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Cardiovascular Risk/Disease in Type 2 Diabetes Mellitus

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Abstract

People with Type 2 diabetes mellitus (T2DM) have a 2–3 times higher cardiovascular risk (CVR) than people without diabetes. Atherosclerotic cardiovascular disease (ASCVD) is the major cause of morbidity and mortality in T2DM. Over 30% of those with T2DM have CVD (cardiovascular disease), and over half die from it, mainly from coronary heart disease. The presence of T2DM reduces life expectancy by 10–14 years. The European Society of Cardiology stratifies the CVR into *moderate* (young patients, with a short duration of diabetes, no risk factors), *high* (duration of diabetes >10 years, no target organ damage, plus any additional risk factor) and *very high* (patients with established CVD, target organ injury three CVD risk factors: age, hypertension, dyslipidemia, obesity, or Type 1 diabetes mellitus (T1DM) over 20 years duration). The American Association of Clinical Endocrinologists (AACE) considers that diabetes per se involves high risk. Heart failure (HF) is the second most common complication after obstructive peripheral arterial disease. T2DM associates a 75% higher risk of CV mortality or hospitalization for HF. A multifactorial approach is required to reduce CV morbidity and mortality.

Keywords: cardiovascular risk, cardiovascular disease, type 2 diabetes mellitus

1. Introduction

Diabetes mellitus (DM), a very complex and heterogeneous chronic disease, is associated with chronic complications generated by alteration of the endothelium at all arterial vascular territory levels. The micro- and macrovascular complications affect the entire body; their pathogenic mechanisms are intricate and involve multiple pathways and risk factors. The main risk factors are insulin resistance/hyperinsulinemia, hyperglycemia, dyslipidemia, hypercholesterolemia, hypertension, smoking, obesity/overweight, all of which cause endothelial dysfunction. Consequently, they appear vasoconstriction, oxidative stress, subclinical inflammation, vascular calcification and thrombosis, essential pathogenic elements in the process of atherogenesis/macroangiopathy and microangiopathy [1].

Cardiovascular disease is considered a major cause of morbidity and mortality among people with diabetes, with a significantly increased prevalence compared with people without diabetes. The risk increases with the level of glycaemia, the duration of diabetes and the number of risk factors. People with T2DM have much earlier and more extensive process of accelerated atherosclerosis, more vulnerable and larger volume atherosclerotic plaques and coronary artery lumen with a smaller

diameter, compared to people without DM. The pathogenic complex is influenced by genetic factors, age, personal history and a pro-risk lifestyle (unhealthy eating, sedentary lifestyle, smoking, sleep disorders, psychosocial stress and depression) [1].

The macrovascular complications mainly refer to the atherosclerotic cardiovascular disease, represented by coronary artery disease (acute and chronic coronary syndrome) (CAD), chronic peripheral artery disease (PAD) and cerebrovascular disease (CBV). A particular complication is heart failure (HF). The pathogenic mechanisms of micro-and macro-angiopathy are extremely complex, with multiple interactions at the molecular-cellular and vascular-organic level.

Although all complications declined in the last decades, the most significant decreases in diabetes-related complications occurred for heart attack and stroke, especially for people aged 75 years and older. The CVD risk and mortality rate has declined in both the general population [2] and the people with diabetes [3]. However, diabetes, mainly T2DM, continues to be an important generator of cardiovascular disease. As the number of patients with diabetes is predicted to increase, reaching 700 million in 2045 [4], it is expected that the number of people with CVD will also increase. Thus, these major diabetes complications continue to place a heavy burden on health care systems.

