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A review of cardiovascular outcome trials in type 2 diabetes

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Abstract

Type 2 diabetes is a complex metabolic disorder associated with a high risk of cardiovascular complications. In December 2008, due to concerns about the cardiac safety of antihyperglycaemic therapies, the Food and Drug Administration (FDA) published a new guidance on special requirements for the demonstration of cardiovascular safety for these medications. In 2012, similar recommendations were made for antidiabetic drug manufacturers by the European Medicines Agency (EMA). Since then, both FDA and EMA recommendations have been applied in cardiovascular outcome trials (CVOTs) for several new antihyperglycaemic drugs. Unlike conventional trials, CVOTs are usually placebo controlled, non-inferiority trials that examine the cardiovascular safety of a drug compared to standard of care in large cohorts of patients with high cardiovascular risk or established cardiovascular disease. Patients in CVOTs are also monitored for a longer observation period than in typical randomised controlled trials to provide data on long-term cardiovascular risk. To date, nine CVOTs involving patients with type 2 diabetes have been completed, and at least 13 are still ongoing. These studies focus on a variety of antihyperglycaemic drugs, including incretin-based agents, sodium-glucose cotransporter 2 inhibitor (SGLT-2) inhibitors, and insulin formulations. This article takes a critical look at these CVOTs and summarises the results of the completed trials. **(Endokrynol Pol 2018; 69 (4): 424–431)**

Key words: *type 2 diabetes mellitus; cardiovascular disease; hyperglycaemia*

Introduction

Diabetes is one of the most dangerous lifestyle diseases in the world. According to epidemiological data from the International Diabetes Federation (IDF) in 2015, 415 million adults aged 20–79 years worldwide suffered from this disease, accounting for 8.8% morbidity (59.8 million people in Europe) [1].

Type 2 diabetes mellitus (T2DM) is a chronic disease, whose incidence is systematically increasing globally. T2DM is responsible for the shortening of average life expectancy by 5–10 years, with the most common direct cause of premature death being cardiovascular complications [2]. In the first 10 years from diagnosis, about 41% of patients with T2DM develop ischaemic heart disease, 12% develop cerebrovascular disease, and 11% develop peripheral vascular disease [3, 4]. While there is a close association between fasting and postprandial glucose levels and future risk of cardiovascular complications, there is no convincing evidence of the protective effect of antidiabetic therapy on the incidence of cardiovascular events [3, 4].

The relationship between glycaemic control assessed by the value of glycated haemoglobin (HbA1c) and cardiovascular risk was documented by the United Kingdom Prospective Diabetes Study (UKPDS), published in 1998 [5]. Based on the analysis of 4209 patients with newly diagnosed T2DM, it was found that a 1% increase in HbA1c level increased the risk of death from diabetes complications by 21%, from myocardial infarction by 14%, from stroke by 12%, from any cause by 14%, and from peripheral arterial disease by 43%. In patients with HbA1c > 7%, a one-unit increase in HbA1c increased the risk of developing macrovascular complications or death by 38%. In turn, the risk HbA1c threshold for microvascular events was 6.5%; above it, the probability of events for each unit increase in HbA1c levels increased by 40%.

Unlike the results of the UKPDS, the ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease), and VADT (The Veterans Affairs Diabetes Trial) studies published in 2008–2009 did not show a statistically significant relationship between decreased HbA1c levels and reduced incidence of cardiovascular events [6–8]. In contrast, a meta-analysis of all four studies (UKPDS, ACCORD, ADVANCE, and VADT) for a five-year follow-up showed a statistically significant 15% (95% CI: 14–16%) reduction in non-fatal myocardial infarction and fatal myocardial infarction in patients using pharmacotherapy in the course of T2DM [9].

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Currently available T2DM therapies, ranging from metformin to insulin and incretin drugs, have been registered on the basis of the results of randomised clinical trials, where the main goal was to demonstrate hypoglycaemic action of the intervention, usually based on reduction of HbA1c as a biomarker of diabetes control. However, due to the short (3–6 month) horizon of these studies, the long-term safety of therapy and its effect on the cardiovascular system in patients suffering from T2DM remains unclear [3].

