Caspian Journal of Internal Medicine 2026 (Spring); 17(2): 319-327
DOI: 10.22088/cjim.17.2.319

Original Article

Initial treatment for uncontrolled type 2 diabetes: A clinical trial comparing basal insulin and modified-release gliclazide

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Received: 12 April 2025
Revised: 28 June 2025
Accepted: 19 July 2025
Published: 10 March 2026

Abstract

Background: The global rise of type 2 diabetes (T2D) presents significant healthcare challenges in diagnosis, prevention, and treatment. This study compares basal insulin and modified-release gliclazide to assess their effectiveness in managing glycemic control and other clinical factors in T2D patients.

Methods: This open-label, randomized controlled trial included 90 patients with type 2 diabetes mellitus (T2DM) exhibiting poorly controlled glycemic levels (HbA1c > 10%), referred to endocrinology clinic of Imam Khomeini Hospital, Urmia, Iran, between 2023 and 2024. The patients were randomly assigned into one of two intervention groups: the Gliclazide-MR group (n=45), receiving 30 mg of modified-release gliclazide twice daily, or the Basal Insulin group (n=45), receiving basal insulin (detemir or glargine) at a dosage of 0.1–0.3 units per kilogram of body weight.

Results: The mean age of participants was 56.4±11.48 years in the gliclazide-MR group and 55.5±13.48 years in the basal insulin group. Baseline demographic characteristics and pre-intervention variables demonstrated no statistically significant differences between the groups ($p > 0.05$). Both intervention groups exhibited statistically significant reductions in three glycemic indices HbA1c, fasting blood glucose (FBS), and 2-hour postprandial blood glucose (BS2hpp) at the 3-month follow-up compared to baseline ($p < 0.001$). The gliclazide-MR group demonstrated comparable efficacy to the basal insulin group in reducing these glycemic indices.

Conclusion: Both basal insulin and modified-release gliclazide demonstrated efficacy in improving glycemic control in patients with severe hyperglycemia. The optimal treatment choice should be individualized based on patient-specific factors and treatment goals.

Keywords: Hyperglycemia, Type 2 diabetes, Basal insulin, Modified-release gliclazide.

Citation:
Mohammadi E, Hooshmand Gharebagh L, Hajiesmaello M. Initial treatment for uncontrolled type 2 diabetes: A clinical trial comparing basal insulin and modified-release gliclazide. Caspian J Intern Med 2026; 17(2): 319-327.

Type 2 diabetes mellitus (T2DM) is recognized as a persistent metabolic condition, primarily defined by elevated blood glucose levels resulting from both reduced insulin sensitivity and the gradual deterioration of pancreatic beta-cell function (1). Maintaining optimal glucose regulation is paramount in the clinical management of T2DM to minimize the potential for developing prolonged microvascular and macrovascular pathologies (2). A significant obstacle to achieving stringent glycemic control is the inherent risk of hypoglycemic episodes (3). Even moderate episodes of hypoglycemia can lead to cognitive deficits, potentially impairing performance in a variety of cognitive tasks essential for daily functioning (4). Furthermore, repeated occurrences of severe hypoglycemia may contribute to diminished awareness of hypoglycemic symptoms and could potentially result in enduring cognitive impairments (4, 5). Although lifestyle adjustments are fundamental to the management of T2DM, pharmacologic interventions are frequently necessary to attain and sustain desired glycemic targets (6).

 Publisher: Babol University of Medical Sciences

A diverse array of oral and injectable antihyperglycemic medications exists; each characterized by unique mechanisms of action and associated safety considerations (7). Despite the established efficacy, safety, and cardiovascular advantages of metformin as the initial therapeutic approach, a substantial proportion of patients necessitate supplementary pharmacological interventions to achieve target glycemic parameters (8). The progression of treatment strategies often entails the addition of oral hypoglycemic agents, such as sulfonylureas, or the introduction of insulin therapy (9). Sulfonylureas, exemplified by gliclazide, have played a pivotal role in the management of T2DM due to their capacity to augment insulin secretion through the stimulation of pancreatic beta cells (10). Formulations designed for modified-release (MR) delivery, such as gliclazide-MR, facilitate prolonged drug release, thereby potentially enhancing patient compliance (11). Gliclazide modified-release (MR) is a once-daily sulfonylurea widely utilized in the therapeutic management of type 2 diabetes across various European nations (12). Clinical studies have demonstrated the efficacy and safety profile of gliclazide MR (11, 13), with some investigations reporting a reduced incidence of hypoglycemic events compared to other sulfonylurea agents (14, 15). Insulin therapy is frequently considered for patients exhibiting HbA1c levels surpassing 10% (16). Although insulin administration can be highly effective, its implementation is often complicated by factors such as injection-related anxiety, technical complexities, and economic considerations, which may contribute to patient hesitancy regarding its initiation (17).

