Review

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Consensus Statement of Endocrinology, Cardiology, and Nephrology(ENCARNE) Experts on Prevention, Diagnosis, and Management of Cardiovascular and Renal Complications of Diabetes

Diyabette Kardiyovasküler ve Renal Komplikasyonların Önlenmesi, Tanısı ve Tedavisi için EndokrinolojiKardiyoloji Nefroloji (ENKARNE) Uzlaşı Raporu

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Abstract

An array of medical practitioners, including endocrinologists, family physicians, internal medicine specialists in nephrology and cardiology, unceasingly investigate, diagnose and treat over 8 million diabetic patients in Turkey. Apart from routine glycemic regulation, several frequent coexisting comorbidities such as obesity, hypertension, dyslipidemia, and their associated complications should also be promptly managed. Due to the concomitant occurrence of complications, the involvement of additional specialties in the precise management of such conditions becomes indispensable. Owing to the ever-expanding knowledge about the prevalence and clinical manifestations of diabetes, various international medical societies publish annual diabetes guidelines, which makes it too cumbersome as well as challenging for the practicing physicians to follow these comprehensive guidelines in clinical practice. There is an unmet need for an easy-to-read and concise document for all physicians working for diabetes management for a standardized approach for better management of diabetes and improved patient care. This consensus report was prepared collectively by the Society of Endocrinology and Metabolism Turkey, Turkish Society of Cardiology, Turkish Society of Nephrology, Turkish Society of Hypertension and Renal Diseases to prevent cardiac and renal complications of diabetes, to timely detect these complications by using pertinent measures and to develop, implement and monitor strategies for managing them effectively.

Keywords: Diabetes mellitus; cardiovascular disease; chronic kidney disease; heart failure; diabetic nephropathy

Özet

Türkiye'deki 8 milyon diyabetlinin tanı ve tedavisinde endokrinoloji ve metabolizma hastalıkları uzmanları, aile hekimleri, iç hastalıkları uzmanları, nefroloji ve kardiyoloji uzmanları başta olmak üzere birçok farklı disiplin de görev almaktadır. Diyabetli bireyde iyi glisemi regülasyonunun yanı sıra, obezite, hipertansiyon, dislipidemi gibi eşlik eden hastalıkları ve gelişen komplikasyonları da uygun biçimde tedavi etmek gereklidir. Diyabet komplikasyonları arttıkça diğer branşların da tedavi yönetimine katılması gerekmektedir. Öte yandan, diyabetle ilgili bilgiler giderek artmakta, çeşitli uzmanlık dernekleri diyabet kılavuzları yayımlamakta ve bu kılavuzları sahada çalışan hekimlerin izlemesi güçleşmektedir. Diyabet tedavisinde görev alan tüm hekimler için kolay okunan, özet bir başvuru kaynağı hazırlamak ve hasta yaklaşımında standardı sağlamak önemlidir. Bu uzlaşı raporu Türkiye Endokrinoloji ve Metabolizma Derneği, Türk Kardiyoloji Derneği, Türk Nefroloji Derneği, Türk Hipertansiyon ve Böbrek Hastalıkları Derneğinin ortak gayretiyle diyabetin kardiyak ve renal komplikasyonlarını önlemek, bu komplikasyonları zamanında ve uygun yönlemlerle tespit etmek ve etkin bir şekilde yönetmek için stratejiler geliştirmek, uygulamak ve izlemek amacıyla hazırlanmıştır.

