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REVIEW

Modern Management of Cardiometabolic Continuum: From Overweight/Obesity to Prediabetes/Type 2 Diabetes Mellitus. Recommendations from the Eastern and Southern Europe Diabetes and Obesity Expert Group

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ABSTRACT

The increasing global incidence of obesity and type 2 diabetes mellitus (T2D) underscores the urgency of addressing these interconnected health challenges. Obesity enhances genetic and environmental influences on T2D, being not only a primary risk factor but also exacerbating its severity. The complex mechanisms linking obesity and T2D involve adiposity-driven changes in β-cell function, adipose tissue functioning, and multi-organ insulin resistance (IR). Early detection and tailored treatment of T2D and obesity are crucial to mitigate future complications. Moreover, personalized and early intensified therapy considering

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the presence of comorbidities can delay disease progression and diminish the risk of cardiorenal complications. Employing combination therapies and embracing a disease-modifying strategy are paramount. Clinical trials provide evidence confirming the efficacy and safety of glucagon-like peptide 1 receptor agonists (GLP-1 RAs). Their use is associated with substantial and durable body weight reduction, exceeding 15%, and improved glucose control which further translate into T2D prevention, possible disease remission, and improvement of cardiometabolic risk factors and associated complications. Therefore, on the basis of clinical experience and current evidence, the Eastern and Southern Europe Diabetes and Obesity Expert Group recommends a personalized, polymodal approach (comprising GLP-1 RAs) tailored to individual patient's disease phenotype to optimize diabetes and obesity therapy. We also expect that the increasing availability of dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) agonists will significantly contribute to the modern management of the cardiometabolic continuum.

Keywords: Type 2 diabetes; Obesity; Treatment; Cardiometabolic continuum; Glucagon-like peptide 1 receptor agonists

Key Summary Points

Diabetes and obesity that share genetic and environmental features are highly prevalent, frequently coexisting and result in serious complications.
Management of obesity can postpone the progression from prediabetes to type 2 diabetes (T2D) and improve hyperglycaemia in patients with T2D.
Intensive lifestyle interventions in combination with anti-obesity pharmacotherapy adjusted to patients' requirements, capabilities and comorbidities are of key importance in the management of obesity and T2D.
The goal of therapy of patients with diabetes and obesity should shift from glucose-centred care to the management of obesity and cardiovascular complications.
Treatment with glucagon-like peptide 1 receptor agonists enables effective glycaemic control and weight loss, improves lipid profiles, decrease systolic and diastolic blood pressure, regulates the immune system and inflammation, etc.

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INTRODUCTION

The prevalence of obesity and type 2 diabetes mellitus (T2D) has been consistently increasing worldwide. Both share powerful genetic and environmental features in their pathogenesis. Obesity amplifies the impact of genetic susceptibility and environmental factors on T2D. Persistent genetic and environmental factors, including a high-fat diet and sedentary lifestyle, favour chronic metabolic inflammation, which in turn can lead to hyperglycaemia, insulin resistance (IR), β-cell dysfunction and ultimately to T2D [1, 2]. Environmental exposure can induce adaptive post-transcriptional modifications of DNA. These epigenetic factors, like DNA methylation, may play a role in the development of both T1D and T2D by causing modifications in pancreatic islets, adipose tissue and the liver [3]. In obesity, epigenetic changes in CpG methylation and miRNA expression pattern during all stages of adipocyte differentiation modify lipid metabolism and insulin sensitivity and cause β-cell dysfunction [4, 5]. Epigenetic alterations have been shown to persist even after the disappearance of stimuli, causing chronic inflammation and subsequent vascular damage, and cardiovascular disease (CVD). It appears that obesity promotes T2D through chronic inflammation that interferes with insulin signalling and IR processes. However, obesity is not only a significant risk factor (RF) for T2D but also contributes to T2D severity [6]. Mechanisms coupling obesity and T2D are complex and involve adiposity-induced alterations in β-cell function, adipose tissue biology and multi-organ insulin resistance (IR), which are often ameliorated and can even be normalized with adequate body weight (BW) loss [7]. The expanding of adipose tissue and increase in adipocyte size result is lower responsiveness to insulin resulting from less efficient glucose transport due to oxidative stress and stretched cell surface of enlarged adipocytes and lead in consequence to insulin resistance [8]. Excessive accumulation of white adipose tissue (WAT) in obesity has been linked with inflammation, hypoxia, fibrosis, disturbed secretion of adipokines and impaired mitochondrial function [9, 10]. Adipose tissue expansion-related steatosis aggravates insulin resistance via cellular dysfunction and apoptosis associated with lipotoxicity [11]. All these mechanisms play key role in the development of diabetes. Under such conditions, β-cells secret more insulin to preserve normal glycaemic homeostasis which promotes the development of insulin resistance.

Epidemiological observations have confirmed that individuals with T2D frequently have obesity (approx. 90%), while persons with obesity are more prone to T2D [12, 13]. In a national cohort of US adults from the National Health and Nutrition Examination Survey (NHANES) Epidemiologic Follow-up Study, even values in the upper range of normal body mass index (BMI) (BMI > 22 kg/m^2) were found to raise the incidence of T2D [14]. BW gain caused by enlargement of visceral adiposity resulting in so-called abdominal obesity triggers phenotypic alterations in adipose tissue and induces chronic low-grade systemic inflammation [15]. Abdominal obesity is associated with many cardiometabolic abnormalities, such as hypertension and IR, followed by pancreatic β-cell dysfunction, dyslipidaemia, metabolic dysfunction-associated steatotic liver disease (MASLD), systemic inflammation, prothrombotic state, endothelial dysfunction and others leading in consequence to the development of metabolic syndrome (MetS) and T2D [16–19].

Adiposity-Related Diabetes and How to Change the Burden of the Cardiometabolic Continuum

Diabesity is a term to describe the combined detrimental effects of obesity and T2D [20]. The results of studies revealed that the reduction of excess BW may counteract the development of T2D [21]. The presence of obesity and T2D is associated with many complications. Long-term uncontrolled T2D promotes inflammation and triggers changes at the cellular level [22]. Obesity directly enhances the risk of CVD

via cardiac adaptions such as higher peripheral resistance, reduced cardiac output, thickening of left ventricular mass/wall and deterioration of left ventricular systolic function [23]. Moreover, individuals with obesity show atherogenic dyslipidaemia characterized by the abundance of small, dense low-density lipoprotein (LDL) particles, increased triglyceride (Tg) levels and reduced levels of high-density lipoprotein (HDL) particles [24]. The presence of chronic, low-grade inflammation and atherogenic dyslipidaemia promotes the development of vascular dysfunction, favours atherosclerotic plaque formation and impairs fibrinolysis leading in consequence to increased CVD risk (e.g. stroke, myocardial infarction and peripheral artery disease) [25]. The results of the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that each one percentile decrement in glycated haemoglobin (HbA1c) translated into a 14% relative risk (RR) reduction for coronary heart disease [26].

Good control of T2D is associated with a lower risk of complications [22]. Apart from obesity and hyperglycaemia, the presence of hypertension and hyperlipidaemia also increases the risk of CV complications in individuals with T2D. A large epidemiological study based on the data from the NHANES III demonstrated significantly higher all-cause mortality risk in patients with diabetes with HbA1c > 8% compared to those with HbA1c < 6.5% (hazard ratio [HR] 1.6, 95% confidence interval [CI] 1.02 to 2.6; $p < 0.0001$) [27]. The understanding of disease-related pathomechanisms, recognition of disease complexity, early diagnosis and the introduction of early adjusted treatment enable effective management of T2D and obesity, the prevention of associated complications as well as improving outcomes [28, 29].

