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POSSIBILITIES OF EARLY COMBINATION THERAPY FOR TYPE 2 DIABETES MELLITUS

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Annotation
Information on early combination therapy options for type 2 diabetes is provided.

Keywords
diabetes mellitus type 2, combination therapy, ACE, metabolic memory, carbohydrate metabolism, decompensation, HbA1c.

Relevance. A number of modern algorithms for the treatment of type 2 diabetes mellitus (T2DM) provide for the start of intensive glucose-lowering therapy when the HbA1c level at the time of diagnosis is more than 7.5%. Possible benefits of combination glucose-lowering therapy in the onset of T2DM are considered.

Introduction. Many recommendations for the treatment of type 2 diabetes mellitus (T2DM), including the recommendations of the Uzbek Association of Endocrinologists [1], the AACE/ACE recommendations (2015) [2] and the joint DA/EASD recommendations [3], suggest intensifying glucose-lowering therapy in in cases where the previous stage of therapy has failed. Specifically, most first-stage algorithms include the use of metformin as monotherapy and the addition of second-line therapy if glycemic control goals cannot be achieved on metformin. This approach forces the doctor to wait for the patient to decompensate carbohydrate metabolism and only then take steps to eliminate it. As a result, a period occurs when patients are outside the target glycemic range and the duration of this period depends on the time the patient seeks medical help. However, an increasing number of studies indicate that with active treatment of patients from the very onset of the disease (careful glycemic control at the onset of T2DM), "metabolic memory" is activated - a state in which complications of T2DM "by

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inertia" do not progress even in conditions of decompensation of carbohydrate metabolism [4]. The concept of "metabolic memory" suggests the need to achieve maximum effective glycemic control at the first signs of impaired carbohydrate metabolism (for example, by initially prescribing a combination of drugs). Given the high risk of developing adverse events during intensive glucose-lowering therapy, it is necessary to be extremely wary of the choice of drugs for initial combination therapy, taking into account their side effect profile and drug interactions. Algorithms for specialized medical care for patients with diabetes, approved by the Uzbek Association of Endocrinologists, stratify treatment tactics for patients with type 2 diabetes depending on the initial level of glycated hemoglobin (HbA1c) [1]. At the onset of T2DM, when the HbA1c level is in the range of 6.5-7.5%, according to the algorithms, it is sufficient to prescribe monotherapy using metformin, dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) or glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists) . These groups of drugs were chosen due to the low risk of hypoglycemia - the main limiting factor in the intensification of glucose-lowering therapy. A starting combination of glucose-lowering drugs is recommended starting with an HbA1c level of 7.6%. AACE/ACE recommendations (2015) also recommend considering starting with a double combination at the same glycemic levels [2]. In the combined ADA/EASD recommendations, a combination of drugs at the onset of the disease can be prescribed at an HbA1c level of 9% or more, since with such a degree of decompensation of carbohydrate metabolism, the effectiveness of one drug alone is unlikely [3]. Thus, these recommendations are based on the principle of achieving glycemic control targets rather than on the need to change the natural history of the disease [5]. An alternative approach may be to use a combination of metformin and another class of antidiabetic drug at the onset of T2DM with an HbA1c level of <7.5%; this combination allows you to preserve the potential of β-cells and thereby prolong the time of compensation for T2DM by using the body's own reserves. To evaluate the effects of early combination therapy, O. Phung et al. [6] in 2014. Conducted a systematic review and meta-analysis of studies that included patients with untreated T2DM who received a combination of metformin with another glucose-lowering drug or metformin monotherapy as first-line therapy. The analysis included 15 randomized clinical trials, with a total number of participants exceeding 6,500 people. The average initial HbA1c level was in the range of 7.2–9.9%, i.e. in some cases, combination therapy was prescribed when the algorithms made it possible to manage with one glucose-lowering drug. Metformin monotherapy was opposed to the combination of metformin with a DPP-4 inhibitor

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in 5 studies, with sulfonylureas (SU) in 3 studies, with glinides in 1, with thiazolidinediones (TZDs) in 5 and with sodium-glucose co-transporter 2 inhibitors type (iNGLT-2) - in 2. The results of comparison of two different treatment regimens were assessed according to two important parameters: the effectiveness of therapy in terms of the degree of reduction in HbA 1c levels and the risk of developing hypoglycemia. It turned out that combination therapy achieved a significantly lower HbA1c value and a significantly higher number of patients achieved target HbA1c levels compared to metformin monotherapy. If the results regarding the effectiveness of combination therapy were expected, then assessing the safety of combination therapy in patients with newly diagnosed T2DM was one of the main objectives of the analysis. When all data were taken into account, the incidence of hypoglycemia when using a combination of glucose-lowering drugs was higher than when using metformin monotherapy. However, when studies using SM and glinide drugs were excluded from the analysis, the differences disappeared, which once again indicates that combination therapy at the onset of the disease with drugs with a low risk of developing hypoglycemia (metformin, incretin-directed therapy, TZDs, SGLT-2) provides some patients with with T2DM significant benefits. Several conclusions can be drawn from the results of this meta-analysis. First, it confirmed that initial combination antihyperglycemic therapy is more effective in individuals without a long history of T2DM with baseline HbA1c levels starting at 7.2%, i.e. from the early stages of the disease. Secondly, combination therapy may be safe in the early stages if drugs with a significant risk of hypoglycemia are not used. The safety of the combination will be further enhanced if drugs with different mechanisms of action are used, as this allows the doses of each component to be reduced. There is evidence that that patients are more adherent to treatment in the form of monotherapy [7], but this problem can be solved by prescribing fixed combinations of drugs [8]. One of the key points in choosing the initial combination of glucose-lowering drugs should be the physiology of the prescribed therapy. After all, the point of an early intensive start of therapy is to try to change the pace of the disease, to preserve one's own insulin reserves for as long as possible. It must be emphasized that both drugs in combination should have a different mechanism of action: on the one hand, this will reduce the likelihood of potential adverse events, on the other hand, it will allow simultaneously influencing different pathways of regulation of carbohydrate metabolism and provide more effective glycemic control. Metformin has long occupied the place of first-line therapy in most international recommendations due to its high efficiency, safety and extensive experience with use. Therefore, it