Anahtar kelimeler: Diabetes mellitus; kardiyovasküler hastalık; kronik böbrek hastalığı; kalp yetersizliği; diyabetik nefropati

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Introduction

The most critical public health issue faced by Turkey currently is the precise management of chronic non-communicable diseases that impose a heavy burden on the healthcare system. Previously conducted research shows that several environmental and lifestyle factors like increased calorie intake, decreased energy expenditure, disturbed sleep-wake homeostasis, and accumulation of continuous chemical pollutants may influence epigenetic and chemical changes to such an extent that at times, the human genome is unable to adapt to environmental changes as well as occasional deplorable living conditions (1). As a result, the prevalence of coexisting risk parameters in Type 2 diabetes mellitus (DM), namely obesity, elevated blood pressure (BP), and dyslipidemia, have been significantly rising worldwide as well as in Turkey (1-3). Owing to the fact that the estimated number of Type 2 DM patients in Turkey is about 8 million (3), Turkey ranks first among the European countries in the incidence of Type 2 DM (4). Furthermore, Turkish studies like the TURDEP-2 study (The Turkish Diabetes Epidemiology) as well as several global studies suggest that one in every two patients suffering from diabetes remains undiagnosed (3,4). Effective identification and management of such a high number of patients require accurate monitoring of patients in every step beginning from the primary care system stage (family medicine) till the final clinical outcome, along with the use of standardized treatment regimes, follow-up, and additional management protocols.

Since Turkey ranks first among the European countries in Type 2 DM-related public health expenditure, (4) treating diabetes-related complications account for nearly 75% of the inpatient costs (5). One of the leading reasons for mortality and morbidity caused by diabetes is cardiovascular (CV) and renal complications (6-8). The TEMD study (**T**urkish nationwide surv**E**y of glycemic and other **M**etabolic parameters of patients with **D**iabetes mellitus), being Turkey's largest national study about the metabolic control of diabetes, demonstrated that out of all accessed cases in pooled data, microvascular complications occurred in half of the patients while macrovascular complications transpired in one-fourth of the patients afflicted with Type 2 DM (9). However, with proper diagnosis, treatment as well as certain lifestyle changes, these complications might be further prevented, thus ensuring efficient usage of Turkey's health resources as well as improving the quality of life and life expectancy in people with Type 2 DM.

Due to a close association between blood glucose levels, macrovascular disorders, and CV risks, managing optimum blood glucose levels is of paramount importance to prevent microvascular and macrovascular complications in patients with diabetes (10). However, maintaining only glycemic control cannot prevent unfavorable cardiac and renal outcomes in patients with diabetes, (11,12) several existing comorbidities accompanying diabetes such as obesity, hypertension (HTN), and dyslipidemia also contribute to increased CV risk in patients through several inadvertent mechanisms, including hyperglycemia, oxidative stress, endothelial dysfunction, and hypercoagulability (13). Therefore, all accompanying diseases and their associated risk factors should be controlled efficiently to manage diabetes effectively and prevent any further complications. Additionally, the TEMD study results also showed that 90% of people with Type 2 DM were either overweight or obese, while 95% had dyslipidemia followed by HTN in 75% of the patients (9,14-16). Unfortunately, the control rate of these comorbidities is very low in Turkey (14-16). The control rate of glycated hemoglobin (HbA1c), arterial BP (ABP), and low density lipoprotein (LDL) cholesterol all together was only 10% in patients with Type 2 DM and 5% of patients with Type 1 DM (9).

The most common CV disorders associated with diabetes in such susceptible patients are coronary artery disease (CAD), peripheral arterial disease, stroke, and systolic/diastolic heart failure (17). Although CAD is the primary cause of CV mortality, systolic/diastolic heart failure, categorized

as a non-ischemic disorder, is also a leading factor resulting in mortality in a substantial number of the cases (18). Therefore, early detection and preventive management strategies are of supreme importance as it is extremely vital for patients with diabetes to undergo timely screening for structural and functional cardiac problems so that crucial management steps can be undertaken to invalidate the effects of these coexisting disorders if required. Accuracy of the definitions of diabetic cardiomyopathy and the likely commen cement of cardiomyopathy by diabetes alone has long been under immense debate and scrutiny (19). Although diabetic cardiomyopathy has been suggested to arise from associated comorbid conditions such as CAD and HTN, it is now widely considered as a separate disease entity in itself (19). There are several mechanisms governing the initiation of diabetes-related cardiomyopathy including left ventricular hypertrophy, diastolic dysfunction, (20) and insulin resistance, thus leading to a plethora of reduced cardiac functional reserve (21), metabolic disorders, and autonomic dysfunction (22). Recent data suggest a potential association between diabetes and valvular heart disease, and the presence of a mild valvular disease may be a poor prognostic indicator (23,24).