Cardiovascular outcome trials (CVOTs)

In 2005, promising results of the second phase trial for muraglitazar were published [10]. This treatment not only reduced the level of HbA1c in T2DM patients but also decreased triglyceride levels and increased HDL levels, which prompted the US Food and Drug Administration (FDA) to use an accelerated pathway for drug approval [11]. However, further clinical trials have shown that muraglitazar therapy is associated with more than twice the risk of stroke, myocardial infarction, and cardiovascular death ($P = 0.03$) compared to standard therapy [12]. This led to the complete closure of all activities related to the introduction of this substance for T2DM treatment. The worrying data published in 2007 in the *New England Journal of Medicine* on the relationship of rosiglitazone therapy with increased risk of myocardial infarction (OR = 1.43; 95% CI: 1.03–1.98; $P = 0.03$) and cardiovascular death (OR = 1.64; 95% CI: 0.98–2.74; $P = 0.06$) in patients with T2DM also pointed to the need to evaluate cardiovascular safety of antidiabetic therapies [13].

In response to these reports, two leading agencies responsible for the registration and market authorisation of medicinal products, the US FDA and the European Medicines Agency (EMA), published recommendations for pharmaceutical companies (FDA in 2008, EMA in 2012) [14, 15]. These recommendations clearly state that for every new drug introduced to treat diabetes, in addition to demonstrating the efficacy of the intervention in reducing HbA1c levels, the sine qua non condition required in the clinical efficacy evaluation in T2DM patients is to demonstrate its acceptable cardiovascular safety profile [14, 15]. The FDA and EMA positions do differ: the EMA guidelines are more general and only state that the medication should not have any effect on or positively influence the cardiovascular risk, while the FDA guidelines state the results of all available clinical trials for antidiabetic agents should be meta-analysed to establish the relative risk (RR) of major cardiovascular events in the population using the intervention versus the comparative intervention. If the upper value of the two-sided confidence interval (95% CI) for RR is > 1.8, the FDA recommends further studies in a larger group of patients, while blocking the authorisation of the drug. If the upper value of the 95% CI ranges from 1.3 to 1.8, the drug is authorised for use, but further post-registration studies are recommended. However, if the upper value of the 95% CI is < 1.3, further post-registration studies are not required. The FDA and EMA guidelines also require patients with cardiovascular disease or an increased risk of cardiovascular events to be included in studies evaluating antidiabetic agents. Data on the cardiac safety of therapy for a period of at least two years should be provided, and the events constituting the endpoints of the study must be assessed by an independent external committee with sample blinding.

The above guidelines are being applied in designing modern cardiovascular outcome trials (CVOTs), which are necessary to register the given drug and aim to determine the effect of long-term antidiabetic therapy on the risk of cardiovascular events in patients with T2DM [16]. Unlike classical clinical trials, CVOTs are performed on large populations of patients (ranging from a few to a dozen or thousands of patients from hundreds of centres in multiple countries) to ensure the highest possible representativeness of the sample and to increase the probability of the endpoint occurrence. All participants in the study are monitored over a long follow-up period lasting at least several years.

CVOTs are event-driven trials. The assumptions of this type of study determine how many events constituting the endpoint (e.g. cardiovascular death or fatal myocardial infarction) have to occur in order to achieve the research goal. In classical randomised clinical trials, the duration of the study is strictly defined, and the difference (between the test and control arms) in the clinical parameters considered study endpoints are assessed.

The required number of events depends on the type of CVOT study, i.e. whether it is intended to determine the cardiovascular safety of the drug in accordance with the FDA and EMA requirements (non-inferiority study) or if it will examine whether it also has a beneficial effect on cardiovascular risk (superiority study) compared to placebo or other intervention. In the first case, 600 to 700 events are considered sufficient to reach the target; this number is much higher in the second case and depends on the assumed positive level of the intervention.

