



IDF Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care

International Diabetes Federation - 2017

IDF Working Group

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Foreword

Diabetes is a global issue. Type 2 Diabetes (T2DM) is the most common form of diabetes. Around 90% of people with diabetes have type 2 diabetes. From the onset of the disease until the symptoms developed, many people with undiagnosed diabetes already have complications such as chronic kidney disease, heart failure, retinopathy and neuropathy. Early detection, diagnosis, and cost-effective treatments can save lives and prevent or significantly delay devastating diabetes-related complications.

In many cases, type 2 diabetes can be prevented by adopting a healthy lifestyle. Much can be done to improve the quality of life, increase physical activity, and reduce morbidity and mortality in people living with diabetes. These **“New IDF Clinical Practice Recommendations for managing Type 2 Diabetes in Primary Care guidelines”** seek to summarise current evidence around optimal management of people with type 2 diabetes. It is intended to be a decision support tool for general practitioners, hospital based clinicians and other primary health care clinicians working in diabetes.

The development of these guidelines has been a highly consultative process, evidence-based, incorporating recent advances in diabetes management and emerging treatment opportunities.

On behalf of the International Diabetes Federation, we would like to appreciate the technical working group that was led by Dr Pablo Aschner from Colombia, all the experts, reviewers and editors who have worked hard to make these guidelines a reality. Thanks to their thorough and realistic advices our recommendations undoubtedly became more user-friendly for practicing clinicians. We therefore wish to express our sincere gratitude and appreciation for their rich contribution.

After all, a guideline is only valuable and useful when it is implemented in the field for the day-to-day clinical practice. Therefore, we would like to recommend to all clinicians from all over the world to use these recommendations for an optimal management of type 2 diabetes in their settings.

Dr Shaukat Sadikot
IDF President (2016-2017)

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Rationale for Guidance

Diabetes is a worldwide epidemic with an estimated 415 million adults living with the disease in 2015, compared with 108 million in 1980. Type 2 diabetes (T2D) is the most prevalent form of diabetes, which has increased alongside cultural and societal changes. It is estimated that almost 200 million people with diabetes are undiagnosed and are, therefore, more at a risk of developing complications, which include kidney failure, blindness, amputations, heart disease and stroke. These complications increase the cost of care and decrease the quality of life.

Diabetes and its complications are the major causes of death in most countries. Diabetes contributed to an estimated 5 million deaths in 2015, with more than 80% of diabetes-associated deaths occurring in low- and middle-income countries.

During the past few years, there have been significant advances in medications, insulin delivery and glucose monitoring technologies. Unfortunately, the majority of the people with diabetes and their health-care professionals have limited or no access to many of these tools due to insufficient financial and/or health-care resources. Approximately 75% of the adults with diabetes reside in low- and middle-income countries. Even in the high-income countries, many communities and practice areas are populated with low-income, underinsured individuals. Additionally, the appropriate use of resources is highly dependent on the education of the health-care team members and people with diabetes. Managing T2D is complex, time-intensive and ongoing. As such, primary care physicians (PCPs) are challenged to meet the changing medical needs of those with the disease. The challenge becomes even more daunting when there is limited access to the most current tools and treatments as well as supporting personnel, notably diabetes educators.

Currently, there are many clinical practice guidelines around the world to manage T2D at the local, regional and international levels. Most are evidence-based, albeit often developed using quite different processes. They all concur in the basic recommendations; however, there are significant differences in some topics that may confuse PCPs when they want to take the best decisions regarding the management of their patients.

Aware of this, the International Diabetes Federation (IDF) Guidelines Task Force decided to analyze the similarities and discrepancies of the currently available guidelines based on their methodological rigor and wide usage, to provide the PCPs and their teams with clinical practice recommendations that will facilitate their decision-making processes in their daily real-world practice.

Purpose and Scope of This Document

The purpose of this document is to provide recommendations based on the current guidelines to PCPs who provide care for people with T2D anywhere in the world. Although the recommendations presented here are derived from the more comprehensive and well-conducted guidelines, our focus is to facilitate the optimal utilization of the available medications and monitoring tools to optimize diabetes outcomes.

Methodology

The following methodology was used

- An external epidemiologist made a search for the latest published version of the current guidelines for the management of T2D around the world, using the main databases: Medline, Embase, SciELO, National Guideline Clearinghouse, and was limited to English and Spanish languages, but most guidelines in other languages had an English version. The search yielded 23 published guidelines until 2015.
- They were appraised by two methodologists using the Agree II scoring system (<http://www.agreetrust.org/practice-guidelines/>) (Table 1A in the appendix).
- Twelve guidelines were finally selected based on their general score (70% or higher) and/or their wide acceptance and use (the case for IDF, ADA/EASD and AACE). The Chinese guideline had no English version available, but was included for the same reason, and one member of the group translated the relevant parts during the meeting. Guidelines on specific issues such as the management of elderly patients and patients with cardiovascular disease (CVD) were also selected.
- Initially the IDF Guidelines Task Force members proposed the questions that were considered most relevant for the management of people with T2D at the primary care level. In all, 40 relevant questions were selected and classified according to various topics (Table 1).

Table 1

Questions addressed in the guidelines for the treatment of T2D	
Topics	Questions
SCREENING AND Dx	<ol style="list-style-type: none"> 1. Is screening for diabetes recommended? If yes, when and which tests? 2. Is prevention of diabetes mellitus considered in the guideline? 3. What is the recommended diagnostic procedure for diabetes? Is HbA1c an option?
TARGETS FOR GLUCOSE	<ol style="list-style-type: none"> 1. Is there a general HbA1c target? If yes, which one? 2. Are there individualized HbA1c goals? If yes, which are the variables to be considered? 3. Do guidelines address hypoglycemia?
LIFESTYLE CHANGES	<ol style="list-style-type: none"> 1. Does the guideline recommend diabetes education? Does it mention a structured program? Does it mention a diabetes educator?

Topics	Questions
LIFESTYLE CHANGES	<ol style="list-style-type: none"> 2. Are lifestyle changes considered the treatment's first step on their own? If yes, under which circumstances? 3. Are there specific requirements on the desired amount and type of physical activity? 4. Are there specific requirements on the macronutrient composition of the diet?
OVERWEIGHT OBESITY	<ol style="list-style-type: none"> 1. Is there a general weight target? If yes, body mass index (BMI) or body weight? 2. Are there specific instructions on the caloric intake of the diet or caloric restriction? 3. Are there any recommendations regarding drugs and other treatments (eg, bariatric surgery) for weight loss?
INITIAL TREATMENT	<ol style="list-style-type: none"> 1. Does the selection of the first pharmacologic step consider the patient's phenotype? if yes, which phenotypes are being considered? 2. Does the selection of the first pharmacologic step consider baseline HbA1c? If yes, which are the cutoffs? 3. Does the selection of the first pharmacologic step consider comorbidities? +If yes, which are they? 4. Is metformin the preferred AHA for monotherapy? If not, then which? 5. Is there a preferred AHA when metformin is not tolerated or is contraindicated as monotherapy? If yes, then which one? 6. Does the guideline recommend a combination of AHA as the initial treatment? If yes, when? 7. If the guideline recommends a combination of AHA as the initial treatment? Which is the preferred one? 8. Is insulin considered as the first pharmacologic step? If yes, under which circumstances?
ADD-ON TREATMENT	<ol style="list-style-type: none"> 1. Is there a preferred combination of AHA recommended when monotherapy fails? If yes, which? 2. Is there a hierarchical order in the choice of the add-on drug? If yes, what is the order? 3. Is there any distinction between the use of glibenclamide/glyburide and other sulfonylureas? If yes, what is the difference? 4. Is insulin considered as a second pharmacologic step? If yes, under which circumstances? 5. Is there a preferred combination for triple therapy? If yes, which?
CARDIOVASCULAR RISK FACTORS	<ol style="list-style-type: none"> 1. Does the guideline consider the management of other CV risk factors? If yes, which? 2. Does the guideline consider a blood pressure target? If yes, which? 3. Does the guideline consider sodium restriction in the diet? 4. Does the guideline consider treatment of high blood pressure? If yes, which drugs and when to start monotherapy or combinations? 5. Does the guideline consider an LDL cholesterol target? If yes, which? 6. Does the guideline consider treatment of high LDL cholesterol, specific recommendations on statins or other lipid-lowering drugs? 7. Does the guideline consider treatment of high triglycerides/low HDL cholesterol? If yes, what is the cutoff to start drugs? What is the target? 8. Does the guideline consider vascular protection with ACEI/ARS even if there is no hypertension? 9. Does the guideline consider vascular protection with low-dose ASA? If yes, when? 10. Does the guideline consider smoking and how to avoid or stop it?
OTHERS	<ol style="list-style-type: none"> 1. Does the guideline specify the target audience: PCPs, specialists or educators? 2. Does the guideline include an algorithm? 3. Does the guideline give any recommendations on referral? 4. Are there any specific recommendations for the elderly? 5. Is the guideline cost-sensitive? If yes, does it include evidence on cost-effectiveness?

