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A Jordanian Multidisciplinary Consensus Statement on the Management of Type 2 Diabetes

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Abstract: *Background:* The prevalence of type 2 diabetes (T2D) is increasing in Jordan and cardiovascular disease (CVD) is considered the leading cause of morbidity and mortality among patients with T2D patients. New data emerged with novel antihyperglycemic agents that demonstrated reduction in cardiorenal outcomes. *Aims:* The aims of the expert panel were to provide a multidisciplinary consensus approach to the screening, diagnosis, controlling cardiovascular risk factors, treatment, and monitoring of T2D. In addition, the panel's aim was to develop an algorithm, incorporating new data to serve as an easy-to-use tool by health care providers (HCPs) to ultimately improve the decision-making process and outcome. *Methods:* A panel of experts from different specialties representing various medical societies met to discuss and review all the relevant T2D literature and the related international clinical practice guidelines on T2D. The panel evaluated and developed a comprehensive understanding of the current situation in Jordan, addressing the screening, diagnosis, pharmacological treatment, management, and monitoring parameters of T2D. *Results:* The expert panel established criteria for screening and diagnosis of patients with T2D driven by international clinical practice guidelines. The panel addressed all the cardiovascular (CV) risk factors associated with T2D and developed a risk stratification strategy. Accordingly, treatment recommendations were proposed based on the evidence of reduction of cardiorenal events and hospitalizations for heart failure (HFF) with the different options of pharmacological treatments. A treatment algorithm was drafted to provide guidance to the HCPs on the management of T2D.

Conclusion: The focus of treatment in T2D has shifted from just controlling hyperglycemia towards reduction in cardio-renal complications. New data with two disease-modifying agents have changed the landscape of T2D treatment. It was important to develop a consensus statement with a multidisciplinary approach to provide HCPs with useful tools to use in the management of T2D, including a treatment algorithm. These recommendations would help increase awareness about the management of T2D in Jordan with the ultimate goal of improving cardiorenal outcomes.

Keywords: Type 2 Diabetes, Consensus Statement, Management, Jordan

1. Introduction

The burden of T2D is well recognized worldwide [1], which accounts for more than 90% of the 537 million estimated diabetic patients globally [2]. The Middle East and North Africa region represents 13.6% of the total diabetics worldwide and has the highest percentage (24.5%) of diabetes-related deaths [3]. In Jordan, the prevalence of T2D was estimated to be at 15.4% last year and it is increasing [4].

It is well known that T2D is associated with a high rate of complications related to CVD and diabetic kidney disease (DKD), retinopathy, and neuropathy [5-7]. The CVD mortality rate among patients with T2D is approximately twice as high as those without diabetes [6-8]. T2D is also the main cause of renal damage and end-stage renal disease (ESRD) and 35% of patients with T2D develop DKD [9, 10]. Patients who have T2D and DKD have a 23% higher mortality rate than those patients without diabetes and normal renal function [11]. In addition, cardiorenal complications are considered the most frequent among T2D patients reaching 60% [12].

Heart failure (HF) is common in patients with T2D, especially in patients with age of 70 years and older. However, there are a considerable number of patients with T2D who have undiagnosed HF [13, 14]. It was reported that 68% of patients with T2D had evidence of asymptomatic left ventricular dysfunction at 5 years after T2D diagnosis. [15]. Patients with established T2D have an increased risk for HHF by 33% compared to those without T2D [14]. Accordingly, a new proposed staging for HF was released in 2021 which recognized T2D as a key risk factor for HF. It was also suggested that patients with T2D without symptoms or structural cardiac changes or elevated biomarkers to be classified as being in the first stage of HF (stage A) [16].

Therapeutic inertia in treating and achieving glycemic target goals in patients with T2D has been demonstrated locally in Jordan. The baseline data of the DISCOVER (DISCOVERing Treatment Reality of Type 2 Diabetes in Real World Settings) study for Jordan showed inertia before the initiation of second-line therapy for patients with T2D. A substantial number of patients were young and obese with multiple CV risk factors and a poor glycemic control with a glycated hemoglobin (HbA1c) of 8.7%, requiring treatment intensification and more comprehensive management [17]. Therefore, it was crucial for a local panel of experts to develop a multidisciplinary consensus statement to provide health care providers with practical clinical information regarding the complexity of the disease and how to successfully manage patients with T2D, recognizing risk factors early to prevent complications. Moreover, it was of paramount importance to provide treatment recommendation with the novel pharmacological options that have favorable CVD, including HF, and renal outcomes.

2. Objectives

The main objectives of the expert panel were to raise awareness and provide guidance regarding screening, diagnosis, risk factors, comorbidities, and risk reduction with the novel antidiabetic agents. In addition, the objective was to provide a consensus statement on the treatment and management of T2D in Jordan, utilizing a multidisciplinary team approach, to guide local HCPs in T2D patient care to ultimately improve patients' outcomes.

3. Methodology

A panel of ten experts with different specialties, representing different societies undertook the initiative to discuss the challenges with the treatment and management of T2D in Jordan and provide recommendations and treatment protocols for health care practices taking into considerations local factors. The panel was comprised of endocrinologists/diabetologists, nephrologists, cardiologists, and internists, including general practitioners. The experts represented Jordanian Society of Endocrinology, Diabetes & Metabolism, the Jordanian Society for the Care of Diabetes, Jordan Cardiac Society, Jordan Society of Nephrology and Renal Transplantation, the Jordanian Society of Internal Medicine, and the Jordanian General Practitioner Society. The local experts also conducted a comprehensive review of the literature, utilizing databases such as Medline, EMBASE and Cochrane and using key terms such as "type 2 diabetes", "treatment and management", "antihyperglycemic agents", "clinical practice guidelines", "glycemic control", "cardiovascular outcome", "kidney disease", " heart failure" "multidisciplinary approach", "patient education" and "patient empowerment". They also researched the International Diabetes Federation, and the World Health Organization, websites. The panel reviewed the international practice guidelines on T2D and the relevant literature to provide a multidisciplinary approach and tailored and easy to use recommendations to the health care providers in Jordan on the management of patients with T2D.