The primary endpoint in CVOT studies is a composite endpoint that should consist of events classified as major adverse cardiovascular events (MACE) such as cardiovascular death, myocardial infarction, and stroke. It may also include hospitalisation for acute coronary syndrome or heart failure and the need for emergency revascularisation.

Measurement of the result through a composite endpoint affects the size of the analysed population. In the case of observation of individual cardiovascular events separately, the number of patients included in the study should be multiplied to demonstrate the statistical significance of the individual endpoint. Analysing multiple events at the same time in a composite endpoint enables optimisation of the population size, but also allows the study horizon to be shortened.

Providing evidence regarding the long-term safety of antidiabetic therapy is a challenge for modern clinical trials because a different approach must be adopted in a CVOT than in traditional studies. First and foremost, it is important to remember that conducting long-term studies in very large patient groups involves the recruitment of participants from multiple centres in different countries, which may differ, for example, in the treatment standard or the characteristics of the study group.

A serious problem in long-term CVOT studies is the low retention of participants — for example, in EXAMINE and SAVOR-TIMI 53, 10% of patients stopped taking the studied drug. Care must be taken to ensure that the loss of patients during the course of the study, either due to withdrawal of consent or discontinuation of the test drug, is low [17]. It is especially important to monitor all patients until the end of the study, even those who have stopped taking the medicine. Lack of complete information and patient loss during the study is critical to the credibility of the endpoint assessed and can completely undermine the value of even well designed, professionally performed, and important clinical trials. An example of this is the RECORD (Rosiglitazone Evaluated for Cardiac Outcome and Regulation of Glycaemia in Diabetes) study, based on which the FDA abrogated restrictions on rosiglitazone in 2013 [13]. Although the RECORD results have not confirmed previous reports of association of rosiglitazone therapy with increased risk of myocardial infarction and death, some medical environments undermine their credibility, inter alia because of the lack of blinding and low retention of patients (8.9% of participants did not complete the study and no data on health status was available for 2.9%).

Results of the completed CVOT studies

There are currently several large CVOTs evaluating antidiabetic therapies. In almost all cases (except for the CAROLINA study where two drugs are compared), the safety of the given drug in addition to standard therapy compared with placebo is assessed. These studies included a population of over 150,000 patients with T2DM. A summary of the completed CVOTs in patients with T2DM is shown in Table I.

In 2013, the results of the first large clinical trials complying with FDA and EMA requirements for cardiovascular risk assessment of antidiabetic therapy in patients with T2DM were published: SAVOR-TIMI (Saxagliptin Assessment of Vascular Outcome Recorded in patients with diabetes mellitus–Thrombolysis In Myocardial Infarction) and EXAMINE (EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE; Table 1) [18, 19].

SAVOR-TIMI, which evaluated the efficacy and safety of saxagliptin (belonging to the dipeptidyl peptidase-4 inhibitor class of drugs) added to standard therapy, included patients with T2DM with evidence of cardiovascular disease or at increased risk of cardiovascular events [18]. Cardiovascular safety assessment showed that the use of the studied drug in comparison to placebo did not significantly increase the incidence of primary endpoint, i.e. cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (7.3% in the saxagliptin group and 7.2% in the placebo group). On the other hand, a significant increase in risk (by 27%) of hospitalisation for heart failure in patients treated with saxagliptin was observed for the secondary endpoint (including primary endpoint plus hospitalisation for heart failure, need for revascularisation, and unstable angina pectoris) (OR = 1.27; 95% CI: 1.07–1.51; $P = 0.007$).

The EXAMINE study assessed the safety of another dipeptidyl peptidase-4 inhibitor, alogliptin, compared to placebo, in addition to standard treatment in patients with T2DM, who had a severe coronary event 15–90 days prior to randomisation [19]. The primary composite endpoint was cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The secondary endpoint included a combination of primary endpoint plus urgent revascularisation due to acute coronary syndrome. There were no statistically significant differences between groups in the incidence of the primary endpoint (11.3% in the alogliptin group vs. 11.8% in the placebo group) or secondary endpoint (12.7% vs. 13.4%, respectively).

