Diabetes, pre-diabetes and cardiovascular diseases in light of the 2019 ESC Guidelines

Cukrzyca i stan przedcukrzycowy a choroby układu krążenia w świetle wytycznych ESC 2019

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Abstract

The prevalence of diabetes mellitus (DM) is steadily increasing all over the world. DM is associated with a doubling of cardiovascular (CV) risk independently of other risk factors. The European Society of Cardiology (ESC) in collaboration with the European Association for the Study of Diabetes (EASD) presented a new set of guidelines on diabetes, pre-diabetes and cardiovascular diseases at the ESC 2019 Congress in Paris. The most important changes in the guidelines include a new assessment of CV risk in DM patients, an algorithm for glucose-lowering treatment, prevention of CV diseases including new targets for the treatment of dyslipidemia taking into account CV risk and recommendations for antiplatelet/antithrombotic drugs. Furthermore, attention focused on the management of DM concomitant with coronary artery disease and heart failure, as well as individualized therapeutic strategies for diabetic patients with arterial hypertension.

Streszczenie

Na świecie narasta epidemia cukrzycy (DM). Cukrzyca zwiększa dwukrotnie ryzyko wystąpienia zdarzeń sercowo-naczyniowych (CV), niezależnie od innych czynników ryzyka. European Society of Cardiology (ESC) we współpracy z European Association for the Study of Diabetes (EASD) przedstawiło w czasie kongresu ESC 2019 w Paryżu nowe wytyczne dotyczące cukrzycy, stanu przedcukrzycowego i chorób sercowo-naczyniowych (*2019 Guidelines on diabetes, pre-diabetes, and cardiovascular diseases*). Najistotniejsze nowe rekomendacje i zmiany w dotychczasowych rekomendacjach dotyczą nowej klasyfikacji ryzyka CV u chorych na DM, algorytmu leczenia hipoglikemizującego, profilaktyki chorób sercowo-naczyniowych, w tym nowych celów terapeutycznych w leczeniu dyslipidemii uwzględniających ryzyko CV oraz rekomendacji dotyczących leczenia przeciwpłytkowego lub przeciwzakrzepowego. Ponadto dużo miejsca poświęcono postępowaniu w DM i chorobie wieńcowej, niewydolności serca oraz indywidualizacji celów terapeutycznych u chorych z nadciśnieniem tętniczym.

Introduction

The prevalence of diabetes mellitus (DM) is steadily increasing all over the world. It has been projected that the number of people with DM will increase by almost 50% in the next two decades [1]. Diabetic patients have a shorter life expectancy than people without cardiometabolic abnormalities [2–4]. DM is associated with a doubling of cardiovascular (CV) risk independently of other risk factors, to a greater extent in women. The increased CV risk of DM patients is mainly dependent on disease duration and presence of microvascular complications [5]. In recent years there has been an unprecedented increase in the new evidence-based data including the results of clinical trials that have reported clear evidence of a CV benefit in DM and pre-DM populations. It is important for practicing healthcare professionals to become familiar with this new data set and incorporate new recommendations into their everyday clinical practice to improve outcomes in this group of high CV risk patients. The European Society of Cardiology (ESC) in collaboration with the European Association

for the Study of Diabetes (EASD) presented a new set of guidelines on diabetes, pre-diabetes and cardiovascular diseases at the ESC 2019 Congress in Paris [5]. The most important changes in the guidelines include a new assessment of CV risk in DM patients, an algorithm for glucose-lowering treatment, prevention of cardiovascular diseases (CVD) including new targets for the treatment of dyslipidemia taking into account CV risk and recommendations for antiplatelet/antithrombotic drugs. Furthermore, attention focused on the management of DM concomitant with coronary artery disease and heart failure, as well as individualized therapeutic strategies for diabetic patients with arterial hypertension.

CV risk assessment in diabetic patients

One of the most notable changes in the updated guidelines is the introduction of a new classification of CV risk in DM patients. Risk scores developed in the general population cannot be accurately used in individuals with diabetes [6]. Diabetes is a significant risk factor for cardiovascular diseases and for this reason there are no individuals at low CV risk among diabetics. Young patients with a DM duration < 10 years are at intermediate CV risk. Patients who have had DM ≥ 10 years and at least one risk factor (age, smoking, arterial hypertension, dyslipidemia, obesity) but without target organ damage are at high risk. Very high risk patients include those with DM and a diagnosis of coronary artery disease or target organ damage (proteinuria, chronic kidney disease defined as the presence of GFR < 30 ml/min/1.73 m^2, left ventricular hypertrophy, retinopathy) or with at least three major risk factors or with an early onset type 1 DM duration of at least 20 years [5]. This classification, as emphasized by the working group experts, provides the opportunity to improve individualization of the diagnostic and therapeutic process, which should translate into better prognosis. It is important to note that some patients will not be unequivocally ascribed to a specific risk group (for instance individuals with a DM duration of > 10 years without target organ damage or other risk factors) or they will be somewhere in between.