4. Results

4.1. Screening and Diagnosis

The panel of experts agreed that patients should be screened for diabetes at a younger age at ≥25 years of age for those who are overweight or obese defined as a body mass index ≥25 and ≥ 30, respectively since diabetes and its related complications are prevalent and occur 10 years earlier in Jordan than Western societies [18-21]. The panel endorses the criteria for diagnosis of diabetes or prediabetes in asymptomatic adults and early interventions such as lifestyle modifications and/or pharmacological treatment related to prediabetic patients that have been published elsewhere [21]. The screening intervals every 3 years is considered a reasonable approach for those adults with an initial normal glucose level. Older age, family history, history of gestational diabetes, history of polycystic ovarian syndrome (PCOS), and dietary and lifestyle are also considered risk factors that should be taken into consideration [22, 23].

According to the American Diabetes Association (ADA), plasma glucose criteria is utilized for the diagnosis of diabetes. The diagnosis can be made based on either the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or HbA1C criteria (table 1) [24].

Table 1. *Diagnosis criteria for T2D.*

Criteria	Cut-off Value
FPG*	≥126 mg/dL
2-h PG	≥200 mg/dL
A random plasma glucose	≥200 mg/dL with classic symptoms of hyperglycemia or hyperglycemic crisis
HbA1c%*	≥6.5%

FPG: Fasting Plasma Glucose; HbA1c: Glycated Hemoglobin; PG: Post-prandial Glucose
*On two separate occasions.

4.2. Metabolic-Cardio-Renal Risk Assessment and Target Goals

T2D is a glucose and lipid metabolism disorder, which is associated with an increased risk of microvascular and macrovascular complications [25]. The expert panel recommends that all T2D patients should be evaluated in terms of metabolic-cardio-renal risk factors. Atherosclerotic cardiovascular disease (ASCVD) is very prevalent in patients with T2D. Approximately one-third of patients with T2D develop CVD, which is attributed to 50% of deaths in patients with T2D [26]. Comorbidities coexisting with T2D (e.g., hypertension and dyslipidemia) are risk factors for ASCVD, and T2D is also considered an independent risk [27]. Patients with T2D have an increased risk of developing DKD by two-folds [10]. Microalbuminuria is considered a good biomarker in predicting clinical proteinuria, poor renal outcomes, and mortality in patients with the T2D [28]. It should be assessed annually if the renal function is normal and every 3 months if the renal function is abnormal. Monthly monitoring of microalbuminuria is recommended if treatment adjustment is required [28, 29]. Requesting serum creatinine is important to calculate the estimated Glomerular Filtration Rate (eGFR) and measuring the urine albumin and creatinine to calculate the urine albumin-creatinine ratio (UACR), which is another important parameter for screening and monitoring of kidney disease. The results of both the eGFR and UACR help identify patients at risk for kidney disease progression who may benefit from established and emerging kidney protective therapies [30]. Furthermore, optimizing treatment to achieve glycemic and BP control may slow decline in kidney function in patients with T2D [27]. The target goal is to reduce albuminuria and provide renoprotection (table 2). Modifying individual CV risk factors improves ASCVD outcome in patients with T2D. Therefore, it is prudent to assess the lipid profile, blood pressure, albuminuria, eGFR, and UACR in addition to the HbA1c at baseline for all patients with T2D [25]. HF and T2D are interrelated, as T2D increases the risk of HF and subsequently HHF. HF is also prevalent in T2D patients, and it is possible that HF increases the risk of developing T2D [31]. T2D patients with HF may present with either preserved ejection fraction (HFpEF), HF mid-range EF (HFmrEF), or with reduced ejection fraction (HFrEF) [16]. The recommendation for screening and diagnosing HF in patients with T2D is an electrocardiogram (ECG), echocardiography (ECHO), and biomarkers such as B-type natriuretic peptide (BNP) or N-terminal (NT)-pro hormone BNP (see table 2 for cardiac assessment) [32].

The HCP should set a target goal to manage and control metabolic-cardio-renal risk factors in patients with T2D. The recommendation of the panel is to have the glycemic target goals individualized. Several studies have demonstrated the reduction of microvascular complications with intensive glycemic control in patients with T2D [33, 34]. The target HbA1c target goal is <7% for the general population. However, in young T2D patients without any evidence of ASCVD with short duration of T2D, the HbA1c target goal should be lower than 6.5% and less stringent HbA1C goals (<8%) in patients with advanced age, long duration of T2D, limited life expectancy, and multiple comorbidities. These targets can be lower and should be discussed with the patients to make sure that they can be achieved safely without significant hypoglycemia or other adverse effects of treatment [35]. The American Association of Clinical Endocrinologists (AACE) guidelines considers HbA1c goal of ≤6.5% optimal if it can be achieved, provided the treatment is safe and affordable. Higher HbA1c target (>6.5%) can be used if adverse events were encountered with the lower target goal [36]. It is also recommended that patients should use continuous glucose monitoring to have optimal glycemic control [31, 36]. The lipid target should be set at a level according to the CV risk stratification of the patient. The European Society of Cardiology (ESC) recommends that LDL-C target of <100 mg/dL for patients with moderate CV risk, <70 mg/dL for patients with high CV risk, and <55 mg/dL for patients with very high CV risk [31]. The American College of Cardiology (ACC) and American Heart Association (AHA) guidelines recommend statins for

primary and secondary prevention in T2D patients and for those with established ASCVD, the highest intensity statin than can be tolerated should be used to decrease the LDL-C level by more than 50%. Moderate intensity statins for primary prevention are recommended while considering age and absolute ASCVD risk. Hypertriglyceridemia should be addressed by proper glycemic control, lifestyle modifications, and pharmacological therapy (statins, fibrates, and others) (table 2.) [37]. Most guidelines recommend a target BP of <130/80 mmHg if tolerated [38]. The ADA recommends a BP target of <140/90 mmHg and <130/80 mmHg for patients with high ASCVD risk [27]. The panel of experts recommend a multidisciplinary with a patient centered decision-making approach as treatment strategy should be considered to ensure patients safety in achieving glycemic, lipid, and BP target goals (table 2).