The long-term effectiveness of lifestyle intervention without added pharmacological treatment may not be sufficient, as the disease may revert. Even in patients whose BW was significantly reduced, there is a 40–50% probability that the impaired glucose tolerance may cause T2D [30]. Similarly, lifestyle interventions are key for the management of obesity; however, even the implementation of most intensive programmes translates into 5–10% BW loss with a tendency for weight regain [31].

A vast body of evidence confirms that appropriate management of obesity can postpone the progression from prediabetes to T2D and improve hyperglycaemia in patients with T2D [32–34]. Modest and maintained weight reduction in patients with T2D who are overweight or obese was associated with decreased need for glucose-lowering medications [21, 32]. The analysis of the effect of BW loss on selected variables in a 0.5 million population from the UK Clinical Practice Research Datalink (CPRD) GOLD database revealed that a median 13% BW loss corresponded with 41% reduced risk of T2D [35]. Moreover, clinical data indicate that weight loss of ≥ 15% can reverse metabolic abnormalities in T2D as well as ameliorate glucose control and improve quality of life [36]. Interesting results concerning the significance of lifestyle modification were obtained from the DiRECT clinical trial. In this trial, an average BW loss of about 10 kg resulting from a low-calorie diet and intense lifestyle modifications was associated with T2D remission in about 46% of patients within 1 year and in approximately 36% of individuals after 2 years [37, 38]. Comparable rates of T2D remission after 1 year were reported in the DIADEM-I trial in which diabetes remission was observed in 61% of participants and normoglycaemia in 33% of participants [39]. The results of the Look AHEAD (Action for Health in Diabetes) study have shown that either a 10% BW loss or a considerable escalation in fitness translates into approximately a 20% reduction in CVD risk [40].

SEARCH METHODS

PubMed and Google scholar electronic databases were searched for articles concerning the scope of this position paper without any limitation by publication date. The primary focus was on clinical studies and most recent guidelines. The following keywords were used during the literature search: cardiometabolic continuum, glucagon-like peptide 1 receptor

agonists, obesity, obesity management, type 2 diabetes mellitus, metabolic dysfunction-associated (previously nonalcoholic) steatotic liver disease, metabolic dysfunction-associated steatohepatitis, metabolic syndrome, prediabetes, inflammation, pathophysiology, and cardiovascular risk. Useful publications cited in selected publications were also searched. All selected articles were in English and were peer-reviewed.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors therefore, ethical approval was not necessary.

MODERN MANAGEMENT OF CARDIOMETABOLIC CONTINUUM

Appropriate management of obesity has been demonstrated to delay the progression from prediabetic state to T2D and to exert beneficial impact on the treatment of patients already with T2D [41–46].

Treatment of Cardiometabolic Risk Factors: Focus on GLP-1 RAs

Figure 1 summarises the effects of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) on cardiometabolic risk factors and cardio-renal-metabolic conditions.

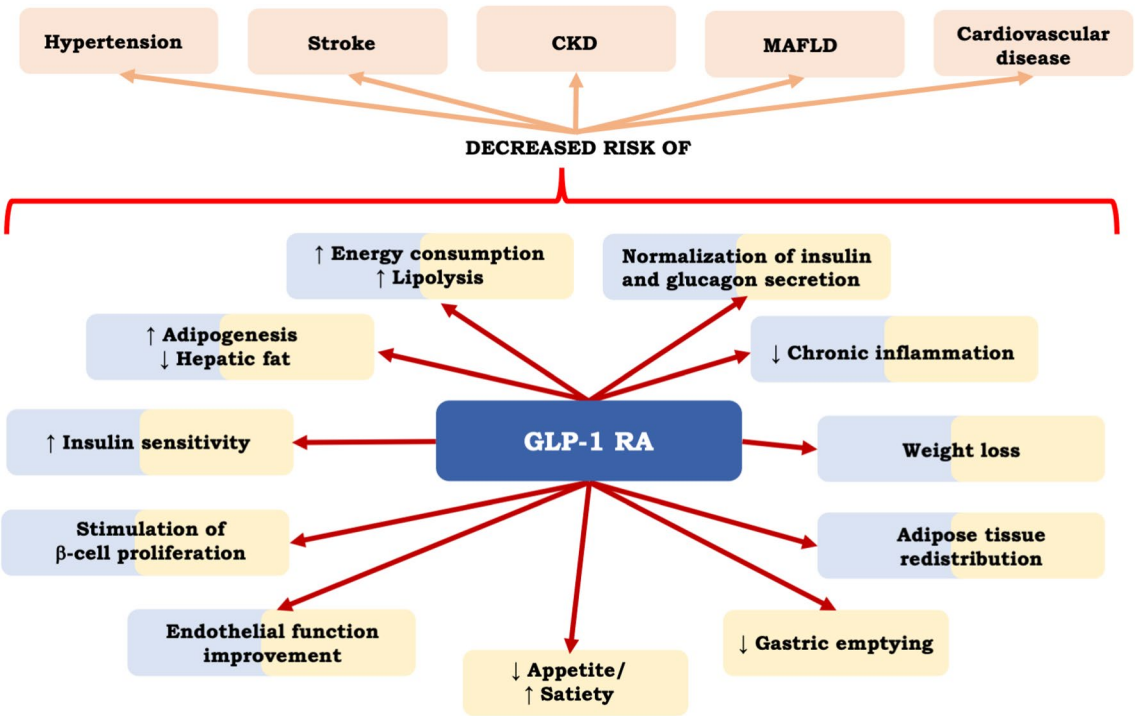

Fig. 1 Beneficial effects of GLP-1 RA in obesity and diabetes. Blue and yellow fields show mechanisms important in diabetes and obesity, while entirely yellow fields show those most important in obesity, ↑ increased, ↓ decreased. *CKD* chronic kidney disease, *GLP-1 RA* glucagon-like peptide 1 receptor antagonists, *MALFD* metabolic associated fatty liver disease

Impact of GLP-1 RAs on Lipids Levels

Several clinical trials showed that GLP-1 RA improved lipid profiles in T2D by modifying levels of LDL cholesterol (LDL-C), total cholesterol (TC), Tg and free fatty acids [47, 48]. In a pilot study on the effect of liraglutide on lipids in patients with T2D, the administration of liraglutide reduced non-HDL-C and calculated TC at 1 and 3 months, and TC and LDL-C levels at 1 month [49]. However, such treatment did not affect cholesterol synthesis and cholesterol absorption markers. Only TC level was found to be reduced in patients with baseline LDL-C > 100 mg/dL (> 2.6 mmol/L). In turn, the administration of exenatide limited postprandial endothelial dysfunction and diminished postprandial Tg levels after a high-fat meal in patients with T2D [50]. GLP-1 RA-stimulated reduction in serum Tg levels was suggested to be related to diminished gastric emptying and intestinal lipid production [51–53].

Lipid-lowering properties have been observed also in the case of other GLP-1 RA, including semaglutide and dulaglutide. In a retrospective cohort study (Sema-MiDiab01), both TC and LDL-C levels were significantly reduced in patients with T2D after 6 months of semaglutide treatment (LDL-C 91.13 vs. 81.88 mg/dl, $p = 0.0002$; TC 167.07 vs. 155.61 mg/dl; $p < 0.0001$) [54]. Tg levels decreased significantly after 12 months of therapy (166.51 vs. 147.18 mg/dl; $p = 0.001$). Moreover, Tuttolomondo et al. [55] demonstrated that at the 9-month follow-up, subjects treated with dulaglutide had significantly lower values of the mean serum TC and LDL-C compared with control subjects treated with conventional therapy.

