The use of GLP-1 analogs in treatment of diabetes in patients with cardiovascular diseases. The expert opinion of the Working Group of Cardiovascular Pharmacotherapy of the Polish Cardiac Society

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a metabolic disease resulting from many pathophysiological processes leading to chronic hyperglycemia, and its incidence in societies is constantly increasing. For many years, it has also been recognized as an independent risk factor for the development of cardiovascular diseases. On the other hand, cardiovascular diseases are the most common cause of mortality in both type 2 and type 1 diabetic patients. There is therefore no doubt that the problem of T2DM and its complications is of the utmost importance. The response to the ever-increasing prevalence of this disease is the intensive development of pharmacological possibilities. In recent years, many new multi-targeted antihyperglycemic drugs have been developed and successfully implemented, including glucagon-like peptide-1 (GLP-1) analogs. Drugs from this group proved to be effective in terms of improving the control of carbohydrate metabolism parameters but also studies clearly indicate that some GLP-1 analogs may also reduce cardiovascular risk and extend lives of T2DM patients. GLP-1 analogs are, therefore, an interesting and attractive therapeutic option for many patients with T2DM and coexisting diseases of the cardiovascular system. This position statement aims to define the role that a cardiologist can play in designing a T2DM pharmacotherapy regimen.

Key words: type 2 diabetes mellitus, cardiovascular risk, GLP-1 analogs

CARDIOVASCULAR COMPLICATIONS IN TYPE 2 DIABETES MELLITUS — UNMET NEEDS IN THE TREATMENT OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

Type 2 diabetes mellitus (T2DM) is a very important epidemiological problem — before COVID-19, the disease was described as the first non-infectious pandemic in the history of the world. According to the data of the International Diabetes Foundation (IDF), in 2021, T2DM affected approximately 68 million people in Europe and 537 million adults worldwide [1, 2]. According to current projections, the estimated number of nearly

650 million T2DM patients worldwide, until recently forecasted for 2045, will be achieved much earlier, already in 2030 [2]. In turn, according to the Polish epidemiological data, T2DM and its complications were the seventh most common cause of death in 2019 [3]. Atherosclerotic Cardiovascular Disease (ASCVD) is the most common cardiovascular disease in patients with T2DM. Studies also show that cardiovascular complications are the leading cause of disability and death in T2DM patients and may occur at a very early stage in type 2 diabetes. It is estimated that at the time of diagnosis of type 2 diabetes, approximately 26% of patients may already have features of retinopathy, and nearly 7% may already have albuminuria [4, 5]. Even up to 45% of T2DM patients suffer from neuropathy [6]. Coronary artery lesions are found in up to 25% of asymptomatic patients with type 2 diabetes, the risk of hospitalization for heart failure (HF) in patients with T2DM is 2-fold higher than in those without diabetes; similarly, T2DM is associated with a 2 to 4-fold increase in the risk of peripheral artery disease (PAD) [7–9]. Finally, within 5 years from the diagnosis of T2DM, the risk of stroke doubles as compared to the control population [10]. It is therefore not surprising that most patients with T2DM are considered to be at least moderate cardiovascular risk patients, and in the course of T2DM and with tests performed, the patient may quickly be reclassified into the group of high or very high cardiovascular risk. Each coronary, cerebrovascular, or peripheral vascular episode, if its cause is atherosclerosis, changes this classification. In practice, a cardiologist will come into contact with diabetic patients during hospitalization or consultation related to the clinical manifestation of atherosclerosis or in connection with symptoms of heart failure. Cardiologists are well aware of the principles of intensifying lipid-lowering treatment, anticoagulant and antiplatelet therapy, and, finally, optimization of antihypertensive treatment. In the last year, drugs originally approved for the treatment of T2DM — flozins (SGLT2i) — have also been included in cardiological guidelines and are increasingly used in patients with heart failure, not burdened with diabetes. It is worth noting, however, that, as in the case of the initiation of anticoagulation in atrial fibrillation in a patient with a significant risk of stroke or a statin in a patient after myocardial infarction, these drugs have the highest class of recommendation— IA. Similarly, the inclusion of a GLP-1 analog in a patient with T2DM and ASCVD or high cardiovascular risk also has the highest class of recommendation — IA [11]. This class of recommendation is based on the proven effect of GLP-1 analogs on the reduction and stabilization of atherosclerotic plaque. The proposed mechanisms of action include inhibition of atherothrombotic changes and improvement in inflammatory markers, and as a result, inhibition of progression of atherosclerotic lesions. These processes occur through antiproliferative effects on smooth muscle cells and vascular endothelial cells, reducing oxidative stress and increasing the production of nitric oxide [12, 68].

The overriding goal of patient care is always to improve prognosis. Until recently, the basic tool used by diabetologists to achieve this goal was intensification of diabetes treatment and improvement of the patient's metabolic control, while the cardiologist focused primarily on reducing cardiovascular risk. It is worth emphasizing, however, that we currently have management strategies that allow for simultaneous improvement of metabolic control and improvement of cardiovascular prognosis. GLP-1 analogs are the drugs most potent in lowering HbA1c, with the simultaneous safety resulting from the lack of risk of hypoglycemia. Hence, apart from cardiovascular protection per se, they ensure effective glycemic control. According to the current standards of cardiological and diabetic management, the premise for the implementation of GLP-1 analogs is the overall cardiovascular risk or a diagnosis of atherosclerotic disease of the cardiovascular system, and not the HbA1c rate or coexistence of obesity. However, we still use GLP-1 analogs too rarely, and looking at the results of many studies conducted over several years where the use of appropriate therapy at an early stage of treatment slowed down complications of T2DM, we can really influence the prognosis of a patient with T2DM. As a result, these patients can avoid or slow disease progression over time, with all the benefits: less use of healthcare or avoiding premature death [13]. From this point of view, the necessity of early prevention of T2DM complications seems crucial.

