Preform A1c, required baseline HbA1c and the Preform DiA1c index as input parameters. The difference between actual HbA1c at A1cW16 and Preform A1c

was <0.5% in 60.0% of participants. Correlation: r = 0.75; p<0.001 [2].

6. An indicator was proposed to evaluate the strength of pharmacological effect in both monotherapy and combined therapy inT2DM [6].

RACTICAL RECOMMENDATIONS

1. Monotherapy with Gliclazide MR and combination therapy of Gliclazide MR with Metformin represent effective and safe pharmacotherapeutic options for T2DM. Depending on financial circumstances, these regimens may be considered as alternatives to newer glucose-lowering agents with additional cardioprotective and nephroprotective effects GLP-1 RA and SGLT2 inhibitors.
2. Clinical follow-up visits for patients with T2DM may be scheduled once every four months, provided that fasting plasma glucose levels are monitored every two weeks.
3. In patients initiating monotherapy with Gliclazide MR or combination therapy with Gliclazide MR plus Metformin, the expected change in HbA1c after four months can be predicted one month after treatment initiation using the "Preform DiA1c" index. This index is based on the following parameters: W0 fasting glucose, change between W0–W2, change between W 2–W4, and W0 HbA1c level.
4. Similarly, one month after initiating therapy with Gliclazide MR (alone or in combination with Metformin), the expected HbA1c value at four months can be predicted using the "Preform A1c" index.
5. If the predicted values do not correspond to predefined target levels, this should be considered an additional indication for intensification of glucose-lowering therapy.
6. The pharmacological effect strength indicator allows assessment of the degree to which the potential of the applied therapy is being utilized.

LIST OF SCIENTIFIC PUBLICATIONS RELATED TO THE DISSERTATION TOPIC

1. Mirzazada, V.A. Evalution of Type 2 Diabetes Treatment with Gliclazide Modified Release in Azerbaijan (the EdiAzer Study) Results from a 16-week Observational Clinical Study / V.A.Mirzazada, R.A. Huseynova, S.A. Mustafayeva [et all.] // - Netherlands: Journal of Diabetology, - 2020. - p.175-182
2. Mirzazada V.A. The HbA1c Lowering Effect Prediction on the Basis of the Edi Azer Study / V.A.Mirzazada, R.A. Huseynova, S.A. Mustafayeva [et all.] // - USA: Journal of Diabetes and İslet Biology, - 2022. - p.1-6
3. Huseynova, R.A. Şəkərli Diabet Tip 2 zamanı qlisemik idarəetmə üçün farmakolojı dərmanlar // - Bakı: Əziz Əliyev elmi- praktik jurnal Tibb və Elm, -2022. 2(32),- p. 108-115.
4. Huseynova, R.A., Mirzazada, V.A. Безопасность терапии гликлазидом MR и метформином в исследовании EdiAzer. Влияние на вес и индекс массы тела // - Bakı: Azərbaycan Metabolizm jurnalı, - 2023. 2(20). - p.37-38.
5. Huseynova, R.A. Анамнестические и антропометрические данные больных сахарным диабетом типа 2 участвовавших в исследовании EdiAzer //- Bakı: Azərbaycan Tibb Universiteti Professor Zərifə Zeynalova 90,-2023.-p.199-207
6. Huseynova, R.A., Mirzazada, V.A. EdiAzer tədqiqatında farmakoterapiyanın qiymətləndirilməsi üçün ümumi farmakoloji təsir göstəricisinin hesablanması //- Bakı: Çagdaş təbabət: Yeniliklər və müasir yanaşmalar mövzusunda Beynəlxalq elmi praktik konfrans. - 2023.- p.44-45
7. Huseynova R.A. "EdiAzer" tədqiqatının ilk həftəsindən sonuncu həftəsinə qədər orta qlikolizələşmiş hemoqlobinin dəyişikliklərinin son nəticələri // - Bakı: Azərbaycan Metabolizm jurnalı, - 2024. №3. - s.18-24
8. Huseynova, R.A., Mirzazada, V.A. Ediazer tədqiqatında istifadə olunan şəkərendirici terapiyanın ilkin və sonraki dozaların təhlili // - Bakı: Azərbaycan Təbabətinin Müasir Nailiyyətləri, - 2024. - s.190-193

9. Huseynova, R.A., Mirzazada, V.A. Достижение первичной конечной точки исследовании «EDIAZER»-процент участников, достигших уровня гликогемоглобина 7,0% //-Moskow: Научный форум: медицина, биология и химия, -2024. 9(72). - с.30-35.

LIST OF ABBREVIATIONS

AH – Arterial hypertension
BMI – Body mass index
DBP – Diastolic blood pressure
DM – Diabetes mellitus
EdiAzer – Evaluation of Type 2 Diabetes Treatment with Gliclazide Modified Release in Azerbaijan
GFR – Glomerular Filtration Rate
GLEI – General Pharmacological Glucose-Lowering Effect Index
GLP-1 Ras – Glucagon-like peptide-1 receptor agonists
HbA1c – Glycated hemoglobin
IDF – International Diabetes Federation
SBP – Systolic blood pressure
SGLT2-Is – Sodium–glucose cotransporter-2 inhibitors
T2DM – Type 2 diabetes mellitus
W0 – Start of the Study
W2 – Second Week of the Study
W4 – Fourth Week of the Study
W6 – Sixth Week of the Study
W8 – Eighth Week of the Study
W16 – End of the Study

The defense of the dissertation will be held at 30 October 2025, at 14:00 o'clock during the meeting of the Dissertation Council FD 2.11 operating under the Azerbaijan State Advanced Training Institute for Doctors named after Aziz Aliyev.

Address: AZ1012, Baku, 35 Muzaffar Hasanov Street

The dissertation is available for review at the library of the Azerbaijan State Advanced Training Institute for Doctors named after Aziz Aliyev.

The electronic versions of the dissertation and the abstract are published on the official website: http://www.adhti.edu.az

Abstract was sent to the required addresses on "26" "September" 2025

Signed for printing: 22.09.2025

Paper size: 60 x 84 1/16

Volume: 39859

Number of hard copies: 20