The impact of GLP-1 RA on lipid profile was suggested to be associated with weight loss. Magkos et al. [56] showed that a 5% weight loss enhanced adipose tissue lipolytic activity and cholesterol flux, while pathways involved in lipid synthesis were reduced. This weight loss significantly lowered triglyceride levels but did not affect free fatty acids, LDL or HDL cholesterol. Weight loss by 16% of body mass translated into progressive linear lowering of intrahepatic triglyceride content and triglyceride concentrations, with a significant decline in plasma free fatty acids observed only following 16% weight loss. These observations were confirmed by gene expression analysis in abdominal subcutaneous adipose tissue which revealed increased expression of cholesterol flux genes (ATP-binding cassette sub-family G member 1, ATP-binding cassette transporter, apolipoprotein E, cholesteryl ester transfer protein) and decreased expression of lipid synthesis genes (stearoyl-CoA desaturase, fatty acid desaturase 1, fatty acid desaturase 2, elongation of very long chain fatty acids protein 6) with progressive weight loss [56]. However, GLP-1 RAs can also alter body fat distribution by influencing lipid remobilization and turnover across various fat depots [57]. Zhao et al. [57] found that liraglutide can reduce visceral fat while increasing subcutaneous fat via bidirectional regulation of lipid metabolism in these fat depots.

Impact of GLP-1 RAs on Blood Pressure (BP)

GLP-1 RAs have been found to decrease systolic BP (SBP) and diastolic BP (DBP). In the meta-analysis of 16 randomized controlled trials (RCTs) enrolling patients with T2D, exenatide BID was demonstrated to lower SBP levels when compared to placebo (mean difference [MD] −5.24, 95% Cl −6.88 to −3.59; $p < 0.00001$) and insulin glargine (MD −3.46 mmHg, 95% CI −3.63 to −3.29; $p < 0.00001$) [58]. Also, the DBP was decreased by −5.91 mmHg (95% CI −7.53 to −4.28; $p < 0.00001$) compared with the placebo group, and by 0.99 mmHg (95% CI −1.12 to −0.87; $p < 0.00001$) compared with sitagliptin. Similarly, the treatment with liraglutide was associated with SBP and DBP reduction by 1 to 5 mmHg compared to glimepiride and placebo [58]. Beneficial impact on BP was hypothesized to result from the vasodilatory effect on the blood vessels, natriuretic/diuretic effects of GLP-1 agonists on kidneys, and interactions with the central nervous system [59–61]. Since the decrease in BP levels is mostly visible within the first 2 weeks of treatment, meaning before the occurrence of BW loss, it has been suggested that GLP-1 RA-related direct hypotensive effect is independent of BW reduction [58, 62].

The analysis of five randomized, placebo-controlled trials included in the AWARD program demonstrated that dulaglutide (1.5 mg) decreased SBP (−2.6 mmHg, 95% CI −3.8 to −1.5; $p<0.001$) and pulse pressure (−2.5 mmHg, 95% CI −3.5 to −1.5; $p<0.001$) in people with T2D [63]. Up to one-third of the impact of dulaglutide on SBP and pulse pressure was associated with BW reduction; however, the major effect was independent of BW. In contrast, the effect of dulaglutide on DBP was limited with only a small weight-mediated effect. Dulaglutide 4.5 mg affected SBP and pulse pressure to a greater extent in comparison to dulaglutide 1.5 mg [63]. Also, semaglutide was found to beneficially influence BP. The results of a 6-month retrospective study in the USA (SCOPE) revealed mean reductions of −4.4 ± 12.3 mmHg (95% CI −5.7, −3.0; $p<0.001$) in SBP and −1.7 ± 8.4 mmHg (95% CI −2.6, −0.7; $p<0.001$) in DBP following the administration of 2.4 mg semaglutide in subjects with overweight and obesity [64]. Similarly, in a systematic review and meta-analysis of 29 RCTs (26,985 T2D participants) weighted MD in SBP of semaglutide vs. placebo or other antihyperglycaemic agents was −2.31 mmHg (95% CI −3.11 to −1.51), and 0.09 mmHg (95% CI −0.16 to 0.33) for DBP [65]. The observed reduction in SBP was similar for semaglutide administered subcutaneously and orally [65].

Impact of GLP-1 RAs on Inflammation

GLP-1 RAs show the capability of regulating the immune system and inflammation [66], and immune cell recruitment [22]. Anti-inflammatory properties of GLP-1 RAs have been confirmed in human trials, which demonstrated a significant reduction of inflammatory biomarkers following GLP-1 RAs treatment compared to other standard antidiabetic treatments [22, 67]. Furthermore, the use of GLP-1 RAs has been demonstrated to reduce inflammatory cytokines and pro-fibrotic factors related to the development of nephropathy, such as tumour growth factor (TGF)-β1 and fibronectin [68, 69]. These additional effects are of importance because the presence of chronic inflammation is associated with the occurrence of long-term chronic complications of diabetes [70]. GLP-1 RAs may diminish inflammation by directly acting on immune cells expressing GLP-1 receptors or indirectly via glycaemic control and BW loss [22, 71]. The results of the study of liraglutide's effect on monocytes obtained from healthy volunteers revealed that it diminished tumour necrosis factor alpha (TNFα) expression and considerably repressed monocyte chemoattractant protein 1 expression [71]. Also semaglutide was found to decrease systemic inflammatory cytokines, TNFα and interferon (IFN)-γ levels as well as immune cell recruitment in a murine model of acute inflammation [72]. GLP-1 RAs are able to limit the migration and infiltration of monocytes irrespective of BW loss. The confirmation of the characteristic immune effect of GLP-1 RAs was provided by the observation of decreased interleukin (IL)-1β production by M1 macrophages and an enhanced synthesis of IL-10 by M2 macrophages in response to these drugs in patients with obesity and T2D [73]. In the study of patients with inadequately controlled T2D on insulin or other antihyperglycaemic drugs, 12-month therapy with either dulaglutide or liraglutide decreased local or systemic inflammation, independently of the changes in glycaemic control and BW [74]. However, reduction in IL-6 significantly correlated with the changes in waist circumference ($r=0.347$; $p=0.006$) [74]. In another study, liraglutide reduced high-sensitive C-reactive protein (CRP) more effectively than metformin [75]. The same effect was reported for both subcutaneously and orally administered semaglutide vs. comparators (placebo, exenatide extended-release or empagliflozin) [76]. Moreover, liraglutide also stimulated a significant reduction in the mean concentration of CRP in a retrospective study of 110 patients with T2D and obesity. A sub-study of a randomized trial of individuals with T2D treated for 26 weeks with liraglutide revealed that this GLP-1 RA drug intensely reduced the production of TNFα and IL-1β but also increased chemokine (C–C motif) ligand 5 in peripheral blood mononuclear cells compared to placebo. Gupta et al. [77] demonstrated significantly diminished cell necrosis and apoptosis following the therapy with GLP-1 RA. Through the modulation of vascular inflammation and beneficial impact on endothelial

dysfunction, GLP-1 RAs may protect patients against atherosclerosis [78, 79].