Personalized clinical evaluation and results of additional risk-modifying tests play a role in the assessment of CV risk. Routine assessment of microalbuminuria is indicated to identify patients at risk of developing renal dysfunction or at high risk of future CVD (class I recommendation). Patients with DM and diagnosis of arterial hypertension or suspected CVD are recommended to undergo ECG at rest. Assessment of carotid and/or femoral plaque burden with arterial ultrasound should be considered (class IIa recommendation) and screening tests for CAD may be considered using a load test or angio-CT of coronary arteries in asymptomatic patients. Furthermore,

similar to the general population, other tests may be considered such as the ankle-brachial index and coronary artery calcium score as risk modifying factors (class IIb recommendation), whereas common carotid artery intima-media complex thickness by ultrasound is not recommended for CV risk assessment (class III recommendation).

A new algorithm for glycemia lowering therapy in the management and prevention of CVD

It has been nearly 100 years since the discovery of metformin (1922), the first oral glucose-lowering drug. In our times, the year 2007 was particularly remarkable in the history of oral hypoglycemic agents. That year a meta-analysis of data from studies on rosiglitazone (now not available in Europe) was published demonstrating that the drug was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from CV causes that had borderline significance [7]. Consequently, a set of new regulations for the approval of novel diabetes drugs came into force in 2008. Previously, the registration of new medications that targeted diabetes depended mainly on the efficacy of glycemic control and study designs were not powerful enough to detect potential harmful effects of the medication on clinical CV endpoints. Since 2008 all novel glucose-lowering agents have been required to demonstrate CV safety to achieve regulatory approval. This has resulted in an increase in trials that assess cardiovascular outcomes in the treatment of diabetes.

The past 5 years have witnessed a spectacular breakthrough in the management of patients with diabetes. Professor Peter J. Grant, who presented the new guidelines during the European Society of Cardiology Congress in Paris in August 2019, emphasized that this was probably the greatest change since the discovery of insulin in 1924. The latest guidelines in diabetes screening and treatment are based on an enormous number of trials which assessed CV safety of novel drugs and thus became the basis for a new algorithm to help guide the management process.

A number of clinical trials of sodium glucose cotransporter 2 (SGLT-2) inhibitors, also called gliflozins (EMPA-REG OUTCOME [8], DECLARE [9], CANVAS [10]) and of glucagon-like peptide-1 (GLP-1) receptor agonists (LEADER [11], Harmony Outcomes [12], EXSCEL [13], SUSTAIN-6 [14], REWIND [15], PIONEER [16]) have documented that drugs in these two classes significantly reduce the risk of MACE (CV death, non-fatal myocardial infarction, non-fatal stroke) in patients with type 2 DM. Significant declines were also observed in hospitalizations for heart failure and CV mortality rates. The EMPA-REG Outcome trial of empagliflozin demonstrated a significant reduction of 32% in cardiovascular mortality,

whereas the number needed to treat (NNT) was 39. It is important to note that the decline of CV mortality risk, which was achieved early in the trial, was maintained throughout the whole duration of the study [8]. Similarly, liraglutide, a GLP-1 receptor agonist in the LEADER study, significantly reduced major adverse cardiovascular events [11].

The first large-scale clinical trial with SGLT-2 inhibitors enrolled mainly patients with the diagnosis of CV disease, whereas several consecutive studies of other SGLT-2 inhibitors included increasing numbers of participants with only CV risk factors. In these circumstances, there was a smaller number of endpoints ("healthier" groups), but at the same time larger sample sizes were required to maintain the statistical power of the study. This, however allowed for broadening the target population of individuals for whom the drug could be effective.