2. Cardiovascular risk

2.1 Cardiovascular risk factors in diabetes

The concept of cardiovascular risk began to be of interest in the 1930s. Studies of cardiovascular disease epidemiology and its causes began in the 1950s, with Framingham Heart Study being one of the first. This extended program has demonstrated the existence of multiple CVR factors over the years, introducing in the literature and medical concept the term “risk factor”. Among the study’s first results, high blood pressure, hypercholesterolemia, and smoking are considered traditional, classic, risk factors. Subsequently, Framingham study and other epidemiological studies, have identified other risk factors, including obesity, diabetes, dyslipidemia, sedentary lifestyle. Thus diabetes is associated with a 2- to 3-fold increase in the risk of developing CVD and glucose intolerance with a 1.5-fold increase [5–7]. In addition to hyperglycemia, diabetes, mainly T2DM, is accompanied by other cardiovascular risk factors, within the metabolic syndrome: insulin resistance, abdominal obesity, atherogenic dyslipidemia (hypertriglyceridemia, low HDL-C (High-density lipoprotein cholesterol), LDL-C (low density lipoprotein cholesterol particles), remnant lipoproteins, postprandial hyperlipidemia), high blood pressure, prothrombotic, proinflammatory and oxidative stress state, microalbuminuria, non-alcoholic fatty liver disease [8].

High blood pressure increases 2–4 times the risk of CVD, kidney and death, atherogenic dyslipidemia induces a residual CVR, even under statin treatment and LDL-C control and abdominal obesity, as a component of metabolic syndrome, significantly increases the risk of coronary heart disease, stroke and death [9–11].

2.2 Cardiovascular risk in T2DM

Overall, people with T2DM have 2 to 4 times increased risk of cardiovascular morbidity and mortality than individuals without diabetes. This risk increases with the increase of fasting glycaemia since the stages of prediabetes. The risk for CAD is rising by 160%, for ischemic heart disease by 127%, for stroke by 56%, for CVD

death by 132% [4], and for HF is 2–4 times higher in men and five times higher in women, compared to those without diabetes [5].

Epidemiological studies have revealed that the excess relative risk of vascular events is more significant in women, at younger ages, in long-standing DM and in the presence of microvascular complications, mainly renal disease or proteinuria [12].

Although T2DM was initially considered a “cardiovascular risk equivalent” [12–14], it has since been shown that CVR, mainly CAD risk, is not similar for all persons with diabetes, but is highly heterogeneous. Thus, the CVR should be differentiated based on the presence of other CVR factors or overt CVD.

For T1DM, The Swedish National Diabetes Register has shown actual results in CVD and CV death prevalence. [13] For T1DM, 27,195 patients were stratified by age and sex. Early-onset at 1–10 years of age was correlated with an HR (hazard ratio) of 7.38 for CV mortality, 30.95 for acute myocardial infarction (MI), and 12.9 for heart failure (HF). Progress of T1DM between 1 and 10 years of age resulted in a loss of 17.7 years of life in women and 14.2 years in men. [13] Notwithstanding, T2DM is more common than T1DM. These results confirm the loss of years of life in both populations, which is more severe in the younger patients and in young-onset female individuals with T2DM, highlighting the need for early and intensive risk-factor interventions in these clusters of patients. [12]

The European Society of Cardiology stratifies the CVR into three risk categories, including T1DM, considering that presence of DM overall represents a significant risk factor for CVD:

- **moderate:** young patients (T1DM aged <35 years or T2DM aged <50 years), with DM duration <10 years, without other risk factors,
- **high:** patients with DM duration ≥ 10 years without target organ damage plus any other additional risk factor, and
- **very high:** patients with DM and established CVD, or further target organ damage (proteinuria, renal impairment defined as $eGFR < 30 \text{ mL/min/1.73 m}^2$, left ventricular hypertrophy, or retinopathy), or three or more major risk factors (age, hypertension, dyslipidemia, smoking, obesity), or early-onset T1DM of >20-year duration [12].

The American Association of Clinical Endocrinologists (AACE) stratifies the CVR into three levels: **high** (DM without other CVR factors), **very high** (DM with at least one CVR factor), and **extreme risk** (overt CVD in those with DM, chronic kidney disease) [15].

T2DM is reputed as an independent risk factor for the development of HF. Higher levels of glycated hemoglobin A1c (HbA1c) in T2DM patients have been associated with significantly more incident HF cases than in patients with T2DM and lower HbA1c levels. The incidence is even higher in patients with established CAD, in which each 1% increase in HbA1c level was associated with a 36% increased risk for HF hospitalization [16].