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occupies one of the positions in combination therapy. The second place in the combination in people with newly diagnosed T2DM should be taken by a drug that has both a pathogenetically substantiated effect and an optimal safety profile, which is especially important for this category of patients with relatively low HbA1c values. Of the 5 combination options analyzed in the work of O. Phung et al. [6], the combination of metformin with a DPP-4 inhibitor meets the requirements to the greatest extent. Combinations of metformin with SM drugs and glinides have demonstrated a large number of hypoglycemia, and the combination of metformin with NGLT-2 inhibitors, although safe from the point of view of the development of hypoglycemia, does not meet the criterion for pathogenetic treatment. The combination of metformin with TZD is extremely effective in combating insulin resistance, but does not affect secretion insulin. Meta-analysis by O. Phung et al. [6] did not include studies of the combination of metformin and GLP-1 receptor antagonists. From the point of view of the mechanism of action of GLP-1 antigens, this combination can also be expected to be highly effective in terms of regulating not only carbohydrate metabolism, but also weight, as well as a favorable safety profile. The use of this combination in patients in the early stages of T2DM may be limited by the need for injection of GLP-1 antigens, but this problem is mitigated by the emergence of drugs administered once a week. The studies included in the meta-analysis were characterized by a relatively short follow-up period (in most cases no more than 24 weeks). To evaluate the long-term effect of an early combination of metformin with a representative of the DPP-4 class of iri (vildagliptin), the VERIFY study, unique in its objectives, was designed [9]. This 5-year, international, randomized, double-blind study will include approximately 2000 patients who have not previously received glucose-lowering therapy or have received metformin for no more than 1 month. Patients will be divided into two groups: one will receive metformin monotherapy, the second will initially receive a combination of metformin and vildagliptin. The main parameter of the study is the time until the initial therapy fails and the need to start insulin therapy. If target glycemic values (HbA1c twice more than 7%) are not achieved in patients of the first group, vildagliptin will also be added to their therapy; in the future, decompensation of carbohydrate metabolism in both groups will be corrected by insulin therapy in accordance with local recommendations. A unique feature of this study is that the baseline HbA1c level should be 6.5-7.5%, i.e. the level at which, according to the algorithms, combination glucose-lowering therapy is not required. The hypothesis underlying the VERIFY study is that targeting two key mechanisms in the development of T2DM (insulin secretion defect and insulin resistance) using

two different classes of drugs from the earliest stages of the disease will determine a more favorable prognosis for patients compared with a regimen of gradual intensification of glucose-lowering drugs. therapy. In addition, DPP-4 inhibitors are the only class of drugs that normalize glucagon secretion in T2DM. The authors of the study [10] hope that the synergism of metformin and vildagliptin, manifested in an increase in the active form of GLP-1, will preserve β-cell function for as long as possible in patients with the initial stages of T2DM. Over a 5-year study period, in patients without severe decompensation of carbohydrate metabolism, it will be difficult to estimate the incidence of micro- and macrovascular complications in the two treatment regimens. Therefore, the VERIFY study does not set itself this goal. However, the study will evaluate all prognostic factors for the development of late complications of T2DM (severity of microalbuminuria, presence of microaneurysms in the fundus, cardiovascular history, etc.). It is possible that differences in the rate of development of T2DM complications will be identified between the mono- and combination therapy groups, which can later be relied upon when planning observational programs. Thus, according to available data, early intensive glucose-lowering therapy in patients with a short history of T2DM allows for more effective glycemic control than monotherapy. Prescribing combination therapy from the very start of the disease with an HbA1c level <7.5% can improve the prognosis of patients due to the "metabolic memory" effect and slow down the development and progression of diabetes complications. However, prospective studies evaluating the long-term effects of this treatment regimen are needed. the level at which, according to the algorithms, combination glucose-lowering therapy is not required. The hypothesis underlying the VERIFY study is that targeting two key mechanisms in the development of T2DM (insulin secretion defect and insulin resistance) using two different classes of drugs from the earliest stages of the disease will determine a more favorable prognosis for patients compared with a regimen of gradual intensification of glucose-lowering drugs. therapy. In addition, DPP-4 inhibitors are the only class of drugs that normalize glucagon secretion in T2DM. The authors of the study [10] hope that the synergism of metformin and vildagliptin, manifested in an increase in the active form of GLP-1, will preserve β-cell function for as long as possible in patients with the initial stages of T2DM. Over a 5-year study period, in patients without severe decompensation of carbohydrate metabolism, it will be difficult to estimate the incidence of micro- and macrovascular complications in the two treatment regimens. Therefore, the VERIFY study does not set itself this goal. However, the study will evaluate all prognostic factors for the development of late complications

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