A consensus meeting was held in Brussels in March 2015, during which the group analyzed the answers to each question found in the selected guidelines. Based on the answers, the group proposed recommendations. Where there were significant differences in the specific recommendations, the group included the various options while providing a rationale that would help the PCPs to choose based on local resources and the individual characteristics of the person with T2D to be treated.

Limitations

- As mentioned before, language was a limitation but the group considered this whenever a question addressed a regional or ethnically sensitive issue, and tried to search for different points of view with the help of the members of the group.
- Some guidelines refer to other guidelines for specific issues such as screening, obesity and lipid management. Whenever possible, the group tried to find the answers in those other guidelines, but it was not always possible.
- The latest update of each guideline as available in 2015 was selected. Since then, significant evidence from recent trials has led some guidelines to update their versions to include new recommendations (Table 2A in the appendix). These changes were included in this document but not in the recommendations.

Although during the consensus, members pointed out evidence-based concepts that differed from those in the guidelines, it was agreed that the recommendations would be guideline-based, assuming the selected guidelines were evidence-based.

A red glucometer is shown in the foreground, partially overlapping a white chart with the text "Blood sugar control". The chart has a grid with numerical values like "2.00" and "4.00".

Screening & diagnosis

1.1 Screening for T2D

Up to 50% of the people with T2D remain undiagnosed (and untreated) for a variable length of time and may develop complications during that period. Therefore, most guidelines recommend screening for T2D in people above 40 to 45 years of age and/or with high risk factors such as family history of diabetes, excess weight (obesity), abdominal obesity (increased waist circumference) and hypertension.

There are differences in the screening tool. Ideally screening should not include blood tests because one of its purposes is to reduce the number of people needing a laboratory test. Screening questionnaires are becoming widely used because they include the main risk factors and can be easily performed by trained personnel and even by the subject being screened. One such tool is the FINDRISC, which is an 8-item questionnaire that provides a measure of the probability of developing T2D over the following 10 years. The assessment tool is available online in English and for download in several languages from the IDF Web site (<http://www.idf.org/about-diabetes/risk-factors>) and takes only a few minutes to complete and score. The Web site also contains links to other risk scores from different countries. Some scores can capture data from electronic records. Screening can be population-based (systematic screening for everyone who meets the criteria for age and risk factors) but most guidelines favor case finding (opportunistic screening) as part of the local health care when resources are limited.

People who have a score considered positive in the screening test must follow the recommended diagnostic procedure. The most widely used procedure is a fasting blood glucose, which is also considered as a screening test by some guidelines. Fasting blood glucose identify people with undiagnosed T2D and also people with intermediate hyperglycemia ("prediabetes"), who should be offered advice on how to follow a healthy lifestyle, preferably by means of a structured program, in order to reduce their risk of progression to T2D.

Most guidelines recommend repeating the screening test at least every three years. If the screening was positive but the diagnostic test was negative,

the subject should be advised on how to follow a healthy lifestyle and the diagnostic procedure should be repeated every year.



Recommendations: Screening for T2D

- Screen people with risk factors for diabetes attending your local health-care facility.
- High risk factors for diabetes include age above 40 to 45 years, obesity, increased waist circumference, hypertension and family history of diabetes.
- Use a locally validated screening test such as the FINDRISC score. If unavailable, use fasting blood glucose.
- People with a positive screening test should proceed to a diagnostic test as described in section 1.3. If the result of that test is normal, they should be advised on healthy lifestyle changes and the diagnostic test should be repeated every year.
- When negative, the screening test should be repeated at least every three years.
- Screening calls to action: this process will identify people with undiagnosed T2D who will benefit from early treatment, and also people with intermediate hyperglycemia ("prediabetes") who will benefit from a diabetes prevention program. Those diagnosed with diabetes should be managed according to the following guidance.

1.2 Prevention of T2D

Some guidelines include recommendations on the prevention of T2D, with some specific guidance on this subject. In general, they all concur on the need for a structured prevention program for people with intermediate hyperglycemia ("prediabetes"). The program should focus on lifestyle modifications aiming to reduce weight in those who are overweight and the goal is to achieve at least a 5% to 7% body weight loss. The program should be conducted by trained educators, coaches or even community workers.

If a prevention program is not available, the PCP should at least give simple advice on lifestyle changes such as control of food portions, avoiding snacks and sweets (notably sugar and sweetened beverages), reducing the frequency of eating out (where size and content of meals cannot be controlled) and increasing physical activity. Some simple aids may be used, such as the healthy dish (<https://www.hsph.harvard.edu/nutritionsource/healthy-eating-plate/>) and the Cooper table for exercise (<http://www.whyexercise.com/cooper-test.html>). Essentially the changes should include cutting the daily caloric intake by 500 to 600 kcal and increasing the physical activity to at least 150 minutes per week.

The consensus strongly encourages PCPs to organize their clinics and have a trained educator who can develop a program. This program can be shared with the prevention of other prevalent chronic conditions such as obesity, hypertension, CVD and HIV.

Some guidelines recommend medications when the lifestyle modification strategy is not enough. The most common drugs are metformin or alpha-glucosidase inhibitors (AGI), although at present most regulatory agencies do not authorize the use of medications for diabetes prevention purposes.



Recommendations: Prevention of T2D

- Prevention of T2D in people with intermediate hyperglycemia ("prediabetes") should focus on lifestyle modifications aimed to achieve at least a 5% to 7% weight reduction and increased physical activity.
- PCP should team with a trained educator and develop a structured prevention program.
- Medications such as metformin and acarbose may be considered in people who fail to achieve goals with lifestyle changes.

1.3 Diagnostic procedure

Most guidelines use the standard diagnostic criteria proposed by IDF and World Health Organization (WHO) (Table 2).

Test	Intermediate Hyperglycemia ("Prediabetes")	Diabetes
Fasting glucose	100-125 mg/dL (6.1-7.0 mmol/L)	≥126 mg/dL (7.0 mmol/L)
OR 2-hour glucose following ingestion of 75-g glucose load	140-199 mg/dL (7.8-11.0 mmol/L)	≥200 mg/dL (11.1 mmol/L)
OR random plasma glucose in symptomatic patient		≥200 mg/dL (11.1 mmol/L)
OR HbA1c		≥6.5% (48 mmol/mol)

Fasting is defined as no caloric intake for at least 8 hours.
The HbA1c test should be performed in a laboratory using a method that is NGSP-certified and standardized to the Diabetes Control and Complications Trial assay.
The 2-hour postprandial glucose test should be performed using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.

They include HbA1c as an option for diagnosis, provided the results of the HbA1c test are standardized to those of the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS), which have established direct associations between HbA1c levels and outcome risks in people with diabetes. The PCP is encouraged to ensure that the local HbA1c test is appropriate by consulting the NGSP Web site (<http://www.ngsp.org/>). Although HbA1c may be expensive and unavailable in many places, it becomes necessary to decide the treatment and monitor its effectiveness in persons with T2D and therefore PCPs are encouraged to ensure that the HbA1c test is available in their local practice.