Table 2. *Glycemic, lipids, BP, and albuminuria target goals in patients with T2D.*

Type of Assessment (parameter)	Target goal recommendations	Comments
Metabolic assessment (HbA1c)	<7% general population <6.5% (young with no evidence of ASCVD and short duration of T2D) <8% (Elderly, long duration of T2D, limited life expectancy, and multiple comorbidities)	Measure at initial visit and every 3 months if drug therapy changes otherwise every 6 months
Metabolic assessment (Lipids)	Assess ASCVD risk (utilizing ASCVD risk calculator to estimate 10-year risk) T2D with established or very high risk for ASCVD-target 50% or more reduction in LDL-C from baseline or LDL-C of < 55 mg/dL T2D with high-risk for ASCVD- target LDL-C of < 70 mg/dL T2D with low-risk for ASCVD- target LDL-C of < 100 mg/dL	Measure at initial visit and every 3 months if drug therapy changes otherwise every year
Cardiac assessment	BP<130/80 mmHg if tolerated Normal ECG, ECHO, and biomarkers	Measure BP every visit An initial non-invasive cardiac exam such as ECG, ECHO, and with or without biomarkers to screen for HF
Renal assessment (kidney function test)	Normal kidney function test, absence of albuminuria or reduction to <30mg/g (UACR)/normal eGFR adjusted according to age	Request serum creatinine to calculate eGFR and request urine albumin and creatinine to calculate the UACR at initial visit and every 6 months or every 3 months in case of renal impairment

BP: Blood Pressure; ECG: Electrocardiogram; ECHO: Echocardiography; eGFR: estimated Glomerular Filtration Rate; LDL-C: Low Density Lipoprotein Cholesterol; UACR: Urine Albumin-to-Creatinine Ratio; HF: Heart Failure.

4.3. Lifestyle Modifications

All patients with T2D should be offered individualized and comprehensive lifestyle modifications that encompasses weight management (weight reduction including bariatric surgery if required), physical activity, dietary counseling, and smoking cessation, as part of the first-line treatment. Patients and physicians should agree on a glycemic and lifestyle goals and the plans should be individualized to attain target glycemic goals. Patients who do not meet their glycemic target goals should revisit their HCPs every 3-6 months for a re-evaluation and adjustment of the management plan as required. Patients' self-monitoring, engagement, and continuous education are considered of paramount importance to achieve glycemic control [36, 39, 40].

4.4. Cardiorenal Risk Reduction in Patients with ASCVD, HF, DKD or Multiple Risk Factors and T2D

4.4.1. The Role of Glucagon-Like Peptide 1 Receptor Agonists (GLP-1RAs)

Data from GLP-1RAs Cardiovascular Outcome Trials (CVOTs) were reviewed in table 3. The following studies have been completed thus far; ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome [41]), LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [42, 43]), SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes [44]), PIONEER-6 (Peptide Innovation for Early Diabetes Treatment [45]), EXSCEL (Exenatide Study of Cardiovascular Event Lowering Trial [46]), HARMONY (HARMONY [Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease [47]), REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes [48]), and AMPLITUDE-O (A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Effect of Efpeglenatide on Cardiovascular Outcomes in Type 2 Diabetes Patients at High Cardiovascular Risk [49]). These CVOTs have differences in the type of patient population whether they have established ASCVD or at high risk for ASCVD with T2D, duration of diabetes, study duration, as well as the baseline HbA1c. The primary endpoint of the study and only statistically significant secondary endpoints were reported in table 3. Patients with established ASCVD ranged from 31% (REWIND) up to 100% (ELIXA and HARMONY). In these clinical trials and over a period of 2.1 to 3.8 years, the HbA1c was decreased on average by 0.3-1% versus placebo. Treatment with GPL-1RAs was associated the weight reduction of 0.8-4.0 kg and a SBP decrease of 0.8-2.6 mmHg. In terms of the primary endpoints of the trials, neither lixisenatide, exenatide, or oral semaglutide have shown to significantly to reduce risk of MACE. However,

liraglutide, injectable semaglutide, and efpeglenatide demonstrated a significant reduction in the risk of MACE by 12-26% (table 3). The primary endpoint of MACE was driven by reduction in CV deaths with liraglutide, decrease in MI with albiglutide, and fewer strokes with subcutaneous (s. c) semaglutide. Recent meta-analyses of GLP-1RAs showed that the risk reduction was 10-12% for 3-point MACE, 12-13% for CV death, 12% for all-cause mortality, 6-9% for MI, and 13-14% for stroke [50, 51]. Liraglutide had a relative risk reduction of the renal events by 22% (composite of persistent macroalbuminuria, doubling of serum creatinine (Sr. Cr), ESRD, or death from ESRD) [43] and s. c semaglutide reduced the composite of UACR >300 mg/g, creatinine, and doubling of SrCr or ESRD) by 36% [44]. Dulaglutide and efpeglnatide also reduced the renal outcome endpoints in REWIND and AMPLITUDE-O trials by 15% and 32%, respectively [48, 49]. According to a meta-analysis, GLP-1RAs had no effect on HHF, but they reduced the relative risk of the broad composite kidney outcome significantly by 18% (HR, 0.82; 95% CI, 0.75–0.89; P<0.001) and the benefit appeared to be driven by reduction in macroalbuminuria [51]. These distinct clinical benefits within the GLP-1RA class of drugs should be considered in the decision-making process when making the treatment selection for patients with T2D. The recent approval of tirzepatide, which is a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1RA, will offer more treatment options for T2D patients. Although, tirzepatide demonstrated superiority over semaglutide in reducing HbA1c and body weight, it carries a box warning with the risks of developing pancreatitis and thyroid C-cell tumors, including medullary thyroid cancer (MTC) like the GLP-1RAs [52]. The ongoing SURPASS-CVOT (A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes) trial should shed some light on CV and renal outcome differences with tirzepatide (dual GIP/GLP-1RA) versus dulaglutide (GLP-1RA) [53].