The relative efficacy of basal insulin compared to gliclazide-MR in the treatment of T2DM patients presenting with HbA1c levels exceeding 10% has not been extensively investigated. While earlier research has indicated significant improvements in HbA1c levels when basal insulin is utilized in conjunction with oral antihyperglycemic medications, as opposed to insulin monotherapy (18), a direct comparison between basal insulin and modified-release gliclazide within this specific patient population is warranted. Therefore, this study aimed to conduct a comparative evaluation of the clinical effectiveness of basal insulin and gliclazide-MR in individuals with T2DM, focusing on their respective effects on glycemic regulation and other pertinent clinical variables. Although both therapeutic modalities are designed to achieve reductions in blood glucose concentrations, they operate through distinct physiological mechanisms and are associated with varying profiles of potential advantages and disadvantages.

Methods

Study design and participants: A prospective, open-label, randomized controlled trial was conducted to assess the efficacy of two therapeutic regimens in patients diagnosed with T2DM exhibiting suboptimal glycemic control, as evidenced by HbA1c levels exceeding 10%. The study population consisted of individuals referred to the endocrinology clinic at Imam Khomeini Hospital in Urmia, Iran, from 2023 to 2024. A total of 90 participants were recruited and subsequently assigned, through stratified block randomization, into one of two equal intervention groups, each comprising 45 individuals. Stratification was based on participants' prior history of antihyperglycemic medication use. The first group designated the Gliclazide-MR group, received 30 mg of modified-release gliclazide administered twice daily. The second group, the basal insulin group, received basal insulin, specifically glargine, at a dosage ranging from 0.1 to 0.3 units per kilogram of body weight at night. Both interventions were administered for duration of three months. Concurrent antihyperglycemic medications, including metformin and other oral agents, were permitted and continued at the discretion of the attending physician.

Participants eligible for inclusion in the study were adults aged 30 years or older, diagnosed with T2DM, and demonstrating HbA1c levels exceeding 10%. Individuals were excluded from participation if they presented with conditions such as renal or hepatic insufficiency, cardiovascular comorbidities (including, but not limited to, ischemic heart disease, heart failure, and cerebrovascular events such as stroke or transient ischemic attacks), pregnancy, a history of prior treatment with gliclazide or insulin, gastrointestinal disorders, current sulfonylurea therapy, or the presence of urinary ketones in conjunction with clinical manifestations suggestive of polyuria or diabetic ketoacidosis (DKA). The study protocol received the ethical approval from the institutional review board of Urmia University of Medical Sciences (Code: IR.UMSU.HIMAM.REC.1402.043), and all participants provided written informed consent prior to enrollment.

Follow-up assessment: Participants in both groups were seen after 3 months. Demographic data, including age, sex, duration of illness, and medication history, were recorded at baseline. Glycemic indices HbA1c, fasting blood sugar (FBS), and postprandial blood sugar (BS2hpp) were measured at baseline (typically conducted in the morning after breakfast) and after three months of intervention all laboratory measurements were performed in local laboratories and each measurement of glycated hemoglobin was standardized as previously reported (19).

Hypoglycemia was defined as a blood glucose of less than 70 mg/dL or the presence of typical symptoms and signs of hypoglycemia without other apparent cause. Patients with transient dysfunction of the central nervous system who required help from other person were considered to have severe hypoglycemia (19).

- **HbA1c levels:** were quantified using the high-performance liquid chromatography (HPLC) method. The analysis was performed on a DanChrom HPLC system (Kianshar Danesh Company), utilizing the TOSOH G8 HbA1c Kit (Tosoh Bioscience, Japan). All measurements were conducted in the Clinical Biochemistry Laboratory at Urmia Imam Khomeini Hospital.
- **FBS:** Determined after at least eight hours of fasting.
- **BS2hpp:** Assessed two hours after meals.