In people with diabetes, albuminuria (>30 mg per day) and/or a reduced glomerular filtration rate (GFR) (<60 mL/min/1.73 m²) persisting more than three months indicate the presence of chronic kidney disease (CKD). Diabetes is the most common cause of CKD. The risk of CKD is at least 2-fold increased in individuals with diabetes and approximately 30-40% of patients with diabetes develop kidney disease (25). The CREDIT (Chronic Renal Disease in Turkey) study conducted by the Turkish Society of Nephrology (TSN) to determine the prevalence of CKD and its association with risk factors revealed that the prevalence of CKD was 32.4% in people with diabetes, which was 2.5 times higher than the general population (26). Diabetes is also the leading cause of the end-stage renal disease (ESRD) that necessitates dialysis or kidney transplantation. The prevalence of diabetes ranges from 10.3 to 66.7% among individuals newly diagnosed with ESRD in various countries (27). According to the 2019 TSN Kidney Registry Report, 39% of people who received hemodialysis in 2019 had diabetes as the underlying etiology (28). These figures truly indicate that nearly 2 out of every five patients undergoing dialysis have diabetes as an initiating factor and promptly demonstrate the magnitude of the relative risk of developing kidney diseases for patients with diabetes. Based on the above-mentioned facts, it is extremely crucial to control both hyperglycemia and associated comorbidities along with risk factors to prevent further mortality and morbidity in people afflicted with diabetes. Healthy eating patterns and regular physical activity should be implemented in patients' lifestyles while certain physiological and physical parameters like body weight, ABP, and blood lipids should be maintained within the target range to pave the way to a positive patient outcome (29,30). Microvascular and macrovascular complications of diabetes should be regularly investigated using age-appropriate methods and should be managed accordingly. Additionally, in diabetic CKD patients, various complications, including CV disorders, anemia, metabolic bone and mineral disorders, malnutrition, and hyperkalemia, are more prevalent (31) and deteriorate more rapidly than in patients having CKD caused by other etiologies (32). People with diabetes have a higher mortality risk due to a synergistic association with CV diseases (CVDs), and the presence of CKD further increases this risk. A previous observational study concluded that the 10-year mortality rate was 7.7% in people who had neither diabetes nor CKD, 11.5% in people with diabetes but without CKD, and 31.1% in people affected with both diabetes and CKD (33) while the reported mortality risk increases from the early stages of kidney disease, and becomes more prominent as the disease progresses to the ESRD.

The presence of albumin in urine and GFR should be regularly monitored for early de-

tection of kidney disease in all patients with diabetes, as early detection of probable kidney disease would substantially increase the benefit of preventive measures and therapies implemented for such patients. Subsequently, the timely detection of kidney function deterioration in such patients might significantly reduce the resultant progression to ESRD as well as halt the initiation of CVDs by precisely controlling and managing adequate blood glucose, BP, and CV risk factors. Early detection and treatment of CV complications are equally essential in patients both for healthy survival as well as protecting the quality of life (34).

This consensus report aims to create standards of knowledge and skills required to prevent cardiac and renal complications of diabetes, to detect these complications using appropriate methods on time, and to manage them effectively for a positive patient outcome. The report was prepared by the collective efforts of the Society of Endocrinology and Metabolism Turkey (SEMT), Turkish Society of Cardiology, (TSC), Turkish Society of Nephrology (TSN) Turkish Society of Hypertension and Renal Diseases (TSHRD) for usage by all physicians involved in Type 2 diabetes management. The outline of the consensus report based on the requisite knowledge and skills to prevent and treat both cardiac and renal complications of diabetes is summarized in Figure 1.