RATIONALE FOR USING GLP-1 ANALOGS IN THE TREATMENT OF TYPE 2 DIABETES WITH HIGH/VERY HIGH RISK OF CVD

GLP-1 analogs

GLP-1 analogs are still a relatively new group of drugs whose strong normoglycemic effect, similar to SGLT2i, is due to their multidirectional action (Figure 1). Already in the 1930s, it was shown that intestinal factors secreted in response to the consumed meal reduce glucose levels [14, 15]. The incretin effect responsible for this observation results from a much greater insulin response after oral glucose ingestion than after intravenous glucose infusion [16]. The incretin effect accounts for over 50% of insulin secretion after meals in healthy subjects [15]. Two intestinal hormones are responsible for this phenomenon: glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP – glucose-dependent insulinotropic peptide). GLP-1 receptors are localized in many organs, and hence, the multidirectional action of the GLP-1 protein [16–28]. GLP-1 receptors are present, *inter alia*, in the pancreas, brain (almost the entire central nervous system, except the cerebellum and cortex), stomach, heart, lungs, and digestive tract. From a clinical point of view, the effect on the pancreatic islets is very important. The GLP-1 protein not only affects beta cells and increases postprandial insulin secretion, but it also inhibits the secretion of glucagon by pancreatic alpha cells; however, this process is strictly

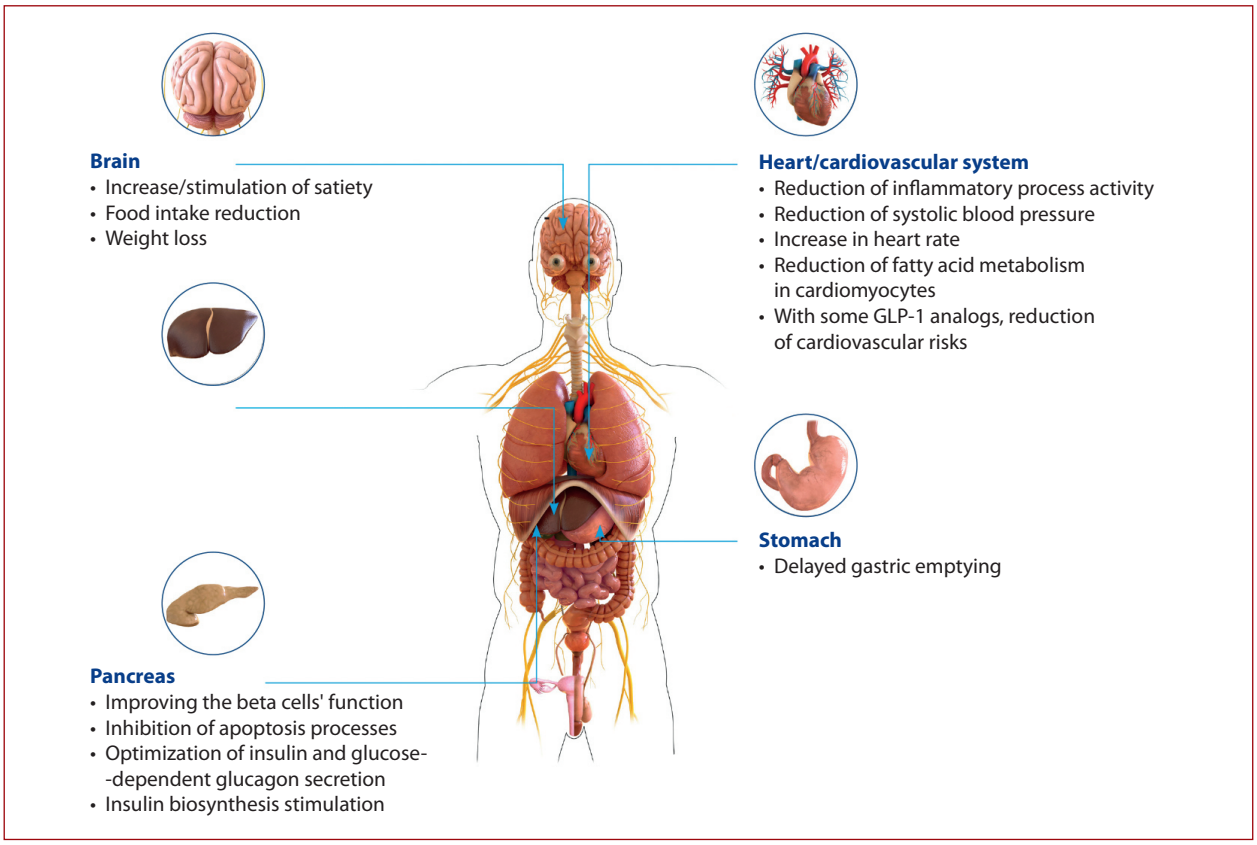

Figure 1. Multidirectional effect of GLP-1 analogs (prepared on the basis of 19–28)

dependent on the level of glycemia (thus the risk of hypoglycemia in the case of therapeutic use of GLP-1 analogs is low). In addition to affecting pancreatic cells, GLP-1, among others, limits excessive hepatic glucose secretion, lowers lipogenesis, delays gastric emptying, and acts on hunger and satiety centers in the hypothalamus [16, 19–26]. The latter processes stimulate the feeling of fullness and satiety, resulting in a reduced caloric intake and translate into a significant reduction in body weight observed in clinical practice. The effect of GLP-1 analogs on weight reduction is multifactorial and independent of diabetes status, which was already observed in the SCALE Obesity and Prediabetes trial evaluating the use of GLP-1 analogs in obese patients without diabetes [18]. These mechanisms, as can be seen, differ from the weight reduction mechanisms in patients receiving SGLT2i [14]. In addition, GLP-1 analogs in the course of clinical trials have also shown a beneficial effect on inflammation (reduction of hs-CRP) and reduction of blood pressure (by improving endothelial function, vasodilatory action, and natriuresis, most likely mediated by natriuretic peptides), thus reducing afterload [19, 29, 68]. The natriuretic effect is also achieved through the influence on the cells of the proximal tubules of the kidney, which is a postulated mechanism of nephroprotective action of this class of drugs, supported by more and more scientific evidence [29]. At present, however, these are the results of early studies, and the results of cardiovascular outcome trials (CVOT) in the case of coexisting diabetes and heart failure or renal failure are available for flozins.