The mechanism of action of gliflozins

In normal individuals renal glomeruli filter 180 g of glucose per day. In patients with type 2 diabetes the expression of glucose transporters is up-regulated, causing increased glucose reabsorption in the tubular epithelial cells. Under normal conditions SGLT2 is responsible for absorbing up to 90% of filtered glucose in the proximal convoluted tubule, whereas SGLT1 scavenges the remaining 10% of the filtered glucose in the distal convoluted tubule, and thus the urine is virtually glucose free. Gliflozins, selective and reversible inhibitors of SGLT2, increase urinary glucose excretion (~ 70 g/day = ~280 kcal/daily). In Poland two drugs in this class are commercially available: empagliflozin used in a dose of 10 mg once daily (maximum dose 25 mg daily) and dapagliflozin with the recommended dose of 10 mg once daily. The most important benefits from use of gliflozins include markedly reduced hyperglycemia, reduction in body mass, no increased risk of hypoglycemia, and, what is more, beneficial cardiovascular and renal effects. According to the registered characteristics of these pharmaceutical products it is not recommended to start treatment when GFR is below 60 ml/min. The treatment should be stopped once the GFR is below 45 ml/min. In the future, it may be formally approved to use these drugs in patients with GFR > 30 ml/min, which has been mentioned in the guidelines.

The mechanism of action of glucagon-like peptide-1 receptor agonists

Incretins are protein hormones which modulate carbohydrate metabolism. One of them is glucagon-like peptide-1 (GLP-1), a 31 amino acid long peptide hormone. It is derived from proglucagon in the intestinal L cells. It is one of the intestinal hormones released to the circulatory system in response to nutrient ingestion. It regulates blood glucose levels through increasing insulin secretion by the β-cells of the pancreatic islets. Glucagon-like peptide-1 receptor agonists (incretin-based drugs) increase insulin secretion, inhibit glucagon secretion, decrease blood glucose level and delay gastric emptying. In Poland liraglutide (under the brand name Victoza) is commercially available for use, initially 0.6 mg subcutaneously once a day, and after 1 week the dose may be increased to 1.2 mg.

Gliptins

Other clinical trials (SAVOR [17], EXAMINE [18], TECOS [19], CARMELINA [20, 21]) focus on gliptins, dipeptidyl peptidase-4 (DPP-4) inhibitors, which work by blocking the breakdown of glucagon-like peptide-1 (GLP-1) in the liver. Data from studies with DPP-4 inhibitors are not consistent for this class of drugs – sitagliptin showed a neutral effect on the risk of hospitalization for HF, whereas saxagliptin was associated with an increased risk of hospitalization for HF. In general, the available evidence shows that gliptins have no effect on MACE risk (CV death, non-fatal myocardial infarction, non-fatal stroke), which means that they are not worse than placebo; however, there is still the potential for higher hospitalization rates due to heart failure.

Summing up, clinical trial data and results served as the basis for changing the treatment paradigm in patients with type 2 DM combined with atherosclerosis and a high/very high risk of CV disease. The updated guidelines recommend a new approach to treating patients depending on whether they are already receiving metformin or not.

The most important change compared to the previous treatment algorithm for DM patients with atherosclerotic cardiovascular disease or at high/very high CV risk is the new recommendation to use SGLT-2 inhibitors as the first choice, and GLP-1 agonists in patients with untreated DM and as an adjunct to metformin in patients already receiving the drug. In view of the proposed changes one may ask about the role of metformin in the new treatment paradigm for DM. According to the latest guidelines metformin should be considered in overweight patients with type 2 DM without cardiovascular disease and at intermediate CV risk (class IIa recommendation, level of evidence C) [5].

The most frequent comment on the updated treatment algorithm incorporating novel drugs is that the guidelines were prepared in collaboration with the EASD. However, despite the fact that EASD members contributed to the development of the ESC guidelines, the EASD has not officially approved the data in this document. In 2018, the American Diabetes Association (ADA) in collaboration with the EASD published a consensus report on the management of hyperglycemia in type 2 diabetes mellitus [22]. One of the dif-

ferences between the ESC 2019 guidelines and the 2018 consensus report is that according to the latter metformin remains the first-line medication for all DM patients, including individuals with CV diseases.

It is interesting to note that the results of randomized clinical trials (RCTs) of SGLT-2 inhibitors and GLP-1 analogues were available during the publication of the ADA/EASD 2018 recommendations. This discrepancy between the ADA/EASD and ESC statements indicates that the ESC experts are strongly convinced of the level of existing scientific evidence that is used to guide recommendations in accordance with EBM standards. In this context, the effectiveness of treatment is truly better determined based upon results of several large-scale RCTs which are assigned the highest level of evidence compared to even long-standing experience and clinical practice supported by observational studies, registries, etc. Time will tell whether it was right to relatively quickly incorporate in the ESC guidelines novel drugs as the first choice in a large group of patients with DM. Paradoxically, we may soon be able to learn the effects of novel drugs used in routine clinical practice in accordance with these guidelines.