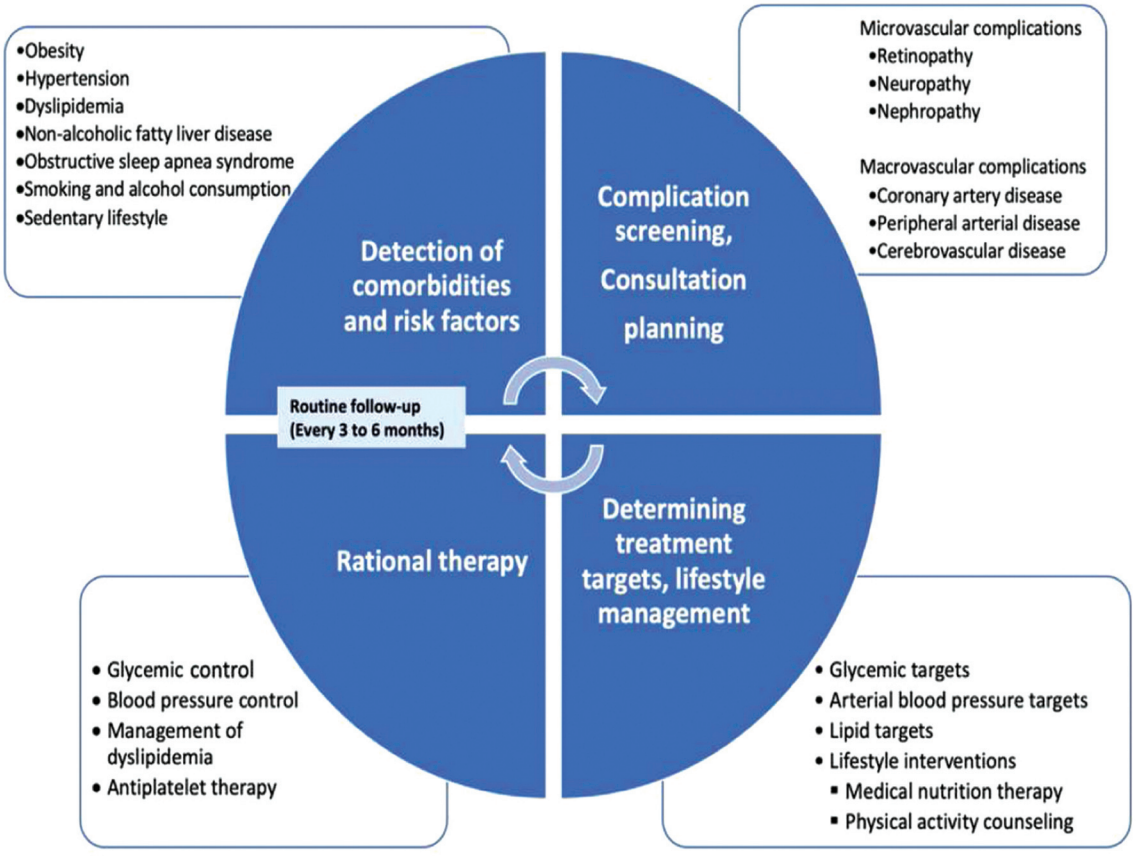

Figure 1. Management of the follow-up and treatment in people with diabetes.

Basic Principles in the Management of Patients With Diabetes With an Emphasis on Cardiac and Renal Complications

1. Determination of comorbidities and risk factors in people with diabetes (29,30,35-37)

a) Patients with Type 1 DM should be screened for the presence of other autoimmune disorders.

b) Common comorbidities accompanying Type 2 DM and risk factors for further investigations are listed below:

i) Obesity

1. Medical history

a) Searching for the obesity duration, possible underlying factors, nutritional habits, and extent of physical activity.

b) Previous weight loss attempts, employed methods, time duration, and outcomes.

c) History of obesity in family members or close relatives.

d) History ofusing medications that may lead to obesity.