Impact of GLP-1 RAs on Liver Functioning

GLP-1 RAs have also been shown to exert beneficial effects on metabolic dysfunction-associated steatotic liver disease (MASLD) which is a hepatic manifestation of MetS and is commonly associated with T2D and obesity [80–82]. GLP-1 RA administration protects against hepatotoxicity and hepatic steatosis [83]. The beneficial effects on liver function could stem from the anti-inflammatory effect of GLP-1 RAs and protection against lipotoxicity [84–86]. The results of a pilot study of liraglutide effects in MASLD with glucose intolerance (LEAN-J) demonstrated that 24 weeks of treatment with liraglutide at the dose of 0.9 mg/day was associated with significant improvement in BMI, visceral fat accumulation and liver function [87]. When the treatment was prolonged and the therapy was continued for 96 weeks, an additional reduction in inflammation, fibrosis and MASLD activity score was reported. The authors suggested that mechanisms behind metabolic dysfunction-associated steatohepatitis (MASH) improvement could be associated with decreased BW and HbA1c [87]. The therapy with liraglutide was also demonstrated to directly decrease liver fibrosis and steatosis in patients with MASLD and T2D compared to sitagliptin and pioglitazone [88].

Similarly, a systematic review and meta-analysis of eight studies including 2413 patients with MASLD/MASH treated with semaglutide revealed that this therapy was associated with a decrease in serum alanine transaminase (ALT) (MD 14.07 U/L, 95% CI 19.39 to – 8.75; $p<0.001$) and aspartate transaminase (AST) (MD 6.89 U/L, 95% CI 9.14 to – 4.63; $p<0.001$) levels as well as significant amelioration of liver fat content (LFC) (MD 4.97%, 95% CI 6.65 to – 3.29; $p<0.001$) and liver stiffness (MD 0.96 kPa, 95% CI 1.87 to – 0.04; $p=0.04$) [89]. Newsome et al. demonstrated that in patients at risk of MASLD (with T2D and obesity) ALT levels were reduced by 6–21% ($p<0.05$ for doses ≥ 0.2 mg/day in BW management trial) and by 9% vs. placebo for 1.0 mg/week semaglutide ($p=0.0024$; in CV outcome trial) [90]. However, no improvement was observed in patients treated with 0.5 mg/week semaglutide in the second trial [90]. The study assessing the impact of dulaglutide on LFC, pancreatic fat content and liver enzyme levels demonstrated that 0.75 mg subcutaneously administered dulaglutide each week for 4 weeks, followed by 1.5 mg weekly for 20 weeks plus standard treatment vs. standard treatment alone revealed a greater decrease in LFC, pancreatic and liver stiffness than that of the control group ($p<0.001$ for all) [91]. In turn, Hartman et al. [92] observed that tirzepatide (a dual agonist of glucose-dependent insulinotropic polypeptide [GIP] and GLP-1 receptors) reduced levels of ALT, AST, keratin-18 (K-18), procollagen III (Pro-C3) and considerably increased adiponectin from baseline compared with placebo after 26 weeks.

Impact of GLP-1 RAs on Adiposity Components

The systematic review of 10 trials, including 625 patients, demonstrated that GLP-1 RA treatment could considerably reduce visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) in patients with diabetes and obesity [93]. It appears that the VAT reduction (11.23%) is preferential over SAT (8.34%). VAT and SAT reduction positively correlate with BW loss. The extent of SAT and VAT is associated with metabolic RFs, i.e. VAT accumulation correlates with a higher risk of T2D hypertension, hyperlipidaemia, heart failure and CV death [94–97]. The VAT-to-SAT rate determines the severity of atherosclerosis and CV risk [98, 99]. Since the abnormal distribution of VAT and SAT is very frequent in patients with T2D, treatments that decrease both glucose level and VAT content appear to be highly beneficial. A meta-analysis of RCTs demonstrated that GLP-1 RA therapy resulted in significant reductions in VAT, SAT and adipose tissues that correlated with BW loss [93]. The observed decrease in VAT could be ascribed to lower appetite and calorie intake due to the treatment [93]. It has been suggested that GLP-1 RA administration may be associated with distinct effects on VAT and SAT since GLP-1 receptors are more abundant in VAT [93].

Impact of GLP-1 RAs on Kidneys

Some studies suggested renoprotective effects of GLP-1 RAs [100, 101]. Renoprotective effects stem from greater glycaemic control and BW loss; however, it is plausible that these drugs may also exert direct effects on renal function, for example via actions on systemic BP and kidney hemodynamics [102]. In the SUSTAIN 6 trial beneficial effects of semaglutide on composite renal outcome (HR 0.64, 95% CI 0.46–0.88; $p=0.005$) and significant reduction (46%) in the risk of developing macroalbuminuria (HR 0.64, 95% CI 0.37–0.77; $p=0.001$) were observed [103]. Moreover, in this trial, semaglutide significantly diminished the estimated urinary albumin-to-creatinine ratio from baseline to end of treatment, compared with placebo (treatment ratio 0.74, 95% CI 0.67–0.81; $p<0.001$) [104]. Also, the results of a post hoc analysis of SUSTAIN 6 and PIONEER 6 trials showed significant differences in the rate of annual estimated glomerular filtration rate (GFR) decline in all GFRs groups. Estimated treatment difference (ETD) was 0.59 (95% CI 0.29, 0.89; $p<0.0001$) for the overall population, 1.06 (95% CI 0.45, 1.67; $p=0.0007$) for the ≥30 to <60 ml/min per 1.73 m^2 subgroup and 0.46 (95% CI 0.12, 0.80; $p=0.0083$) for the ≥60 ml/min per 1.73 m^2 subgroup [104]. However, it should be underlined that not all GLP-1 RAs exert renoprotective effects and there are safety issues in advanced renal disease for some GLP-1 RAs. Exenatide, which is mostly eliminated via the kidneys, is not recommended for patients with severe renal impairment or end-stage renal disease; in those with moderate renal disease, this drug should be administered with caution [105]. In general, all GLP-1 RAs should be used cautiously in patients with T2D and severe (creatinine clearance < 30 mL/min) renal impairment since there is not enough evidence confirming their safety in this population [106, 107].

Impact of GLP-1 RAs on Cardiovascular System

Apart from the beneficial impact on glucose control and BW management, most GLP-1 RAs (liraglutide, semaglutide and dulaglutide) positively influence the CV risk profile [107]. They diminish CV risk, lower the incidence of myocardial infarctions and strokes as well as improve quality of life and prolong the survival of patients [108–111]. Many clinical trials confirmed the favourable impact of GLP-1 RAs on the CV system. Liraglutide, dulaglutide and subcutaneously administered semaglutide were shown to decrease major adverse cardiovascular events (MACEs) [112]. Beneficial CV properties of GLP-1 RAs appear to be associated with their impact on blood lipids, endothelial function and BP decrease as well as anti-inflammatory state. Long-acting GLP-1 RAs were found to be superior to placebo in reduction of the primary MACE endpoint in the following trials: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) (liraglutide), SUSTAIN 6 (semaglutide QW), REWIND (dulaglutide), Harmony Outcomes (albiglutide) and Effect of Efpeglenatide on Cardiovascular Outcomes (AMPLITUDE-O) (efpeglenatide) [113]. The LEADER trial [111] showed the superiority of liraglutide compared to placebo in decreasing cardiovascular mortality and nonfatal cardiovascular events (e.g. MI, stroke) (HR 0.87, CI 0.78–0.97; $p=0.01$). SUSTAIN 6 trial demonstrated a 26% lower rate of CV death, nonfatal MI or nonfatal stroke in patients with T2D administered injectable semaglutide (0.5 mg or 1.0 mg) in comparison to placebo (HR 0.74 (0.58; 0.95), number needed to treat 45 over 24 months) [110]. Also, a systematic review and meta-analysis of aforementioned RCTs demonstrated that GLP-1 RAs reduced the risk of MACEs by 14%, with a HR of 0.86 (95% CI 0.80–0.93; $p<0.0001$), all-cause mortality by 12% (HR 0.88, 95% CI 0.82–0.94; $p=0.0001$) and hospital admission for heart failure by 11% (HR 0.89, 95% CI 0.82–0.98; $p=0.013$) [114]. Recently published data from the randomized, double-blinded SELECT trial, which included individuals who were overweight or presented obesity accompanied with established CVD but without T2D, demonstrated that 2.4 mg of semaglutide once-weekly significantly decreased MACE, defined as CV death, non-fatal MI or nonfatal stroke, compared with placebo [115]. The results from the SELECT trial may have indeed a significant impact on future