When a person is asymptomatic and the result of the diagnostic test is close to the normal range, the diagnosis should be confirmed with a second test.



Recommendations: Diagnostic procedure

- Use the diagnostic criteria currently proposed by the WHO and IDF.
- Consider HbA1c as a diagnostic test, particularly in those who are very likely to have the disease, since it will also be necessary to decide treatment and monitor its effectiveness.
- A standardized HbA1c test should be available in every primary care clinic.



Targets for glucose control

2.1 General target for glucose control of T2D

Most guidelines consider HbA1c <7% (53 mmol/mol) as the general target for glucose control. Some consider that HbA1c should be <6.5% (48 mmol/mol).

Although the risk of diabetic complications decreases with lower values of HbA1c down to the normal range, the main concern in decreasing HbA1c to a target far below 7.0% (53 mmol/mol) is doing more harm than benefit with aggressive treatments that induce hypoglycemia and weight gain.

Clinically significant hypoglycemia usually starts around a plasma glucose value of 3 mmol/L (54 mg/dl) and should always be avoided. Levels between 3 and 3.9 mmol/L (54-70mg/dl) are considered alert values, particularly for patients taking SUs, glinides or insulin alone or in combination with other GLD, because they call for behavioural changes, dose adjustments and/or changes in the choice of GLD.

The PCP may encourage a patient to reach a near-normal HbA1c target if drugs that cause hypoglycemia are not used and the patient adheres to the treatment.

Some guidelines mention diabetes remission as the ultimate target. Remission is defined by most guidelines as HbA1c \leq 6% (42 mmol/mol) during 6 months without medication, and it may be feasible if the patient starts treatment early in the course of the disease and achieves the targets for lifestyle changes.

HbA1c values above 8% (64 mmol/mol) are generally unacceptable by all guidelines.



Recommendations: General target for glucose control of T2D

- The general target for glucose control in T2D should be less than 7% (53 mmol/mol).
- Lower HbA1c targets are desirable or at least should be considered, as long as hypoglycemia and weight gain can be avoided using appropriate treatments.
- Values of HbA1c above 8% (64 mmol/mol) are generally unacceptable.
- Blood glucose below 3 mmol/L (54 mg/dl) should be always avoided

2.2 Targets for glucose control in special populations

Many guidelines specifically consider that the general HbA1c target may not be appropriate in patients with a higher risk of side effects associated with tight control or may derive little benefit from it, such as short survival life, cognitive impairment and advanced chronic kidney disease (CKD). Some include established CVD, although this may only be a concern when CVD is severe and associated with multiple comorbidities. In those cases, an HbA1c target in the range of 7.5% to 8% (58-64 mmol/mol) may be safer; however, the patient should be referred to specialized care.

2.3 Monitoring glucose control

Most guidelines recommend self-monitoring of blood glucose (SMBG) for patients using insulin or sulfonylurea (SU). SMBG is particularly useful in special situations such as intense exercise or before and during driving, when treatment is being adjusted or during acute illness. In non-insulin and non-SU users, glucose monitoring could be useful if accompanied with education on self-care.

Some guidelines propose blood glucose targets that may be equivalent to the HbA1c target. A fasting capillary blood glucose <6 mmol/L (roughly 110 mg/dL) and post-prandial blood glucose <10 mmol/L (180 mg/dL) in most measurements may predict an HbA1c <7% (53 mmol/mol) but do not replace it.



Recommendations: Target for glucose control in special populations

- An HbA1c target between 7.5% and 8% (58 to 64 mmol/mol) may be more appropriate in patients using multiple medications including glucose-lowering drugs (GLDs) where predicted survival is short (eg, <10 years), with cognitive impairment, CKD or severe CVD associated with multiple comorbidities.
- Patients with those conditions should be referred to specialized care.



Recommendations: Monitoring glucose control

- Glucose monitoring is mandatory for patients using insulin.
- Glucose monitoring is useful during treatment adjustment, acute illness or as an education tool for self-care.



Lifestyle changes

3.1 Education

All guidelines consider diabetes education as one of the cornerstones of diabetes management. Many guidelines emphasize the role of a trained diabetes educator who should organize and conduct an education program. There is an IDF initiative to train health professionals as diabetes educators around the world. Group education seems to work well for people with T2D and these patients should be referred to a structured education program at the time of diagnosis, with an annual review of their progress.

One of the guidelines (NICE) has established quality standards for such a program, which should be evidence-based, suit the needs of the individual, have specific aims and learning objectives and support the learner plus family and caregivers in developing attitudes, beliefs, knowledge and skills to self-manage diabetes. It should have a structured curriculum and should be delivered by trained educators. This program should be quality-assured and reviewed by trained competent independent assessors and the outcomes from this program should be regularly audited. The "Train the Trainer" centers should be familiar with this kind of program and teach it during their courses. Ideally all PCPs should encourage at least one of the health professionals in their team to take the course. Trained diabetes educators can be shared by nearby primary care clinics to fill the gap. Quality improvement initiatives such as patient education, self-management, task allocations, case management, incentives and integrated care have been shown to effectively improve diabetes control and are mentioned by some guidelines.



Recommendations: Education

- Patients with T2D should be referred to a diabetes education program at the time of diagnosis and the program should be available at the primary care level.
- The program should be conducted by a trained diabetes educator.
- Every primary care unit should facilitate the training of at least one of their health professionals to become a diabetes educator.
- At minimum, the PCP and a health professional should team to organize group education for their patients with T2D and strive to organize a structured education program.
- Patients with T2D should attend the diabetes education program periodically.

3.2 Lifestyle changes

The variable recommendations between guidelines reflect the controversy around starting management of the patient with T2D with lifestyle changes alone and postponing medication, which would be started only in those cases in whom lifestyle changes were not sufficient to achieve the metabolic targets. Those in favor consider that this strategy emphasizes the role of diet and exercise in diabetes control. Those against this strategy consider that usually this strategy fails and the patients should also start a medication (metformin) from the time of diagnosis. The choice of strategy may depend on the availability of a structured and effective education program and the patient's compliance, but in any case, inertia should be avoided and the targets of glucose control should be reached within 3 to 6 months to avoid prolonged hyperglycemia.

3.3 Diet

All guidelines recommend a hypocaloric diet for overweight or obese people with T2D in order to aim for a normal body weight or to achieve a clinically significant reduction in body weight. This means that moderately obese people have to lose at least 10 kg (22 pounds) and therefore some guidelines recommend that their daily caloric intake should be limited to 800 to 1200 calories (low-calorie diet) in order to achieve the necessary weight loss within 6 months. Severely obese people may not be able to achieve this with diet and may need bariatric surgery as discussed later.

As discussed in the prevention section, the PCP can start by giving simple advice on diet changes such as to avoid snacks, sweets and eating out (where size and content of meals cannot be controlled) and reduce the daily caloric intake by 500 to 600 calories. Referral to a dietician can be very useful to learn how to translate the caloric restriction into feasible meals and how to manage some barriers for caloric restriction such as emptiness and hunger.

Some guidelines specifically consider the composition of the macronutrients in the diet and describe the Mediterranean diet as a beneficial example. It may not be appropriate everywhere, but the patient should be advised to prefer high-fiber and low-glycemic index foods, which may be found in local lists of foods. Three to five daily portions of vegetables and/or fruits, fish, grains and monounsaturated fats are good choices. Sugar, sweets and sweetened beverages should be avoided.



Recommendations: Lifestyle changes

- Persons with T2D must improve their lifestyle from the time of diagnosis to reach the metabolic targets as soon as possible. This can be achieved best assisted with an effective education program.
- The PCP may consider starting medication (metformin) from the time of diagnosis together with lifestyle modification, or may postpone it for 3 to 6 months when he anticipates that lifestyle changes may be sufficient to reach metabolic targets.
- In all cases inertia and prolonged hyperglycemia must be avoided.



Recommendations: Diet

- Overweight and obese patients with T2D should reduce daily caloric intake by 500 to 600 calories and when possible they should be referred to a dietician who will help them to follow a low-calorie diet (800 to 1200 calories per day).
- People with T2D should be advised to prefer high-fiber and low-glycemic index foods.
- Sugar, sweets and sweetened beverages should be avoided.