2. Physical examination

a) Height and weight measurements, calculating body mass index (BMI).

b) Waist circumference.

c) Neck circumference.

ii) Hypertension

1. Medical history

a) Duration of HTN, medications, and home ABP recordings.

b) Queries to determine the role of secondary causes (BP levels, comorbidities, episodic episodic BP elevations, past medical history, medications, etc.).

c) Checking for the attainment of ABP targets.

2. Physical examination

a) ABP should be measured and recorded by the physician at each visit.

b) Standardized procedures should be followed during ABP measurements both at home and in outpatient clinics.

c) Patients should rest for five minutes before their ABP is measured, both feet should be placed flat on the floor, and the arm from which the measurement will be taken should be supported at the level of the heart. The cuff size should be appropriate for the arm circumference.

d) Home ABP monitoring may be requested if the office ABP measurement is consisten tly high (≥140/90 mmHg).

e) Ambulatory BP monitoring should be done if indicated.

f) The office ABP measurement should be repeated at the next visit for an accurate assessment of home ABP readings.

3. Diagnosis

a) A diagnosis of HTN is made if either of the following conditions occurs:

i) Home ABP readings ≥ 135/ 85 mmHg with an automated measurement device.

ii) A 24-hour mean ambulatory BP of ≥130/80 mmHg or a mean daytime BP of ≥135/85 mmHg.

iii) Two consecutive office measurements of ≥140/90 mmHg.

b) Resistant HTN is defined as follows:

i) Uncontrolled BP despite treatment with at least three antihypertensive drugs containing one diuretic.

ii) Conditions listed below should be excluded before a diagnosis of resistant HTN is made:

1) White-coat HTN.

2) Non-adherence to treatment.

3)Secondary HTN.

iii) Dyslipidemia

a) Medical history
i) Self-history or a family history of dyslipidemia.
ii) Previous and current history of medications.
iii) The history of early CV death or events in first-degree relatives.
b) Physical examination
(i) Physical signs of familial dyslipidemia.
1. Corneal arcus.
2. Tendon Xanthoma.
3. Xanthelasma palpebrarum.
c) Laboratory investigations
i) Lipid profile should be measured at the time of diagnosis, during the firstmedical assessment, and thereafter annual measurements should be taken.
1. Total cholesterol.
2. LDL cholesterol.
3. Triglycerides.
4. HDL cholesterol.
5. Non-HDL cholesterol
d) Assessment of the CV mortality risk
i) Patients with diabetes with any of the following criteria should be considered as having a very high risk of CVD (10-year CV mortality risk ≥10%):
1. Macrovascular disease [silent myocardial infarction (MI), silent ischemia, peripheral arterial disease, carotid artery disease, or cerebrovascular event].
2. Other target organ damage (nephropathy and retinopathy in particular).
3. The presence of three or more risk factors for CVD (age, HTN, dyslipidemia, obesity, smoking, family history of early coronary vascular disease and/or cerebrovascular events).
4. Type 1 diabetes with disease duration longer than 20 years.
ii) Patients listed below should be considered at a higher risk for CVD (10-year CV mortality risk 5 to 9%):
1. Diabetes duration longer than 10 years, without end-organ damage or additional CVD risk factors.
iii) Patients listed below should be considered at moderate risk for developing CV events (10-year CV mortality risk 1 to 4%):
1. Type 1 DM patients younger than 35 years, with disease duration shorter than 10 years and without any additional risk factors.
2. Type 2 DM patients younger than 50 years old without any additional risk factors.
iv) Nonalcoholic fatty liver disease (NAFLD).
a) Medical history
i) An overview of previous radiology reports searching for the presence of NAFLD. Any previous report showing excessive fat accumulation in the liver should be noted.
b) Physical examination
i) If the liver is palpable, the size, consistency, the distance from the cos-tal edge should be noted.
c) Laboratory
i) Hepatobiliary ultrasound.
1) Every overweight patient with diabetes, particularly patients with elevated serum transaminase levels, should have a hepatobiliary ultrasound scan.
v) Obstructive sleep apnea syndrome (OSAS).
a) Medical history
i) Loud snoring during sleep, daytime sleepiness, noted breathing interruption by other individuals during sleep.
b) Physical examination
i) BMI>35 kg/m^2.