In the course of T2DM, there is a deficiency of GLP-1 protein [16, 17], but its biological activity is largely preserved, which makes GLP-1 an attractive therapeutic target. Since the native GLP-1 protein has a very short half-life (it is broken down by the dipeptidyl peptidase 4 [DPP 4] enzyme in about 2 minutes), molecules that enhance or mimic the action of GLP-1 protein are of great interest. GLP-1 analogs belong to the GLP-1RA group, which consists of two subgroups: drugs based on exendin-4 (a protein hormone isolated from salivary glands of the *Heloderma suspectum* lizard [Gila monster], which is similar in structure to GLP-1 and retains its activity), which include exenatide and lixisenatide, and drugs based on native human GLP-1, GLP-1 analogs, which include liraglutide, dulaglutide, and semaglutide [30-35]. In the first subgroup of GLP-1 receptor agonists, the homology to human GLP-1 is approximately 53% for exenatide and approximately 50% for lixisenatide [30, 31]. Liraglutide and semaglutide are human GLP-1-based molecules whose amino acid sequences share a homology of 97% and 94%, respectively, with the reference peptide [32–34]. Unlike dulaglutide, they are classified as small molecules. Dulaglutide, classified as a large molecule, has a dimer structure in which two chains of amino acids are covalently linked to a modified human immunoglobulin

Figure 2. Basic dosing regimens of GLP-1 analogs currently available on the Polish market, based on summaries of product characteristics (SmPC) [30–35]

A. Dosing once a day:

Lixisenatide (Lyxumia®) [31]	Liraglutide (Victoza®) [32]	Liraglutide (Saxenda®)[a] [32]	Semaglutide (Rybelsus®) [34]
• Initial dose: 1 µg once a day • Target dose. 20 µg once a day • Injections should be administered one hour before a meal (it is recommended to administer the drug before the same meal every day) • Dose reduction should be considered when co-administering basal insulin or sulfonylureas	• Initial dose, 0.6 mg once a day for a minimum one week • Intermediate dose, 1.2 mg once a day for a least one more week • Maximum recommended dose, 1.8 mg once a day • Injections should be administered preferably at the same time of the day, independently of meals	• Initial dose, 0.6 mg once day for a minimum one week • The dose should be increased to 3 mg once daily in increments 0.6 mg with at least one-week intervals • Intermediate dose, 1.2 mg once a day for at least one more week (1.8 mg/2.4 mg in other weeks) • Maximum recommended dose, 3 mg once a day • Injections should be administered preferably at the same time of the day, independently of meals	• ORAL FORM • Initial dose, 3 mg once a day for four weeks • Suggested maintenance dose, 7 mg once a day • Maximum dose, 14 mg once a day
• **Do not use with eGFR <30 ml/min/1.73 m²**	• **No dose adjustment is necessary based on age or renal function**	• **No dose adjustment is necessary based on age or renal function**	• **There is no need to adjust the dose of the drug depending on age, liver, or kidney function, but it is not recommended for use in end-stage CKD**

B. Dosing once a week:

Exenatide extended-release (Bydureon®) [30]	Semagludite (Ozempic®) [33]	Dulaglutide (Trulicity®) [35]
• Recommended dose, 2 mg once a week • If it is necessary to change the day of administration of the drug, there should be an interval of at least 3 days from the last dose	• Initial dose, 0.25 mg once a week • The dose can be doubled every 4 weeks up to a maximum dose of 2 mg once a week • The initial dose should not be a maintenance dose	• In monotherapy, 0.75 mg once a week • In combination therapy, a dose of 1.5 mg once a week is suggested • The dose of the drug can be increased by another 1.5 mg (i.e. up to 3 mg once a week and a maximum of 4.5 mg once a week) at 4-week intervals
• **Do not use with eGFR <30 ml/min/1.73 m²** • No dose adjustment is required in elderly patients	• **There is no need to adjust the dose of the drug depending on age, liver, or kidney function, but it is not recommended for use in end-stage CKD**	• **There is no need to adjust the dose of the drug depending on age, liver, or kidney function, but it is not recommended for use in end-stage CKD**

[a]Saxenda® is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management. [b]A dose of 1 mg is available in Poland

G4 Fc fragment, with the linkage additionally mediated by a linker peptide [35–37].

Until now, all GLP-1RA approved for T2DM treatment, with a different structure and duration of action, have been administered by subcutaneous injection. However, after the publication of the results of the PIONEER 6 study, the US Food and Drug Administration (FDA) approved oral semaglutide in September 2019 and soon after that, the preparation was also approved by the European Medicines Agency (EMA). To date, only GLP-1 analog is available in tablet form. Oral semaglutide is a preparation made by combining semaglutide with a molecule that facilitates its absorption, the so-called SNAC (Sodium N-[8-{2-hydroxybenzoyl} amino] caprylate). SNAC causes a local increase in the pH of the gastric mucosa, which protects the semaglutide molecule against proteolytic degradation and enables its absorption through the gastric wall in a concentration-dependent manner [34, 38]. The basic dosing schedules for these molecules are shown in Figure 2. Although the basic indication common to all GLP-1 receptor agonists (GLP-1RA) is T2DM therapy, individual molecules also differ in their activity in terms of reducing cardiovascular risk, hence diabetes and cardiological guidelines suggest selecting molecules with appropriate studies in this matter.

Guidelines for GLP-1 analogs in the treatment of type 2 diabetes mellitus

The current guidelines of the Polish Diabetes Association (*Polskie Towarzystwo Diabetologiczne*, PTD) clearly indicate that metformin should still be the basis of T2DM treatment [39]. Polish diabetologists emphasize, however, that in the case of unsatisfactory glycemic control, treatment intensification should be considered without undue delay, within 3-6 months from the diagnosis of T2DM. Then a second oral drug, GLP-1 receptor agonist or basal insulin, should be added [39]. At the same time, however, both the ADA (American Diabetes Association) and EASD (European Association for the Study of Diabetes) agree that the first injectable drug to be implemented in T2DM should be GLP-1 analogs [40]. Therefore, the suggestion of the possibility of including GLP-1 analogs in the treatment appears very early after the diagnosis of T2DM. Moreover, according to the Polish guidelines, in justified cases, therapy with a combination of metformin and a second antihyperglycemic drug may be considered at the time of diagnosis of T2DM (Figure 3).