In 2015, the results of two large, multicentre CVOT studies on incretin drugs were published: TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) and ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome; Table I) [20, 21]. In the randomised, double-blinded, placebo-controlled TECOS study, the efficacy and safety of sitagliptin added to standard therapy were evaluated [20]. The study included 14,671 patients with T2DM, aged ≥ 50 years, with baseline HbA1c levels of 6.5–8% and cardiovascular disease. The primary composite endpoint consisted of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalisation for unstable coronary artery

Table I. *Summary of completed cardiovascular outcome trials in patients with type 2 diabetes*

Trial acronym	Drug	Number of patients	Follow-up period (median)	Primary composite endpoint	Hazard ratio (HR) for primary endpoint	Hazard ratio (HR) for individual components of the primary composite endpoint	HbA1c change	Body weight change	Risk of hypoglycemia
SAVOR--TIMI 53	Saxagliptin	16,492	2.1 years	Cardiovascular death Non-fatal myocardial infarction Non-fatal stroke	HR 1.00; 95% CI 0.89–1.12; P < 0.001 for non-inferiority, P = 0.99 for superiority	Cardiovascular death: HR 1.03; 95% CI 0.87–1.22; P = 0.72 Non-fatal myocardial infarction: HR 0.95; 95% CI 0.80–1.12; P = 0.52 Non-fatal stroke: HR 1.11; 95% CI 0.88–1.39; P = 0.38	Decreased by 0.20% more in saxagliptin group vs. placebo (P < 0.001)	Decrease was 0.5 kg higher in saxagliptin group vs. placebo (P = 0.46)	Severe hypoglycemia in 2.1% in saxagliptin group and 1.7% in placebo (P = 0.047)
EXAMINE	Alogliptin	5,380	1.5 years	Cardiovascular death Non-fatal myocardial infarction Non-fatal stroke	HR 0.96; the bound for one-sided repeated CI: 1.16; P < 0.001 for non-inferiority, P = 0.32 for superiority	Cardiovascular death: HR 0.79; 95% CI 0.6–1.04; P = 0.10 Non-fatal myocardial infarction: HR 1.08; 95% CI 0.88–1.33; P = 0.47 Non-fatal stroke: HR 0.91; 95% CI 0.55–1.50; P = 0.71	Decreased by 0.36% more in alogliptin group vs. placebo (P < 0.001)	Decrease was 0.06 kg higher in alogliptin group vs. placebo (P = 0.71)	Severe hypoglycemia in 0.7% in alogliptin group vs. 0.6% in placebo (P = 0.86)
TECOS	Sitagliptin	14,671	3 years	Cardiovascular death Non-fatal myocardial infarction Non-fatal stroke Hospitalization due to unstable coronary artery disease	HR 0.98; 95% CI 0.88–1.09; P < 0.001 for non-inferiority, P = 0.65 for superiority	Cardiovascular death: HR 1.03; 95% CI 0.89–1.19; P = 0.71 Myocardial infarction (fatal and non-fatal): HR 0.95; 95% CI 0.81–1.11; P = 0.49 Stroke (fatal and non-fatal): HR 0.97; 95% CI 0.79–1.19; P = 0.76 Hospitalization due to unstable coronary artery disease: HR 0.90; 95% CI 0.70–1.16; P = 0.42	Decreased by 0.29% more in sitagliptin group vs. placebo (P < 0.001)	No data	Severe hypoglycemia in 2.0% in sitagliptin group vs. 1.7% in placebo (P = 0.31)
ELIXA	Lixisenatide	6,068	2.1 years	Cardiovascular death Non-fatal myocardial infarction Non-fatal stroke Hospitalization due to unstable coronary artery disease	HR 1.02; 95% CI 0.89–1.17; P < 0.001 for non-inferiority, P = 0.81 for superiority	Cardiovascular death: HR 0.98; 95% CI 0.78–1.22; P = 0.85 Non-fatal myocardial infarction: HR 1.03; 95% CI 0.87–1.22; P = 0.71 Non-fatal stroke: HR 1.12; 95% CI 0.79–1.58; P = 0.54 Hospitalization due to unstable coronary artery disease: HR 1.11; 95% CI 0.47–2.62; P = 0.81	Decreased by 0.27% more in lixisenatide group vs. placebo (P < 0.001)	Decrease was 0.7 kg higher in lixisenatide group vs. placebo (P < 0.001)	Hypoglycemia in 16.6% in lixisenatide group vs. 15.2% in placebo (P = 0.14) Severe hypoglycemia in 14 patients (16 episodes) in lixisenatide group vs. 24 patients (37 episodes) in placebo