3.4 Physical activity

All guidelines consider physical activity or exercise as part of lifestyle modifications. Some specify moderate aerobic physical activity such as walking for at least 150 minutes per week at intervals of no longer than 48 hours. Resistance exercise such as moderate weight lifting or yoga can also be included. A more intensive physical activity program including at least 275 minutes per week may be needed to assist weight loss and avoid regain.

3.5 Habits

All guidelines warn against smoking, which should be stopped whenever present. PCPs should use whatever resources are available locally to help smokers to stop.

Alcohol when taken in excess and cannot be self-controlled should also be stopped. Alcohol taken in moderation as a habit may be continued as long as it does not exceed 1 to 2 units per day. Alcohol intake should be avoided when planning a low-calorie diet because it has considerable caloric value (7 kcal/g), and particularly beer, which has additional calories. People with very high levels of triglycerides or signs of liver inflammation should avoid alcohol altogether.



Recommendations: Physical activity

- People with T2D should increase their physical activity. Start by walking for at least 150 minutes per week at intervals of no longer than 48 hours.
- Overweight people with T2D may need a more intensive physical activity program to facilitate weight loss and avoid regain.



Recommendations: Habits

- Avoid smoking.
- Avoid excess alcohol intake.
- Alcohol may be continued in moderation when it is customary, but minimized in a low-calorie diet.



Obesity

4.1 Anti-obesity drugs

Some guidelines recommend anti-obesity drugs with proven efficacy and approved by regulatory agencies when patients with T2D have a BMI ≥ 27 kg/m².



Recommendations: Anti-obesity drugs

- Effective and approved anti-obesity drugs may be indicated in people with T2D and a BMI ≥ 27 kg/m².

4.2 Bariatric surgery

Guidelines consider bariatric surgery for people with T2D who have a BMI ≥ 35 kg/m² (32.5 kg/m² in Asian populations). They should be referred to a multidisciplinary team where the bariatric surgeon is included but is not exclusive. Those patients need a thorough evaluation and a long-term follow-up after surgery to avoid weight regain and malnutrition.

Some guidelines such as NICE and IDF also consider bariatric surgery in people with T2D who have a BMI between 30 and 35 kg/m² (equivalent to 27.5 and 32.5 kg/m² in Asian populations) when the metabolic response to regular treatment has been poor.

A significant proportion of patients (up to 80%) may achieve diabetes remission when operated early in the course of the disease. Remission is defined by most guidelines as an HbA1c below 6% (42 mmol/mol) without medication for 6 months or more. PCPs should inform and discuss this option with their patients.



Recommendations: Bariatric surgery

- PCPs should consider bariatric surgery in patients with T2D and a BMI ≥ 35 kg/m² (32.5 kg/m² in Asian populations) and refer them to a multidisciplinary bariatric team with long-term follow-up.
- PCPs should inform about bariatric surgery to people with T2D and a BMI between 30 and 35 kg/m² (27.5 and 32.5 kg/m² in Asian populations) when the metabolic response to regular treatment has been poor.



Initial pharmacologic treatment

5.1 Monotherapy

Previous versions of some guidelines considered the patient's phenotype to decide the first drug. In general, for overweight patients with T2D, metformin was the best option, whereas for lean patients, particularly Far East Asians, SU or AGI was preferred.

Now all the guidelines recommend metformin as the first choice for initiating pharmacologic treatment in people with T2D. Titration from 500 to 2000 mg per day, administration with or after meals and use of extended-release (XR) preparations can maximize tolerance. Metformin dose should be reduced to 1000 mg per day when renal function is in stage 3A and contraindicated when renal function is in stage 3B or above (Table 3 and Section 8.2.2).

In the event of definitive metformin intolerance or when it is contraindicated, there are discrepancies on which is the best choice to replace it. Some guidelines consider that any GLD with approved indication as monotherapy can be used and the choice would depend on the profile of the drug (efficacy, safety and local cost-effectiveness) and the preference of the patient (compliance, quality of life and affordability). This may be cumbersome at the primary care level considering the limited time to make decisions, and therefore some guidelines specify the best options. SU, AGI or DPP4 inhibitor is the first option, but one guideline (AACE) considers that weight loss is a main consideration and therefore GLP-1 receptor agonists or SGLT2 inhibitors should be the first options. Side effects must be considered, particularly hypoglycemia with SU, and therefore glibenclamide/glyburide is not recommended as it is associated with the greatest risk for hypoglycemia. When starting an SU, the patient must learn how to prevent, recognize and treat hypoglycemia.



Recommendations: Monotherapy

- Metformin is the preferred choice to start monotherapy and the PCP should make efforts to maximize tolerance by titrating the dose from 500 to 2000 mg per day, prescribe it with or after meals and use XR preparations, if necessary.
- When metformin is not tolerated, other GLDs can be used, preferably SU (except glibenclamide/glyburide), AGI or DPP4 inhibitor.

5.2 Initial combination therapy

Some guidelines consider starting with a combination of metformin and another GLD because the baseline HbA1c is 1% to 2% points above target. The baseline HbA1c threshold to start with the initial combination therapy varies from 7.5% to 9% (58-75 mmol/mol).

The choice of the drug to combine with metformin is subject to the same considerations discussed in the previous section on how to replace metformin. In particular, the mechanism of action of the other drug should be complementary to metformin and there should not be unacceptable added side effects. Therefore, the combination with an SU (except glibenclamide/glyburide), a DPP4 inhibitor or an SGLT2 inhibitor may be the preferred option.

Whenever possible, use fixed-dose combinations to increase adherence. When starting an SU, the patients must learn how to prevent, recognize and treat hypoglycemia.

5.3 Initial insulin therapy

Most guidelines recommend the use of insulin alone or in combination with other GLDs when persons with T2D are unstable, with symptoms and signs of acute decompensation including dehydration, acute weight loss, acute illness, very high glucose levels and presence of ketones.

Basal insulin should be preferred and it can be temporary. Most insulin algorithms start with 10 unit or 0.2 units/kg and titrate once or twice weekly at 1 to 2 units each time to achieve a target fasting blood glucose between 3.9 and 7.2 mmol/L (70 and 130 mg/dL).



Recommendations: Initial combination therapy

- The PCP should consider starting with a combination of metformin and another GLD when the baseline HbA1c is 1% to 2% points above target.
- The preferred combinations may be metformin plus SU (except glibenclamide/glyburide), DPP4 inhibitor or SGLT2 inhibitor.



Recommendations: Initial insulin therapy

- Consider starting insulin alone or in combination with other GLDs when people with T2D is unstable, with symptoms and signs of acute decompensation.
- Basal insulin should be preferred and it can be temporary.
- When starting insulin, the patient must learn how to titrate it with self-monitoring and how to recognize and treat hypoglycemia.



Add-on therapy

6.1 Dual therapy

When monotherapy with metformin (or its replacement) is not sufficiently effective to reach the HbA1c target, or it fails afterwards, a second GLD is recommended by all guidelines.

The considerations for the choice of the second drug are the same as for initial combination. Therefore, the best choices of add-on to metformin are SUs (except glibenclamide/glyburide), DPP4 inhibitors or SGLT2 inhibitors. Both DPP4 inhibitors and GLP1 receptor agonists have been reported to be more effective in Asian than in white European patients in several meta-analyses. AGI is also a preferred choice to add to metformin in Asian patients. Gastrointestinal side effects may be potentiated when combining an AGI with metformin, but less severe if combined with XR metformin. A GLP1 receptor agonist may also be considered if there is a concern about an insufficient rate of weight loss.

The patient should not remain longer than 3 to 6 months with an HbA1c above target before adding a second GLD.

Table 3(next page) describes the main risks and benefits of the common GLDs.