In the case of using a combination therapy from the beginning of T2DM pharmacotherapy, the second antihyperglycemic drug should have a proven beneficial effect

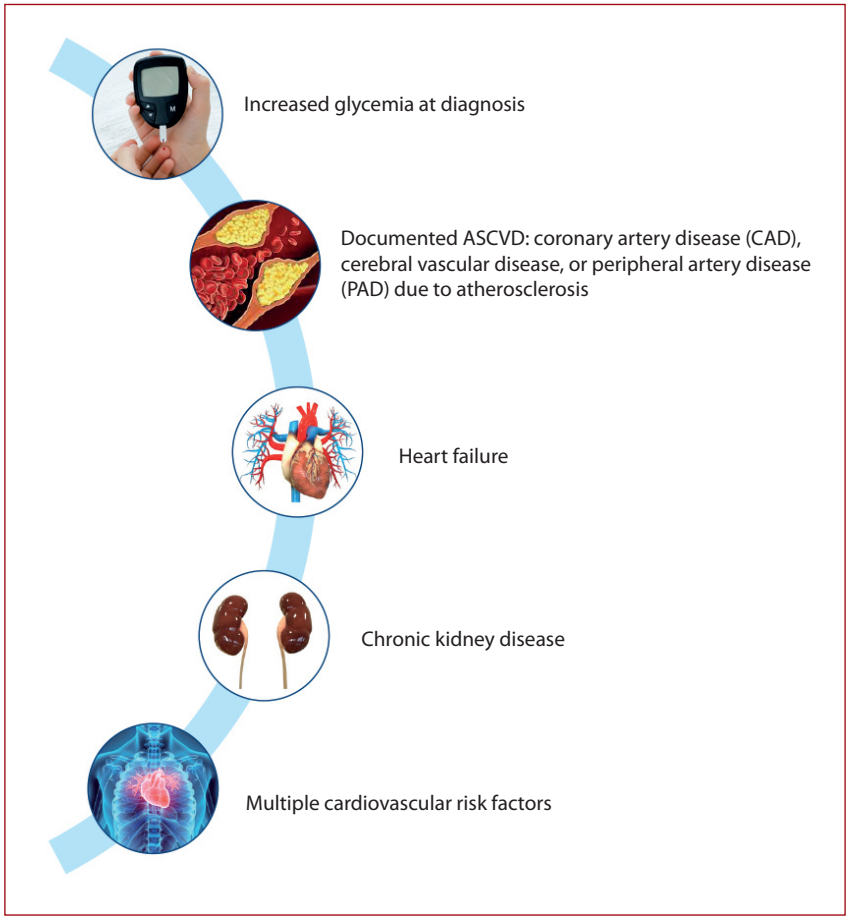

Figure 3. Indications for starting pharmacotherapy in newly diagnosed type 2 diabetes patients from the combination therapy according to PTD (Polish Diabetes Association [39])

on cardiovascular prognosis. Both the Polish guidelines and the current ADA guidelines indicate that the choice in this respect should be made between GLP-1 analogs and SGLT-2 inhibitors (flozins) [39, 40]. It is also worth emphasizing that the combination of these two groups of drugs is acceptable at an early stage of T2DM treatment in the case of patients at high risk [39, 40]. In the current guidelines, there are also strong indications for the management of acute coronary syndromes without ST-segment elevation for these groups of drugs [42]. After carefully analyzing the ADA guidelines, it can also be noticed that the authors allow the use of a drug other than metformin as the first-choice drug in the treatment of newly diagnosed T2DM while emphasizing that it will most often be a derivative of biguanide, well-known for many years [40]. The authors of both ADA and PTD guidelines emphasize the role of individualization of therapy, taking into account patients' preferences and financial resources' [39, 40]. The economic barrier is certainly one of the main limitations for using modern antihyperglycemic drugs, a problem we describe later in this article. First of all, however, it is worth paying attention to different goals that should guide the choice of the aforementioned groups of drugs. From the point of view of diabetes, the main goal is to extend lives of diabetic people. In patients with high cardiovascular risk, the combination of GLP-1 analog or flozin with metformin is currently recommended from the diagnosis of T2DM regardless of blood glucose levels; i.e. dual drug therapy [39, 40]. From a cardiological point of view, the premise for implementing a specific antihyperglycemic drug is the possibility of reducing the risk of cardiovascular events, including death. It should be emphasized that in this respect the use of GLP-1 analogs (preferably in the case of patients with a history of stroke) or flozins (preferably in the case of the coexistence of CKD or HF) has the following strength and class of recommendations:

- At the stage of the first step planning, a pharmacological treatment regimen IA for patients with CVD and IIb for patients with coexisting diabetic target organ damage (TOD: retinopathy, nephropathy, or neuropathy)
- At the stage of the second step planning, a pharmacological treatment regimen, if not already implemented — IA [11].

The indications for the use of GLP-1 analogs are also presented in the 2019 European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) cardiological guidelines for the treatment of diabetes and pre-diabetes coexisting with cardiovascular diseases. These guidelines recommend liraglutide, semaglutide, or dulaglutide even as a first-line treatment in patients with T2DM and diagnosed cardiovascular disease or at high/very high cardiovascular risk (age 55, more than

50 percent narrowing of the coronary arteries, internal carotid artery, or arteries of the lower limb, or left ventricular hypertrophy) to reduce the risk of cardiovascular events (IA), regardless of the percentage of HbA1c in the blood [41]. These guidelines were the first to indicate the possibility of using GLP-1 analogs and flozins (SGLT2i) even before using metformin as the basis of diabetes treatment although this approach may be viewed as controversial also in the context of interpreting the registration records of these groups of drugs.

