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GUIDELINES

Latin American Expert Consensus for Comprehensive Management of Type 2 Diabetes from a Metabolic–Cardio–Renal Perspective for the Primary Care Physician

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ABSTRACT

Growing scientific evidence from studies on type 2 diabetes (T2D) has recently led to a better understanding of the associated metabolic–cardio–renal risks. The large amount of available information makes it essential to have a practical guide that summarizes the recommendations for the initial management of patients with T2D, integrating different aspects of endocrinology, cardiology, and nephrology. The expert consensus presented here does not attempt to summarize all the evidence in this regard but rather attempts to define practical summary recommendations for the primary

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care physician to improve the clinical prognosis and management of patients with T2D, while ensuring economic sustainability of health systems, beyond glycemic control.

Keywords: Antidiabetic drugs; Cardiovascular disease; Heart failure; Hypoglycemia; Type 2 diabetes mellitus

Key Summary Points
Background
Recent reports indicate that the disease and economic burden of type 2 diabetes (T2D) is increasing steadily in the Latin American region.
Primary care physicians (PCPs), who in most cases diagnose and manage patients with T2D, face multifactorial challenges that hinder translating the guidelines, which are often developed by specialists.
PCPs also face patient-specific barriers, such as social influences, perceptions and beliefs, education and lifestyle, patient compliance, paternalistic attitude, vertical communication, and lack of support related to diet at home, while managing patients with T2D.
In this regard, the consensus document presented here provides the following recommendations (from the metabolic–cardio–renal perspective) to PCPs from Latin American region:
Recommendations
At the first visit, it is recommended to confirm the diagnosis of diabetes and evaluate the metabolic–cardio–renal baseline status through measurement of glycosylated hemoglobin (HbA1c), low-density lipoprotein cholesterol (LDL-C), blood pressure (BP), microalbuminuria, estimated glomerular filtration rate (eGFR), and renal hyperfiltration.
Next, it is important to set HbA1c, BP and LDL-C targets that may vary depending on the patient's history (duration of diabetes, cardiovascular [CV] disease, other CV risk factors, renal status, and other comorbidities).
Management of each risk factor (metabolic, cardiac, and renal) includes:
Patient counseling on the asymptomatic and progressive nature of the disease, importance of the need to check blood sugar regularly despite being on treatment, treatment adherence, and continuous glucose monitoring.
Pharmacological treatment for each risk factor: angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers [ACEI/ARB]) for BP; statins for LDL-C; sodium-glucose co-transporter-2 inhibitors for renal hyperfiltration; ACEI/ARB for microalbuminuria/hypertension; close monitoring of potassium, creatinine levels and GFR.
Consultation with a specialist (diabetologist, cardiologist, and nephrologist) when required.
Other general recommendations for glycemic control include balanced isocaloric diet comprising all nutrients, moderate to vigorous physical activity, smoking cessation, and cautious use of antiplatelet drugs (dual therapy with aspirin and clopidogrel).

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13142708.

INTRODUCTION

According to International Diabetes Federation (IDF) estimates, there were globally 463 million people with diabetes in 2019 (9.3% of all adults worldwide aged 20–79 years). By 2045, it is estimated that 700 million people will be affected, an increase of 51% in 26 years. The mortality rate due to diabetes is estimated to be 11.3% worldwide, with 46.2% of these deaths occurring in people aged < 60 years [1]. The total diabetes-related health expenditure in 2019 (USD 760 billion) increased by 4.5% compared to 2017 (USD 727 billion) for adults aged 20–79 years and is projected to increase 11.2% by 2045 [1].

More than 90% of patients with type 2 diabetes (T2D) report micro- and macrovascular complications, such as retinopathy, nephropathy, neuropathy, and cardiovascular diseases (CVD), resulting in significant physical and psychological distress and imposing a greater burden on healthcare systems [2]. The IDF estimated that approximately 4.2 million adults died because of diabetes and its complications in 2019, which is equivalent to one death every 8 s [1]. Atherosclerotic events remain the most important driver of mortality and morbidity in patients with T2D, and the manifestation of heart failure (HF) is common in these patients, negatively influencing life expectancy and quality of life [3]. The Framingham Heart Study reported that the risk of HF is twofold higher in men and threefold higher in women with T2D [4].

Data from the Pan American Health Organization (PAHO) and the World Health Organization (WHO) for 2014 indicate that the prevalence of diabetes in the Americas is 8.6% in men and 8.4% in women [5]. From this data set, the prevalence of macro- and microvascular complications in the Latin American T2D cohort was 13.8% and 15.2%, respectively. Additionally, approximately half of the Latin American patients had hypertension (55.5%) and hyperlipidemia (45.9%) [6]. Despite a great deal of updated information being available, many patients fail to achieve their treatment goals. Furthermore, the IDF Atlas 2019 listed Brazil and Mexico among top ten countries with high healthcare expenditure due to diabetes in 2019 [1]. It is projected that, by 2025 the economic burden of diabetes care would be highest in Mexico (USD 8604 million) followed by Brazil (USD 7230 million), Argentina (USD 1048 million), Colombia (USD 828 million), and Venezuela (USD 742 million). Taking into account the increasing disease and economic burdens, it is important to prevent complications by achieving treatment goals which can result in cost-effective management of diabetes [7].