ii) A neck circumference of >41 cm in females and >43 cm in males.

c) Laboratory investigation

i) People meeting the above-described criteria should be assessed by polysom nography for OSAS.

vi) Smoking and alcohol consumption.

a) The duration and amount of smo king should be noted in smokers. Any smoking cessation attempt should be questioned and encouraged.

b) The quantity and frequency of alcohol consumption should be questioned.

2. Screening for Complications

a) Screening frequency

i) Patients with Type 1 DM should be annually screened after the onset of puberty in pediatric patients, while in adults, screening should commence from the fifth year after the diagnosis.

ii) People with Type 2 DM should be first screened at diagnosis, and then annual screening is required.

iii) The screening interval for retinopathy may be increased to two years if retinopathy has not been detected over several successive years.

b) Microvascular complications

i) Screening for retinopathy.

1) Patients should be referred to an ophthalmologist for retinal assessments at appropriate intervals.

2) Women with diabetes who want to get pregnant should be screened before the pregnancy, during the third trimester of the pregnancy, and after delivery.

ii) Screening for neuropathy.

1) Patients should be examined for the signs of neuropathy at every outpatient visit.

2) Medical history

a) Bilateral symmetrical sensory neuropathy

i) Typical symptoms (Symmetrical bilateral paresthesia and pain, particularly in the lower limbs).

ii) Any other possible etiology should be excluded (cancer, chemotherapeutics, vitamin B_{12} deficiency, hypothyroidism, etc.).

b) Autonomic neuropathy

i) Tachycardia at rest, orthostatic hypotension, gastroparesis, urinary incontinence, impotence, sudomotor dysfunction, etc.

c) Motor neuropathy

i) Cranial neuropathy (commonly affects the sixth cranial nerve and less commonly the third cranial nerve).

ii) Focal neuropathy (carpal tunnel syndrome, ulnar neuropathy, etc.).

iii) Thoracolumbar radiculopathy.

iv) Lumbosacral radiculopathy.

iii) Screening for nephropathy (Figure 2) (38,39)

1) Urinalysis (at every visit)

2) Serum creatinine measurements and eGFR calculation (CKD-Epidemiology Collaboration (CKD-EPI) equation)

a) Measurements should be undertaken at the time of diagnosis and thereafter at annual visits.

b) Measurements should be repeated in one week to exclude acute kidney damage if GFR<60 mL/min/1.73 m^2.

c) Two more tests should be performed within three months to diagnose CKD if the repeat test results are similar to the previous one.

d) All eGFR measurements should be repeated every three to 6 months in CKD diagnosed patients.

3) Albuminuria

a) Albumin/creatinine ratio in a spot urine sample (Preferably in a first-morning void)