Table 3. *The GLP-1RAs cardio-renal outcome trials.*

Study	Drug	Study population	N	Endpoints HR (95% CI)	Comments
ELIXA [41]	Lixisenatide	T2D with h/o ACS <180 days	6,068	1° endpoint: 4-point MACE 1.02 (0.89-1.17)	Median follow-up 2.1 yrs T2D duration 9.3 yrs Baseline HbA1c 7.7% Difference in HbA1c -0.3%
LEADER [42, 43]	Liraglutide	T2D and preexisting CVD, CKD, HF, or CKD at ≥50 yrs of age or CV risk at ≥60 yrs of age	9,340	1° endpoint: 3-point MACE 0.87 (0.78-0.97) Sig. 2° endpoints: Expanded MACE 0.88 (0.81-0.96) CV death 0.78 (0.66-0.93) All-cause mortality 0.85 (0.74-0.97) Worsening nephropathy 0.78 (0.67-0.92)	Median follow-up 3.8 yrs T2D duration 12.8 yrs Baseline HbA1c 8.7% Difference in HbA1c -0.48%
SUSTAIN-6 [44]	S. C Semaglutide	T2D and preexisting CVD, CKD, HF, or CKD at ≥50 yrs of age or CV risk at ≥60 yrs of age	3,297	1° endpoint: 3-point MACE 0.74 (0.58-0.95) Sig. 2° endpoints: Expanded MACE 0.74 (0.62-0.89) Stroke 0.61 (0.38-0.99) Worsening nephropathy 0.64 (0.46-0.88)	Median follow-up 2.1 yrs T2D duration 13.9 yrs Baseline HbA1c 8.7% Difference in HbA1c -0.7-1%
EXSCEL [46]	Exenatide	T2D with or without preexisting CVD	14,752	1° endpoint: 3-point MACE 0.91 (0.83-1.00) Sig. 2°endpoints: All-cause mortality 0.86 (0.77-0.97)	Median follow-up 3.2 yrs T2D duration 12 yrs Baseline HbA1c 8% Difference in HbA1c -0.5%
REWIND [48]	Dulaglutide	T2D and prior ASCVD event or risk factors for ASCVD	9,901	1° endpoint: 3-point MACE 0.88 (0.79-0.99) Sig. 2° endpoints: Composite microvascular outcome (eye or renal) 0.87 (0.79-0.95) Stroke 0.76 (0.61-0.95) Worsening nephropathy 0.85 (0.77-0.93)	Median follow-up 5.4 yrs T2D duration 10.5 yrs Baseline HbA1c 7.4% Difference in HbA1c -0.48-0.61%
PIONEER [45]	Oral Semaglutide	T2D and high CV risk (age ≥50 yrs with established CVD or CKD, or age ≥60 yrs with CV risk factors only	3,183	1° endpoint: 3-point MACE 0.79 (0.57-1.11) Sig. 2° endpoints: CV death 0.49 (0.27-0.92) All-cause mortality 0.51 (0.31-0.84)	Median follow-up 1.3 yrs T2D duration 14.9 yrs Baseline HbA1c 8.2% Difference in HbA1c -0.7%
HARMONY [47]	Albiglutide	T2D and established CVD	9,463	1° endpoint: 3-point MACE 0.78 (0.68-0.9 for non-inferiority and 0.88 (0.7-0.99) for superiority	Median follow-up 1.5 yrs T2D duration 13.8 yrs Baseline HbA1c 8.7% Difference in HbA1c -0.63%

AMPLITUDE-O (A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Effect of Efpeglenatide on Cardiovascular Outcomes in Type 2 Diabetes Patients at High Cardiovascular Risk); ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome); EXSCEL (Exenatide Study of Cardiovascular Event Lowering Trial); HARMONY (HARMONY [Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease); LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results); PIONEER-6 (Peptide Innovation for Early Diabetes Treatment); REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes); SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes).

4.4.2. The Role of Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2is)

(i). SGLT2is CVOTs in Patients with T2D

Several randomized placebo controlled CVOTs with the SGLT2is were conducted are shown in table 4; EMPA-REG (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients [54, 55]), CANVAS (Canagliflozin Cardiovascular Assessment Study [56]), DECLARE–TIMI 58 (Dapagliflozin Effect on Cardiovascular Events trial [57]), VERTIS-CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes trial [58]), and SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk [59]). Most of these large-scale trials included patients with T2D with pre-existing ASCVD or at ASCVD risk. In the EMPA-REG and VERTIS-CV, all enrolled patients had an established ASCVD. In CANVAS, DECLARE-TIMI 58, and SCORED 66%, 41%, and 51% had an established ASCVD at baseline, respectively. The HbA1c was reduced in the range of 0.36-0.58%, SBP by 2-3.9 mmHg, and weight by 1-2.8 kg over different periods varying from 1 to 4 years in duration. A similar reduction in MACE of 14% was demonstrated with empagliflozin and canagliflozin in the EMPA-REG and CANVAS trials, respectively [54, 56]. The reduction of the primary endpoint was driven by 38% in CV mortality reduction in the EMPA-REG trial [54]. DECLARE-TIMI 58 and VERITS-CV demonstrated a non-significant reduction in MACE of 7% and 3%, respectively [57, 58]. However, in DECLARE-TIMI 58, dapagliflozin showed a 17% relative risk reduction of CV death or HHF [57]. Meta-analyses of the SGLT2i of 3 CVOTs that are listed in table 4 (EMPA-Reg, CANVAS, and DECLARE-TIMI 58) showed reduction of MACE, CV mortality or HHF, all-cause mortality, MI, and CV death by 11%, 23%, 15%, 11%, and 16%, respectively. There was no reduction in stroke that is noteworthy in these CVOTs. The reduction of HHF and renal endpoints were seen in patients independent of the presence or absence of ASCVD or HF [51].