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Table I (cont.). *Summary of completed cardiovascular outcome trials in patients with type 2 diabetes*

Trial acronym	Drug	Number of patients	Follow-up period (median)	Primary composite endpoint	Hazard ratio (HR) for primary endpoint	Hazard ratio (HR) for individual components of the primary composite endpoint	HbA1c change	Body weight change	Risk of hypoglycemia
EMPA-REG	Empagliflozin	7,020	3.1 years	Cardiovascular death Non-fatal myocardial infarction Non-fatal stroke	HR 0.86; 95% CI 0.74–0.99; P < 0.001 for non-inferiority, P = 0.04 for superiority	Cardiovascular death: HR 0.62; 95% CI 0.49–0.77; P < 0.001 Non-fatal myocardial infarction: HR 0.87; 95% CI 0.70–1.09; P = 0.22 Non-fatal stroke: HR 1.24; 95% CI 0.92–1.67; P = 0.16	Decreased by 0.24% more in 10 mg empagliflozin group vs. placebo and by 0.36% more in 25 empagliflozin group vs. placebo (both P < 0.001)	Decrease was 0.51 kg higher in 10 mg empagliflozin group vs. placebo and 0.7 kg higher in 25 mg empagliflozin group vs. placebo	Severe hypoglycemia in 1.4% in 10 mg empagliflozin group vs. 1.3% in 25 mg empagliflozin group vs. 1.5% in placebo
LEADER	Liraglutide	9,340	3.8 years	Cardiovascular death Non-fatal myocardial infarction Non-fatal stroke	HR 0.87; 95% CI 0.78–0.97; P < 0.001 for non-inferiority and P = 0.01 for superiority	Cardiovascular death: HR 0.78; 95% CI 0.66–0.93; P = 0.007 Non-fatal myocardial infarction: HR 0.88; 95% CI 0.75–1.03; P = 0.11 Non-fatal stroke: HR 0.89; 95% CI 0.72–1.11; P = 0.30	Decreased by 0.40% more in liraglutide group vs. placebo (P < 0.001)	Decrease was 2.3 kg higher in liraglutide group vs. placebo (95% CI 2.5–2.0)	Severe hypoglycemia in 2.4% in liraglutide group vs. 3.3% in placebo (P = 0.02)
SUSTAIN-6	Semaglutide	3,297	2.1 years	Cardiovascular death Non-fatal myocardial infarction Non-fatal stroke	HR 0.74; 95% CI 0.58–0.95; P < 0.001 for non-inferiority and P = 0.02 for superiority	Cardiovascular death: HR 0.98; 95% CI 0.65–1.48; P = 0.92 Non-fatal myocardial infarction: HR 0.74; 95% CI 0.51–1.08; P = 0.12 Non-fatal stroke: HR 0.61; 95% CI 0.38–0.99; P = 0.04	Decreased by 0.70% more in 0.5 mg semaglutide group vs. placebo (P < 0.001) Decreased by 1% more in 1 mg semaglutide group vs. placebo (P < 0.001)	Decrease was 2.9 kg higher in the 0.5 mg semaglutide group and 4.3 kg higher in the 1.0 mg semaglutide group vs. placebo (P < 0.001 for both)	Severe hypoglycemia in 23.1% in 0.5 mg semaglutide group and 21.7% in 1 mg semaglutide group compared with placebo (21.5% and 21.0%, respectively; (P>0.05)
CANVAS; CANVAS-R	Canagliflozin	CANVAS: 4,330 CANVAS-R: 5,812	3.6 years	Cardiovascular death Non-fatal myocardial infarction Non-fatal stroke	HR 0.86; 95% CI 0.75–0.97; P < 0.001 for non-inferiority and P = 0.02 for superiority	Cardiovascular death: HR 0.87; 95% CI 0.72–1.06; P = not significant Non-fatal myocardial infarction: HR 0.85; 95% CI 0.69–1.05; P = not significant Non-fatal stroke: HR 0.90; 95% CI 0.71–1.15; P = not significant	Decreased by 0.58% more in canagliflozin group vs. placebo (P < 0.001)	Decrease was 1.6 kg higher in canagliflozin group vs. placebo (P < 0.001)	Severe hypoglycemia rate of 50 events per 1000 patient years in canagliflozin group and 46.4 events per 1000 patient years in placebo (P = 0.2)