Recommendations: Dual therapy

- A second GLD should be added if monotherapy with metformin (or its replacement) is not sufficiently effective to reach the HbA1c target or fails afterwards.
- The best choice of add-on is an SU (except glibenclamide/glyburide), a DPP4 inhibitor or a SGLT2 inhibitor. An AGI can be used as well. GLP1 receptor agonist can be used if weight loss is a priority and the drug is affordable.
- The PCP may consider patient's profile (age, body weight, complications and duration of disease) when choosing the best GLD to add.

Table 3. Risks and Benefits of Common GLDs (Excluding Insulin)

	Metformin	Sulfonylurea	Glinides	Pioglitazone	Alpha-Glucosidase Inhibitors	DPP4 Inhibitors	GLP1 Receptor Agonists	SGLT2 Inhibitors
Hypo	Neutral	Moderate/severe	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral
Weight	Slight loss	Gain	Gain	Gain	Neutral	Neutral	Loss	Loss
CKD stages 3A, 3B	Reduce dose in stage 3A Contraindicated in stage 3B	Caution higher risk hypo	Caution higher risk hypo	Neutral	Neutral	Neutral but must reduce dose except linagliptin	Caution with exenatide ER	Contraindicated in stage 3B
CKD stages 4, 5	Contraindicated	Contraindicated except glipizide and gliclazide	Contraindicated		Contraindicated		Contraindicated	Contra indicated
GI SE	Moderate	Neutral	Neutral	Neutral	Moderate	Neutral	Moderate	Neutral
Other SE				Edema and bone fracture		Pancreatitis Heart failure (not a class effect)		Mycotic genital infections, fractures, amputations Bone Fractures and Amputations (may not be a class effect)
Major CV events	Benefit	Neutral	Neutral	Neutral	Neutral	Neutral	Benefit (2RCT*)	Benefit (2 RCT*)
CHF	Neutral	Neutral	Neutral	Increased risk	Neutral	Neutral	Neutral	Benefit (2 RCT**)

CKD, chronic kidney disease; CH, chronic heart failure; CV, cardiovascular; hypo, hypoglycemia; GI, gastrointestinal; SE, side effects; RCT, randomized controlled trial.
 * Reduced risk in RCTs designed for non-inferiority with liraglutide, semaglutide, empagliflozin and canagliflozin
 ** Reduced risk in RCT designed for non-inferiority with empagliflozin and canagliflozin

The profile of the patient (ABCD) may guide the selection of the second GLD and help to define the HbA1c target:

- A** Age: younger people may benefit from lower targets.
- B** Body weight: people with excess weight may benefit from drugs that enhance weight loss.
- C** Complications: people with CKD or severe CVD or who are more susceptible to hypoglycemia, may benefit from a GLD with proven benefit and safety under those circumstances.
- D** Duration: people with longer duration may harbor complications requiring treatment adjustments including the need for insulin.

6.2 Triple therapy

Many guidelines consider basal insulin as the best option when the HbA1c target has not been achieved or has been lost with two oral GLDs. However, some consider a GLP1 receptor agonist as an alternative to insulin, particularly if the patient is still obese and clinically stable. When a GLP1 agonist is added, the DPP4 inhibitor should be stopped (they both utilize the same mechanism of action).

Some guidelines suggest that triple therapy with three oral GLDs could be an alternative before starting injectable. The usual triple combinations are metformin + SU + pioglitazone or metformin + SU + DPP4 inhibitor, but recently SGLT2 inhibitors have been considered as an option to add to metformin + SU or metformin + DPP4 inhibitor. Metformin + SGLT2 inhibitor + GLP1 receptor agonist may be a useful combination for those who have not lost sufficient weight.

Avoiding injection should not be a reason to delay insulin; however, if the patient can remain on target without insulin, there is less need for glucose monitoring and less education time spent explaining how to use insulin and how to recognize and manage hypoglycemia.

Recently the fixed-dose combinations of a long-acting insulin with a GLP1 receptor agonist have been approved for clinical use. Although the GLP1

receptor agonist may not always reach its most effective dose when the long-acting insulin is titrated to achieve the fasting glucose target without hypoglycemia, the combination at least avoids weight gain with insulin.

The patient should not remain longer than 3 to 6 months with an HbA1c above target before adding a third GLD. Some guidelines suggest changes in the medications if HbA1c fails to fall by eg, 0.5% with adequate adherence.



Recommendations: Triple therapy

- A third GLD should be added if a combination of a GLD with metformin is not sufficiently effective to reach or maintain the HbA1c target.
- The most common choice to add to two oral GLDs is basal insulin. GLP1 receptor agonist can be added instead, if weight loss has been insufficient.
- Triple therapy with three oral GLDs may be effective before adding an injectable.

Cardiovascular effects of GLD

Some of the guidelines selected for this document already consider the cardiovascular safety trials with three DPP4 inhibitors (saxagliptin, alogliptin and sitagliptin) and with a short-acting GLP1 receptor agonist (lixisenatide). All these GLDs demonstrated cardiovascular safety, but not superiority. There was some concern with one DPP4 inhibitor (saxagliptin), which significantly increased hospitalizations for heart failure but this was not found with others.

Since the completion of the review of guidelines for this document, new cardiovascular safety trials have been reported with two SGLT2 inhibitors (empagliflozin and canagliflozin) and with two long-acting GLP1 receptor agonists (liraglutide and semaglutide). They all showed a significant reduction in the incidence of major cardiovascular events. This may be taken into consideration when selecting a GLD in patients with established CVD where most of the benefit was observed; however, to date, only one guideline

(Canadian) has considered this in their new algorithm. They recommend empagliflozin or liraglutide as add-on to metformin when the priority is clinical CVD. The FDA recently added a new indication for empagliflozin, to reduce the risk of cardiovascular death in adults with type 2 diabetes and cardiovascular disease.



Cardiovascular risk factors

7.1 High blood pressure (hypertension)

High blood pressure is recognized by all guidelines as a major risk factor for CVD and CKD. They also agree that 80 mmHg should be the diastolic blood pressure (DBP) target for people with T2D. It is an achievable and safe target. There is a discrepancy on the systolic blood pressure (SBP) target, which varies between 140 and 130 mmHg. If complications are present (additional risk factors and small vessel disease, particularly albuminuria), a tighter target may be appropriate. People above the age of 80 years may find it difficult to achieve a blood pressure below 145/85 mmHg if stiff vessels are present.

Some guidelines consider salt restriction for people with hypertension. The restriction should be the same for people with and without diabetes. The simplest strategy is not to add table salt to meals.

All guidelines recommend the commencement of antihypertensive therapy with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) as monotherapy and then add a calcium channel blocker or a thiazide diuretic if targets are not reached. Initial combination therapy may be needed when SBP is >20 mmHg and/or DBP is >10 mmHg above target, but this may vary with ethnicity and age. Most guidelines also recommend an ACE inhibitor or an ARB in the absence of high blood pressure if the patient has persistent microalbuminuria. One of

them (Canadian) recommends this treatment for people with CVD or older than 55 years plus cardiovascular risk factors for vascular protection.



Recommendations: High blood pressure

- Patients with T2D and hypertension should be treated to a DBP target of 80 mmHg and an SBP target of 130 to 140 mmHg. Consider the lower target when they are younger or when additional cardiovascular risk factors or microvascular disease are present.
- Salt restriction strategies such as avoiding the addition of table salt are useful to help control high blood pressure.
- Patients with high blood pressure should start treatment with an ACE inhibitor or an ARB and then add a calcium channel blocker or a thiazide diuretic if targets are not achieved.
- An ACE inhibitor or an ARB should also be started if the patient has persistent microalbuminuria in the absence of high blood pressure.

7.2 Smoking

All the guidelines strongly recommend against smoking and chewing tobacco. Many offer suggestions to facilitate stopping smoking. Electronic substitutes can be used to replace cigarettes but not as an alternative to start smoking. If available, the patient should be sent to a structured program to quit smoking.



Recommendations: Smoking

- Patients with T2D should not smoke.

7.3 Dyslipidemia

All guidelines consider high blood lipid levels as a major cardiovascular risk factor and particularly high LDL cholesterol. They also agree that statins are the best choice to start the treatment of dyslipidemia in patients with T2D. Many consider that statins should be given to every person with T2D above 40 years of age or below if they have an additional cardiovascular risk factor.