Effect of GLP-1 analogs on cardiovascular prognosis

Quite significant differences in the structure of individual drugs belonging to the group of GLP-1 receptor agonists (GLP-1RA) suggest that while the main effect resulting from the activation of receptors for the GLP-1 protein is probably common, yet one should be careful with the extrapolation of the results of studies on one molecule on others. This precautionary assumption has already been confirmed in studies investigating the effects of individual GLP-1 receptor agonists on endpoints typical of diabetes studies. In the context of reducing HbA1c levels, liraglutide was found to be more effective than exenatide in the LEAD-6 and DURATION-6 studies, more effective than lixisenatide in the LIRA-LIXI study, and it showed a similar effect to dulaglutide in the AWARD-6 study [43-45]. In the AWARD-6 and DURATION-6 studies, the use of liraglutide was also associated with a significantly greater reduction in body weight compared to dulaglutide and exenatide, respectively [44, 45]. The Phase III SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) clinical trial program investigated the efficacy and safety of semaglutide in comparison to oral and subcutaneous drugs (46-55). This program comprised 16 international clinical trials comparing semaglutide with placebo (SUSTAIN 1, 5, 6, 9, FLOW), sitagliptin (SUSTAIN 2, SUSTAIN JP, SUSTAIN China), dulaglutide (SUSTAIN 7), canagliflozin (SUSTAIN 8), liraglutide (SUSTAIN 10), semaglutide 2 mg (SUSTAIN Forte), exenatide (SUSTAIN 3), and insulin (SUSTAIN 4, 11). In most of the above studies (SUSTAIN 1-5, 7, 8, 9, 10), the primary and secondary confirmatory endpoints were HbA1c change and weight loss at week 26 or week 52 from baseline, respectively. The results of the above studies showed that semaglutide at a dose of 1 mg proved the highest effectiveness in the context of HbA1c reduction and weight reduction in relation to all comparators [46–55]. In the course of the SUSTAIN-7 study, semaglutide was also more effective than dulaglutide in reducing HbA1c, with the percentage of patients achieving the target HbA1c value and reducing body weight [52] similar to canagliflozin in the SUSTAIN 8 study [53]. The effects of oral semaglutide were investigated against both oral and subcutaneous drugs in the phase III clinical trial program: PIONEER (Peptide InnOvatioN for Early diabEtes tReatment). This program comprised 10 international studies: PIONEER 1-8 [56–63] and 2 Japanese studies, PIONEER 9 and 10. The program enrolled T2DM patients with various lengths of medical history, using a variety of background therapies, and representing a broad spectrum of patients, including patients with moderately impaired renal function. In those studies, oral semaglutide was compared with placebo (PIONEER 1, 4, 5, 6, and 8) [56, 59-61, 63], with 25 mg empagliflozin (PIONEER 2) [57], 100 mg sitagliptin (PIONEER 3 and 7) [58, 62], with 1.8 mg liraglutide (PIONEER 4) [59], and 0.9 mg (PIONEER 9), and 0.75 mg dulaglutide (PIONEER 10). In most studies, except for PIONEER 6, 7, and 10, the primary and secondary confirmatory endpoints were HbA1c change and weight reduction at week 26 from baseline, respectively. In the course of the tests carried out under the PIONEER program, oral semaglutide in 7 and 14 mg doses showed the highest effectiveness in the context of HbA1c reduction in relation to all comparators, including all oral drugs used so far in T2DM therapy [56-63]. A beneficial effect was also seen on the secondary endpoint of weight loss where oral semaglutide (doses of 7 and 14 mg) was also the most effective treatment option. In PIONEER 2, the weight loss achieved with oral semaglutide was similar to that achieved with empagliflozin (ETD, 0.1 kg; $P = 0.76$) at week 26 and 0.2 kg ($P = 0.62$) at week 52. It should be remembered, however, that empagliflozin at a dose of 25 mg was used, which is not available in Poland [57]. In the PIONEER program, an improvement was also observed in the context of other components of the cardiometabolic risk, such as blood pressure, lipid metabolism parameters, or reduction of hs-CRP concentration [56–63, 38]. However, cardiologists should be interested primarily in the results of studies on the influence of the molecules in question on hard endpoints related to cardiovascular events. From this point of view, in the entire group of GLP-1 receptor agonists (GLP1RA), only GLP-1 analogs (liraglutide, semaglutide, dulaglutide) are relevant. Derivatives of exendin 4 (exenatide, lixisenatide), characterized by a weaker metabolic effect, did not show a beneficial effect on the reduction of cardiovascular risk [64, 65].

The ELIXA study assessed the effect of lixisenatide on the cardiovascular prognosis of T2DM patients after myocardial infarction [64]. Over 6000 patients were enrolled in the study, with a median follow-up of 25 months, and the primary endpoint was defined as CV death, myocardial infarction, stroke, or hospitalization associated with unstable coronary artery disease (major adverse cardiovascular events, MACE). The use of lixisenatide has not been shown to be associated with a higher risk of MACE than that that observed in the placebo group (hazard ratio [HR], 1.02; 95% confidence interval [CI], 0.89–1.17). The study did not demonstrate the superiority of lixisenatide over standard management in terms of cardiovascular risks in patients with type 2 diabetes (*P*-value for the superiority analysis 0.081), but it was not shown that the treatment was harmful in this respect either (*P*-value for the noninferiority analysis <0.001) [64]. It is worth underlining here

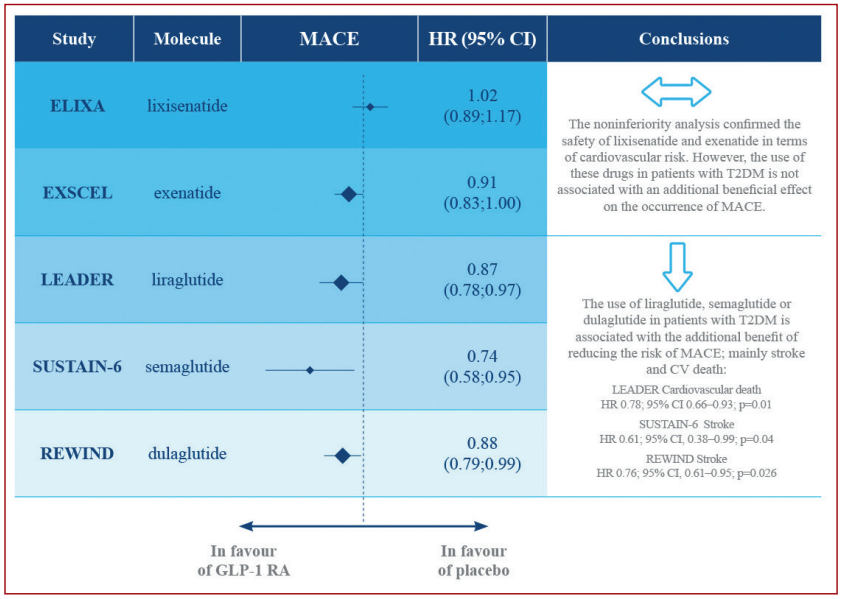

Figure 4. Key results of cardiovascular outcome trials (CVOT) with GLP-1 analogs [51, 64–67]

that noninferiority analysis in the context of cardiovascular risk is a standard analysis in the case of new drugs in the treatment of T2DM.