disease. During the follow-up (median three years), there was no statistically significant difference in the incidence of primary composite endpoints between groups (11.5% vs. 11.6%; HR = 0.98; 95% CI: 0.88–1.09; $P < 0.001$ for non-inferiority, $P = 0.65$ for superiority). The TECOS study did not confirm the SAVOR-TIMI study observation of a statistically significant increase in risk of hospitalisation for heart failure (HR = 1.00; 95% CI: 0.83–1.20; $P = 0.98$) with a dipeptidyl peptidase-4 inhibitor. The increased incidence of acute pancreatitis (P = 0.07) or pancreatic cancer (P = 0.32) was not observed in patients treated with sitagliptin.

In the randomised, double-blind, placebo-controlled ELIXA study, the efficacy and safety of lixisenatide, a glucagon-like peptide 1 (GLP-1) receptor agonist, added to the standard treatment was assessed [21]. This study included 6068 participants with T2DM, who had an episode of acute coronary syndrome within 180 days before the randomisation. The primary composite endpoint (i.e. cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalisation for unstable angina pectoris) was reported in 406 (13.4%) patients in the lixisenatide group and in 399 (13, 2%) patients in the placebo group (HR = 1.02; 95% CI: 0.89–1.17; $P < 0.001$ for non-inferiority, $P = 0.81$ for superiority). There was no statistically significant difference between the groups in hospitalisations due to heart failure (in the lixisenatide group HR = 0.96; 95% CI: 0.75–1.23) or death for any reason (HR = 0.94, 95% CI: 0.78–1.13). Taking the drug did not significantly increase the risk of severe hypoglycaemia, pancreatitis, or pancreatic cancer.

In 2015, the results of EMPA-REG OUTCOME, a multicentre, randomised, double-blinded, placebo-controlled study were published (Table I) [22]. This study evaluated the efficacy and safety of empagliflozin, a selective inhibitor of the sodium-glucose co-transporter 2, added to standard treatment in patients with T2DM at high-risk of cardiovascular events. The study involved 7020 patients, and the observation time was 3.1 years (median). The study was completed by 97% of patients (data on health status were available for 99.2% of patients); however, 25.4% of patients stopped taking the drug prematurely. In accordance with the assumptions of CVOT studies, the study was discontinued following a number of events that constituted a primary composite endpoint, i.e. cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (691 events). The primary composite endpoint occurred in a significantly lower number of patients in the empagliflozin group than in the placebo group (10.5% vs. 12.1%; 14% risk reduction; HR = 0.86; 95% CI: 0.74–0.99; $P < 0.001$ for non-inferiority and $P = 0.04$ for superiority). The main secondary endpoint (including primary endpoint plus hospitalisation for unstable angina pectoris) occurred in 12.8% of patients in the empagliflozin group and in 14.3% of patients in the placebo group (HR = 0.89; 95% CI: 0.78–1.01; $P < 0.001$ for non-inferiority and $P = 0.08$ for superiority). There was no significant difference in the occurrence of non-fatal myocardial infarction or stroke between groups. However, significantly lower cardiovascular mortality (3.7% vs. 5.9%; 38% risk reduction; HR = 0.62; 95% CI: 0.49–0.77, $P < 0.001$) and mortality for any reason (5.7% vs. 8.3%; 32% risk reduction; HR = 0.68; 95% CI: 0.57–0.82; $P < 0.001$) was observed in the empagliflozin group, which is important for the clinical practice.