The guidelines differ in the need for lipid targets to guide the treatment with statins. Most continue to recommend an LDL cholesterol target <70 mg/dL (1.8 mmol/L) in people with T2D and established CVD (secondary prevention) or at a high risk based on the estimated 10-year risk calculated with the UKPDS risk engine (<https://www.dtu.ox.ac.uk/riskengine/download.php>) or the ASCVD pooled equation (<http://my.americanheart.org/cvriskcalculator>). The LDL cholesterol target for people with T2D without established CVD (primary prevention) and without a high 10-year CVD risk should be <100 mg/dL (2.6 mmol/L). One guideline (Canadian) recommends that everyone over 40 years of age should be on a statin with a target LDL cholesterol <77mg/dL (2.0 mmol/L).

The selection and dose up-titration of the statin, including the need for combination with ezetimibe and/or a PCSK9 inhibitor, would depend on the achievement of the target or the convenience of reaching the lowest LDL cholesterol level. Recent RCTs with ezetimibe and PCSK9 have shown additional reduction of CV risk when added to statins in patients with CVD including people with diabetes.

Recently some guidelines have adopted the strategy proposed by the American Cardiologists (AHA/ACC), which recommends that all people with T2D aged between 40 and 75 years and with a LDL cholesterol >70 mg/dL (1.8 mmol/L) should start at least a moderate-intensity statin therapy. If the patient has established CVD or LDL cholesterol \geq 190 mg/dL (4.9 mmol/L) or a high 10-year CVD risk (ASCVD risk score \geq 7.5%), the statin therapy should be high-intensity (atorvastatin or rosuvastatin in the highest approved dose). Once the risk has been established, there would be no specific LDL target and therefore monitoring blood lipids to guide treatment might not be necessary. On the contrary, if the patient is younger than 40 years or older than 75 years and/or has LDL cholesterol under 70 mg/dL (1.8 mmol/L), the treatment with statin would depend on a clinician-patient agreement based on the consideration of additional factors.

Once a PCP considers that the patient needs statin therapy, it should be maintained lifelong.

Regarding triglycerides (TG), the desired levels and the treatment indications are not consistent. Some guidelines consider treatment (mainly fibrates) if the levels are very high because of the risk of pancreatitis (TG above 500-1000 mg/dL, 5.7-11.4 mmol/L). Lifestyle changes and improved glycemic control are effective to lower TG, and if they remain high, consider using insulin, avoiding alcohol and intensification of weight loss.



Recommendations: Dyslipidemia

- All people with T2D and established CVD should start treatment with a statin (secondary prevention). They would benefit from the highest recommended dose of atorvastatin or rosuvastatin, or the statin should be selected and up-titrated to reach an LDL cholesterol target <70 mg/dL (1.8 mmol/L).
- All people with T2D and without established CVD who are \geq 40 years old and have LDL cholesterol >100 mg/dL (2.6 mmol/L), should start treatment with a statin (primary prevention).
- People with T2D and without established CVD who have LDL cholesterol >70 mg/dL (1.8 mmol/L) may also benefit from statin therapy, particularly if they have a high 10-year CVD risk calculated with a validated risk score (primary prevention).
- When a PCP considers that the patient needs statin therapy, it should be maintained lifelong.
- People with levels of triglycerides >500 to 1000 mg/dL (5.7-11.4 mmol/L) despite lifestyle changes and improved glycemic control should start a fibrate to prevent acute pancreatitis.

7.4 Antiplatelet treatment

Most guidelines recommend low-dose aspirin (75-350 mg/d) for people with T2D and established CVD (secondary prevention). Some guidelines suggest that aspirin could do more benefit than harm in those without established CVD but with a high CVD risk (primary prevention) but emphasize that there is still no good evidence for this.



Recommendations: Antiplatelet treatment

- Low-dose aspirin (75-350 mg/d) should be started and maintained lifelong in people with T2D and established CVD (secondary prevention).



Other recommendations

8.1 Depression

Some guidelines draw attention to psychological aspects, particularly depression, which may affect treatment adherence and worsen prognosis. Some guidelines recommend screening with validated screening tools such as the patient health questionnaire-2 (PHQ2) (see table 4). If the score is three or more, the probability of any depressive disorder is 75% or more and the PCP should consider referring the patient to a specialist for full evaluation.



Recommendations: Depression

- Screening for depression with a validated tool should be encouraged in primary care diabetes clinics.

Table 4. Patient health questionnaire PHQ2 for screening for depression

PHQ-2
Over the past two weeks, how often have you been bothered by any of the following problems?
Little interest or pleasure in doing things
0 = Not at all
1 = Several days
2 = More than half the days
3 = Nearly every day
Feeling down, depressed or hopeless
0 = Not at all
1 = Several days
2 = More than half the days
3 = Nearly every day

8.2 Screening for chronic complications

Comprehensive guidelines include screening for microvascular complications in people with T2D from the time they are diagnosed and thereafter every 1 to 2 years.

8.2.1 Retinopathy

To screen for retinopathy, the preferred test is the non-mydratiac retinal photography using a fundus camera. It is simple, can be performed by a technician and interpreted by an expert using telemedicine. It is very sensitive for identifying people who should be referred to an ophthalmologist. Its main barrier is the initial cost, but a single camera could be shared by different clinics. Other methods to look at the retina, such as direct ophthalmoscopy by a trained health professional may be used if validated locally. IDF has recently issued a Guide on Diabetes Eye Health for health professionals for further consultation (http://www.idf.org/sites/default/files/Diabetes_Eye_Health.pdf).

8.2.2 Nephropathy

Screening for nephropathy includes measuring albumin excretion rate (AER) and glomerular filtration rate (GFR).

AER (albuminuria) can be measured in early morning or random spot urine and calculated by the albumin-creatinine ratio (urine albumin per gram of urine creatinine in the same sample). Persistent albuminuria (2 of 3 measurements, 4-6 weeks apart) equal to or greater than 30 micrograms per gram of creatinine in an isolated urine sample indicates microalbuminuria and requires treatment with an ACE inhibitor or an ARB even in the absence of hypertension. Albumin can also be measured in a 24-hour urine sample and the AER calculated directly (without measuring urine creatinine).

GFR can be estimated (eGFR) by measuring serum creatinine and using any of the available formulae. Most guidelines recommend MDRD or CKDEpi in people with T2D and renal impairment. There are many eGFR calculators in the web (eg, https://www.kidney.org/professionals/kdoqi/gfr_calculator)

Diabetic kidney disease (DKD, diabetic nephropathy) is identified when eGFR is <60 mL/min/1.73 m² and albuminuria >30 mg/g creatinine.



Recommendations: Retinopathy

- Screen the retina every 1 to 2 years using the best available test, preferably a non-mydratiac retinal photography.



Recommendations: Nephropathy

- Screen for albumin in urine every year (microalbuminuria)
- Persistent albuminuria requires treatment with an ACE inhibitor or an ARB.
- Measure serum creatinine every year to calculate eGFR once albuminuria is detected and/or when other risk factors are present (eg, hypertension).

8.2.3 Peripheral neuropathy

Although peripheral neuropathy may produce symptoms such as nocturnal symmetrical pain in the feet, the silent loss of sensation is the main risk factor for the diabetic foot and the risk threshold is best identified by the absence of sensation using the 5.07 monofilament, which gives a pressure of 10 g, in which case the patient should be educated on foot hygiene, nail cutting, treatment of calluses, appropriate footwear and recognition of the diabetic foot (when an ulcer is present).

8.2.4 Macrovascular disease

Most guidelines do not recommend screening for macrovascular complications, unless the patient is symptomatic. The symptoms of coronary artery disease (CAD) may be atypical, such as sudden dyspnea. The electrocardiograph has a poor sensitivity for CAD but may identify a previous unrecognized myocardial infarction.