Primary care physicians (PCPs), who in most cases diagnose and manage patients with T2D, face multifactorial challenges that hinder translating the guidelines, which are often developed by specialists. Barriers to the effective management of T2D include limited resources, environmental constraints, limited knowledge and skills, lack of treatment adherence, or patient-related factors, such as social influences, perceptions and beliefs, education, lifestyle, among others [8–10]. Additionally, PCPs are often concerned about the medication issues, the complexity in developing personalized approach in the case of comorbidities, and cost of the medications [11]. The DEAL survey conducted among general practitioners from Latin American countries identified patient compliance issues in the T2D patients with regards to medication, glucose self-monitoring, diet, and exercise [12]. Additionally, Blasco et al. identified patient-specific barriers, such as paternalistic attitude, vertical communication, lack of patient-centric communication by healthcare professionals, and lack of support related to diet at home, in the Latin American region [13]. Education of PCPs and ensuring coordinated activity among different levels of health care is necessary for improved outcomes. The Municipality of Buenos Aires introduced an online diabetes care education program at the primary care level that reported significant improvement not only in the clinical outcomes at 1 year but also higher treatment adherence, better T2D control, and reduced cost of care [14]. Although multiple detailed guidelines provide guidance to specialists, very few guidelines have been developed to help the PCPs who treat patients with T2D [15, 16].

This document provides consensus recommendations for PCPs to guide the diagnosis, assessment, and management of metabolic–cardio–renal risks in patients with T2D from the Latin America region. The primary objective of this consensus document is to integrate the metabolic, cardiac, and nephrological views in a single practical and simple guideline for the management of patients with T2D in Latin America, starting from the first contact with their PCP.

METHODOLOGY

The recommendations presented in this document are the result of a discussion among medical specialists (four endocrinologists, five cardiologists, and three nephrologists) and experts in clinical research. Existing scientific evidence on the prevention of complications in diabetes with a metabolic–cardio–renal approach was critically reviewed and discussed to formulate recommendations.

The level of evidence and the strength of the recommendation associated with each of them were not included in the development of the recommendations because of the complexity involved in exchanging the different scales used by the medical societies. Reference was made to the latest consensus guidelines from the European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD), and American Association of Diabetes (ADA) for additional recommendations.

A questionnaire comprising 20 questions on different aspects of T2D management (including treatment inertia, early diagnosis and management of CV and renal diseases, and holistic perspective on T2D management) was sent to the respective experts prior to the meeting, which was held on 11 July 2019 at the University of Campinas, Sao Paulo State, Brazil. The consensus statements were drafted and reviewed by all the authors; sections of the manuscript were further refined through correspondence until a consensus was reached.

The recommendations are summarized in five steps:

1. Diagnosis.
2. Assessment of metabolic–cardio–renal risk.
3. Determination of target glycosylated hemoglobin (HbA1c), blood pressure (BP), and low-density lipoprotein cholesterol (LDL-C) levels.
4. Management of each risk factor.
5. Other general recommendations.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

STEP 1: CONSENSUS RECOMMENDATIONS ON DIAGNOSIS OF DIABETES

Diabetes occurs (particularly because of ethnicity) at a younger age (before 45 years) in the Latin American region, resulting in long-term exposure to hyperglycemia and, consequently, a greater risk of early complications [17]. Hence, the expert panel emphasizes a prompt evaluation and diagnosis of T2D. The consensus recommends similar diagnostic criteria (with some modification) as proposed by the ADA [18], as shown in Fig. 1. Diabetes can be diagnosed based on the fasting plasma glucose (FPG) value or on the 2-h PG value following oral consumption of 75 g glucose (oral glucose tolerance test), or on the HbA1c value. However, patients exhibiting classical symptoms of hyperglycemia can undergo a random plasma glucose test. Similar recommendations are provided by the Latin American consensus published in 2019 for T2D patients with hypertension [19].

STEP 2: CONSENSUS RECOMMENDATIONS ON THE ASSESSMENT OF METABOLIC–CARDIO–RENAL RISKS

The scientific evidence published between 2007 and 2017 report that, overall, 32.2% of patients with T2D developed CVD, attributing to 50% of