Similar conclusions, as in the case of lixisenatide, were provided by the EXCEL study on exenatide. Nearly 15 000 patients with T2DM were enrolled in the study, 73% of whom had already been diagnosed with cardiovascular disease [65]. The median follow-up was 3.2 years. The primary endpoint was defined as non-fatal cardiovascular event, myocardial infarction, or stroke. The use of exenatide, compared with placebo, as an adjunct to standard therapy for T2DM, was not associated with a higher risk of MACE (HR, 0.91; 95% CI, 0.83–1.00; P <0.001 for noninferiority analysis; P = 0.06 for superiority analysis) [65].

The breakthroughs in this regard turned out to be the LEADER, SUSTAIN-6, and REWIND studies [66, 51, 67].

Over 9000 patients with T2DM and high cardiovascular risk were qualified for the LEADER study. The follow-up period was nearly 4 years. The primary endpoint was defined as cardiovascular death, non-fatal stroke, and non-fatal myocardial infarction (three-point MACE) [66]. The use of liraglutide was associated with a significant 13% reduction in the risk of MACE (HR, 0.87; 95% CI, 0.78–0.97; P <0.001 for noninferiority; P = 0.01 for superiority). Therefore, for the first time, the use of a GLP-1 analog turned out to be more effective than placebo in reducing cardiovascular risk [66]. In the SUSTAIN-6 study, the use of semaglutide (weekly injection) in T2DM patients with high cardiovascular risk also proved to be more effective than placebo in terms of its effect on cardiovascular prognosis [51]. The obtained significant 26% reduction in the risk of MACE (HR, 0.74; 95% CI, 0.58–0.95; P <0.001 for noninferiority) was mainly due to the decrease of the risk of stroke (HR, 0.61; 95% CI, 0.38–0.99; P = 0,04). In the group treated with semaglutide, fewer heart attacks were also observed, but the difference was not statistically significant [51]. There are also ongoing oral semaglutide trials (the SOUL study; clinicaltrials.gov/ct2/show/NCT03914326) to confirm the same favorable cardiovascular profile as has already been demonstrated with semaglutide injectable form. So far, a pre-approval PIONEER 6 trial has been conducted to assess the cardiovascular safety of oral semaglutide (14 mg vs. placebo) [61]. The primary endpoint was the three-point MACE. In this study, the safety of oral semaglutide was not inferior to placebo and although the hazard ratio (HR, 0.79; 95% CI, 0.57–1.11) for this drug was similar to that of subcutaneous semaglutide in SUSTAIN 6 (HR, 0.74; 95% CI, 0.58–0.95), the superiority of the drug over placebo could not be demonstrated. However, with oral semaglutide, there was a 51% statistically significant reduction in cardiovascular deaths (HR, 0.49; 95% CI, 0.27–0.92) and a statistically significant 49% reduction in all-cause death (HR, 0.51; 95% CI, 0.31–0.84) [61, 38].

Finally, the REWIND study compared the effects of dulaglutide and placebo on the cardiovascular prognosis of over 9000 T2DM patients with previously diagnosed cardiovascular disease or at high cardiovascular risk [67]. The median follow-up was nearly 5.5 years, the primary endpoint was defined as in the previously cited studies. The use of dulaglutide compared to placebo resulted in a significant 12% reduction in the risk of MACE (HR, 0.88; 95% CI, 0.79–0.99; P = 0.026) [67]. The main results of the studies discussed above are presented in Figure 4.

In conclusion, those clinical trials demonstrated that among the GLP-1 analogs currently available on the market: liraglutide, semaglutide, and dulaglutide are superior to placebo in reducing the risk of MACE in T2DM patients diagnosed with ASCVD or at high risk of its occurrence.

SAFETY OF USE OF GLP-1 ANALOGS

Cardiologists' concerns about side effects of the above-mentioned drugs and the conviction that their implementation should be decided by diabetologists may delay the implementation of the described therapeutic options. For this reason, it should be clearly emphasized that the very mechanism of action of the discussed group of drugs shows that the use of GLP-1 analogs is associated with a very low risk of hypoglycemia. In the studies performed so far, hypoglycemia has occurred only in patients receiving concomitant insulin and/or sulfonylurea therapy. Therefore, caution is recommended in these cases and the dose of insulin and/or sulfonylurea should be verified [32-35]. In most cases, it is necessary to gradually reduce the dose of insulin and/or sulfonylurea to reduce the risk of hypoglycemia. The most common (although still rare and usually temporary) side effects include gastrointestinal discomfort. Most cases are nausea, vomiting, and diarrhea. They are usually most severe when initiating treatment and increasing the dose. Nausea is typically reported in 25% of patients, while vomiting and diarrhea in approximately 10% of patients treated with GLP-1 analogs. Most patients have short episodes which resolve spontaneously within a few days, even with continued treatment [68, 69]. The patient should be informed about possible side effects and instructed to respond to the first feeling of satiety and eat smaller meals. In most cases, this contributes to a reduction in the incidence of side effects and increases treatment satisfaction [68, 69]. Also, as with any injectable drug, injection site reactions are possible. Significant but rare side effects include cholelithiasis and cholecystitis, and acute pancreatitis. Overall, the safety profile and tolerability of GLP-1 analogs are very good, and renal function (can be used in patients with eGFR> 15 ml/min/1.73 m^2) does not affect the dosage of the three analogs most important for cardiologists: liraglutide, semaglutide, and dulaglutide. Similarly, in the case of hepatic dysfunction or in elderly patients, there is no need to reduce the dose [32–35]. The tolerance profile of oral semaglutide is consistent with that of the entire GLP-1 analog class. The most common side effects observed were gastrointestinal symptoms, mainly nausea and diarrhea. Similarly, the safety profile is consistent with the safety profile of other drugs in this group [34, 38].

The influence of GLP-1 analogs on the heart rate (HR) requires additional commentary. The observed increase in HR is small (by a few beats per minute), and no negative effects on the cardiovascular prognosis of patients with T2DM have been observed so far, but it is believed that the sustained increase in HR may potentially adversely affect the prognosis for patients with coexisting HF [70]. A cardiologist introducing a GLP-1 analog to the treatment of a patient with T2DM should be aware of the potential impact of the new drug on HR and consider adequate modifications to the treatment regimen.