2.3 Cardiovascular risk assessment

A rational and successful approach to reducing the CVR involves stratifying risk and the periodic evaluation of the outcomes. Accurate CVD risk estimation in people with T2DM without established CVD can identify patients at high risk of developing CVD and can thus be used to adapt the intensity and complexity of

appropriate treatment. For practice, CVR assessment scores which can be applied in diabetes are beneficial. Several CVR calculation scores in DM have been developed. The first is the result of the United Kingdom Prospective Diabetes Study (UKPDS), in which, in people newly diagnosed with T2DM, the effect of intensive treatment on the evolution of chronic complications compared to conventional treatment was followed. UKPDS Risk Engine estimates the risk of fatal and non-fatal coronary events and fatal and non-fatal stroke at 15 and 30 years, in people with T2DM without CV disease, considering the duration of DM, age, gender, ethnicity, smoking, presence of atrial fibrillation, the level of HbA1c, systolic blood pressure, total cholesterol and HDL-C (<https://www.dtu.ox.ac.uk/riskengine/>) [17].

Another score (Advance Risk Engine) is based on ADVANCE and ADVANCE-ON studies. It refers to patients with T2DM without CVD, is based on the usual parameters and estimates the risk of major CV events at four years, the risk of renal events at five years and the risk of major vascular disease at ten years (www.advanceriskengine.com) [18].

The American Heart Association (AHA) and American College of Cardiology (ACC), developed a risk score to estimate the ten-year risk for the first ASCVD event (non-fatal myocardial infarction or CHD death, or fatal/non-fatal stroke) (available online at tools.acc.org/ASCVD-Risk-Estimator-Plus) [19].

Based on the ACCORD trial population, the BRAVO risk engine has been recently developed. It contains three separate modules addressed to events (stroke, MI, HF, angina, revascularization surgery, renal events, blindness, hypoglycemia), risk factors and mortality [20].

None of these CVR estimation scores is perfect, so clinical judgment and consideration of CVR factors are important for setting and selecting appropriate therapeutic goals and interventions.

3. Cardiovascular disease

The high impact that T2DM has on the CVD has generated numerous studies, and population analyzes in order to determine the prevalence of the cardiovascular pathologies in people with diabetes. Although the description and the diagnostic criteria used to define the different manifestations of CVD were different across the epidemiologic studies, overall, the results show that CVD is a major cause of comorbidity and mortality among patients with T2DM. Thus, the CVD, including myocardial infarction, stroke, angina, heart failure, atherosclerosis and coronary artery disease, is present in 32.2% of people with T2DM. The most frequent type of CVD seems to be the CAD (21.2%), males having higher rates (18.7%) than females (14.3%) [21]. A large cohort of 1,921,260 individuals, 1.8% with T2DM, followed 5.5 years, has been analyzed in terms of the most common initial manifestations of CVD. In T2DM individuals, peripheral artery disease was the most frequent first presentation (16.2%) followed by HF (14.1%), significantly higher compared with those without diabetes [22]. The prevalence of CVD and the incidence of primary adverse outcomes is higher in women with T2DM than their male counterparts (RR = 9.29; $P < 0.0001$ for CVD and RR = 5.25; $P < 0.0001$ for incident major adverse outcomes [23]. Data from the UK Biobank showed that a cardiovascular event's excess risk was approximately 50% higher in women (HR = 1.96) than in men, and more importantly, the incidence of myocardial infarction (MI) [A1] was higher in men than in women (28.8%). This observation was exciting since the sex differences were the same in all age-related groups and were attenuated with increasing age, from 0.27 (0.18 to 0.41), in 45 years age cluster versus 0.45 (0.40 to 0.50) in 65 years age cluster. [24].

Although diabetes-related excess mortality is lower in the contemporary era than previously, T2DM is associated with a two to six times increased risk of CVD mortality than people without diabetes. Cardiovascular disease accounts for 52% of deaths in type 2 DM [25]. MI is considered to be the main cause of death for individuals with diabetes mellitus.

T2DM is a significant predictor of HF, independent of the simultaneous presence of hypertension and coronary heart disease. In diabetes, HF has multiple risk factors: hyperglycemia, insulin resistance, age, ischemic heart disease, high blood pressure, left ventricular hypertrophy, diffuse, accelerated and severe atherosclerosis. Even in the absence of CAD, microvascular complications, arterial thickening and fibrosis, endothelial and vasomotor dysfunction, increase the risk of HF. The risk of HF is 2–4 times higher in men and five times higher in women compared to those without diabetes, according to Framingham Heart Study [5, 16].