1. FBS and BS2hpp were indeed measured weekly, primarily through patient self-monitoring at home with results reported during subsequent clinic visits or via telecommunication for review, during which dose adjustments were made based on these weekly glucose readings and the patient's clinical status, adhering to a pre-specified protocol.

Hypoglycemia was defined as blood glucose levels below 70 mg/dL. The patients report typical neurogenic (autonomic) or neuroglycopenic symptoms, such as:

- *Neurogenic*: Sweating, trembling, palpitations, hunger, anxiety.
- *Neuroglycopenic*: Confusion, dizziness, weakness, blurred vision, seizures, or loss of consciousness.

While formal blood glucose measurement (<70 mg/dL or <3.9 mmol/L) is ideal, some patients may self-report fingerstick readings or describe symptoms strongly suggestive of hypoglycemia. The patients confirm that symptoms resolve after consuming carbohydrates (e.g., juice, candy, or glucose tablets).

Sample size and sampling method: The sample size calculation was based on Zhou et al.'s study (20), which demonstrated a target blood sugar achievement rate of 48.94% in the combined treatment group versus 20.75% in monotherapy groups. To achieve statistical significance at a 95% confidence interval and 80% power, a minimum of 45 patients per group was determined. A total of 90 participants were enrolled and randomly allocated into two groups using stratified block randomization, stratified by history of drug use.

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \times [P_1(1-P_1) + P_2(1-P_2)]}{(P_1 - P_2)^2}$$

Statistical analysis: Quantitative variables were expressed as mean±standard deviation (SD), while qualitative variables were presented as frequencies and percentages. Statistical analyses were performed using the following methods:

1. Between-Group Comparisons: Independent t-tests or Mann-Whitney U tests were used to compare continuous variables between the two groups. Chi-square tests or Fisher's exact tests were employed for categorical variables.
2. Within-Group Comparisons: Paired t-tests or Wilcoxon signed-rank tests were applied to evaluate changes within each group before and after the intervention.
3. Adjustment for Baseline Values: Analysis of covariance (ANCOVA) was utilized to adjust for baseline differences when comparing outcomes between groups. Statistical analyses were performed using the SPSS software Version 21. Significance was set at $p < 0.05$ for all analyses.

Results

The study included 45 patients in the glyclazide-MR group and 45 patients in the basal insulin group for analysis. A comparison of demographic characteristics and baseline variables between the two groups was conducted, revealing no significant differences before the intervention (p>0.05). The mean age of participants in the glyclazide-MR group was 56.4±11.48 years with 20 males and 25 females, while in the basal insulin group, it was 55.5±13.48 years with 25 males and 20 females (P= 0.84). The mean duration of illness was 5.95±3.71 years in the glyclazide-MR group and 7.52±5.03 years in the basal insulin group (P= 0.1). Weight (P=0.21), gender distribution (P= 0.29), and types of medication used (P=0.63) were also similar between the groups (table 1). Comparison of the mean glycemic indices before and after the intervention in each group, as well as their mean changes between the two groups, is shown in table 2. The results showed that all three glycemic indices (HbA1c (P=0.29), FBS (P=0.2), and BS2hpp (P=0.3)) had a significant decrease in both groups at 3 months after the intervention compared to before the intervention. The gliclazide-MR group had similar effects in reducing glycemic indices compared to the basal insulin group. The mean changes in HbA1c in the gliclazide-MR and basal insulin groups were -0.93±4.61% and -1.05±4.77%, respectively (P=0.42). The mean changes in FBS were -41.42 ± 84.51 mg/dL and -29.85±95.09 mg/dL, respectively (P=0.17). The mean changes in BS2hpp were -37.4±127.44 mg/dL and -38.87±125.82 mg/dL, respectively (P=0.84). There was no significant difference between the two groups in the changes of any of the glycemic indices. Comparison of hyperglycemia (P=0.8) and hypoglycemia (P=0.67) symptoms showed that there was no significant difference between the two groups (table 3).