Another important CVOT study concerning incretin therapies is the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results) study, which was published in 2016 [23]. Its purpose was to assess cardiovascular safety of liraglutide added to standard treatment compared with placebo in T2DM therapy. Liraglutide, a long-acting GLP-1 analogue that enhances insulin secretion and simultaneously inhibits glucagon secretion in a glucose-dependent manner, was registered by the EMA in 2009 as an antidiabetic drug for adults with T2DM. Clinical studies have demonstrated the efficacy of liraglutide in the reduction of HbA1c, glycaemia, and body weight; it has also shown efficacy in combination with metformin or sulfonylurea derivatives [24–26]. According to some clinical trials, inclusion of GLP-1 into therapy improves left ventricular function in patients with myocardial infarction undergoing cardiac revascularization [27]. Moreover, in patients with heart failure, the addition of GLP-1 to standard therapy improves the ejection fraction and the use of oxygen by cardiac muscles [28].

LEADER is a randomised, double-blinded phase III study, which started in 2010, involving over 9340 patients from 410 centres worldwide (including 388 patients from 13 centres in Poland) [23]. The study included patients with T2DM aged ≥ 50 years (and ≥ 60 years without cardiovascular disease), with HbA1c ≥ 7.0%, who had cardiovascular risk factors or cardiovascular disease, cerebrovascular disease, peripheral arterial disease, or chronic renal failure or heart failure. The subjects were randomised (1:1) to a once-daily subcutaneous dose of 1.8 mg (or maximum tolerated) liraglutide or placebo. The observation time was 3.8 years (median), and 96.8% of patients completed the study (health status data was available for 99.7% of patients).

The primary composite endpoint was cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. Secondary endpoints were measurements of the same events as those of the primary endpoint, with the additional need for coronary revascularisation in the course of ischaemic heart disease and for hospitalisation

associated with unstable angina or heart failure, time to death from any cause, and time to occurrence of particular primary endpoint components.

The primary composite endpoint occurred in a significantly lower number of patients in the liraglutide group than in the placebo group (13.0% vs. 14.9%; HR = 0.87; 95% CI: 0.78–0.97; $P < 0.001$ for non-inferiority and $P = 0.01$ for superiority). Fewer patients taking liraglutide died of cardiovascular causes (4.7% vs. 6.0% in the placebo group, HR = 0.78; 95% CI: 0.66–0.93; $P = 0.007$) and of any reason (8.2% vs. 9.6% in placebo group, HR = 0.85; 95% CI: 0.74–0.97; $P = 0.02$). There were also fewer non-fatal myocardial infarctions, non-fatal strokes, and hospitalisations for heart failure in patients in the liraglutide group than in the placebo group, but these differences were not statistically significant. The number of adverse events found in both groups was similar (62.3% in the liraglutide group and 60.8% in the placebo group) and did not differ significantly ($P = 0.12$). The incidence of pancreatitis was not significantly lower, but the incidence of pancreatic cancer was not significantly higher, in the liraglutide group than in the placebo group. The most common side effects of liraglutide leading to discontinuation of the therapy were gastrointestinal symptoms.

Semaglutide is another promising long-acting GLP-1 analogue, which has been assessed in preapproval SUSTAIN-6 trial (Table I) [29]. SUSTAIN-6 was a randomised, double-blinded, placebo-controlled, parallel group trial involving patients with T2DM on a standard care regimen to receive once-weekly semaglutide (0.5 mg or 1.0 mg; n = 1648) or placebo (n = 1649) for 104 weeks. Patients with T2DM aged ≥ 50 years with established cardiovascular disease (previous cardiovascular, cerebrovascular, or peripheral vascular disease), chronic heart failure (New York Heart Association class II or III), chronic kidney disease (stage 3 or higher), or ≥ 60 years with at least one cardiovascular risk factor were included.