Peripheral artery disease can be screened by palpating the foot pulses and/or by measuring the ankle and brachial systolic pressures (ankle needs a Doppler) and calculating the ankle/brachial index, which should be >0.9.

8.3 Referral

Most guidelines do not include specific recommendations for the referral of the patient to a specialist. Since this document is addressed mainly to the primary care health professionals, they should refer to an endocrinologist or diabetologist those people with poor metabolic control as well as those who have multiple morbidities and/or need complex treatment and/or resetting of the target, such as those who need more than three GLD including basal insulin. PCPs should also refer people with atypical presentation of diabetes such as young onset T2D with strong family history (MODY?), rapid failure to oral GLD (LADA?) or atypical features suggestive of another endocrinopathy (eg, Cushing's syndrome, Conn's syndrome, pheochromocytoma and acromegaly).

If the screening for retinopathy is positive or if the patient has unexplained reduced visual acuity with or without retinopathy, the individual should be referred to an ophthalmologist.



Recommendations: Peripheral neuropathy

- Screen for neuropathy using the 5.07 monofilament to identify if the foot is at risk.
- Inspect the feet at every visit when they are at risk and educate the patient on prevention of diabetic foot



Recommendations: Macrovascular disease

- Screen for CAD when the patient has typical or atypical symptoms.
- Screen for peripheral artery disease by palpating the foot pulses and/or measuring the SBP to calculate the ankle/brachial index.

People should be referred to a nephrologist when they have DKD stage 4 or 5 (eGFR <30 mL/min/1.73 m²) or unexplained heavy proteinuria with or without hematuria in the absence of retinopathy or with short disease duration (eg, other causes of renal disease) or with a rapid fall in the eGFR.

People should be referred to a vascular surgeon if they have severe intermittent claudication.

Persons with diabetic foot ulcers should be referred to a diabetic foot clinic, where the treatment by a multidisciplinary specialized team will reduce the risk of amputation and the time to functional recovery considerably.

Women in the reproductive age range should have special advice if they desire pregnancy because glucose control should be optimal in order to reduce maternal and fetal risks.

People with suspected gastroparesis and/or persistent vomiting should also be referred.

In general, people with T2D benefit from a referral to a diabetes-specialized center for a complete assessment every 1 to 3 years, although they should continue their treatment at the primary care level.

8.4 Elderly

Most diabetes guidelines do not consider special targets for healthy elderly people with T2D but do call for a higher target when the patient has multiple comorbidities.

Specific guidelines for elderly people with T2D recommend screening for frailty defined by a combination of significant fatigue, recent weight loss, severe restriction in mobility, increased propensity to falls and increased risk of institutionalization. There are scales to assess frailty (<https://www.nscphealth.co.uk/edmontonscale-pdf>).

If frailty is present, a higher HbA1c target should be considered, such as <8% (64 mmol/mol). Consider the balance between harm and benefit when prescribing GLDs to elderly people and avoid those with a risk of hypoglycemia.

Treatment of people at the end of life should aim to avoid symptoms and signs due to very high blood glucose levels.



Recommendations: Referral

- Refer to an endocrinologist or diabetologist people with an atypical presentation of T2D (when suspecting MODY, LADA and other endocrinopathies).
- Refer to an endocrinologist or diabetologist or to the appropriate specialist people with T2D who have screened positive for chronic complications and may need special treatment.
- Refer people with diabetic foot ulcers to a diabetic foot clinic when available.



Recommendations: Elderly

- Healthy elderly people with T2D should have the same glucose control targets as younger adults.
- Screen for frailty and consider a higher target in people with a high frailty score.
- Avoid GLDs with a risk of hypoglycemia.
- Treatment of people at the end of life should aim to avoid symptoms and signs of hyperglycemia.

8.5 Ramadan

The recent IDF and Diabetes and Ramadan (DAR) International Alliance guidelines proposed three categories of risk for Muslim patients during Ramadan fasting. Those patients with T2D classified in the very high and high risk groups are being advised not to fast. This includes patients with sustained poor glycemic control including severe hypoglycemia, hyperosmolar hyperglycemic coma or unexplained ketoacidosis within 3 months prior to Ramadan. Also patients with history of recurrent hypoglycemia and/or unawareness, acute illness, pregnancy, CKD stage 3 or higher, advanced macrovascular complications, comorbid conditions that present additional risk factors, treatment with drugs that may affect cognitive function including multiple dose or premix insulin therapy and elderly with ill health.

Patients taking SUs or insulin will need to make adjustments to dose and/or timings to reduce the risk of hypoglycemia and SMBG is recommended. Fasting should be interrupted if BG values are under 70 mg/dl (3.9 mmol/L) or

above 300 mg/dl (16.7 mmol/L). Newer GLD including basal insulin analogs are associated with a lower risk of hypoglycemia and may be preferable for use during Ramadan.



Recommendations: Ramadan

- Very high and high risk patients are advised not to fast
- Fasting should be interrupted if BG values are under 70 mg/dl (3.9 mmol/L) or above 300 mg/dl (16.7 mmol/L)

8.6 Cost-effectiveness

Most guidelines consider cost as a barrier for the use of new GLDs, but only a few include cost-effectiveness analyses. The results may not be applicable to different economies and health systems. Local cost-effectiveness studies are important in the process of local guideline development and should be included. Expensive drugs may become cost-effective, whereas the inexpensive ones may not.

Abbreviations

AACE, American Association of Clinical Endocrinologists
ACE, angiotensin-converting enzyme
ADA, American Diabetes Association
AGI, alpha-glucosidase inhibitor
ARB, angiotensin receptor blocker
BG, blood glucose
BMI, body mass index
CKD, chronic kidney disease
CV, cardiovascular
CVD, cardiovascular disease
DBP, diastolic blood pressure
DCCT, Diabetes Control and Complications Trial
DKD, diabetic kidney disease
DPP4, dipeptidyl-dipeptidase 4
GLD, glucose-lowering drug
GLP1, glucagon-like peptide 1
HbA1c, glycosylated hemoglobin
HIV, human immunodeficiency virus
IDF, International Diabetes Federation
NGSP, National Glycohemoglobin Standardization Program
NICE, National Institute for Health and Care Excellence
PCP, primary care physician
RCT, randomized clinical trial
SBP, systolic blood pressure
SGLT2, sodium-glucose co-transporter 2
SMBG, self-monitoring of blood glucose
SU, sulfonyleurea
T2D, type 2 diabetes
UKPDS, United Kingdom Prospective Diabetes Study
WHO, World Health Organization
XR, extended release

APPENDIX

Table 1A. Appraisal of Guidelines for the Treatment of Type 2 Diabetes with AGREE II