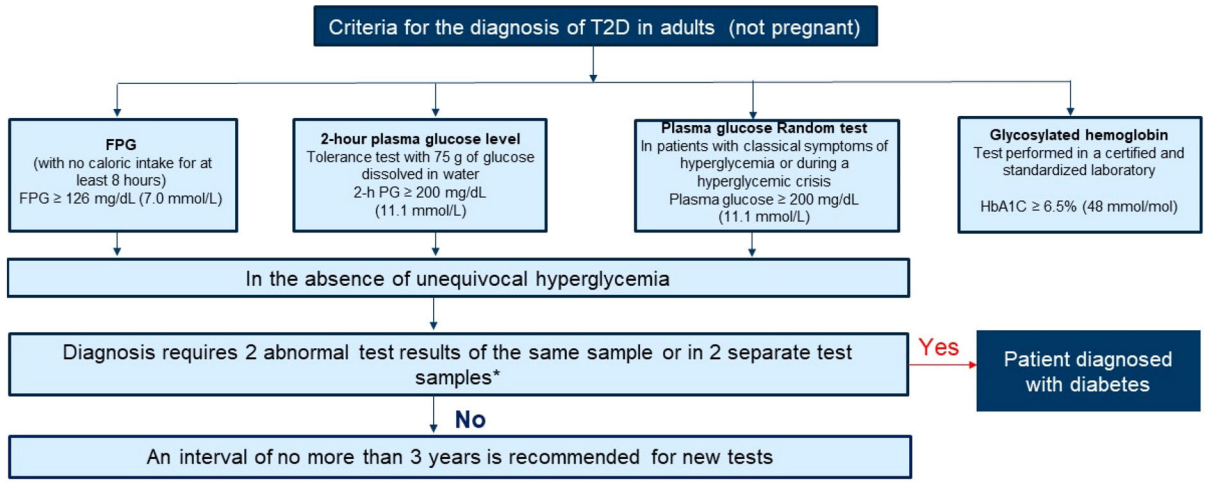


Fig. 1 Criteria for the diagnosis of type 2 diabetes in adults (not pregnant). Asterisk: The same tests can be used for screening and for diagnosis of patients with diabetes. *FPG* Fasting plasma glucose, *HbA1c* glycated hemoglobin, *PG* plasma glucose, *T2D* type 2 diabetes

all deaths in T2D patients [20]. In addition, patients with diabetes have twofold higher odds of developing chronic kidney disease [21]. Given the higher disease and economic burdens in the Latin American region, the expert panel recommends independent consideration for metabolic–cardio–renal risk factors. In this regard, the evaluation of baseline status with respect to metabolic–cardio–renal risk factors (HbA1c, LDL-C, BP, microalbuminuria, and estimated glomerular filtration rate [eGFR]) should be performed at the first visit. Thus, the evaluation of each patient should focus on immediately identifying and categorizing their metabolic–cardio–renal situation, which would allow prompt prioritization of measures to bring these levels under control.

The timely determination of initial hyperfiltration and the presence or absence of microalbuminuria is essential. Both renal hyperfiltration and microalbuminuria should be incorporated as monitoring and treatment goals along with the other classic risk factors (BP, lipids, and HbA1c). A study by Cachat et al. explored the assessment and definition of glomerular hyperfiltration (GH) from the medical literature ($N = 405$ studies). Of the 405 studies included in the review, the 225 studies that used threshold to define GH (199 studies used a single threshold and 26 studies used several or continuous thresholds adjusted for patient age and/or sex) reported that the median GH was 135 (range 90.7–175) mL/min/1.73 m^2 [22]. As GH is considered to be a mechanism of damage and progression of kidney disease, it should be considered to be present in patients with decreased or normal kidney function [23].

Since the early 1980s, microalbuminuria has been considered to be a well-known marker of proteinuria, poor renal outcomes, and mortality in patients with T2D [24, 25]. When the renal function is normal, microalbuminuria should be measured annually, whereas in the case of renal impairment or abnormalities, microalbuminuria should be assessed every 3 months [26]. In addition, the expert panel also recommends that it is possible to assess microalbuminuria on a monthly basis if there is a need to adjust treatment, until the objectives of the therapeutic change are reached. Recommendations from the ADA on the assessment of albuminuria and eGFR are in line with these recommendations [27]. The different recommended equations used for measuring eGFR are indicated in Box 1.

Box 1 Recommended equations for measuring estimated glomerular filtration rate

1. Cockcroft–Gault (CG) equation:

([140 − age] × weight [kg])/(sCr [mg/dL] × 72) (× 0.85 for females) [74]

2. Four-variable Modification of Diet in Renal Disease (MDRD) equation traceable to IDMS reference:

$(175 \times [\text{sCr}]^{-1.154} \times [\text{age}]^{-0.203}$ [× 1.212 if black race] [× 0.742 if females] [75]

3. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation:

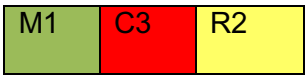
$141 \times \min.(\text{sCr}/\kappa, 1)^{\alpha} \times \max.(\text{sCr}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}}$ [× 1.018 for females] [× 1.159 for black race][a] [76]

The American Diabetes Association (ADA) guidelines recommend the MDRD formula while the present expert panel recommended using the CKD-EPI equation for measuring estimated glomerular filtration rate (eGFR)
IDMS Isotopic dilution mass spectrophotometry, *sCr* serum creatinine
[a] κ is 0.7 for females and 0.9 for males; α is − 0.329 for females and − 0.411 for males; min. is sCr minimum value/κ or 1, max. is the sCr maximum value/κ or 1

The risk parameters that a PCP should consider from the metabolic–cardio–renal perspective to identify T2D patients at a higher risk of developing associated morbidities are shown in Table 1 [26, 28]. This evaluation method is aimed at not only identifying the patient with T2D but also at identifying some of the elements of associated CVD risks. This stratification is used to define a patient's health status and allows a rapid assessment of metabolic–cardio–renal risk factors from the initial consultation. In the case of CVD and renal risk, the higher of the two values exhibited by the patient at the time of assessment is used. However, CVD risk and kidney disease are highly interrelated, and renal insufficiency is the most important CVD risk factor, even higher than tobacco use and dyslipidemia. Furthermore, albuminuria is, in addition to being an indicator of renal impact, a marker of endothelial damage [29]. In this context, we provide an example of a 75-year-old patient, weighing 94 kg, undergoing evaluation.

The patient's BP is 145/85 mmHg, and test results are as follows: HbA1c, 6.9%; creatinine, 1.5 mg/dL; albuminuria, 185 mg/day; lipid profile: total cholesterol, 205 mg/dL; triglycerides, 165 mg/dL; high-density lipoprotein cholesterol, 23 mg/dL; and LDL-C, 149 mg/dL. The GFR estimation by the Cockcroft–Gault equation is 56.6 mL/min/1.73 m^2.