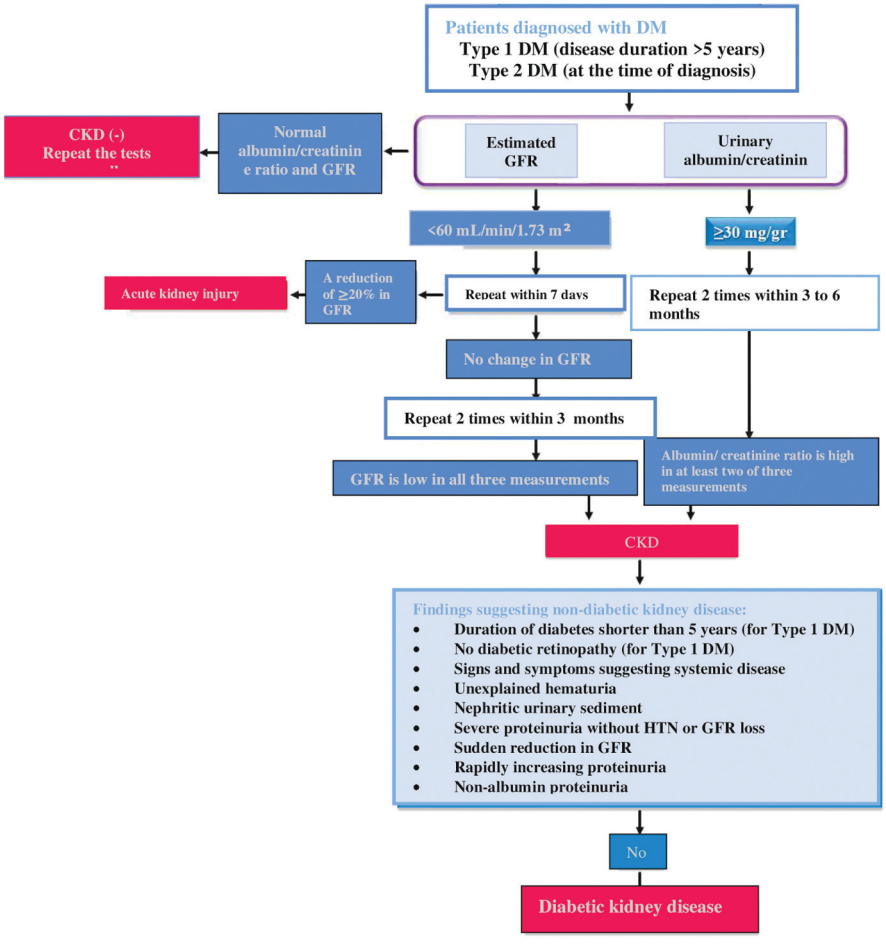

Figure 2. Diagnostic algorithm for kidney disease.
DM: Diabetes mellitus; GFR: Glomerular filtration rate; CKD: Chronic kidney disease; HTN: Hypertension.

i) Assessment should be done at the time of diagnosis and thereafter on annual visits.

ii) Reference level <30 mg/g creatinine.

iii) To diagnose albuminuria, at least two out of three measurements should remain high over the last three to 6 months.

iv) Albumin/creatinine ratio calculations should be repeated every three to 6 months in all CKD patients.

1) Following conditions may lead to false high results

a) Vigorous physical activity within the last 24 h.

b) Infection.

c) High body temperature.

d) Congestive heart failure.

e) Uncontrolled blood sugar and elevated BP.

A nephropathy screening test should be delayed until the issues mentioned above are resolved.

c) Macrovascular complications

i) Medical history:

1) History of (CAD), peripheral artery disease, or cerebrovascular disease should be investigated. If present, relevant events, interventions, treatments, etc., should be noted.