The presence of DM in those hospitalized for HF worsens the prognosis, prolongs hospitalization, and increases the number of hospitalizations and the risk of death. In stable forms of HF, T2DM is an independent predictor of hospitalization and mortality, regardless of the ejection fraction [26]. Patients with T2DM have a 2.5-fold increased risk of developing HF and a 75% higher risk of CV mortality or hospitalization for HF than those without DM [27].

HF with preserved ejection fraction (HFpEF) is a frequent phenotype in T2DM and is related to an important risk of morbidity and mortality than those without diabetes, with multiple comorbidities, reduced exercise capacity, increased markers of inflammation, fibrosis, endothelial dysfunction, congestion, increased left ventricular pressure [28].

At similar ejection fraction values, patients with T2DM have a higher NYHA functional class, and more expressed symptoms than those without diabetes. Left ventricular (LV) diastolic dysfunction can be detected in approximately 75% of patients with T2DM, even in the early stages. The degree of hyperglycemia and its duration correlate with LV diastolic dysfunction's severity, with the increased risk of HF and CV mortality [16].

A retrospective cohort study that included 208,792 adults with diabetes has analyzed the impact of varying combinations of heart disease, stroke, moderate chronic kidney disease (CKD) on mortality, over a median follow-up of 8.5 years [29]. The effect of heart diseases, stroke, CKD, and the combination of these conditions on all-cause mortality has been found to be independent and cumulative. The mortality risks were 1.75 times, 2.63 times, and 3.58 times greater for patients with one, two, and all three above mentioned conditions, and life expectancy for a 40-year-old with one, two, and three conditions was reduced with 20, 25, and 30 years for men and 25, 30, and 35 years, respectively, for women, compared with patients without these diseases [29].

Diabetes is the most known cause of CKD, and end-stage renal disease, more than 50% of people with DM are likely to develop CKD. CKD, especially severe CKD, has a significant impact on life expectancy and mortality risk in patients with diabetes. The risk of CV death increases as renal function declines (eGFR <60 ml/min/1.73 m² and/or ACR (albumin-creatinine ratio) ≥10 mg/g) [30]. Rates of HF are approximately 3-times higher in patients with eGFR <60 ml/min/1.7 m² [31].

The CardioRenal Metabolic Syndrome (CaReMe) has been introduced as terminology to describe the ongoing relationship between obesity, diabetes, kidney disease and heart failure with preserved systolic function, with significant mortality implications rate and therapeutic interventions [32].

Within CVD, diabetic cardiomyopathy or “cardiac microvascular disease”, is a phenotype with distinct manifestations, described as a “structural and functional alteration of the myocardium, in the absence of hypertension, ischemic

coronary heart disease, valvulopathies, or other FRCV, in patients with diabetes, especially with long-term diabetes and poor control.” Fibrosis, stiffness, and cardiac hypertrophy are basic changes, which are initially associated with diastolic dysfunction, LV hypertrophy and reduced compliance with preserving the ejection fraction, later evolving into systolic dysfunction clinically manifest HF [16, 33]. As risk factors of diabetic cardiomyopathy, hyperglycemia, dyslipidemia, altered energy metabolism, dysregulated insulin signaling, inflammation, endoplasmic reticular stress, mitochondrial dysfunction, oxidative stress and accumulation of advanced glycation end-products (AGEs) and activation of the renin-angiotensin-aldosterone system (RAAS) are described [33].

4. Hyperglycemia and CVD relationship

Compared with individuals without diabetes, patients with T2DM are disproportionately affected by CVD morbidity and mortality. Most of this excess risk is associated with an increased prevalence of risk factors such as hypertension, dyslipidemia, and obesity in these patients. However, hyperglycemia, as a distinct characteristic of DM, appears to be an independent risk factor for all-cause and CVD mortality independent of other modifiable CVD risk factors:

- Increased HbA1c is associated with coronary heart disease [34],
- Long-term intraindividual variability of HbA1c or basal blood glucose is associated with micro- and macro-vascular complications and with an increased risk of important adverse CV events [35–37],
- 24-hour glycemic variability, greater than 35.9 mg/dl, is independently associated with an increased risk of left ventricular diastolic dysfunction, even in asymptomatic patients and with a preserved ejection fraction (odds ratio: 3.67; $p < 0.05$) [38],
- Basal glycemia >126 mg/dl was associated with a risk of fatal/non-fatal coronary heart disease, fatal/non-fatal stroke of 39% in women and 48% in men [39],
- Each 1-point increase in HbA1c is associated with an 8% increase in the risk of HF and a 36% increased risk for HF hospitalization [16, 39],
- The onset of diabetes in young people and the long duration of diabetes, are associated with an increased risk of mortality, mainly CV, due to ischemic disease and stroke [40, 41],
- The risk of coronary artery disease increases in diabetic patients by 11% for each 1% increment in HbA1c greater than 6.5%. In adults with diabetes, but without baseline CVD, an HbA1c of 9% is correlated with an increased risk of myocardial infarction or acute coronary syndrome (odds ratio [OR] = 1.18), stroke (OR = 1.29) and heart failure (OR = 1.37) [42],
- Severe hypoglycemia is linked with an increased risk of recurrence (especially in T1DM) and an increased risk of CV events, including death. In the Veteran Affairs Diabetes Trial, severe hypoglycemia was associated in the following 3 months with CV events (HR = 1.9; $p = 0.03$), CV mortality (HR = 3.7; $p = 0.01$) and mortality of any cause (HR = 2.4; $p = 0.02$) [43].

5. Therapeutic approach

The major objectives of clinical management in T2DM are preventing or delaying chronic complications, increasing life expectancy, and quality. The basic principle of clinical management is the “patient-centred” approach, respectively, the intervention’s individualisation [19]. The significant reduction of cardiovascular morbidity/mortality implies a multifactorial approach, addressed simultaneously to all CV risk factors. The 7.8-year STENO-2 study, which included patients with T2DM with increased CV risk (microalbuminuria), showed that the multifactorial approach significantly reduced mortality from any cause (20% reduction in absolute risk), 13% in CV mortality and 29% in the absolute risk of CV events [44, 45]. The 21-year assessment showed that life expectancy was extended by eight years in the intensive care group, and the relative risk of HF was reduced by 76% [45]. Analysis of data from an extensive registry has shown that in people with T2DM, simultaneous control of major CV risk factors (blood glucose, blood pressure, cholesterol and lifestyle, no smoking), can reduce over 60% of cardiovascular and coronary atherosclerotic events [46]. Patients with diabetes who have five risk-factor variables within the target ranges (HbA1c, LDL-cholesterol, blood pressure, no albuminuria and no smoking) seem to have lower or no excess risk of overall death or myocardial infarction and/or stroke, as similar to the general population, as shown in a study that included 271,174 patients with T2DM registered in the Swedish National Diabetes Register [47].

5.1 Specific therapeutic targets

The specific targets of clinical management are presented in **Table 1**.

5.2 Lifestyle optimization

Lifestyle interventions addressed to optimize nutrition, increase physical activity, control body weight, stop smoking, are the cornerstone for T2DM therapy, for both glycemic and other CV risk factors [19, 50]. In terms of CV risk control, lifestyle management aims to, and it is proven to achieve [51]:

- Control of body weight and improvements of obesity-related complications,
- Improvement of glycemic control,
- Lowering of blood pressure,
- Improvement of the lipid profile
- Improvement of fitness, well-being and mental health.

Although the Look AHEAD (Action for Health in Diabetes) study did not show that intensive lifestyle optimization reduces CV events in people with diabetes and obesity, it showed significant control of CV risk factors, with fewer medication requirements and long-term weight loss maintenance (4.7% at eight years) [52].