Based on the test results, the patient is diagnosed with diabetes, with a higher CV risk compared to renal or metabolic risk:



Stratifying patients based on their metabolic (M), cardio (C), and renal (R) risk factors, as shown in color-coded image, will allow PCPs to identify patients who are at a greater risk and prioritize the treatment.

STEP 3: CONSENSUS RECOMMENDATIONS ON ESTABLISHING HbA1c, BP, and LDL-C Goals

The HbA1c, BP, and LDL-C goals may vary depending on the patient's history and are indicated in Table 2 as recommended by the ESC guidelines [30]. From the renal point of view, the objective is that every patient maintains glomerular filtration within normal limits (90–120 mL/min) without microalbuminuria. A Latin American consensus published in the same year recommends HbA1c of at least 6.5% and classifies hypertension into grade 1 (between 140/90 and 159/99 mmHg), grade 2 (between 160/100 and 179/109 mmHg), and grade 3 (≥ 180/110 mmHg) [19]. Another Latin American consensus published in 2010 proposed treatment goals for HbA1c as < 7%, BP ≤ 130/80 mmHg, and LDL-C target as < 100 mg/dL [31].

The guideline published by the ESC in 2019 has amended lipid targets according to the CVD

Table 1 Initial assessment of patients with type 2 diabetes

Area	Risk Parameter	Treatment Objectives or Goals →		
		3	2	1
Metabolic	HbA1c	>8%	7%-8%	<7%
	Hypoglycemia	Severe hypoglycemia	Mild hypoglycemia	Without hypoglycemia
Cardiac	BP (mm Hg)	>140/90	>130/80 and <140/90	<130/80 and >120/70
	LDL-C (mg/dL)	>130	>100 and <130	<100
Renal	GFR (mL/min/1.73 m^2)	<30 to >150	30-90	90-150
	Albuminuria	Macroalbuminuria >300 mg/g (albumin/creatinine)	Microalbuminuria from 30 to 300 mg/g (albumin/creatinine)	Absent or <30 mg/g

BP blood pressure, *GFR* glomerular filtration rate, *HbA1c* glycosylated hemoglobin, *LDL-C* low-density lipoprotein cholesterol

risk in patients with T2D. The ESC recommends an 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 [30].

STEP 4: CONSENSUS RECOMMENDATIONS ON THE MANAGEMENT OF EACH RISK FACTOR

Metabolic Control

Glycosylated Hemoglobin

Given the asymptomatic nature of diabetes, patients remain with high HbA1c values for years without treatment intensification, increasing the risk of microvascular complications. The DISCOVER study found that in Latin America, 80% of patients had an average HbA1c of 8.5% (vs. 7%, suggested by the treatment guidelines). The study highlighted the clinical inertia in treatment intensification and the need for intensive risk factor screening to improve the prognosis of these patients from the Latin American region [6]. Additionally, it is mandatory to acknowledge strategies between physicians and patients to improve adherence and lifestyle changes. It is a process of communication and commitment.

Some recommendations to avoid clinical inertia are:

Table 2 Glycosylated hemoglobin, blood pressure, and low-density lipoprotein cholesterol goals that may vary depending on special situations [30]

Risk factor	Target
BP	SBP should be 130 mmHg in patients with DM; < 130 mmHg if tolerated, but not < 120 mmHg
	Older people (> 65 years): SBP goal is to maintain between 130 and 139 mmHg
	DBP target is < 80 mmHg but not < 70 mmHg
HbA1c	Younger patients with a short duration of DM and no evidence of CVD should maintain HbA1c 6.0–6.5%
	Fragile, elderly patients with a long history of DM, limited life expectancy, and multiple comorbidities should maintain HbA1c < 8% or ≤ 9%
LDL-C	DM patients with very high CV risk: < 55 mg/dL
	DM patients with high CV risk: < 70 mg/dL
	DM patients with moderate CV risk: < 100 mg/dL

BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure

- Do not delay therapeutic escalation while awaiting adherence to lifestyle changes. Evidence-based clinical practice recommendations should be followed.
- Adapt a language that is appropriate to each patient.
- Agree on therapeutic goals with the patient; emphasize the importance of treatment adherence and the risk of poor metabolic control with the patient and seek his/her commitment.
- Discuss the asymptomatic nature of the disease and the need for periodic control with the patient.
- Discuss with the patient the progressive nature of the disease and the need to check blood sugar regularly despite being on treatment.
- Design a written follow-up agenda and set reminders.

The ESC guideline recommends structured self-monitoring of blood glucose (SMBG) and/or continuous glucose monitoring (CGM) to facilitate optimal glycemic control [30]. Continuous glucose monitoring (real-time or intermittent) helps overcome many limitations associated with the traditional HbA1c testing and SMBG by providing uniform tracks of the glucose concentration, thus reflecting intra- and inter-day glycemic excursions [32]. The international consensus recommends using CGM in conjunction with HbA1c in all patients with diabetes who are not achieving glycemic targets despite insulin therapy. Furthermore, it also emphasizes patient education and training for interpreting glucose data and improving treatment adherence [32].