treatment recommendations for GLP-1 RAs as well as guidelines for people with obesity and pre-existing atherosclerotic CVD (ASCVD), and therefore the results of the tirzepatide cardiovascular outcome trial in patients with overweight/obesity are now highly anticipated [116]. In addition, a 4-month retrospective, real-world study of individuals with T2D revealed that injectable semaglutide significantly decreased HbA1c levels and carotid intima-media thickness, which means that this drug appears effective in the treatment of subclinical atherosclerosis, irrespective of disease duration [117]. However, not all drugs from this class showed a beneficial impact on CV events. Lixisenatide and exenatide QW failed to significantly decrease the risk of MACE in the corresponding CV outcome trials—ELIXA and EXSCEL [118, 119].

Treatment of Overweight/Obesity Focus on GLP-1 RAs

The recommendations for the treatment of obesity in patients with T2D have been changing over time. Currently, in addition to diet and physical activity modifications, behavioural therapy as well as metabolic surgery and new pharmacotherapies are suggested [120, 121]. Moreover, there is a strong focus on obesity management which reaches beyond BW loss alone, as it covers risk reduction and health improvement [122]. The European guidelines for obesity management state that even a modest BW loss of 5–10% of initial BW combined with lifestyle modification brings significant clinical benefits [122]. Loss of at least 15% of BW can exert a disease-modifying effect in T2D, which extends the results obtained using glucose-lowering intervention. The results of clinical trials have demonstrated that in 25–60% of patients with prediabetes, the progression to T2D can be prevented via lifestyle intervention that also leads to weight loss [123].

Furthermore, according to these guidelines, obesity management should not only concentrate on the reduction of weight and BMI but also on waist circumference (indicating a decrease of visceral adiposity) and the improvement in body composition (improvement of fat-free mass and reduction of fat mass). BW loss targets should be established individually for each person, and they ought to be realistic in the long term. Focus should be also put on the long-term maintenance of BW loss, as repeated loss and regain of BW (weight cycling) was found to increase the risk of hypertension, dyslipidaemia and gallbladder disease [124]. Moreover, BW variability was shown to increase the risk of CV complications of diabetes [125].

According to the US guidelines, in patients with a BMI > 30 kg/m^2 or with a BMI > 27 kg/m^2 and weight-related comorbidities, including T2D, dyslipidaemia and hypertension, pharmacotherapy is recommended as an adjunct to lifestyle modifications [126, 127]. However, the options for anti-obesity pharmacotherapy are because the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved only a few drugs, including phentermine/topiramate extended-release (ER) (only in the USA, not approved by EMA), orlistat, naltrexone (ER)/bupropion (ER), tirzepatide and the GLP-1 RAs liraglutide 3.0 mg daily and semaglutide 2.4 mg weekly [128]. EMA and FDA-approved second-generation anti-obesity medications such as semaglutide and tirzepatide have created a paradigm shift in the current management of obesity and are currently predominantly used for the treatment of diabetes with comorbidities. Many guidelines recommend GLP-1 RAs in the treatment of patients with T2D and concomitant obesity owing to their high efficiency in BW management and glycaemic control of T2D [129–131]. Despite the fact that subcutaneous injections of GLP-1 RA may be less tolerated/accepted by patients compared to oral obesity treatments, the efficacy and safety profile of these drugs appear superior to oral treatments and give hope for the reduction of obesity burden and greater prevention of T2D [132] also according to the American Diabetes Association Standards of Care in Diabetes 2024 [133].

The impact of GLP-1 RAs on BW loss has been demonstrated in many clinical trials. In the phase III SCALE Obesity and Prediabetes clinical trial, the treatment of patients without diabetes with a BMI of at least 30 or a BMI of at least 27 with dyslipidaemia or hypertension with

once-daily subcutaneous injections of liraglutide at a dose of 3.0 mg was associated with a mean BW loss of 8.4 ± 7.3 kg (a difference between treatment and control groups of − 5.6 kg, 95% CI − 6.0 to − 5.1; $p < 0.001$) [134]. The mean total BW loss described in SCALE studies was in the range of − 6% to − 8% with liraglutide 3.0 mg used in individuals with overweight/obesity, dyslipidaemia, prediabetes, T2D and hypertension [48, 135, 136]. In patients with obesity but with normal glucose tolerance, the treatment with GLP-1 RAs has been demonstrated to effectively protect against the development of overt T2D [108]. GLP-1 RAs are also recommended for initial diabetes treatment intensification [28]. In the PIONEER 3 study, orally administered semaglutide at a dose of 7 mg proved more effective than sitagliptin in terms of HbA1c reduction as well as BW reduction [137]. Semaglutide 2.4 mg has been found to promote the greatest BW loss compared to other GLP-1 RAs. In a phase II clinical trial, BW loss was higher in patients on orally administered semaglutide at doses of 2.5–40 mg once daily (dosage-dependent range, − 2.1 to − 6.9 kg) and subcutaneously administered semaglutide (− 6.4 kg) compared to placebo (− 1.2 kg) [138]. Recently, the EMA's Committee for Medicinal Products for Human Use has recommended the approval of semaglutide 2.4 mg/day for the management of obesity as an adjunct to a reduced-calorie diet and increased physical activity for weight management. Such treatment is indicated in either patients presenting obesity (≥ 30 kg/m^2) or overweight individuals with at least one weight-related comorbidity (e.g. prediabetes or T2D, CVD, dyslipidaemia, hypertension, obstructive sleep apnoea, etc.) [139].

A systematic review and meta-analysis of head-to-head, phase 3 RCTs demonstrated that compared to other GLP-1 RAs, semaglutide induced a significantly higher reduction in HbA1c levels (by 0.44%), in fasting plasma glucose (by 0.48 mmol/L), as well as in BW (by 2.53 kg) and BMI by 0.91 kg/m^2 [140]. Individuals treated with semaglutide had significantly higher odds of achieving target HbA1c, and BW loss > 5% and 10% [140].

Treatment of T2D: Focus on GLP-1 RAs

According to the American Diabetes Association Standards of Care 2024, metformin should be used as the initial first-line therapy for T2D in patients not meeting the criterion for the presence of ASCVD/increased risk for ASCVD, heart failure or chronic kidney disease [141]. The 2019 European Society of Cardiology guidelines [142] advocate the use of GLP-1 RAs (or sodium-glucose cotransporter 2 [SGLT2] inhibitors) as first-line therapy in drug-naïve patients with T2D and ASCVD, or high/very high CV risk (target organ damage or multiple RFs). Moreover, GLP-1 RAs are suggested as a second line of therapy, when metformin monotherapy does not allow one to reach the glycaemic target, in drug-naïve patients without ASCVD or those with high/very high CV risk. However, in patients with metformin intolerance or other contraindications, GLP-1 RA can be initiated straight away after the diabetes diagnosis. The introduction of GLP-1 RAs should also be considered in patients who failed to achieve glycaemic goals with other antidiabetic medications or if their HbA1c exceeds the target by 1.5% or more [143].