THE ROLE OF A CARDIOLOGIST IN TREATING A PATIENT WITH TYPE 2 DIABETES MELLITUS

According to the current PTD guidelines, "cooperation of specialists from related fields is also necessary due to the multidisciplinary nature of late diabetes complications and comorbidities". This recommendation is formally classified as B, but there is no doubt that a cardiac patient is often a diabetic patient and vice versa. In Poland, there are no precise data on the frequency of GLP-1 analog use by representatives of different specializations; however, we believe that these drugs are still not used as often as suggested by both diabetes and cardiological guidelines. The price of the drugs in question may certainly be off-limits for patients. However, it is worth remembering that many new molecules are affected by this problem, and physicians should not assume a priori that the patient will not use the drug for economic reasons. Class IA recommendations oblige us, in principle, to at least inform the patient about the existence of a given therapeutic option, its benefits, risk balance, and costs. This should also include comparing the cardiovascular benefits and side effects of the two most suitable classes of antihyperglycemic drugs today: GLP-1 analogs and flozins.

Another potential barrier may be the form of drug administration – a subcutaneous injection. However, it is worth noting in this context that GLP-1 analogs can be used once a day (liraglutide) or once a week (semaglutide or dulaglutide), which means that the number of injections is potentially much smaller than with insulin therapy. Moreover, the aforementioned oral formulation of semaglutide has recently appeared on the market, which enables the use of this GLP-1 analog in the form of tablet (once a day). The new formulation of the drug requires good patient adherence; however, this condition is well known to many patients treated, for example, for hypothyroidism (Figure 5).

At the turn of 2019 and 2020, the retrospective IGNITE study (InvestiGating New InitiaTors on oral semaglutidE in routine clinical practice) was conducted in the USA based on data from electronic health records (EHR) to assess how the results of clinical trials of oral forms of semaglutide translate into its use in everyday clinical practice [71]. The results of this study indicate that in the US, oral semaglutide therapy was ordered in 66% of cases (a total of 516 patients of the 782 patients enrolled in the study) by general practitioners (GPs). The authors of that study also noted that mainly basal doses were used without their subsequent titration (37% of patients received a prescription for the initial dose of 3 mg only) [71]. This indicates the need for further education in the medical community and stronger involvement of cardiologists in helping primary care physicians to control cardiovascular risk factors in people with T2DM.

Taking into account the cardiometabolic benefits associated with the use of GLP-1 analogs, proven in clinical trials, we developed a practical decision-making algorithm

Figure 5. Directions for use of the oral form of semaglutide [34]

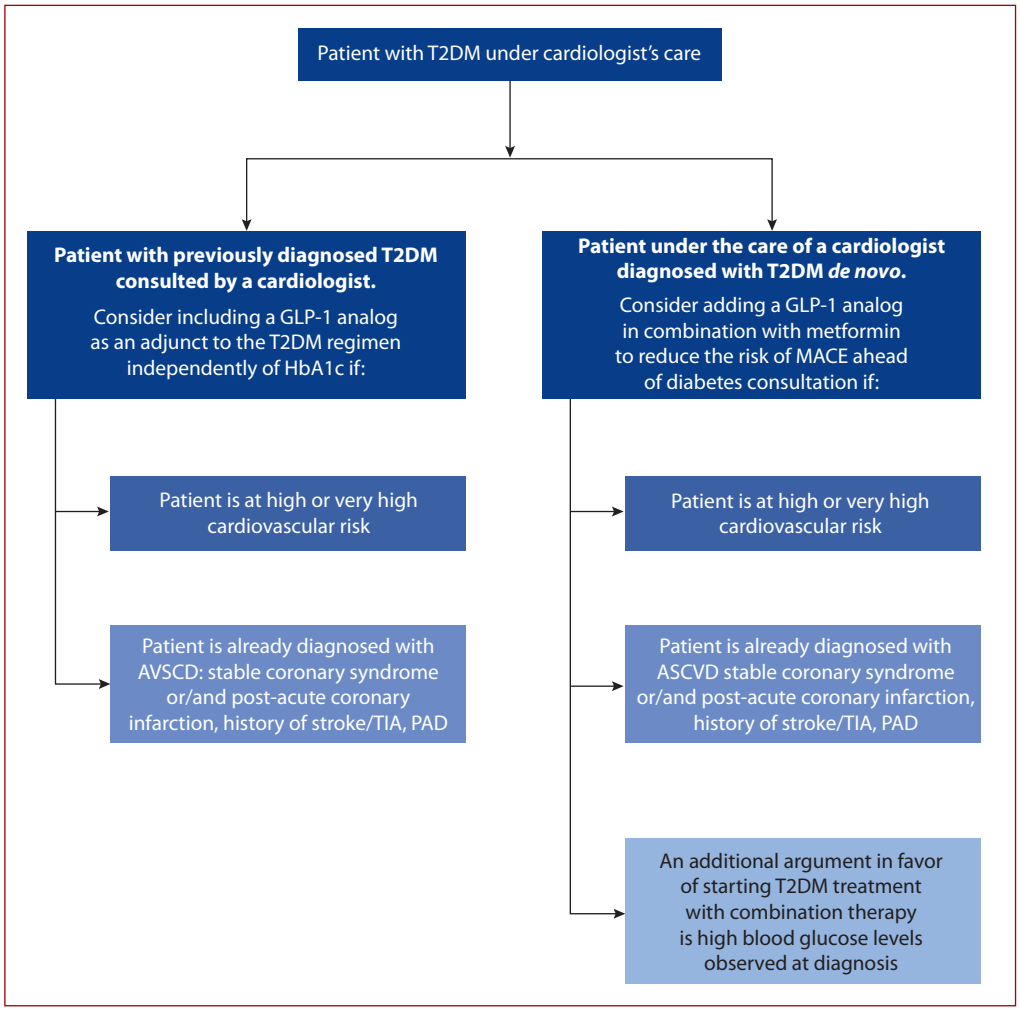

Figure 6. Algorithm supporting the decision to include GLP-1 analog by a cardiologist in a patient with T2DM

Abbreviations: ASCVD, atherosclerotic cardiovascular disease, GLP-1, glucagon-like peptide-1; PAD, peripheral artery disease; T2DM, type 2 diabetes mellitus; TIA, transient ischemic attack

for the inclusion of this class/group of drugs in this group of patients with T2DM. The algorithm is presented in Figure 6.