Therapeutic Management

Recommendations for the Therapeutic Management of Blood Glucose Levels The expert panel recommends following a step-wise approach when the patient fails to achieve the HbA1c goal. The ADA/EASD guideline [33] and the ESC guideline [30] recommend sodium-glucose co-transporter 2 (SGLT2) inhibitors or glucagon-like peptide-1 (GLP-1) receptor agonists regardless of HbA1c level or individualized HbA1c target for patients with atherosclerotic CVD or high CVD risk. When HbA1c is ≥ 1.5% (12.5 mmol/mol) higher than the blood glucose target, many patients will require a combined dual therapy to achieve their HbA1c target level. In addition to pharmacological strategies, lifestyle changes and intensification of statin therapy are recommended to prevent CV complications [30]. However, if the patient is not at high CV risk, patient characteristics should be considered and relevant medication should be recommended.

The treatment decision algorithm (Fig. 2) is proposed as per the CVD risk categories defined by the ESC guidelines. The ESC guidelines

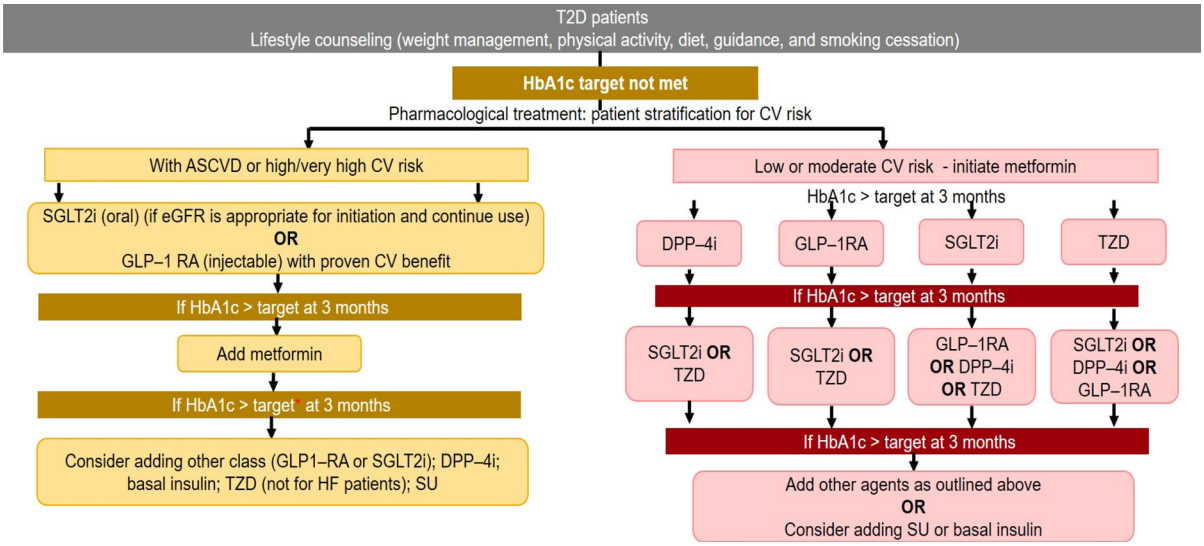


Fig. 2 Decision tree on recommendations for therapeutic management of blood glucose levels. Red asterisk: If HbA1c is 1.5% (12.5 mmol/mol) higher than the blood glucose target, consider adding SGLT2 to metformin monotherapy. ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; DPP–4i, dipeptidyl peptidase–4 inhibitor; eGFR, estimated glomerular filtration rate; GLP1–RA, glucagon like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HF, heart failure; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SU, sulfonylureas; T2D, type 2 diabetes; TZD, thiazolidinedione

Table 3 Cardiovascular risk categories in patients with diabetes [30]

CV risk level	Patient details
Very high risk	Patients with DM AND established CVD OR with target organ damage[a] OR ≥ 3 major risk factors[b]
High risk	Patients without target organ damage and any other additional risk factor but with DM duration ≥ 10 years
Moderate risk	Young patient with T2D (aged < 50 years) without any risk factors but with diabetes duration of < 10 years

CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; T1D, type 1 diabetes; T2D, type 2 diabetes

[a] Proteinuria, renal impairment defined as eGFR > 30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy

[b] Age, hypertension, dyslipidemia, smoking, and obesity

stratify patients with T2D into very high risk, high risk, and moderate risk on the basis of the presence or absence of CVD, organ damage, risk factors (such as age, hypertension, dyslipidemia, smoking, and obesity), and the duration of diabetes (Table 3) [30].

The order for management recommendations is based on the following:

- When glycemic targets are not achieved with healthy lifestyle management alone, metformin should be preferred as the initial pharmacological therapy, unless contraindicated (when GFR < 45 mL/min/1.73 m^2). Early intensive glucose control reduces progression of microvascular complications [34, 35]. When the HbA1c target is not achieved within 3 months, dual therapy can be considered with other classes of medication, including sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitors, SGLT2 inhibitors, GLP-1 receptor agonist, or basal insulin.
- SGLT2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) offer high levels of

Table 4 Timeline for follow-up of parameters

Parameter	Initial Visit	Follow-up	Yearly
BP	Yes	Each visit	Yes
HbA1c	Yes	3 months after drug change (otherwise, every 6 months)	Yes
Lipid profile (TC, LDL-C, HDL-C, TG)	Yes	3 months after drug change (otherwise, yearly)	Yes
Ionogram	Yes	Every 3 months in case of CRD or change in medication	Yes
Microalbuminuria	Yes	Every 6 months or more frequently in case of renal impairment	Yes
Estimation of glomerular filtration	Yes	Every 6 months or more frequently in case of renal impairment	Yes

CRD, chronic renal disease; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides

CVD prevention and nephroprotection and hence can be considered as a primary recommendation in patients with high CVD risk [36–40]
- GLP-1 receptor agonists (liraglutide, semaglutide) offer CV benefits [41–43].