Table 1. Comparison of demographic and basal characteristics between the two groups of gliclazide-MR and basal insulin

Variables	Glyclazide-MR Group (45=n)	Basal insulin group (45=n)	P-value
Mean Age (years)	56.4 ± 11.48*	55.5±13.48	0.84
Mean Duration of illness (years)	5.95± 3.71*	7.52±5.03	0.1
Mean Weight (kg)	70.31±6.13	72.2± 6.75	0.21
Gender(%) n **Male** **Female**	 20 (44.4) 25 (55.6)	 25 (55.6) 20 (44.4)	0.29¶¶
Type of used medicine **Metformin** **Metformin + empaglifosine** **Metformin + Sitagliptin** **Metformin + Empaglifosan + Sitagliptin**	 20 (44.4) 10 (22.2) 10 (22.2) 5 (11.1)	 19 (42.2) 8 (17.8) 15 (33.3) 3 (7.6)	0.63¶¶
HbA1C	11.75±0.98	12.09±1.19	0.14
FBS	203.02±33.37	206.75±31.36	0.59
BS2hpp	299.45±39.63	292.35±34.55	0.36

Mean comparison using the Independent T-test. ¶¶: Frequency comparison using the Chi-square test. *: Data are reported as SD±mean
Hemoglobin A1C (HbA1C), Fetal Bovine Serum (FBS), Blood Sugar 2-hour Postprandial (BS2hpp)

Table 2. Comparison of the mean changes in blood glucose indices before and after the intervention between the two groups

Variables	Glyclazide-MR Group (n=45)	Basal insulin group (n=45)	¶p-value
Mean HbA1C **Before intervention** **Three month after intervention** **Within group changes** **¶¶p-value**	 11.75±0.98 7.14±0.76 -4.61±0.93 <0.001	 12.9±1.19 7.31±0.8 -4.77±1.05 <0.001	 0.14 0.29 0.42
Mean FBS (mg/dl) **Before intervention** **Three month after intervention** **Within changes** **¶¶P-value**	 203.02±33.37 118.5163±32.7 -84.51±41.42 <0.001	 206.75±31.36 111.67±14.01 -95.09±29.85 <0.001	 0.59 0.2 0.17

Variables	Glyclazide-MR Group (n=45)	Basal insulin group (n=45)	¶p-value
Mean BS2hpp (md/dl)			
Before intervention	299.45±39.63	292.35±34.55	0.36
Three month after intervention	172.48±39.63	166.53±20.28	0.3
Within changes	-127.44± 37.4	-125.82±38.87	0.84
¶¶P-value	<0.001	<0.001	

Independent t-test , ¶¶ :Paired t-test

Hemoglobin A1C (HbA1C), Fetal Bovine Serum (FBS), Blood Sugar 2-hour Postprandial (BS2hpp)

Table 3. Comparison of the frequency of hyperglycemia and hypoglycemia between the two groups

Variables	Glyclazide-MR Group (n=45)	Basal insulin group(n=45)	P-value
before intervention			
Polyuria and polydipsia			
No	10 (2.22)	11 (24.4)	0.8¶
yes	35 (8.77)	34 (75.6)	
Post-intervention polyuria			
No	42 (3.93)	45 (100)	0.08¶
yes	3 (7.6)	0	
Complications (hypoglycemia)			
No	43 (6.95)	41 (1.91)	0.67¶¶
yes	2 (4.4)	4 (8.9)	

Chi-square test, ¶¶ : Fisher`s exact test

Discussion

The therapeutic approach to glycemic regulation in type 2 diabetes mellitus has evolved into a more multifaceted and debated area of clinical practice, characterized by the expanded availability of diverse pharmacologic interventions (21, 22), heightened scrutiny regarding potential adverse reactions, and revised perspectives on the impact of aggressive glycemic control on macrovascular outcomes (23). Therefore, this investigation aimed to conduct a comparative analysis of the effectiveness and safety profiles of basal insulin and modified-release gliclazide in the management of severe hyperglycemia within a cohort of individuals diagnosed with type 2 diabetes. HbA1c measurement serves as the primary metric for evaluating glycemic control, and its use has been pivotal in clinical trials demonstrating the advantages of glucose reduction (24). For the majority of non-pregnant adults with a life expectancy sufficient to realize microvascular benefits (typically exceeding 10 years), an HbA1c target of approximately 7% (53 mmol/mol) or lower is generally recommended (25). However, individualized glycemic targets should be established, taking into account patient preferences, treatment goals, the potential for adverse effects such as hypoglycemia and weight gain, and patient-specific factors including frailty and comorbidities (26). Epidemiological investigations have consistently demonstrated a strong correlation between HbA1c levels and the risk of both macrovascular and microvascular complications (27). Although the degree to which HbA1c reduction influences macrovascular disease prevention remains a subject of ongoing discourse, a consensus exists regarding its critical role in mitigating microvascular disease (28). Nevertheless, recent meta-analyses of clinical trials involving patients with type 2 diabetes have indicated that HbA1c reduction can yield modest decreases of approximately 9% in macrovascular events, with more substantial reductions of around 15% observed in myocardial infarction (29). Consequently, effective glucose management and HbA1c lowering are considered paramount for the prevention of vascular disease in individuals with type 2 diabetes (30).