Semaglutide, dulaglutide and liraglutide have been found to exert the strongest effect on HbA1c reduction [144–146]. Semaglutide received approval for the treatment of T2D inadequately controlled on at least one oral glucose-lowering medication [147, 148]. The phase 2, randomized, parallel-group, dosage-finding, 26-week trial demonstrated that semaglutide both orally administered at doses of 2.5-40 mg once daily (dosage-dependent range, − 0.7% to − 1.9%) and subcutaneously (− 1.9%) considerably reduced HbA1c level compared to placebo [138]. Also phase III clinical trials confirmed the efficacy of GLP-1 RA drugs. The effectiveness of once-weekly subcutaneously administered semaglutide in decreasing HbA1c and BW was confirmed in phase 3 SUSTAIN clinical trials [149]. The efficacy of orally administered semaglutide at doses of 3, 7 and 14 mg was also confirmed in a series of 10 phase 3 multicentre, RCTs—the Peptide InnOvatioN for the Early diabEtes tReatment (PIONEER) programme [150]. In terms of HbA1c reduction from baseline, PIONEER 2–4

trials indicated that in patients with established T2D on oral antidiabetic drugs, orally administered semaglutide at a dose of 14 mg was more effective than empagliflozin 25 mg (ETD −0.4%; $p<0.0001$), sitagliptin 100 mg (ETD −0.5%; $p<0.001$) and similar to liraglutide 1.8 mg (ETD −0.1%; $p=0.0645$) after 26 weeks [137, 151, 152]. The effectiveness of dulaglutide in the reduction of fasting plasma and BW was evaluated in the AWARD clinical trial program. HbA1c decrease was −1.36 ± 0.08% versus exenatide BID in AWARD-1 trial and −1.08 ± 0.06% versus insulin glargine in the AWARD-2 trial [153–155]. In turn, the efficacy of BW lowering was −0.30 ± 0.29 kg (AWARD-1 trial) and −1.87 ± 0.24 kg (AWARD-2 trial) [153–155].

Treatment of Both Diabetes and Obesity: Focus on GLP-1/Insulin Fix Ratio Combinations and Dual GLP-1/GIP Agonists

The administration of many drugs used to lower glucose levels, such as insulin, most sulfonylureas (SUs) and glinides causes BW gain due to several mechanisms, including defensive overeating to avoid hypoglycaemia [156]. Therefore, when making a decision concerning treatment, the problem of BW gain should be considered. Drugs that both treat hyperglycaemia and facilitate BW loss, especially GLP-1 RAs and SGLT2is, should be considered in patients with diabetes and obesity [157, 158]. Since the obesity and diabetes form a vicious circle in which one disorder aggravates the other, only the therapy of both can bring expected and satisfactory effects. The administration of GLP-1 RAs promote weight loss; however, the extent depends on type of drug from this class. While lixisenatide (0.7 kg difference vs. placebo) and dulaglutide (1.5 kg vs. placebo) induce small but considerable weight loss, the effects are more pronounced with liraglutide (−2.3 kg vs. placebo) and semaglutide (−4.3 subcutaneous and −3.4 kg oral vs. placebo) [109–111, 159]. In cases in which the use of antihyperglycaemic drugs with BW-reducing effects is not possible for any reason, medications that have a neutral impact on BW, including metformin and dipeptidyl peptidase 4 (DPP4) inhibitors, should be administered [121, 157, 160]. The selection of appropriate treatment requires careful analysis of existing comorbidities, as well as patient preferences and therapy costs [108]. Treatment with SGLT2i is associated with modest BW reduction [161–163].

Patients requiring insulin therapy are often recommended to use a fixed-ratio combination comprising long-acting insulin and GLP-1 RA (e.g. degludec/liraglutide or glargine/lixisenatide) since GLP-1 RA neutralizes the insulin-induced BW gain and mitigates the risk of hypoglycaemia associated with insulin. This prevents the drug-related increase in weight [157]. The combination of insulin with GLP-1 RAs was found to mitigate insulin-related BW gain [164, 165]. Moreover, the results of a clinical trial assessing the efficacy and safety of iGlarLixi (a fixed-ratio combination of insulin glargine and lixisenatide) compared with insulin glargine in inadequately controlled, basal insulin-treated patients with T2D showed that iGlarLixi not only promoted beneficial reductions in HbA1c (from baseline) but also BW loss by 0.7 kg as compared to the increase in patients' body mass by 0.7 kg with iGlar (1.4 kg difference, $p<0.0001$) [164]. In a phase 3b clinical trial (NCT02420262) estimating the effects on BW, IDegLira (insulin degludec/liraglutide fixed-ratio combination) was compared with iGlar U100 and insulin aspart up to four times per day [165]. This trial demonstrated that IDegLira reduced BW, while basal bolus insulin increased it (ETD −3.6 kg, 95% CI −4.2 to −2.9). Moreover, the occurrence of hypoglycaemic events was significantly lower in the IDegLira group. However, no differences between these two treatment alternatives were observed in terms of HbA1c reductions [165].

The results of large-scale trials (e.g. SURPASS-3, SURMOUNT-1) indicated that the use of dual GLP-1/GIP agonist tirzepatide provided greater BW loss benefits in patients with obesity with/without T2D compared with GLP-1 RAs [166, 167]. The effects were even greater when tirzepatide treatment was accompanied by the implementation of moderate intensity lifestyle interventions [31, 166]. Tirzepatide has been demonstrated to exert various favourable effects on most 'cardiometabolic continuum' components and suggested that its beneficial

effectiveness related to insulin sensitivity, glycaemia, BW control and β-cell function might be higher compared to GLP-1 RAs [168]. Moreover, it appears to show comparable safety as GLP-1 RAs. In the double-blind, randomized, placebo-controlled, phase 3 SURPASS-1 trial [169] tirzepatide in different doses (5 mg, 10 mg and 15 mg) not only significantly improved HbA1c and fasting blood glucose levels vs. placebo but also induced a dose-dependent BW loss ranging from 7 to 9.5 kg. Moreover, more than 80% of patients receiving the study drug met HbA1c level targets of < 7% (87–92% vs. 20% on placebo) and ≤ 6.5% (81–86% vs. 10%) without facing increased risk of hypoglycaemia. The safety profile of tirzepatide was consistent with that of GLP-1 RA [169]. Similarly, another clinical study demonstrated that significant reduction in BW associated with the administration of other dual GLP-1/GIP RA (NNC0090-2746, also known as RG7697) was accompanied by improved HbA1c in individuals with T2D, over a 12-week period [170, 171]. BW loss was greater than that of liraglutide [170, 171].

Intensive lifestyle interventions (such as low-calorie diets, structured exercise) in combination with anti-obesity pharmacotherapy adjusted to patients' requirements, capabilities and comorbidities are of key importance in management of obesity and T2D. Greater physical activity and exercise help to normalize BW as well as ameliorate glycaemic control, insulin sensitivity, levels of lipids, blood pressure and inflammatory biomarkers in T2DM [172–174].