Concomitant use of GLP-1 receptor agonists and DPP-4 inhibitors is not recommended as this combination therapy provides marginal and nonsignificant glycemic control, offers minimal weight loss, and is not cost-effective [44, 45]. Thiazolidinediones (pioglitazone and rosiglitazone) are associated with a higher risk of incident HF (serious/severe) and should not be recommended in patients at risk of HF or with history of HF [46–48]. SGLT2 inhibitors and metformin should be the first-choice drugs (Tables 4, 5).

Consultation with Specialists in Diabetes is indicated in the Following Cases

- In case of hyperglycemia that is difficult to manage with drugs (patients with HbA1c above target even after combination therapy including two to three oral antidiabetic drugs), patients with atherosclerotic CVD, or patients at the beginning of complex (basal-bolus) insulin regimen.
- In case of microvascular complications, such as diabetic neuropathy, retinopathy, and nephropathy.
- In the presence of hypoglycemia episodes despite adjustments in treatment where hypoglycemia is defined as glucose levels < 70 mg/dL (symptomatic or asymptomatic).

Cardiac Control

Recommendations for the Therapeutic Management of BP
Pharmacological Treatment

- Evidence suggests that treatment should be started with an angiotensin-converting enzyme inhibitor (ACEI); patients who are intolerant to ACEI should receive an angiotensin receptor blocker (ARB). ACEIs or ARBs have beneficial effects on CV and non-CV mortality in patients with high CV risk [49].
- BP control frequently requires a combined pharmacological treatment with a renin–angiotensin system (RAS) blocker and a calcium blocker or a thiazide-type diuretic, particularly in the presence of proteinuria and microalbuminuria [50–52].
- A combination of two classes of drugs (RAS or ACEIs or ARBs combined with a calcium channel blocker or thiazide), preferably

Table 5 Summary of consensus recommendations

Summary of consensus recommendations
Step 1: Criteria for confirming diagnosis
FPG $\geq$ 126 mg/dL (7.0 mmol/L)
2hPG $\geq$ 200 mg/dL (11.1 mmol/L)
HbA1c $\geq$ 6.5% (48 mmol/mol)
RPG $\geq$ 200 mg/dL (11.1 mmol/L)
Step 2: Assessment of metabolic–cardio–renal risk
At the first visit, it is recommended to evaluate the metabolic–cardio–renal baseline status through measurement of HbA1c, LDL-C, BP, microalbuminuria, eGFR and renal hyperfiltration
Patients should be further stratified into very high risk, high risk, and moderate risk on the basis of the presence or absence of CVD, organ damage, risk factors (such as age, hypertension, dyslipidemia, smoking, and obesity), and the duration of diabetes
Step 3: Establish HbA1c, BP and LDL-C goals
HbA1c, BP, and LDL-C goals may vary depending on the patient's history (duration of diabetes, CVD, other CV risk factors, renal status, and other comorbidities)
Step 4: Management of each risk factor
Metabolic control
Improved prognosis of patients from the diagnosis is needed to overcome clinical inertia
Patients with ASCVD or high CV risk should receive SGLT2 inhibitor (oral) or GLP1 agonist (injectable) before initiating metformin therapy [30]
Patient characteristics should be considered and relevant medications (starting with metformin, followed by DPP-4i, GLP-1 agonist, SGLT2 inhibitor, and TZD) should be recommended for patients with low or moderate CV risk
When HbA1c is $\geq$ 1.5% (12.5 mmol/mol) over the blood glucose target, patients should receive a dual therapy including metformin
Consult a diabetes specialist when hyperglycemia is difficult to manage with drugs, or at the beginning of a complex insulin regimen, microvascular complications such as diabetic neuropathy, retinopathy and nephropathy, and incidence of hypoglycemia episodes (glucose levels $<$ 70 mg/dL) despite adjustments in treatment
CVD control
It is recommended to start treatment with ACEI; however, ARB can be recommended to patients intolerant to ACEIs [49]
Statins are recommended as the first line at the doses required to achieve LDL-C goals [53]
If LDL-C target is not achieved with statins at maximum doses, ezetimibe should be indicated
Consult cardiologist if the patient has a history of CVD or multiple risk factors, suspicion or history of HF, CAD, or hypertension

Table 5 continued

Summary of consensus recommendations
Nephrological control
Prescribe a SGLT2 inhibitor to reduce renal hyperfiltration and protect the kidneys [55–57]
Consult a nephrologist when GFR < 60 mL/min, accelerated decrease (> 15%) in GFR within 12 months, or increase in serum creatinine (> 20% from baseline) or albumin (> 30 mg/dL) occurs
Step 5: General recommendations
Low- to moderate-carbohydrate diets have a greater effect on achieving glycemic control compared with high-carbohydrate diets [61]
The Mediterranean diet supplemented with olive oil and/or nuts reduces the incidence of CV events [60]
Moderate to vigorous physical activity of ≥ 150 min/week is recommended [30]
Advise all patients not to use cigarettes or other tobacco products or electronic cigarettes because of health risks
Aspirin use is not recommended as primary prevention, but it may be considered in patients with high CV risk in the absence of contraindication. Other antiplatelet drugs such as clopidogrel is recommended in aspirin intolerant patients or in combination with low-dose aspirin as dual antiplatelet therapy [30]