Table 4. *SGLTis CVOTs in T2D patients with established ASCVD or with multiple risk factors for ASCVD.*

Study	Drug	Study population	N	Endpoints HR (95% CI)	Comments
EMPA-REG [54, 55]	Empagliflozin	T2D and preexisting CVD (MI, multivessel CAD, CAD with ischemia/UA, stroke, or PAD)	7,020	1° endpoint: 3-point MACE (0.86; 0.74-0.99) Sig. 2° endpoint: CV death 0.62 (0.49-0.77) HHF 0.65 (0.5- 0.85) All-cause mortality 0.68 (0.57-0.82) Worsening nephropathy 0.61 (0.53-0.7)	Median follow-up 3.1 yrs T2D duration 57%>10 yrs Baseline HbA1c 8.1% Difference in HbA1c -0.3%
CANVAS [56]	Canagliflozin	T2D and preexisting CVD at ≥30 years of age or >2 CV risk factors at ≥50 years of age	10,142	1° endpoint: 3-point MACE 0.86 (0.75–0.97 Sig. 2° endpoint: HHF 0.67 (0.52–0.87)	Median follow-up 3.6 yrs T2D duration 13.5 yrs Baseline HbA1c 8.2% Difference in HbA1c -0.58%
DECLARE-TIMI 58 [57]	Dapagliflozin	T2D and established ASCVD or multiple risk factors for ASCVD	17,160	1° endpoint: 3-point MACE 0.93 (0.84-1.03) CV death or HHF 0.83 (0.73–0.95) Sig. 2° endpoints: Renal composite (≥40% decrease in eGFR rate to <60 mL/min/1.73 m^2, new ESRD, or death from renal or CV causes 0.76 (0.67–0.87) HHF 0.73 (0.61- 0.88) Worsening nephropathy 0.53 (0.43-0.66)	Median follow-up 4.2 yrs T2D duration 11 yrs Baseline HbA1c 8.3% Difference in HbA1c -0.43% T2D with established ASCVD 59% T2D with multiple risk factors 41%
VERTIS CV [58]	Ertugliflozin	T2D and ASCVD	8,246	1° endpoint: 3-point MACE 0.97 (0.85-1.11) Sig. 2° endpoint: HHF 0.7 (0.54-0.9)	Median follow-up 3 yrs T2D duration 12.9 yrs Baseline HbA1c 8.2% Difference in HbA1c -0.48-0.5%

(ii). SGLT2is CVOTs in Patients with Heart Failure and Reduced Ejection Fraction (HFrEF)

The SLT2i trials demonstrated the largest CV benefit in reducing HHF by 27-35%. Both trials, DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure [60]) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction [61]), have shown reduction in the composite endpoints of HHF and CV death in patients with preexisting HFrEF irrespective of whether patients had T2D or not. However, dapagliflozin demonstrated reduction in CV death while empagliflozin did not. In the Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial, the dual SGLT1/2 inhibitor also demonstrated benefit in reducing the primary endpoint of the total number of deaths from CV causes and hospitalizations and urgent visits for HF versus the placebo group (51.0 vs. 76.3; HR, 0.67; 95% [CI], 0.52 to 0.85; P<0.001) table 5 [62].

Table 5. *SGLT2i CVOTs in patients with HFrEF.*

Study	Drug	Study population	N	Endpoints HR (95% CI)	Comments
DAPA-HF [60]	Dapagliflozin	NYHA class II, III, or IV HF and an EF ≤40%, with or without T2D	4,744	1° endpoint: Worsening HF or death from CV causes 0.74 (0.65–0.85) Sig. 2° endpoints: CV death or HHF 0.75 (0.65-0.85) CV death 0.82 (0.69-0.98) HHF 0.7 (0.59-0.83) All-cause mortality 0.83 (0.71-0.97)	Median follow-up 1.5 yrs Patients with T2D 42%
EMPEROR-Reduced [61]	Empagliflozin	NYHA class II, III, or IV HF and an EF ≤40%, with or without T2D	3,730 (1856 with T2D)	1° endpoint: CV death or HHF 0.75 (0.65–0.86) Sig. 2° endpoints: Composite renal outcome 0.5 (0.32-0.77)	Median follow-up 1.3 yrs Patients with T2D 50%
SOLOIST-WHF [62]	Sotagliflozin*	T2D with HHF and received IV diuretics	1,222	1° endpoint: deaths from CV causes and hospitalizations and urgent visits for heart failure 0.67 (0.52 to 0.85) Sig. 2° endpoint: HHF 0.64 (0.49-0.83) Deaths from CV causes, HHF for HF, nonfatal MI, and nonfatal strokes 0.72 (0.56 to 0.92)	Median follow-up 9.2 months

DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure); EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction); SOLOIST-WHF: (Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure trial).

(iii). SGLT2is CVOTs in Patients with Heart Failure with Preserved Ejection Fraction (HFpEF)

Two major trials were conducted in patients with HFpEF or with left ventricular ejection fraction (LVEF >40%) in table 6. The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) trial demonstrated a relative risk reduction of 21% in the composite endpoint of CV death or HHF with empagliflozin versus placebo (HR, 0.79; 95% [CI], 0.69 to 0.90; P<0.001), which was mainly related to a 29% lower risk of HHF [63]. Most recently, the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial results showed that dapagliflozin significantly reduced the primary composite endpoint of CV death or HHF or urgent visit for HF compared to placebo by 18% (HR 0.82; 95% [CI], 0.73-0.92; p<0.001) [64]. These data with the SGLT2i provided further evidence to support their use as an essential drug therapy for HF patients regardless of the status of LVEF or the presence of T2D.

Table 6. *SGLTis CVOTs in patients with HFpEF.*

Study	Drug	Study population	N	Endpoints HR (95% CI)	Comments
EMPEROR-Preserved [63]	Empagliflozin	Patients with NYHA class II–IV HF and EF> 40% with or without T2D	5988	1°endpoints: HHF or CV death 0.79 (0.69–0.90) Sig. 2° endpoints: Total number of HHF 0.73 (0.61-0.88) eGFR decline 1.36 (1.06-1.66)	Median follow-up of 2.18 years Patients with T2D 49%
DELIVER [64]	Dapagliflozin	Patients with LVEF > 40% with or without T2D, with structural heart disease and elevated natriuretic peptide	6263	1°endpoints: composite endpoint of (HHF or urgent visit for HF, HHF, urgent visit for HF, CV death) 0.82 (0.73-0.92) Sig. 2° endpoint: Total number of worsening HF events and CV deaths 0.77 (0.67-0.89)	Median follow-up 2.3 years Patients with T2D 45%

EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction); DELIVER: (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure).