SAFETY ISSUES RELATED TO GLP-1 RA THERAPY

The results of studies have demonstrated that GLP-1 therapy may increase the risk of gastrointestinal adverse events, including biliary disease bowel obstruction and gastroparesis in patients with diabetes [175–179]. Such events have been reported by 40–70% of treated patients in RCTs [180–182]. Real-world data analysis (the United Kingdom Clinical Practice Research Datalink and liked databases including over 25,000 patients on GLP-1 RA) indicated that GLP-1 RA use was associated with higher risk of intestinal obstruction compared with SGLT1 inhibitors (HR 1.69, 95% CI 1.04–2.74) [183]. In an IQVIA database health claim analysis, the semaglutide-related incidence of biliary disease in people with obesity was 11.7 (per 1000 person-years), and 4.6 for pancreatitis [178]. The incidence of these two adverse events was higher in the case of liraglutide and amounted to 18.6 and 7.9, respectively. In the STEP trials, the rate of cholelithiasis episodes mirrors the established links between rapid weight reduction and higher susceptibility to cholelithiasis and also aligns with earlier findings of gallbladder-related issues associated with GLP-1 RAs. Notably, there were no significant rises in acute pancreatitis occurrence observed with semaglutide 2.4 mg [184–186]. Similarly, meta-analysis based on real-world data of 1,324,515 patients suggests no association between the incretin-based therapy and the risk of acute pancreatitis, while the evidence for the impact of such treatment on pancreatitis is very weak [187]. Analysis of data from SUSTAIN 1–6, SUSTAIN 8 and SUSTAIN 11 trials revealed that gastrointestinal problems, such as vomiting, diarrhoea, abdominal pain and constipation [188] occurring in ≥ 5% of patients were the most frequent adverse reactions in these trials. In turn, dyspepsia, eructation, flatulence, gastroesophageal reflux disease and gastritis occurred in < 5% of patients. In the pool of placebo-controlled trials, gastrointestinal adverse reactions occurred more commonly among patients administered semaglutide (0.5 mg—32.7%, 1 mg—36.4%) compared to placebo (15.3%), especially during dose escalation. In turn, in the trial with semaglutide 1 mg and 2 mg, gastrointestinal adverse reactions were reported in 34.0% of patients treated with the dose of 2 mg and 30.8% in those on semaglutide 1 mg. In SUSTAIN 7, SUSTAIN 9–10 and SUSTAIN FORTE trials, no intestinal obstruction or related adverse events were reported [189]. Pharmacological studies in rodents have linked GLP-1 RAs to medullary thyroid cancer (MTC), leading to a black box warning for at-risk patients [190]. While this association is biologically plausible in rodents, it is unclear for non-MTC in humans. Clinical

trials, observational studies and meta-analyses indicate that thyroid cancer is rare and does not provide consistent evidence of increased risk from GLP-1 RA use. A cohort study performed in three countries found no substantial increase in thyroid cancer risk over 3.9 years of GLP-1 RA use, with a slight increase in the first year possibly due to detection bias [191]. Two large meta-analyses reported an odds ratio of 1.49 (95% CI 0.83–2.66) and a risk ratio of 1.30 (95% CI 0.86–1.97) for thyroid cancer with GLP-1 RAs [192, 193]. Analysis of nationwide real-world data (French national health care insurance system (SNDS) database) demonstrated increased risk of thyroid cancer and medullary thyroid cancer with the use of GLP-1 RA, especially after 1–3 years of treatment [194]. Pharmacovigilance studies show an increased reporting of thyroid cancer in GLP-1 RA users [195, 196]. Therefore, it appears reasonable to review patients' past medical and family history for medullary thyroid carcinoma prior to initiating GLP-1 RA. Moreover, the SUSTAIN 6 study demonstrated higher occurrence of diabetic retinopathy in semaglutide-treated patients compared to those on placebo (3.0% vs. 1.8%; $P=0.02$) [197]. These events could be probably ascribed to a rapid reduction in hyperglycaemia in patients with advanced retinopathy and poor glycemic control, already on insulin [198]. In turn, in the LEADER trial, liraglutide was associated with a non-significant 15% increase in retinopathy events [199]. However, no differences in retinopathy rates were observed between semaglutide and comparators in the SUSTAIN 1–5 trials or Japanese regulatory trials [200]. As a result of the concern of diabetic retinopathy worsening in patients treated with semaglutide, screening for this complication is recommended among people with T2D prior to initiation of GLP-1 RA as well as frequent monitoring in patients with retinopathy at the initiation of therapy.

GLP-1 DRUGS IN LOCAL SETTINGS (CLINICAL INERTIA AND REIMBURSEMENT ISSUES)

In spite of good clinical guidelines, some real-world evidence shows that many patients with diabetes do not receive adequate care, especially in terms of prescribing modern medications, including SGLT2 inhibitors and GLP-1 RAs [201]. Data from the international CAPTURE trial show that only 21.5% of subjects with T2D and CVD receive such medications despite having the indication (according to current guidelines) [202]. The non-adherence of clinicians to the changing guidelines, poor training and unawareness of the efficacy and safety of therapeutic regimens have been suggested to be some of the reasons for clinical inertia [203]. Moreover, some physicians ascribe inertia to heavy workload, lack of appropriate organization and burnout. The slow adoption of new medications is likely due to prescribing inertia and a lack of knowledge or familiarity among clinicians. The numerous treatment options available can be overwhelming for healthcare providers [204]. Additionally, in some countries high cost and insurance pre-authorization approvals present significant barriers. Other factors include discomfort among non-endocrinologists with adjusting other glycaemic agents (such as SUs and insulin) to incorporate GLP-1 RAs [205]. In turn, the patient-related factors favouring clinical inertia involve drug side effects, poor understanding of the severity of the disease, lack of compliance, limited access to specialist consultation, restricted doctor–patient communication as well as financial issues [206]. The barriers generated by the National Healthcare System depend on individual country legislation and they are mostly related to the need for reimbursements, poor coordination between planning and data exchange between the members of a health team as well as insurance coverage [206]. These elements translate into frequent use of "traditional" diabetes drugs (metformin, insulin and SUs) instead of the administration of combined therapies or newer disease-modifying drugs which do not cause

hypoglycaemia [207]. The results of studies confirm that clinical inertia remains an important problem. In a large study that focused on the assessment of therapeutic inertia, 26.2% of patients with HbA1c more than 7% and 18.1% of patients with HbA1c more than 8% who were treated with two oral drugs did not receive intensification of therapy [208]. Third oral drug or insulin was added in patients with mean HbA1c of 8.7% (± 1.3) and 9.4% (± 1.5), respectively [208]. Also, the SOLVE study has demonstrated that average HbA1c, in patients in North America, Europe and Asia, reached 8.9% before insulin was initiated and nearly 50% of these patients had HbA1c ≥ 9.0% despite treatment with combinations of oral hypoglycaemic agents [209]. The percentage of patients who achieved HbA1c ≤ 7% was as low as 53.6% and 62.6% in GUIDANCE and PANORAMA studies respectively [210, 211]. Moreover, another study revealed that patients wait approximately 7 years for therapy intensification and the introduction of a third antidiabetic drug [212].

A proactive approach, including, in addition to the treating physician, the support of nurses, pharmacists, etc., in the management of the disease has proved effective since patients respond better when they feel that somebody responds to their needs and problems [213, 214]. Also, education and training for physicians on the new guidelines, new drugs and their efficacy and adverse reactions should help to decrease clinical inertia. Finally, the National Health System focus on the treatment of chronic diseases as well as the improvement of the exchange of data and information between the healthcare facility and the patient and the introduction of reimbursement strategies would promote more adequate treatment strategies [215].