2hPG, 2-hour plasma glucose; ACEI, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARB, angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GFR, glomerular filtration rate; GLP1-RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HF, heart failure; LDL-C, low density lipoprotein cholestrol; RPG, random plasma glucose; SGLT2i, sodium-glucose co-transporter 2 inhibitor; SU, sulfonylureas; T2D, type 2 diabetes; TZD, thiazolidinedione

combined in a single pill for improved adherence, can be recommended as the first-line treatment [19, 52]. In case the dual treatment fails, a triple combination (RAS and calcium channel blocker combined with diuretic) can be considered. However, combined therapy with an ACEI and ARB must be avoided [19, 52].

Controlling LDL-C

- Statins are recommended as the first-line treatment at the doses required to achieve LDL-C goals [53].
- If the LDL-C target is not achieved with statins at maximum doses, ezetimibe should be added to the treatment regimen.
- In patients with high CV risk (multiple risk factors or CV history) who do not achieve target levels with a statin and ezetimibe or with intolerance to statins, a consultation with a cardiologist or endocrinologist is indicated to consider the need of protein convertase subtilisin-kexin 9 (PCSK9) inhibitors.

Consult a Cardiologist in the Following Circumstances

- The patient has a history of CVD or multiple risk factors.
- If there is a suspicion or history of HF (patients presenting with dyspnea, orthopnea, fatigue, edema in extremities, irregular heartbeat, and reduced ability to exercise).
- If there is a suspicion of coronary artery disease (patients presenting with pain and/or discomfort, tightness, burning sensation in chest, arms, shoulders, etc., dyspnea).
- Difficult to manage patients whose hypertension is not controlled even on three different classes of hypertensives including

diuretics (office BP is > 130/90 mmHg) and dyslipidemia (LDL-C of > 100 mg/dL) despite on maximum tolerated dose of statins and ezetimibe.

Renal Control

Renal hyperfiltration and microalbuminuria should be included as treatment goals in patients with diabetes [23–25]. As both of these are prognostic markers of renal and CV risk, the expert panel recommended monitoring a pathophysiological mechanism of renal damage.

Initial GH is triggered by excess glucose at the proximal glomerular tubules, with a consequent increase in proximal reabsorption of glucose and sodium, which results in the activation of the tubuloglomerular feedback system. This leads to a reduction in sodium reaching the distal segments. The macula densa detects a decrease in distal sodium concentration, leading to the vasodilation of afferent arterioles and, consequently, an increase in intraglomerular pressure. Blocking glucose and sodium reabsorption in the proximal tubules corrects this situation and improves renal and CV prognosis from the early stages of the disease [54].

Pharmacological Treatment

- SGLT2 inhibitors have been shown to significantly reduce eGFR decline, risk of microalbuminuria, macroalbuminuria, end-stage renal disease, and nephropathy compared to controls. Furthermore, SGLT2 inhibitors reduced serum creatinine doubling, and renal death in patients with eGFR > 60 and < 60 mL/min/1.73 m^2 [55, 56]. These outcomes were supported by the recently published DAPA-CKD trial that reported a significantly lower risk of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal causes after dapagliflozin treatment compared to placebo in patients with CKD regardless of the presence or absence of diabetes [57]. An SGLT2 inhibitor should be prescribed to reduce renal hyperfiltration and to protect the kidneys in patients with T2D.
- Prescribe an ACEI or ARB, but not as combined therapy at the same time, in case of microalbuminuria or hypertension [52].
- Monitor potassium and creatinine levels and GFR if ACEI, ARB, or diuretics are used
- Avoid nephrotoxic drugs, such as non-steroid anti-inflammatory drugs, aminoglycosides, and iodinated contrast media.

Consult a Nephrologist in the Following Circumstances

- If GFR < 60 mL/min/1.73 m^2.
- When an accelerated decrease in GFR occurs (> 15% in 12 months).
- In case of increase in serum creatinine (> 20% from baseline).
- In case of persistent albuminuria despite treatment (> 30 mg/dL).

STEP 5: OTHER GENERAL RECOMMENDATIONS

Diet and Physical Activity

As patients with diabetes are often overweight, changing dietary intake to bring about a reduction in energy consumption is a key component in the treatment of diabetes. A number of patient-specific factors, such as patient adherence, beliefs, and knowledge of diabetes and how it affects self-management

[58, 59]. In this regard, PCPs need to identify patient-specific barriers and provide counseling to influence patient perception of diabetes and compliance to self-management. The physician's expertise is essential in the development, implementation, and evaluation of any intervention designed to reduce and/or control overweight, obesity, and other comorbidities.

The Mediterranean diet supplemented with olive oil and/or nuts reduces the incidence of CV events in patients at high CV risk [60]. In addition to glucose-lowering therapy, low- to moderate-carbohydrate diets have been shown to have a greater effect on achieving glycemic control compared with high-carbohydrate diets [61].