In 2019 the ADA/EASD updated their recommendations, based on research findings, focusing on cardiovascular and renal benefits of SGLT-2 inhibitors and GLP-1 receptor agonists [23]. The updated guidelines highlight the role of the novel drugs in the management of hyperglycemia and identify which patients are likely to benefit most from therapy, without however changing the position of metformin in the standards formulated by these organizations.

Prevention and treatment of cardiovascular disease in diabetes mellitus

Tight glycemic control as an important element of the management of diabetes

The new guidelines place great emphasis on an important grouping of CV risk factors in patients with DM. The insulin resistance syndrome includes obesity and other atherosclerotic risk factors (hyperglycemia, hyperinsulinemia, lipid disorders, arterial hypertension). Such patients have also been shown to have elevated levels of proinflammatory and prothrombotic factors, which play a significant role in vascular injury.

Chronic hyperglycemia is associated with increased morbidity and is a leading cause of microangiopathy affecting the eyes, nerves and kidneys. There is a 40-fold increase in CV risk in diabetic patients with kidney disease. For this reason in the new guidelines it is recommended to apply tight glycemic control targeting individualized levels of $HbA_{1c} < 7\%$, especially in young adults with a short duration of DM. Tight glycemic control has been found to lower the CV risk, but its effects are visible only after a relatively

long time – this fact, however does not cast doubt on the validity of glycemic control, which – in line with the new guidelines – is an important element of DM treatment [5]. At the same time the class I recommendation is to avoid hypoglycemia, which occurs quite frequently in patients under treatment for DM. Analysis shows that repeated hypoglycemic events correlate with a poorer CV prognosis [24, 25]. However, there is no evidence to confirm a causal relationship; therefore it is not clear whether hypoglycemia is a predictor of poor outcome or an indicator of the patient's serious health status.

Drug treatment of lipid disorders

The recommendations for the management of lipid disorders in DM patients are consistent with the recommendations for the treatment of dyslipidemia [26]. There are no individuals with low CV risk among diabetic patients. In patients with type 2 DM and intermediate CV risk it is recommended to target an LDL level < 2.5 mmol/l (< 100 mg/dl), and in patients at high CV risk an LDL level < 1.8 mmol/l (< 70 mg/dl) or at least a reduction of ≥ 50%. In patients with type 2 DM at very high CV risk it is recommended to target an LDL level < 1.4 mmol/l (< 55 mg/dl) or at least a reduction of ≥ 50%. In patients with type 2 DM a non-HDL-C level < 2.2 mmol/l (< 85 mg/dl) is recommended as a secondary target of lipid-lowering in patients with very high CV risk, whereas targeting an LDL level < 2.6 mmol/l (< 100 mg/dl) can be used in patients with high CV risk.

Statins are recommended as first-choice lipid-lowering medication in DM patients (class I recommendation, level of evidence A). The new guidelines present a recommendation not considered in the previous edition (class IIa recommendation) to use high-intensity statins before initiating combination therapy. If the therapeutic goal has not been achieved with statin monotherapy it is recommended to combine statins with ezetimibe (class I recommendation, level of evidence B) [5]. In patients at very high CV risk and with elevated LDL levels despite maximum tolerated doses of statin and ezetimibe or with statin intolerance it is recommended to use a PCSK9 inhibitor (class I recommendation, level of evidence A). Subgroup analyses in the ODYSSEY OUTCOMES trial [27] demonstrated twice the absolute reduction in MACE among patients with DM as in non-diabetic individuals and those with pre-DM. This finding shows that the treatment not only works in DM patients but also reduces the residual risk of MACE in pre-diabetic individuals.

Antiplatelet and antithrombotic therapy

Antiplatelet therapy in the primary prevention of CVD

In the 2013 guidelines [28] antiplatelet therapy with ASA was not recommended in DM patients at

low CV risk (class III recommendation, level of evidence A). The guidelines were based on evidence generated from two RCTs presented in 2008 and a meta-analysis published in 2009 [2, 29, 30]. Although the results showed a tendency towards decreased rates of myocardial infarction and stroke in DM patients receiving ASA in primary prevention, the effect was too small and insignificant, so according to the authors of the previous guidelines there was no basis for recommending ASA for primary prevention of CVD.