(iv). SGLT2i CVOTs in Patients with DKD

Canagliflozin demonstrated CV benefit in patients with T2D, CKD, and proteinuria in the CREDENCE (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation [65]) trial. Canagliflozin demonstrated a 30% a relative risk reduction of the primary renal endpoint (composite of ESRD, doubling of serum creatinine, or death from either renal or CV cause) versus placebo (HR =0.70; [95% CI, 0.59-0.82]). In addition, in the DAPA-CKD (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease) trial dapagliflozin reduced the risk of the composite outcome (a composite of 50% decline in eGFR, ESRD, death from renal or CV cause) by 39% (HR, 0.61 [95% CI, 0.51–0.72]) among CKD patients with or without T2D [60].

4.4.3. Cardiorenal Protection in Patients with T2D and Multiple Risk Factors (Primary Prevention)

Both the GLP-1 RAs and the SGLT2is demonstrated reduction in MACE by a similar magnitude of 12%, with the

treatment effect restricted to patients with T2D and ASCVD. However, SGLT2 inhibitors, unlike GLP-1 RAs, demonstrated risk reductions for HHF and progression of kidney disease in a broader spectrum of patient population (primary and secondary prevention population). The SGLT2is reduced the risk of HHF by 31% (HR, 0.69; 95% CI, 0.61–0.79; *P*<0.001) and they also reduced the risk of worsening eGFR, ESKD, or renal death by 45% (HR, 0.55; 95% CI, 0.48–0.64; *P*<0.001) [51]. The same analysis showed that the SGLT2is also had a similar robust reduction of 23% in HHF or CV death across primary and secondary T2D patients with and without history of HF [51].

Table 7. *SGLT2i CVOT in patients with DKD.*

Study	Drug	Study population	N	Endpoints HR (95% CI)	Comments
CREDENCE [65]	Canagliflozin	T2D and Albuminuric kidney disease	4,401	1^{O} endpoint: ESRD, doubling of creatinine, or death from renal or CV cause 0.70 (0.59–0.82) Sig. 2^{o} endpoint: HHF 0.61 (0.47-0.8)	Median follow-up 2.6 yrs T2D duration 15.8 yrs Baseline HbA1c 8.3% Difference in HbA1c -0.31%
DAPA-CKD [66]	Dapagliflozin	Albuminuric kidney disease, with or without diabetes	4,304	1^{O} endpoint: 50% decline in eGFR, ESKD, or death from renal or CV cause 0.61 (0.51–0.72) Sig. 2^{o} endpoint: All-cause mortality 0.69 (0.53-0.88)	Median follow-up 2.4 yrs Baseline HbA1c 7.1% and 7.8% with T2D Patients with T2D 68%

CREDENCE: (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation trial); DAPA-CKD (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease).

4.5. Current Clinical Guidelines Recommendations of Pharmacological Treatment in Patients with T2D

According to the current ADA guidelines, the recommendation for first-line treatment generally includes metformin with lifestyle modification. Several factors should be taken into consideration such as comorbidities, patient-centered treatment factors, cost, and management needs when initiating or adding drug therapy for the treatment of T2D patients [67]. The AACE recommends monotherapy for HbA1c <7.5% with any of the following antihyperglycemic (metformin, GLP-1RAs, SGLT2i,, thiazolidinediones (TZD), dipeptidyl peptidase-4 inhibitors (DPP-4i), glinides (GLN), alpha-glucosidase inhibitors (AGi)). However, they recommend long acting GLP-1RAs and SGLT2is as initial therapies independent of glycemic control in patients with established/high risk for ASCVD, stage 3 CKD, and HFrEF [36]. The ESC guidelines/European Association for the Study of Diabetes and the ACC 2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients with T2D guidelines advocate the use of GLP-1RAs or SGLT2is as first-line therapies in patients with established or at high risk for ASCVD [31, 68]. A recent consensus report provided a clear guidance to practitioners on the best approaches for screening and diagnosing HF in patients with T2D and also incorporated the SGLT2i as a treatment recommendation in addition to the standard HF therapies to prevent progression of HF for those with HFrEF and also HFpEF [69].

Metformin has been widely, as it has been shown to be a cost-effective treatment option for lowering blood glucose level with fewer hypoglycemic episodes than sulfonylurea or insulin and it has been associated with weight loss [70-73]. In a meta-analysis that included 40 studies comprising 1,066,408 patients, the cardiovascular mortality, all-cause mortality, and incidence of CV events were reduced with metformin in patients with CAD. In addition, a subgroup analysis demonstrated that metformin reduced all-cause mortality in MI and HF and the incidence of CV events in patients with HF and T2D [74]. However, another meta-analysis showed uncertainty about whether metformin reduces risk of CVD among patients with T2D [75]. More recently, an 18-year follow-up to the landmark Diabetes Prevention Program (DPP) outcome trial, treatment with metformin was no better than placebo at reducing the risk of major CV events (MACE; HR 1.03, 95% CI 0.78-1.37, P=0.81) [76]. Metformin has been known for its gastrointestinal side effects in 25% of patients, especially in women and elderly [77, 78]. These side effects can be overcome by dose titration and the use of delayed-release formulation of metformin [79, 80]. In order to avoid clinical inertia, dual treatment should be considered 3 months after initiating first-line treatment and in patients who have a high HbA1c level ≥1.5% at baseline to have a better glycemic control. Due to the progressive nature of T2D, glycemic control with monotherapy is not usually sustainable over time, and subsequently treatment with dual or triple therapy is required to attain glycemic control [67]. The VERIFY (Vildagliptin efficacy in combination with metformin for early treatment of type 2 diabetes) trial demonstrated the superiority of early combination therapy to the sequential method of adding drug therapy in extending treatment failure [81]. These data suggest that more early intensive antidiabetic treatment has benefits and it should be considered, especially in patients who have high HbA1c at baseline.