5.2.1 Medical nutrition therapy

Medical nutrition therapy is based on healthy eating principles. Its goals are to promote and support healthful eating patterns, with various nutrient-dense foods

Risk factors	Therapeutic targets
HbA1c [19]	<p>< 7% (53 mmol/mol), for most patients</p> <p>< 6,5% (48 mmol/mol), if the target can be achieved without hypoglycemia† (usually younger patients, short duration of diabetes, longer life expectancy, no complications)</p> <p>< 8% (64 mmol/mol), for patients with long-standing diabetes, complex glucose-lowering treatment including insulin, history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular, multiple complications and comorbidities</p>
Fasting glycemia, postprandial glycemia, glycemic variability [19]	<ul style="list-style-type: none"> • Fasting/pre-meal glycemia = 80–130 mg/dl • Postprandial glycemia (1–2 hours) < 180 mg/dl • Reduced glycemic variability (< 36%) • Avoidance of hypoglycemia: <ul style="list-style-type: none"> > 70% time in range (70–180 mg/dL/3.9–10.0 mmol/L) < 4% glucose range below 70 mg (3.9 mmol/L)
Blood pressure [18, 19]	< 130/80 mmHg (≥ 65 years = 130–139/70–79 mmHg)
Lipids [12]	<ul style="list-style-type: none"> • LDL-cholesterol: <ul style="list-style-type: none"> < 100 mg/dl - moderate CV risk < 70 mg/dl and > 50% reduction - high CV risk < 55 mg/dl and > 50% reduction – very high CV risk • Non-HDL-col <85 mg/dl in patients at very high CVR, and < 100 mg/dl in those at high CVR • HDL-cholesterol >40 mg/dl in men and > 45 mg/dl in women * • Triglycerides <150 mg/dl *
Body weight [19]	<p>> 5–10% weight loss and</p> <ul style="list-style-type: none"> • long term weight loss maintenance
Lifestyle [19]	<ul style="list-style-type: none"> • Physical activity • Healthy nutrition, caloric adjusted • No smoking • No/moderate alcohol intake

†Glucose range below 70 mg/dl in less than 4% of the measurements determined by continuous glucose monitoring or ambulatory glycemic profile per day [19, 49].

*Not a goal but indicates a lower risk.

Table 1.
Therapeutic targets in T2DM (adapted by [12, 19, 48, 49]).

in appropriate portion sizes. To ensure adherence and effectiveness, nutritional interventions should be individualized by meeting individual's needs, personal and cultural preferences, access to healthy foods, the pleasure of eating, and providing practical tools to implement the recommendations [50].

Dietary interventions can reduce HbA1c with up to 2% [50]. Caloric intake should be adapted to maintain body weight control. General recommendations are to avoid saturated lipids and foods with a high glycemic index. The Mediterranean diet, the DASH diet (Dietary Approaches to Stop Hypertension), plant-based diets, are recommended for their proven benefits. Carbohydrates should come from foods rich in fibers: vegetables, legumes, whole grains, fruits. Lipids should be mainly mono- and polyunsaturated and omega-3. Supplementation with minerals or vitamins is only recommended in case of deficiency. Hydration is important, with the selection of non-caloric drinks. Consumption of alcohol in moderate amounts is acceptable, but special attention should be paid to the risk of hypoglycemia, hyperglycemia and additional caloric intake. Sodium intake should be <2,300 mg/day [50].

5.2.2 Physical activity

Most patients' recommended physical activity is at least 150 minutes/week, at least three times/week, moderate/high intensity, aerobic, 2–3 sessions/week of endurance and flexibility exercises. Reducing the time spent in sedentary lifestyle is also an important recommendation [50].

5.3 Pharmacotherapy

5.3.1 Pharmacotherapy of hyperglycemia

The pharmacotherapy of hyperglycemia should be patient-centred, addressed to reduce glycemia and the overall CVR [53]. Metformin remains the first step of the treatment. It is initiated simultaneously with lifestyle optimization, from the diagnosis, and is continued throughout the treatment, associated with the other therapeutic classes. It is stopped in case of intolerance and at an eGFR <30 mL/min/1.73 m². For patients with established ASCVD or indicators of high ASCVD risk, established kidney disease, or heart failure, the guidelines recommend the medication with demonstrated CVD benefit, independent of the HbA1c value: SGLT-2 inhibitor (sodium-glucose cotransporter 2 inhibitor – empagliflozin, canagliflozin, dapagliflozin) or GLP-1RA (glucagon-like peptide 1 receptor agonist – semaglutide, liraglutide, dulaglutide, long-acting exenatide, lixisenatide) (**Table 2**) [12, 19, 53–59].