Observational studies conducted in real-world clinical settings have documented disparities in the baseline characteristics of patients commencing insulin therapy

versus those initiating glucagon-like peptide-1 receptor agonists (GLP-1 RAs). Specifically, individuals initiating basal insulin tend to be older, exhibit higher initial HbA1c levels, present with a greater burden of comorbid conditions, and have lower body weights compared to those initiating GLP-1 RA therapy (31). This observation underscores the necessity for rigorous adjustment for patient heterogeneity when conducting comparative effectiveness studies between these treatment modalities. In the present investigation, prior to the application of matching techniques, individuals in the basal insulin group also demonstrated higher baseline HbA1c values and a greater prevalence of comorbidities compared to the gliclazide-MR group. Notably, a prior study reported a more pronounced reduction in HbA1c and a lower cost per 1% HbA1c reduction associated with insulin glargine, a finding that contrasts with the results obtained in the current analysis (32).

Following the intervention, both treatment groups achieved a mean final HbA1c value of 7% from their respective baseline measurements. The results of this study demonstrate that both basal insulin and modified-release gliclazide effectively enhanced glycemic regulation, as evidenced by statistically significant reductions in HbA1c, fasting blood glucose (FBS), and postprandial glucose levels. Nevertheless, a slightly greater reduction in HbA1c was observed in the basal insulin group, implying its potentially enhanced capacity to facilitate the attainment of rigorous glycemic targets (33). These findings align with prior clinical trials that have documented sustained glycemic control with dulaglutide, as well as other long-acting GLP-1 RAs, compared to basal insulin (34). Specifically, an open-label, randomized trial reported that once-weekly administration of dulaglutide 1.5 mg resulted in greater improvements in HbA1c, a higher proportion of patients achieving HbA1c levels below 7.0%, and greater weight loss compared to insulin glargine (35). These observed effects were maintained throughout a 78-week follow-up period. Similarly, studies utilizing basal insulin, administered with standardized glucose target titration, have demonstrated comparable efficacy in improving blood glucose control, with significant reductions observed as early as three weeks following treatment initiation (36).

Extensive, multi-center, randomized controlled trials have been conducted to evaluate the comparative effectiveness of neutral protamine Hagedorn (NPH) insulin and insulin glargine in individuals diagnosed with type 2 diabetes mellitus. These trials encompassed varying durations, ranging from four weeks to five years (37, 38). The baseline characteristics of the study participants varied, with body mass index values spanning from 27 to 35 kg/m², ages ranging from 55 to 62 years, and initial HbA1c levels ranging from 8.3% to 9.7%. In the majority of these investigations, insulin was administered once daily at bedtime; however, one particular study (39) specifically examined the differential effects of morning versus bedtime administration of insulin glargine. Insulin doses in all trials were individualized and titrated to achieve predetermined glycemic targets, typically focusing on fasting blood glucose levels (40). Due to the distinct visual characteristics of the two insulin formulations glargine being a clear solution and NPH being a cloudy suspension blinding was not feasible in these trials (41).