As a result of all the CVOTs with GLP-1RAs and SGLT2is, there has been a paradigm shift in therapeutic focus from reducing HbA1c to prevent microvascular complications to also reducing risk of CV outcomes [67]. To date, two disease modifying drug (DMD) classes for the treatment of T2D, GLP-1RAs and SGLT2is have been shown to significantly reduce the risk of major CV events (composite endpoint of MI, stroke, and CV death or MACE) in patients with or without ASCVD with T2D [41, 43, 44, 47, 48, 55-57]. Both of these DMD classes have also shown benefits in reducing the progression of DKD [63, 65, 66]. Furthermore, the use of SGLT2is was demonstrated to be beneficial in the treatment of HF (HFrEF and HFpEF) in

patients with or without T2D, as they reduce rate of HHF [60-64]. Current international practice guidelines recommend the use antidiabetic agents based on evidence of ASCVD or risk factors assessment of T2D patients [67]. For patients with an established or at high risk of ASCVD and DKD, it is recommended to initiate therapy with GLP-1RA or SGLT2is in this patient population irrespective of baseline HbA1c or metformin use. Patients with T2D and at risk for HF, SGLT2is are recommended to be used in these patients and either GLP-1RAs or SGLT2is for patients with CKD.

4.6. Treatment Considerations

Treatment selection should be based on the evidence of reducing CV events and preventing complications before they occur including HHF and renal progression for patients with T2D. With the existing data and more emerging data with DMDs, the evidence clearly shows that only the GLP-1RAs and the SGLT2is have demonstrated beneficial cardiorenal outcomes in patients with established ASCVD and T2D and the SGL2is have shown consistent reduction of HHF and delay in progression of kidney disease in patients with or without T2D, irrespective of glycemic control [51]. There is one trial that demonstrated reduction in fatal or non-fatal stroke or MI with pioglitazone in patients with insulin resistance ischemic and post-stroke or transient ischemic attacks [82]. However, TZDs should be avoided in patients with HF. Insulin or pioglitazone can be used in patients with T2D and ASCVD after other options have been exhausted to meet glycemic goals, but GLP-1RAs are recommended before insulin as an injectable treatment since they have been proven to reduce CV events [67]. In a recent meta-analysis, insulin treatment in patients with HF has been shown to have a higher risk of death and HHF, regardless of duration of diabetes [83]. In general, treatment should focus on glycemic control to prevent and treat diabetic nephropathy and other microvascular complications as well as reduce CV events. However, treatment with metformin should be used with caution and should be stopped if there is a severe renal impairment (eGFR falls below 30 ml/min/1.73m^2) [84]. The use of SUs and other secretagogues in patients with CKD depends on the renal excretion of the drug, the level of renal impairment, and the hypoglycemia risk [85]. Newer agents such as the SGLT2is and GLP-1RAs tend to reduce weight and BP, and they have minimal risk of severe hypoglycemia [42-48, 55-58]. However, there is higher risk of genital mycotic infections and dehydration, related to glucosuria and polyuria, respectively, with SGLT2is [85]. Patients should be educated on proper hygiene methods to minimize potential infections [86]. Common concerns with the GLP-1RAs are pancreatitis, pancreatic cancer, and medullary thyroid cancer, as they were reported in clinical trials [42-48]. Therefore, treatment of patients with T2D and any history of any of these should be contraindicated.

4.7. Local Consensus Statement and Treatment Algorithm

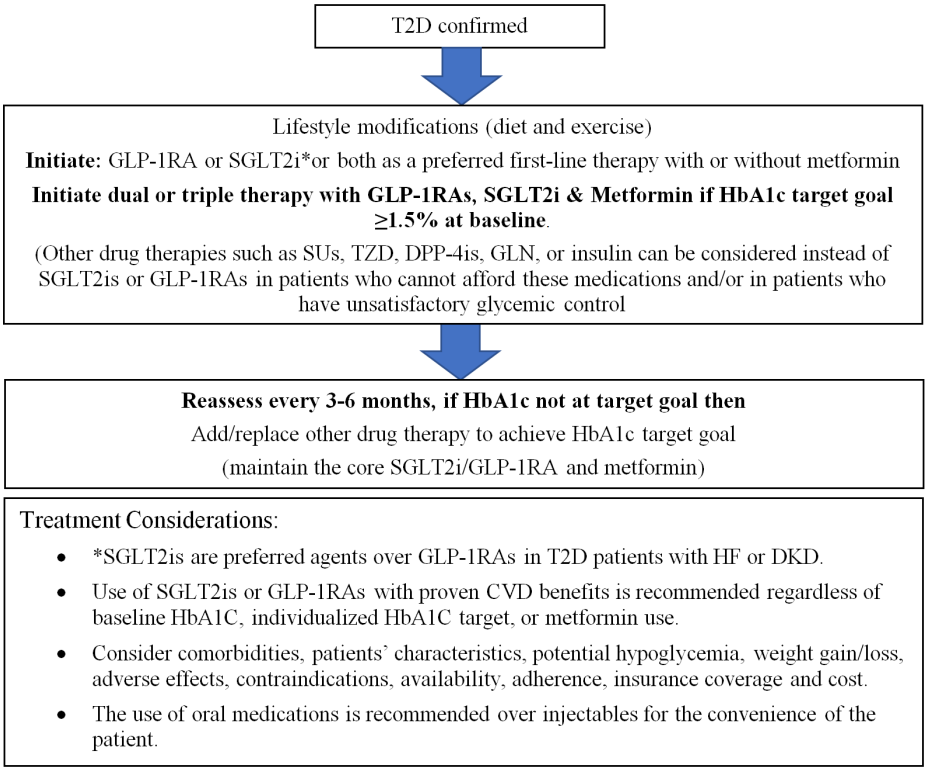

Figure 1. *Local treatment algorithm consensus.*

Recent CVOTs had clinical implications, which impacted the strategy in treating patients with T2D, focusing on CVD risk reduction, as CVD remains the leading cause of death in this patient population. The consensus of the panel of experts

in Jordan have taken into consideration that CVOTs have clearly shown that GLP-1RAs and SGLT2is reduced CV events. The GLP-1RAs and SGLT2is have shown similar benefits in patients with established ASCVD while the SGLT2is have demonstrated greater reduction in HHF and DKD across a wider spectrum of patient population with or without T2D. The panel recommended that the selection of first-line pharmacotherapy to be either GLP-1RAs or SGLT2i with or without metformin for all T2D patients (figure 1). The consensus recommendation was to use the SGLT2is for T2D patients with history of HF or DKD. They also preferred the use of oral medications over injectables for the convenience of patients.