RECOMMENDATIONS FOR TREATMENT OF THE CARDIOMETABOLIC CONTINUUM

On the basis of current evidence, and clinical experiences, Eastern and Southern Europe Diabetes and Obesity Expert Group members developed the following recommendations on the management of obesity and T2D. We believe that the goal of therapy should focus on the shift from glucose-centred care to the management of obesity and cardiovascular complications. Such an approach would translate into beneficial clinical outcomes of therapy.

Recommendations:

- The introduction of a first-line drug for T2D is recommended immediately at diagnosis but should always be combined with non-pharmacological measures of a healthy lifestyle.
- In most cases, the first-line treatment is metformin combined with lifestyle intervention. However, we may also choose to introduce other antihyperglycaemic drugs as a first-line option depending on the patient's cardiovascular and renal comorbidities. The decision should be individually based, taking into account comorbidities and baseline and target glycaemia levels.
- If metformin is contraindicated or not tolerated, treatment can be started with a drug from another pharmacological group, depending on the clinical priority of treatment.
- Intensive individualised management of T2D should be introduced to postpone disease progression, and lower the risk of cardiorenal complications even if intensive hyperglycaemic therapy is not continued:
  - HbA1c < 6.5% (48 mmol/ml) in young subjects without complications and using medication with minimal hypoglycaemia risk.
  - HbA1c < 7.0% (53 mmol/mol) if achievable without causing hypoglycaemia.
  - HbA1c 7.5–8.0% (59–64 mmol/mol) in older patients with significant comorbidities (including CVD), or individuals who are prone to hypoglycaemia.
- Disease-modifying approach in prediabetes, T2D and obesity is recommended meaning early lifestyle interventions accompanied by appropriate treatment to enable disease development hampering or even diabetes remission.

- The identification of patients who are at a higher risk of delay in the intensification of the treatment (treatment intensification should be offered after 3 months from the failure to achieve metabolic goals).
- Risk stratification should be performed in patients with obesity and/or T2D to define their treatment goals and adjust therapy.
- CV and renal status should be checked at least once a year. Efficacy assessment as well as evaluation of possible side effects and adherence to existing pharmacological treatment are needed.
- Early combination therapy is recommended in patients with T2D and obesity.
- If HbA1c levels are ≥ 1.5–2.0% above the individual's target goal, another antihyperglycaemic drug can be introduced together with metformin to increase the likelihood of achieving the glycaemic target.
- Antidiabetic drug dosing adjustments, substitutions and/or addition of new antihyperglycaemic group drugs are necessary to maintain or achieve HbA1c targets. The introduction of antihyperglycaemic therapy should be monitored at 1- to 3-month intervals initially or more frequently at the discretion of the physician. Subsequently, monitoring is usually recommended within a period of 3 to 6 months.
- GLP-1 RAs, especially liraglutide, semaglutide or dulaglutide, should be used in the treatment of patients with T2D and established CVD.
- GLP-1 RAs are recommended as a treatment in patients with obesity to limit the risk of T2D development and decrease additional risk of other comorbidities.
- The use of dual GLP-1/GIP agonist tirzepatide is recommended since it provides a stronger HbA1c decrease and additional BW loss benefit in patients with obesity and T2D compared with GLP-1 RAs alone.
- Non-pharmacological measures should be regularly monitored and repromoted at all follow-up examinations.
- It is recommended to use an individualised approach and to adjust intensive lifestyle interventions (such as low-calorie diets, and structured exercise) in combination with pharmacotherapy to patients' requirements, capabilities and comorbidities.
- Recommended healthy dietary patterns should include vegetables, fruits, healthy protein sources, legumes, whole grains and vegetable oils, e.g. Mediterranean diet, DASH (Dietary Approaches to Stop Hypertension) diet and the low-carbohydrate diet (to a lesser extent)
- Apart from focusing on the achievement of short-term weight loss goals, support actions to establish attained effects and to intensify them are recommended since maintaining the achieved BW is as important as the initial weight loss itself.
- Bariatric surgery deserves attention in the treatment of T2D and obesity, especially in patients failing to attain glycaemic goals with pharmacotherapy plus lifestyle intervention.
- Education of patients and physicians is recommended to decrease therapeutic inertia.

CONCLUSIONS

Substantial and durable BW loss and long-term BW loss maintenance are the keys to effectively addressing obesity-related cardio-renal-metabolic conditions. Successful weight reduction exceeding 15% has significant implications such as prevention of T2D, probable disease remission as well as improvement in cardiometabolic risk factors and in already developed obesity-related complications. Our recommendations highlight the need to look at the patient from a broader perspective. Here, we stress the importance of early diagnosis and treatment of T2D and obesity to reduce future risk for complications. Such therapy should be individualised and intensified early to postpone disease progression and lower the risk of cardiorenal complications. In all patients, the presence of CVD, obesity and other comorbidities should be taken into consideration while adjusting medication and treatment goals. The use of combination therapy and the adoption of a disease-modifying approach is of high importance. The efficacy and safety of GLP-1 RAs use have been confirmed in clinical trials, and therefore these drugs are strongly

recommended. Apart from effective glycaemic control and BW reduction, they can also diminish the risk of CV events in patients with T2D, obesity and established CVD. We have previously made some recommendations on the importance of translating the results from the cardiovascular outcomes trials with GLP-1 RAs into clinical practice and in the present document we emphasize the importance of modern management of the cardiometabolic continuum: from overweight/obesity to prediabetes/type 2 diabetes mellitus. We strongly support to use a polymodal approach in a personalized manner depending on the patient's disease phenotype, and we also expect that the increasing availability of dual GLP-1/GIP agonists will significantly contribute to the modern management of the cardiometabolic continuum.

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Declarations

Conflict of Interest. The authors have given lectures, received honoraria and research support, and participated in conferences, advisory boards, and clinical trials sponsored by many pharmaceutical companies. Yet, no pharmaceutical company had any role in the scientific content of the present article, which has been written independently, and reflects only the opinion of the authors, without any role of the industry. The following conflict of interests were reported: Andrej Janez has served as a consultant and is on Speakers Bureaus for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Medtronic, Abbott, Novo Nordisk, Novartis and Swixx. Emir Muzurovic has given lectures, participated in conferences and advisory boards sponsored by several pharmaceutical companies, including Novo Nordisk, Sanofi, AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Novartis, Medtronic and Servier. Pawel Bogdanski has participated in a Data Safety Monitoring Board or Advisory Board of Novo Nordisk, Boehringer Ingelheim, Eli Lilly, Valeant and received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Novo Nordisk, Boehringer Ingelheim, Eli Lilly, Valeant and Sanofi Aventis. Ľubomíra Fábryová has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Eli Lilly, Novo Nordisk (Slovakia), Boehringer Ingelheim, Sandoz, Servier and Krka. Cristian Guja has participated in scientific advisory boards and received lecturing fees from AstraZeneca, Berlin Chemie Mennarini, Boehringer Ingelheim, Eli Lilly, Krka, Novo Nordisk, Pfizer, Sandoz, Sanofi, Servier and Viatris. Martin Haluzík has received consulting fees and payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from AstraZeneca, Boehringer Inghelheim, Eli Lilly, Merck, Novo Nordisk, Novartis, Pfizer, Sandoz, Sanofi, Krka. Martin Haluzik is an Advisory Board Member of *Diabetes Therapy*. He was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Péter Kempler has

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