Beyond metformin, gliclazide stands as the sole oral antihyperglycemic medication included in the 2017 iteration of the World Health Organization's List of Essential Medicines (13). Similarly, several national clinical practice guidelines currently recognize gliclazide as a second-line therapeutic option, with one guideline advocating for the early introduction of gliclazide modified-release (MR) or glimepiride (42). Notably, gliclazide MR is recommended and extensively utilized in the management of diabetes during Ramadan (24–27), a period characterized by prolonged fasting, which can pose significant challenges to glycemic control (43). These professional recommendations underscore the continued relevance of gliclazide MR in contemporary diabetes management. In the present study, the gliclazide-MR group demonstrated a reduced frequency of hypoglycemic episodes, a noteworthy advantage in light of the inherent risks associated with insulin therapy. The safety profile of gliclazide MR was demonstrably superior, exhibiting approximately a 50% reduction in hypoglycemic episodes compared to glimepiride (44). It is particularly noteworthy that the occurrence of hypoglycemia was exceptionally low in patients treated with gliclazide MR who presented with moderately elevated baseline HbA1c levels (≤ 7%) and/or experienced HbA1c reductions of less than 6.5% during treatment, populations traditionally considered at increased risk for hypoglycemia. This observation suggests that gliclazide MR can be safely employed in accordance with current guidelines advocating for intensive treatment to achieve HbA1c targets within the range of 6.5% to 7% (44).

The basal insulin group demonstrated significant improvements in glycemic regulation, as indicated by substantial reductions in FBS and BS2hpp when compared to the gliclazide-MR group (45). Consistent with these findings, another investigation reported that prolonged maintenance of near-normal fasting plasma glucose and glycated hemoglobin levels, extending beyond six years,

could be achieved through daily basal insulin injections, with or without concurrent oral antihyperglycemic agents, when patients at elevated risk utilized self-monitored fasting glucose levels to guide insulin glargine dosage adjustments (46). Specifically, the mentioned study documented that fasting plasma glucose levels below 95 mg/dL were attained and maintained for a minimum of five years in over 50% of the insulin-glargine treated participants, while levels below 108 mg/dL (6.0 mg/dL) were maintained in excess of 75% of the same cohort.

In this comparative analysis of individuals initiating basal insulin therapy and gliclazide-MR for the management of type 2 diabetes mellitus, both treatment groups exhibited a comparable incidence of hypoglycemic events necessitating medical intervention during the initial three-month period following treatment initiation. The clinical and economic repercussions of hypoglycemia may potentially be mitigated through the utilization of contemporary basal insulin analogs, which are associated with reduced hypoglycemia risks, such as insulin glargine U300 and insulin degludec, available within the US market or recently approved by the US Food and Drug Administration, respectively (47). While basal insulin effectively regulates fasting plasma glucose (FPG) levels, its impact on postprandial glucose (PPG) levels may be limited. Achieving target HbA1c levels often necessitates the normalization of both FPG and PPG levels (48).

This investigation possesses several methodological strengths, including its randomized controlled trial design, thorough evaluation of clinical outcomes, and the inclusion of a heterogeneous patient cohort, all of which enhance the external validity of the study's conclusions. However, certain limitations warrant acknowledgement. The relatively brief follow-up period restricts the assessment of long-term effects, such as the incidence of cardiovascular events and changes in patient-reported quality of life. Furthermore, akin to other observational studies, the potential for confounding bias due to unmeasured variables, encompassing patient-related factors (e.g., age, diabetes duration, weight, and educational attainment) and provider-related characteristics, cannot be entirely excluded. Finally, rigorous monitoring during the study did not reveal any previously undocumented adverse events associated with basal insulin therapy.In conclusion, both basal insulin and modified-release gliclazide demonstrated efficacy in improving glycemic control in patients with severe hyperglycemia. The optimal treatment choice should be individualized based on patient-specific factors and treatment goals. Continued research is necessary to refine treatment recommendations and improve patient outcomes.

Acknowledgments

The authors would like to express their gratitude to the clinical research development unit of Imam Khomeini Hospital, Urmia University of Medical Sciences, for English editing.

Funding: The authors did not receive support from any organization for the submitted work.

Ethics approval: The study protocol received the ethical approval from the institutional review board of Urmia University of Medical Sciences (Code: IR.UMSU.HIMAM.REC.1402.043).

Conflict of interests: The authors have no competing interests to declare that are relevant to the content of this article.

Authors' contribution: E M: Conceptualization, investigation, writing including reviewing and editing and formal analysis; L H Gh: Conceptualization, investigation, and formal analysis; M H: Supervision, and project administration

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