In our opinion, the results of the meta-analysis of CVOT studies with GLP-1 analogs carried out by Sattar et al. [72] are conclusive on this topic. It is worth emphasizing that the CVOT studies aimed to compare the effects of the new drug with the best available therapeutic option without this drug. That meta-analysis showed that the use of GLP-1 analogs allows for a 14% reduction in the occurrence of MACE (HR, 0.86; 95% CI, 0.80–0.93; P <0.0001), a 12% reduction in total mortality (HR, 0.88; 95% CI, 0.82–0.94; P = 0.0001), an 11% risk reduction in HF hospitalization (HR, 0.89; 95% CI 0.82–0.98; P = 0.013), and a 21% risk reduction in developing the composite renal endpoint of the studies

(HR, 0.79; 95% CI 0.73–0.87; *P* <0.0001) [50]. The cited meta-analysis also confirmed a very good safety profile of the discussed group of drugs — when analyzing the results of over 60 000 patients, the authors did not observe any association between GLP-1 analogs and a significant risk of hypoglycemia, retinopathy, or pancreatic side effects [72].

CONCLUSIONS

GLP-1 analogs constitute a valuable group of drugs with proven efficacy in the treatment of T2DM. According to the current international and Polish guidelines, these are one of the first groups of drugs, next to SGLT2 inhibitors, which we should use when designing the pharmacotherapy regimen for T2DM. Their more frequent use than today is supported not only by the proven effectiveness in improving metabolic control, expressed primarily by the effective reduction of HbA1c levels but also by the weight reduction effect that is very beneficial in most T2DM patients. These prerequisites are decisive if the diabetes pharmacotherapy regimen is planned or modified by a diabetologist. Three of the GLP-1 analogs available on the Polish market, however, may also be valuable therapeutic tools in the hands of cardiologists. Current cardiological guidelines clearly indicate GLP-1 analogs (liraglutide, semaglutide, or dulaglutide) as drugs with proven efficacy in reducing cardiovascular risk in patients with T2DM and already diagnosed with atherosclerotic disease or with high/very high cardiovascular risk. In this group of patients, from the cardiological point of view, the inclusion of GLP-1 analogs does not require additional diabetic indications, especially that these drugs, apart from the aforementioned beneficial effect on HbA1c and body weight, have a positive impact on cardiometabolic risk factors: systolic blood pressure, improvement of the lipid profile, or reduction of hs-CRP protein. The only slightly unfavorable effect is the increase in heart rate, which requires individual assessment and observation by a cardiologist or implementation of appropriate modifications in pharmacotherapy. In practice, therefore, almost every T2DM patient, who has had a myocardial infarction or has been diagnosed with stable coronary syndrome, has had a stroke or a TIA, has a documented PAD, or a total cardiovascular risk assessed as high, should be offered to supplement the treatment regimen with a GLP-1 analog. A new option worth mentioning here is the oral form of semaglutide. It gives a chance to overcome the patient's resistance to injection and to early initiate a therapy that, in the course of T2DM, will not only effectively balance glycemia and reduce body weight but will also have a positive effect on cardiometabolic risk factors. Finally, it may also improve adherence. Due to their potent normoglycemic action and valuable cardiovascular protective properties, drugs from the GLP-1RA group should be considered as the first step in the escalation of hypoglycemic therapy in patients for whom traditional oral drugs are not sufficiently effective. An extension of the National Health Fund's reimbursement criteria will be essential for the wider use of this valuable therapy.

PRACTICAL TIPS FOR THE USE OF GLP-1 ANALOGS

- Phase II clinical trials have shown that the rate of reported adverse reactions drops when treatment is initiated at a lower dose. Therefore, it is recommended to initiate treatment with the lowest registered dose (then the dose should be increased following the recommendations for a given drug).
- In the case of a patient not previously treated with GLP-1 analogs, it is recommended to inform him/her about possible side effects and instruct them to reduce the volume of meals and pay attention to the first feeling of satiety.
- In the case of oral semaglutide, the patient should be informed about the need to take the drug immediately after waking up (on an empty stomach), swallow it with a small amount of water (max. 120 ml), and take another drug or a meal after at least 30 minutes.
- If a GLP-1 analog is injected, the drug should be administered to the abdomen, thigh, or arm, at any time of the day, independently of meals.
- If a GLP-1 analog is used in combination with metformin and/or flozin or thiazolidinedione, the current doses of these drugs may remain unchanged.
- If a GLP-1 analog is used in combination with sulfonylureas or insulin, consideration should be given to gradual reduction of the dose of sulfonylureas or insulin, up to and including discontinuation to reduce the risk of hypoglycemia and to facilitate therapy.
- No dose adjustment of a GLP-1 analog is required for patients with mild, moderate, or severe renal impairment (eGFR >15 ml/ min/1.73 m^2), hepatic impairment, and elderly patients.

Highlights

- Atherosclerotic cardiovascular disease (ASCVD) is the most common cardiovascular disease in patients with T2DM.
- The studies also show that cardiovascular complications are the leading cause of disability and death in T2DM patients and may occur at a very early stage in T2DM.
- The results of many studies conducted over several years showed that the use of appropriate therapy at an early stage of treatment slowed down complications of T2DM and had a positive influence on the prognosis of T2DM patients.
- If we decide to use a combination therapy from the beginning of T2DM pharmacotherapy, the second antihyperglycemic drug should have a proven beneficial effect on cardiovascular prognosis. Both the Polish guidelines and the current guidelines of the American Diabetes Association (ADA) indicate that the choice in this respect should be made between GLP-1 analogs and SGLT-2 inhibitors (flozins).
- Due to their potent normoglycemic action and valuable cardiovascular protective properties, drugs from the GLP-1RA group should be considered as the first step in the escalation of hypoglycemic therapy in patients for whom traditional oral drugs are not sufficiently effective.
- This position statement aims to define the role that a cardiologist can play in designing a T2DM pharmacotherapy regimen.

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