Therapy with additional agents can be considered if patients do not meet their HbA1c target goal with the initial therapy of SGLT2i or GLP-1RA or the combination of the two with metformin, including other medications such as SUs, TZD, DPP-4is, GLN, or insulin. Special patients' conditions have to be considered such as baseline HbA1c, risk of hypoglycemia, impact on weight, potential adverse effects, availability of drug therapy in Jordan, insurance coverage, cost, patient preferences and local experience with drug therapy. Dual or triple therapy is recommended initially if the HbA1c is ≥1.5% rather than sequentially. Subsequently, the local panel of experts have developed the following treatment algorithm based on the evidence from CVOTs, meta-analyses, as well as international clinical practice guidelines for the treatment of T2D (figure 1).

4.8. A Multidisciplinary Approach in T2D Patient Care

T2D is a complex disease and involves multiple organs, requiring multidisciplinary collaboration of HCPs to achieve optimal management. Therefore, having a panel of experts with different specialties, providing practical recommendations is important to establish collaborative efforts for implementation. The panel of experts recommend that the HCP should refer patients to the endocrinologist or diabetologist, especially the T2D cases are difficult to manage such as those who fail to achieve glycemic target despite many interventions or in the frequent occurrence of an adverse event that warrants special attention such as hypoglycemia. The HCP should consult the nephrologist if the renal function is deteriorating (>20% increase from baseline in serum creatinine or eGFR is <60ml/min or a decrease of >15% of eGFR over a period of 12 months or albuminuria >30 mg/dL. The HCP should refer the T2D patient to a cardiologist or a nephrologist if patients have difficult to control high blood pressure. The cardiologist should be consulted for HF assessment, especially if the patient has signs and symptoms of HF or ASCVD or multiple risk factors predisposing them to HF or CVD such as uncontrolled hypertension or hyperlipidemia despite appropriate interventions. The HCP should also refer the patient to the ophthalmologist to check for retinopathy and vascular medicine/surgeon if there is a suspicion of peripheral neuropathy or peripheral vascular disease. Data revealed that a multidisciplinary collaborative care can improve clinical, humanistic, and economic outcomes in patients with uncontrolled T2D over a period of 3-12 months [88].

4.9. Patient Education and Empowerment

T2D is a complex disease that requires patients to make numerous daily decisions regarding nutrition, physical activity, and medications. The involvement of patients in their own care is considered a cornerstone of care in T2D. All patients with T2D should participate in T2D self-management education to acquire the knowledge, skills, and abilities necessary for self-care as well as be involved in the treatment decision-process regarding treatment and glycemic targets [39]. The HCP should facilitate this process to empower the patient with T2D to make the right decisions. Patient empowerment is considered a continuous process to build knowledge, motivation, and capacity within the patient to take control of the disease [89].

5. Conclusion

T2D is a complex disease that leads to both microvascular and macrovascular complications. The HCPs are on the frontline and in contact with T2D patients. Therefore, it was important to develop consensus statements to help the HCPs identify and manage patients with T2D, assessing all levels of metabolic and cardiorenal risks. Because T2D is a progressive disease, it is important to achieve glycemic control, however, it is more important to prevent CV events, including HHF, and progression of kidney disease to reduce morbidity and mortality. Therefore, it is equally important to identify and manage cardiorenal risk factors simultaneously with controlling glycemia to improve the overall outcome. Moreover, HCPs should be aware that HF is very common in patients with T2D, and assessment of cardiac function is crucial in this patient population. HCPs have to know that treatment with DMDs such as GLP-1RAs and/or SGLT2is reduce MACE in patients with T2D and established ASCVD. In addition, treatment with the SGLT2is reduce HHF and provide renoprotection, irrespective of glycemic control in patients with or without T2D. The importance of lifestyle modification, including diet counseling, physical activity, and tobacco cessation should also be emphasized along with the appropriate treatment. The HCPs are encouraged to manage patients with T2D in a multidisciplinary collaborative care approach to improve clinical outcome.

Consensus Statement Key Points Summary

1) Screen patients for T2D at a younger age, especially if they are overweight. (≥25 years of age for those who are overweight or obese defined as a body mass index ≥25 and ≥ 30, respectively).
2) It is recommended to confirm the diagnosis of T2D and evaluate the metabolic–cardio–renal baseline status through measurement of HbA1c, LDL-C, BP, microalbuminuria, eGFR and UACR.

3) Request serum creatinine to calculate the eGFR and request the urine albumin and creatinine to assess the UACR for a complete initial renal risk assessment and monitoring purposes.
4) Optimize treatment to achieve glycemic and BP control, which may slow decline in kidney function in patients with T2D.
5) Modify individual CV risk factors to improve CV outcome in patients with T2D.
6) It is recommended that all T2D patients should be screened for HF, as T2D increases the risk of HF development.
7) GLP1-RAs and SGLT2is are used as glucose lowering therapies, with additional benefits of weight loss and BP reduction.
8) Both GLP1-RAs and SGLT2is confer cardiovascular benefits in patients with established ASCVD, whereas SGLT2i have additional benefits in preventing HHF and providing renoprotection in broad spectrum of patients.
9) GLP-1RAs and/or SGLT2is with or without metformin are preferred agents as first-line therapies in patients with T2D and established ASCVD, regardless of glycemic control.
10) The SGLT2is with or without metformin are preferred agents as first-line therapies in patients with T2D and HF or DKD, irrespective of glycemic control.
11) Other antidiabetic agents can be used as add-ons to attain glycemic control.
12) Consider adverse effects, cost, and availability of these drugs.
13) Consult the specialist (s) for further management and treatment of patients with T2D.
14) Involve the patient in the treatment plan and educate them gain the knowledge and the skills about T2D.

Conflict of Interest

The authors received fair market honorarium for their time spent attending the consensus meeting.

Disclosures

AstraZeneca reviewed the manuscript for medical accuracy only before journal submission. The authors are fully responsible for the content of this manuscript, and the views and opinions described in the publication reflect solely those of the authors.

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