The new working group decided to change the recommendations based on the results of the large (more than 15 000 participants) randomized clinical trial ASCEND, which demonstrated a significant reduction in the occurrence of the first serious vascular events (myocardial infarction, stroke, transient ischemic attack (TIA) or death from any vascular cause) in DM patients receiving ASA at a dose of 100 mg daily. However, the benefits of taking daily aspirin were counterbalanced by the increased risk of major bleeding (mainly gastrointestinal bleeding) [31]. Because of a relatively wide definition of serious bleeding, the trial may overestimate effect sizes and the actual net benefits of aspirin may be greater among DM patients. For this reason the new guidelines state that aspirin at a dose of 75–100 mg daily might be considered for primary prevention in DM patients at very high/high CV risk in the absence of clear contraindications (class IIb recommendation, level of evidence A). In contrast, aspirin is not recommended for primary prevention in DM individuals at immediate CV risk (class III recommendation, level of evidence B) [5].

Antiplatelet therapy in the secondary prevention of CVD

Antiplatelet drugs in monotherapy or combination treatment are the cornerstone of secondary CVD prevention. In general, DM patients with symptomatic CVD should be treated in the same way as individuals without DM [5]. Diabetic patients requiring pharmacological treatment by definition belong to a group of patients at high risk for ischemic events. Prolonged dual antiplatelet therapy (ASA plus a single dose of clopidogrel or low-dose ticagrelor 60 mg BID) for up to 3 years should be considered in DM patients at low risk of bleeding (class IIa recommendation, level of evidence A). Beside aspirin, a second alternative antithrombotic drug is rivaroxaban, which should be considered at a dose of 2.5 mg BID for long-term secondary prevention in patients at low risk of bleeding (class IIa recommendation, level of evidence A). The results of COMPASS and ATLAS-ACS trials showed significant survival benefits in patients with peripheral vascular disease. Rivaroxaban is the first anticoagulant to have beneficial effects on peripheral vascular disease. In the 6391 patients with peripheral artery disease in the COMPASS study, rivaroxaban reduced the risk of amputation by 58% ($p < 0.01$), peripheral vascular interventions by 24% ($p = 0.03$), and of all vascular events by 24% ($p = 0.02$) [32, 33].

Individualized treatment targets for patients with arterial hypertension

Individualized treatment targets are recommended for patients with arterial hypertension. In general, the accepted systolic blood pressure (SBP) goal is ~130 mm Hg. A study carried out in 2011 showed that although a more aggressive SBP goal ≤ 130 mm Hg was associated with a continuously falling risk of stroke, there was no benefit regarding the risk of other cardiovascular events [34]. A 2015 meta-analysis of data from more than 100 000 patients with DM confirmed this finding [35]. A reduction of SBP < 130 mm Hg (each 10 mm Hg lower SBP) was associated with a significantly lower risk of stroke and albuminuria. If these target levels are well tolerated, it is reasonable to maintain SBP < 130 mm Hg, but SBP lowering below 120 mm Hg is not recommended. In patients aged 65 years and older treated SBP values should be targeted to a range of 130–139 mmHg. Diastolic blood pressure should be lowered to < 80 mm Hg, but not to below 70 mm Hg [5]. Optimal blood pressure control reduces the risk of micro- and macrovascular complications of diabetes mellitus. Only limited data are available on the benefits of lowering BP levels.

β-blockers in patients with coronary artery disease and diabetes mellitus

β-blockers may be considered to reduce mortality and morbidity (class II recommendation). Despite numerous studies which have confirmed the utility of β-blockers in daily cardiovascular treatment, this recommendation is weak because there is evidence (subgroup analysis in the ACCORD study [36] and a large observational study [37]) to suggest that there may be significant harm to DM patients who are treated with β-blockers. Additional studies are required to further elucidate the role of β-blockers, which probably should be used only in selected patients with DM and CAD, for instance in individuals after myocardial infarction, with heart failure and EF < 40%. Carvedilol, a third generation β-blocker, may be preferable because of its ability to improve insulin sensitivity without negative effects on glycemic control – this observation is based on a 2004 study which compared metoprolol and carvedilol in patients with type 2 diabetes mellitus and arterial hypertension [38].

Recommendations for lifestyle modifications

The guidelines advocate lifestyle changes as an important element of successful therapy in DM patients. The working group placed a strong emphasis on lifestyle intervention also in the context of delaying/pre-

venting the conversion of pre-diabetic states to type 2 diabetes mellitus (class I recommendation, level of evidence A) [5]. For this reason, intensive management of risk factors is required in both groups of patients, which is clearly highlighted in the new guidelines.

Conflict of interest

The authors declare no conflict of interest.

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