APPRAISAL OF TYPE 2 DIABETES GUIDELINES WITH AGREE II							
GUIDELINES Treatment of Type 2 Diabetes	DOMAIN						TOTAL
	1	2	3	4	5	6	
National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care (update). London: Royal College of Physicians, 2008. ISBN 978-1-86016-333-3. Type 2 diabetes in adults: diagnosis and management of type 2 diabetes in adults. NICE guideline. Draft for consultation, January 2015.	100	94	95	100	93	100	97%
Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2013;37(Suppl 1): s1-s212.	88	91	81	97	47	95	83%
Guías ALAD sobre el diagnóstico, control y tratamiento de la diabetes mellitus tipo 2 con medicina basada en la evidencia. Edición 2013. Rev Asoc Lat Diab ALAD 2013.	97	97	73	78	58	88	81%
Gaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2012;156(3):218-31.	94	63	77	97	52	100	80%
Redmon B, Caccamo D, Flavin P, Michels R, O'Connor P, Roberts J, Smith S, Sperl-Hillen J. Institute for Clinical Systems Improvement. Diagnosis and Management of Type 2 Diabetes Mellitus in Adults. Updated July 2014. https://www.icsi.org/	86	55	88	86	75	91	80%
Scottish Intercollegiate Guidelines Network SIGN. Management of diabetes. A national clinical guideline 116. March 2010. isbn 978 1 905813 58 2. www.sign.ac.uk	86	91	73	83	83	62	79%
Gil-Velazquez LE, Sil-Acosta MJ, Dominguez-Sanchez ER, Torres-Arreola LP, Medina Chavez JM. Practice guideline: diagnosis and treatment of type 2 diabetes mellitus. Revista Médica del Instituto Mexicano del Seguro Social 2013;51(1):104-19.	97	68	74	79	55	83	76%
Working group of the Clinical Practice Guideline for type 2 Diabetes. Clinical Practice Guideline on type 2 Diabetes. Madrid: National Plan for the NHS of the MSC. Health Technologies Assessment Agency of the Basque Country; 2008. Clinical Practice Guidelines in the Spanish NHS: OSTEBA No. 2006/08. http://www.guiasalud.es/GPC/GPC_429_Diabetes_2_Osteba_comp1_en.pdf	91	88	59	80	50	91	76%
Colagiuri S, Dickinson S, Girgis S, Colagiuri R. National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes. Diabetes Australia and the NHMRC, Canberra 2009. https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/di19-diabetes-blood-glucose-control.pdf	89	50	81	94	54	91	76%
Ministry of Health of Malaysia. Clinical Practice Guidelines on Management of type 2 Diabetes Mellitus. 4th Edition. 2009; MOH/PAK/184.09 (GU) http://www.moh.gov.my/index.php/file_manager/dl_item/554756755a584a69615852686269394859584a7	80	44	53	77	6	75	55%
American Diabetes Association. Standards of Medical Care in Diabetes—2015. Diabetes Care 2015;38(suppl 1)	63	22	28	75	35	79	50%
Handelsman Y, Mechanick JI, Blonde L, et al; AACE Task Force for Developing Diabetes Comprehensive Care Plan.	55	25	50	44	20	79	45%
American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. Endocr Pract 2011;17(Suppl 2):1-53.	22	41	6	55	54	41	36%

GUIDELINES Treatment of Type 2 Diabetes	DOMAIN						TOTAL
	1	2	3	4	5	6	
Garber AJ, Abrahamson MJ, Barzilay JI, et al; American Association of Clinical Endocrinologists. AACE comprehensive diabetes management algorithm 2013. <i>Endocr Pract</i> 2013;19(2):327-36. See comment in PubMed Commons below	63	22	28	75	35	79	50%
Ministerio de Salud. Guía Clínica diabetes mellitus 2 tipo. Santiago de Chile: Minsal, 2010. ISBN: 978-956-8823-48-1. http://www.bibliote-caminsal.cl/wp/wp-content/uploads/2016/04/Diabetes-Mellitus-tipo-2.pdf	72	44	34	47	31	71	50%
Ministry of Health Singapore. Clinical practice guidelines Diabetes Mellitus. MOH Clinical Practice Guidelines 1/2014. ISBN 978-981-09-0006-9.	78	83	40	83	27	63	62%
Special populations and specific morbidities (CVD)							
Sherifali D, Fitzpatrick-lewis D, Peirson L, et al. Screening for Type 2 Diabetes in Adults. <i>CMAJ</i> . 2012;	88	80	80	97	68	95	84%
The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Guidelines on Diabetes, Pre-diabetes and Cardiovascular diseases: executive summary. <i>Eur Heart J</i> 2007; 28:88-136. The Task Force on Diabetes, pre-diabetes and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). ESC Guidelines on Diabetes, Pre-diabetes and Cardiovascular diseases developed in collaboration with the EASD. <i>Eur Heart J</i> 2013;34: 3035-87.	75	50	67	91	70	100	75%
Colagiuri S, Davies D, Girgis S, Colagiuri R. National evidence based guideline for case detection and diagnosis of type 2 diabetes. Diabetes Australia and the NHMRC, Canberra 2009.	80	50	78	94	54	91	74%
New IDF Guideline for managing type 2 diabetes in older people. <i>Diabetes Res Clin Pract</i> 2014;103(3):538-40	83	56	33	81	65	58	62%
Instituto de Salud Carlos III M de C e I, Spain and Institute for Diabetes in Old People (IDOP) U. European Diabetes Working Party for Older People 2011 Clinical Guidelines for Type 2 Diabetes Mellitus (EDWPOP). 2011;37(3).	55	47	26	66	37	66	49%
Guidelines that were not suitable for appraisal but were considered in the discussion and recommendations (see Methodology section)							
Task Force on Conceptual Model and Preventive Protocols. Working Group on Primary Care. Hong Kong Reference Framework for diabetes care for adults in primary care settings 2013 http://www.pco.gov.hk/english/resource/files/RF_DM_full.pdf							
Chinese Diabetes Society. 2013 CDS-T2DM-Diabetes-Guideline. http://www.cdschina.org/guideline.jsp							
The Japan Diabetes Society. Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013. http://www.jds.or.jp/modules/en/							

Table 2A. Updated versions of the Guidelines that were taken into consideration during the final preparation of the present document

Region	Updated guidelines
Europe	1. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management NICE guideline NG28. 2015 updated 2016-2017. Available from: https://pathways.nice.org.uk/pathways/type-2-diabetes-in-adults
North America and Caribbean	1. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Pharmacologic Management of Type 2 Diabetes: 2016 Interim Update. <i>Can J Diabetes</i> 2016;40(6):484-6. 2. Qaseem A, Barry MJ, Humphrey LL, Forcica MA; Clinical Guidelines Committee of the American College of Physicians. oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American college of physicians. <i>Ann Intern Med</i> 2017. doi: 10.7326/M16-1860. 3. Cefalu WT. American Diabetes Association standards of medical care in diabetes 2017. <i>Diabetes Care</i> 2017;40(Suppl 1) 4. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2017 Executive Summary. <i>Endocr Pract</i> 2017. doi: 10.4158/EP161682
South America Central America	1. Claudio G, Victor C, Julio B et al. Sociedad Argentina de Diabetes. Guías para el Tratamiento de la Diabetes Mellitus Tipo 2. <i>Revista de la Sociedad Argentina de Diabetes</i> 2016;50(2):64-90 2. Sociedade Brasileira de Diabetes. Conduta Terapêutica no Diabetes Tipo 2: Algoritmo SBD 2015. Posicionamento Oficial SBD n 02/2015. Available from: http://www.diabetes.org.br/ 3. Aschner PM, Muñoz OM, Girón D, et al. Clinical practice guideline for the prevention, early detection, diagnosis, management and follow up of type 2 diabetes mellitus in adults. <i>Colombia Med (Cali)</i> 2016;47(2):109-31.
Western Pacific	1. The Royal Australian College of General Practitioners. General practice management of type 2 diabetes: 2016-18. East Melbourne, Vic: RACGP, 2016. Available from: http://www.racgp.org.au/your-practice/guidelines/diabetes/ 2. Ministry of Health of Malaysia. Clinical Practice Guidelines Management of Type 2 Diabetes Mellitus. 5th ed. MOH/P/PAK/303.15 (GU). Available from: http://www.acadmed.org.my/ 3. Weng J, Ji L, Jia W, et al; Chinese Diabetes Society. Standards of care for type 2 diabetes in China. <i>Diabetes Metab Res Rev</i> 2016;32(5):442-58. 4. Korean Diabetes Association. 2015 Treatment Guidelines for Diabetes. 5th ed. 2015. Available from: http://www.diabetes.or.kr/bbs/
Other	1. Hassanein M, Al-Arouj M, Hamdy O, WMW Bebakar, Jabbar A, Al-Madani A, Lessan N, Basit A, Tayeb K, M Omar, Hanif W, Abdallah K, Al Twaim A, Buyukbese MA, El-Sayed AA, Ben-Nakhi A, On behalf of the International Diabetes Federation (IDF), in collaboration with the Diabetes and Ramadan (DAR) International Alliance. Diabetes and Ramadan: Practical guidelines. <i>Diabetes Res Clin Pract</i> 2017; 126: 303– 316 2. International Hypoglycemia Study Group. Glucose concentrations of less than 3.0 mmol/l (54 mg/dl) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. <i>Diabetologia</i> 2017; 60:3–6 and <i>Diabetes Care</i> . 2017; 40(1):155-157



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