Moderate to vigorous physical activity substantially reduces CV and overall mortality risks in patients with type 1 diabetes and T2D [62–64]. ESC/EASD guidelines recommend $\geq$ 150 min/week of moderate to vigorous physical activity [30]. A Latin American consensus guideline recommends consuming a balanced isocaloric diet comprising all nutrients (with 50–55% energy from carbohydrates, 20–25% from protein, and 20–30% from fats, maintaining a ratio of 1:1:1 among saturated, unsaturated, and polyunsaturated fats) [19].

Tobacco Withdrawal: Tobacco and Electronic Cigarettes

Smoking, passive or active, significantly increases the risk of diabetes, CVD, and premature death [65–68]. Advise all patients not to smoke cigarettes, other tobacco products, or electronic cigarettes. Although motivational interviewing, smoking cessation counseling, and other forms of treatment are considered to be a routine component of diabetes care, evidence is lacking on the efficacy and safety of these interventions [69–73].

Antiplatelet Drugs

Clinical judgment should be used regarding antiplatelet drugs because of the risks of bleeding. Aspirin use is not recommended for primary prevention, but may be considered in patients with high CV risk in the absence of contraindications. Alternatively, the ESC guideline recommends clopidogrel in aspirin-intolerant patients or in combination with low-dose aspirin as dual antiplatelet therapy (DAPT). Furthermore, patients with diabetes and acute coronary syndrome and those who undergo percutaneous coronary intervention or coronary artery bypass graft can receive ticagrelor or prasugrel with aspirin for 1 year [30].

LIMITATIONS

This consensus guideline has some limitations. As the main objective of this consensus document was to provide a pragmatic guide to busy PCPs on the diagnosis, assessment, and management of metabolic–cardio–renal risks in patients with T2D, it does not provide the level of evidence or the grade of the recommendation, and it does not discuss published evidence in detail. These recommendations are based on expert opinion. Secondly, specific recommendations focusing on special patient populations, such as elderly and frail patients, patients with type 1 diabetes, patients with a history of HF, CKD, and obesity, are not discussed in detail. Thirdly, the consensus document does not include other micro- and macrovascular complications.

RECOMMENDATIONS AND ACTIONS

Although patients and PCPs are at the core of diabetes management, multilevel efforts at the community, regional, and national level will help increase the awareness, early diagnosis and detection of associated comorbidities, resulting in the effective management of T2D (Box 2).

Box 2 Recommendations and actions

At the national level:

Frequent updates of treatment guidelines

Facilitate access to drug treatment

Include SGLT2 inhibitors in the guidelines for the prevention and treatment of diabetic nephropathy and CV mortality

Recommend GLP-1 receptor agonists to reduce CV events

Change the paradigm of only looking for albuminuria in the face of evidence of increased chronic kidney disease without proteinuria

Improve access to treatments with statins or antihypertensive agents (depending on the case) that prevent CV events

Recognition in the guidelines that glycemic control is an essential part of treatment, but now that we have medications that impact CV outcomes, we must prioritize this evaluation and treatment because not all antidiabetic drugs will have the same impact on CVD

At the regional level:

Facilitate access to specialized healthcare

Facilitate access to HbA1c measurement

Medical education to key decision-makers

Facilitate access to biomarkers for the diagnosis of HF

Develop high-level risk factor care centers for referral

At the local level:

Regular interdisciplinary meetings with discussion of clinical cases

Education by physicians to patients and families; involving family members in achieving goals

Audits to evaluate processes and allow the expression of the impact of different measures

Internal protocols and self-assessments on goals and protocol adherence and incentives for the achievement of therapeutic goals

Electronic medical record with alerts when HbA1c is out of range and confirm with the physician if the same treatment continues

Report the results of studies with SGLT2 inhibitors with benefit in renal events and CV disease (especially HF and CV death)

Improve awareness of HF risk in diabetes and how to screen for it

Education on medications with CV impact

Continuing medical education on how to translate clinical studies into practice and management of risk factors

Engagement of the PCP in the management of patients with high metabolic–cardio–renal risk and referral to specialists

CV cardiovascular, *CVD* cardiovascular disease, *GLP-1* glucagon like peptide-1, *HbA1c* glycated hemoglobin, *HF* heart failure, *PCP* primary care physician, *SGLT2* sodium-glucose transport protein 2

CONCLUSION

Primary care physicians are the first point of contact for patients with T2D and can play a unique role in providing a patient-centric approach in T2D management. Although multiple treatment options for T2D are available, in most cases, detailed guidelines have been developed for specialists. Very few guidelines are drawn up with the intention to provide PCPs with practical approaches to treat patients with T2D.

This statement aims to provide a practical comprehensive approach for PCPs to address multifactorial (metabolic–cardio–renal) assessment of patients with diabetes. As diabetes is progressive in nature, not only glycemic control but also the prevention of CV events and renal injury is important to reduce morbidity and mortality. In this regard, identifying and managing specific risk factors and treating them with an equal priority is important.

The existing clinical evidence suggests that SGLT2 inhibitors and GLP-1 receptor agonists not only provide effective glycemic control but also independently improve CV outcome. Additionally, PCPs can recommend SGLT2 inhibitor for nephroprotection in patients with T2D. PCPs also need to emphasize the importance of lifestyle modification and include counseling on diet, physical activity, and tobacco cessation in their management regimen. Additionally, multilevel efforts at the community, regional, and national level are necessary for the effective management of T2D.

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