The primary composite endpoint was cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. As shown in Table I, the primary composite endpoint occurred in a significantly lower number of patients in the semaglutide group than in the placebo group (6.6% vs. 8.9%; HR = 0.74; 95% CI: 0.58–0.95; $P < 0.001$ for non-inferiority and $P = 0.02$ for superiority). There were fewer cases of non-fatal myocardial infarction in the semaglutide group than in the placebo group, although this difference was not significant (2.9% vs. 3.9%; HR = 0.74; 95% CI: 0.51–1.08; $P = 0.12$). There were also fewer non-fatal strokes in the semaglutide group than in the placebo group (1.6% vs. 2.7%; HR = 0.61; 95% CI: 0.38–0.95; $P = 0.04$). Rates of death from cardiovascular causes were similar between the two groups. Patients in the semaglutide group showed significant and sustained reductions in HbA1c levels compared with placebo, and similar rates of hypoglycaemia.

Semaglutide-treated patients had a higher risk of retinopathy complications (HR = 1.76; 95% CI: 1.11–2.78; $P = 0.02$) but a lower risk of new or worsening nephropathy compared to placebo (HR = 0.64; 95% CI: 0.46–0.88; $P = 0.005$). Overall, fewer serious adverse events occurred in the semaglutide group than in the placebo group; the incidence of both pancreatitis and pancreatic cancer was lower in the semaglutide group than in the placebo group. Nonetheless, treatment discontinuation due to adverse events was more frequent in the semaglutide group than in the placebo group, mainly from gastrointestinal symptoms.

Finally, the effects of the sodium-glucose cotransporter 2 (SGLT2) inhibitor canagliflozin on cardiovascular, kidney, and safety outcomes has been investigated in two related CVOTs: the Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-Renal (CANVAS-R) [30]. An integrated analysis of these two trials was recently published, involving a total of 10,142 participants with T2DM (mean age 63.3 years) and high cardiovascular risk, who were randomised to receive canagliflozin (300 mg or 100 mg; n = 5,795) or placebo (n = 4,347) for a mean follow-up of 188.2 weeks.

The primary composite endpoint was cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. As shown in Table I, the rate of the primary composite endpoint was significantly lower in canagliflozin-treated patients than in the placebo group (26.9 vs. 31.5 participants per 1000 patient-years; HR = 0.86; 95% CI: 0.75–0.97; $P < 0.001$ for non-inferiority and $P = 0.02$ for superiority). All three individual components of the primary outcome showed evidence of increased benefit in the canagliflozin group compared to placebo, although these did not reach significance (Table I). In terms of renal outcomes, there was some benefit of canagliflozin on the progression of albuminuria (HR = 0.73; 95% CI: 0.67–0.79) and the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes (HR = 0.60; 95% CI: 0.47–0.77), although again, these effects were not statistically significant.

Overall, fewer serious adverse events occurred in the canagliflozin group than in the placebo group (104.3 vs. 120.0 participants with an event per 1000 patient-years; HR = 0.93; 95% CI: 0.87–1.00). However, canagliflozin-treated patients had a higher risk of amputation of the toes, feet, or legs (6.3 vs. 3.4 participants per 1000 patient-years; HR = 1.97; 95% CI: 1.41–2.75), primarily at the level of the toe or metatarsal. This was

a new finding, and it prompted the FDA to add a *Boxed Warning* to canagliflozin drug labels to describe this specific risk in 2017. However, the mechanism behind the increased risk of amputation with canagliflozin requires further investigation.

Conclusions

CVOT studies provide data on the predicted effect of the assessed antidiabetic drug on the distant prognosis of survival in patients with T2DM, and they may help to explain the mechanism of the disease itself. They are extremely important for decision-making processes, including drug registration and post-registration changes, and for future public funding. The guidelines published by the FDA and EMA provide direction for further actions, whose primary goal is to improve cardiovascular safety of T2DM drugs, including eliminating existing areas of uncertainty and updating previous reports on treatment safety.

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