For patients without the conditions mentioned above, a second or third agent's choice as an add-on to metformin is based on CV safety, the effect on body weight, and avoidance of hypoglycemia. Sulfonylureas have controversial CV effects. To date, the ADVANCE study (Action in Diabetes and Vascular Disease: Preterax

GLP-1 RA/Study				
	MACE	CV mortality	hHF	Renal effects
Liraglutide (LEADER) [54]	HR = 0.87 (0.78–0.97)	HR = 0.78 (0.66–0.93)	NS	HR = 0.78 (0.67–0.92)
Semaglutide (SUSTAIN) [55]	HR = 0.74 (0.58–0.95) *	NS	NS	HR = 0.64 (0.46–0.88)
Dulaglutide (REWIND) [56]	HR = 0.88 (0.79–0.99)	NS	NS	HR = 0.85 (0.77–0.93)
SGLT2-inh/Study				
Empagliflozin (EMPAREG-OUTCOME) [57]	HR = 0.86 (0.74–0.99)	HR = 0.62 (0.49–0.77)	HR = 0.65 (0.50–0.85)	HR = 0.61 (0.53–0.70)
Canagliflozin (CANVAS) [58]	HR = 0.86 (0.75–0.97)	HR = 0.78 (0.67–0.91) (CV mortality and hHF)	HR = 0.67 (0.52–0.87)	HR = 0.60 (0.47–0.77)
Dapagliflozin (DECLARE-TIMI 58) [59]	NS	HR = 0.83 (0.73–0.95) (CV mortality and hHF)	HR = 0.73 (0.61–0.88)	HR = 0.53 (0.43–0.66)

Table 2. Antihyperglycemic agents with proven CVD/CKD/hHF benefits [12, 19, 53–59].

and Diamicon MR Controlled Evaluation) is the only one that has shown that gliclazide is CV neutral and has beneficial effects in reducing kidney disease [60]. The PROactive study (PROspective pioglitAzone Clinical Trial In macroVascular Events) which included patients with T2DM treated with pioglitazone in secondary prevention, demonstrated benefits of reducing events (myocardial infarction, stroke), but also increased risk for heart failure [61]. DPP-IV-inhibitors (dipeptidyl peptidase IV), are CV safe, body weight neutral, and with low risk for hypoglycemia. Insulin therapy is initiated at HbA1c values above 10%, or in the presence of symptoms of hyperglycemia. New generations of basal insulin analogues are recommended, preferably in association with GLP-1 RA [53].

Mention: only the statistically significant results are included in the table; HR-hazard ratio; NS-non statistically significant; MACE-major adverse cardiovascular events: CV mortality, non-fatal myocardial infarction and non-fatal stroke; hHF- hospitalization for heart failure; Renal effects: new or worsening nephropathy (persistent macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance of less than 45 ml per minute per 1.73 m² of body-surface area, or the need for continuous renal-replacement therapy); LEADER- Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; SUSTAIN-Efficacy and Safety of Semaglutide Once-weekly Versus Placebo in Drug-naïve Subjects With Type 2 Diabetes; EXSCEL- Exenatide Study of Cardiovascular Event Lowering Trial; EMPA-REG-OUTCOME-The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose; CANVAS- Canagliflozin Cardiovascular Assessment Study; DECLARE-TIMI 58-Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58.

Unfortunately, the Exenatide Study of Cardiovascular Event Lowering (EXSCEL) was unable to demonstrate that once-weekly exenatide can achieve a statistically significant reduction in the incidence of major adverse cardiovascular events, compare to placebo [62].

DAPA-HF study (“Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure”), which included patients with heart failure (ejection fraction <40% and NYHA class II-IV or symptoms) has demonstrated, after a median of 18.2 months of treatment with dapagliflozin vs. placebo, a significant reduction (HR = 0.74) of the primary composite outcome (worsening heart failure or death from cardiovascular causes) and the secondary outcomes (cardiovascular death or heart-failure hospitalization) (HR = 0.75) [63]. A similar design has been used in EMPEROR-Reduced trial (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction). Compare to placebo, empagliflozin has significantly reduced the primary composite outcome of death from cardiovascular causes or hospitalization for HF (HR = 0.75) and the total number of hospitalizations for heart failure (HR = 0.70) [64].

5.3.2 Pharmacotherapy of hypertension

At a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, drug therapy is necessary in combination with non-pharmacological treatment [12, 19]. An association of antihypertensive classes is often needed, with a renin-angiotensin-aldosterone system (RAAS) blocker, and a calcium channel blocker or diuretic. A RAAS blocker is recommended particularly in the presence of microalbuminuria, albuminuria, proteinuria, or LV hypertrophy. Dual therapy is recommended as first-line treatment, with a combination of a RAAS blocker with a calcium channel blocker or thiazide/thiazide-like diuretic. It is recommended that at least one antihypertensive drug to be administered

in the evening [12]. In the case of resistant hypertension, if therapeutic targets are not met with three classes of antihypertensive drugs (including a diuretic), a mineralocorticoid receptor antagonist (spironolactone) is added. Fixed combinations are preferred to increase adherence [12, 19].

5.3.3 Pharmacotherapy of dyslipidemia

LDL-cholesterol is the first therapeutic target. Depending on the risk class, statins are used in moderate doses (Atorvastatin 10–20 mg, Rosuvastatin 5–10 mg, Simvastatin 20–40 mg) or high doses (Atorvastatin 40–80 mg, Rosuvastatin 20–40 mg) [12, 19, 48]. If LDL-C target is not reached, ezetimibe or PCSK9 inhibitors (evolocumab or alirocumab) are added. In the presence of atherogenic dyslipidemia (persistent triglycerides >200 mg/dl), the fenofibrate can be added to statin. The lipid arm of ACCORD study showed a further 31% reduction in CV events' relative risk in this combination. Omega-3 fatty acids can further reduce the level of triglycerides in a dose of >2 g/day. The “Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT) study”, showed that 2 grams icosapent ethyl (EPA), administered twice daily, was associated with 25% relative risk reduction ($P < 0.001$) in major adverse CV events (MACE), compared to placebo [65].

5.3.4 Antithrombotic/anticoagulant pharmacotherapy

If there is no contraindication, in individuals with T2DM over the age of 50, at high/very high CV risk, in the presence of the family history of premature atherosclerotic disease, hypertension, dyslipidemia, smoking, chronic kidney disease, aspirin (75–100 mg/day) may be considered in primary prevention. Aspirin (75–162 mg/day), or clopidogrel (75 mg/day) are recommended for secondary prevention. Dual antiplatelet therapy (low-dose aspirin and P2Y12 inhibitors: ticagrelor, clopidogrel, prasugrel) is recommended after an acute coronary syndrome, for a period of one year, possibly with benefits and longer use [12, 19].

Rivaroxaban 2.5 mg administered twice daily in combination with 100 mg aspirin, in T2DM patients with stable atherosclerotic vascular disease, has been shown to significantly reduce the primary outcome of CV death, stroke, myocardial infarction and major adverse limb events including amputation, but with more major bleeding events than those assigned to aspirin alone [66, 67].

5.3.5 Surgical procedures

a. Bariatric surgery is associated with the most important and sustained weight loss, with significant improvements in CV risk factors, including remission of T2DM, cardiac functional parameters and coronary events. The criteria for recommending bariatric surgery in people with T2DM are [68, 69]:

- BMI ≥ 40 kg/m²
- BMI = 35.0–39.9 kg/m² if long-term weight loss and improvement of comorbidities by non-surgical methods could not be achieved
- BMI = 30.0–34.9 kg/m² in certain situations [69]

b. Myocardial revascularization strategies, either percutaneous coronary intervention (PCI) with drug-eluting stents (DES), preferably the newer-generation

everolimus-eluting stents, or coronary artery bypass graft surgery (CABG), are strongly recommended in patients with T2DM. Based on the coronary anatomy complexity, PCI may represent an alternative to CABG for lower complexity, while CABG is recommended for intermediate-to-high anatomical complexity [19].

6. Conclusions

T2DM is a major cardiovascular risk factor. CVD is frequent, associated with high mortality.

The clinical management of T2DM must be early, multifactorial, intensive, and patient-centred. Lifestyle intervention and a combination of several classes of drugs should be addressed to all cardiovascular risk factors.

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