a) Coranary artery disease should be invastigated in the following conditions:
i) Atypical cardiac symptoms (unexplained dyspnea, chest discomfort, etc.).
ii) History of transient ischemic attack (TIA).
iii) Intermittent claudication.
iv) Angina, shortness of breath, exercise intolerance, claudication, arrhythmia, presyncope, or syncope should be questioned in the systemic inquiry.
ii) Physical examination:
1) Examination of the heart and respiratory system.
2) Examination of peripheral arteries.
3) Carotid artery murmurs.
4) Examination of the limbs (edema, venous circulation, etc.).
5) Ankle-brachial index (ABI):
a) ABI is used for peripheral artery screening in patients presenting with typical or atypical symptoms.
b) Screening is also necessary for asymptomatic patients when the following findings are present:
i) Asymptomatic patients aged >50 years.
ii) Patients aged <50 years, with a risk factor for peripheral artery disease.
iii) Diagnostic tests:
1) Electrocardiogram (ECG):
a) ECG monitoring is recommended in patients with diabetes for the following objectives:
i) Detection of silent MI (40,41).
ii) Assessment of increased heart rate and possible arrhythmias (42).
b) Frequency intervals for ECG monitoring in asymptomatic patients (40,41).
i) Baseline resting ECG recorded while diagnosing enables accurate comparisons with future ECGs as well as detecting signs associated with silent MI (40).
ii) It is recommended to evaluate the ECGs every one to two years in patients meeting the following criteria (43):
1) Patient's age >40 years.
2) Patient's age >30 years if the duration of diabetes >15 years.
3) End-organ damage present (microvascular or macrovascular).
4) Single or multiple risk factors for CVD (smoking, HTN, dyslipidemia, family history of premature CVD, CKD, obesity).
2) Echocardiogram (41,44)
a) Indications for an echocardiogram in patients with diabetes include:
i) Shortness of breath at rest or recent deterioration in functional capacity.
ii) Signs and symptoms of hypervolemia (edema, neck vein distention).
iii) Presence of angina symptoms.
iv) Presence of dynamic ischemic ECG alterations.
v) Arrhythmias detected by ECG.
vi) A diagnosis of heart failure with preserved ejection fraction (EF) requires:
1) High levels of natriuretic peptide in the blood and the presence of at least one of the following ECG criteria:
a) Left ventricular hypertrophy.
b) Atrial enlargement.
c) Sinus tachycardia.
3) Following are the indications for a stress test in patients with diabetes: (41,43)
a) Baseline ECG abnormalities suggesting ischemia or infarction (such as Q waves).
b) Cardiac symptoms (unexplained dyspnea, chest discomfort, or a decline in exercise capacity).
c) Asymptomatic diabetic individuals who perform competitive, intensive activities.
d) Prior to any moderate to high-risk surgery.

e) Individuals having sedentary lifestyle and will initiate a vigorous-intensity physical activity program.

f) Pharmacological stress echocardiogram or pharmacological stress nuclear imaging is recommended if an exercise test cannot be performed due to ECG abnormalities (left bundle branch block or ST/T alterations) in the baseline ECG or comorbid conditions, including peripheral vascular disease, stroke or, TIA.

4) It is not recommended to use interventional or non-interventional imaging modalities other than ECG for routine CAD screening in asymptomatic patients with diabetes.

3. Conditions Requiring A Consultation With A Cardiologist or Nephrologist

a) Conditions requiring nephrology consultation (38,39)

i) Kidney disease with unidentified etiology:

1) Kidney dysfunction in patients with Type 1 DM, with disease duration less than 5 years.

2) Presence of dysmorphic erythrocytes and/or urinary casts in urinary sediment microscopy.

3) An >30% increase in serum creatinine levels within four weeks after the initiation or dose escalation of an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB).

4) Signs and symptoms suggesting a systemic disease (skin rash, hemoptysis, arthralgia/arthritis, fever, etc.).

ii) Rapidly progressive or advanced kidney disease:

1) Suspected acute kidney injury or a reduction in eGFR.

2) Rapid progression in CKD (a GFR reduction more than >5 mL/min/1.73 m^2 per year).

3) eGFR value <45 mL/min/1.73 m^2.

4) Urinary albumin/creatinine ratio >300 mg/g creatinine (or protein/creatinine ratio >500 mg/g creatinine).

iii) Therapeutic challenges:

1) Resistant HTN.

2) Electrolyte disturbances.

3) Anemia.

4) Secondary hyperparathyroidism.

5) Metabolic bone disease.

b) Conditions requiring a cardiologist consultation (Advanced tests that are requested here may vary depending on the abilities of the site or clinical status of the patient)

i) Typical or atypical cardiac signs or symptoms (unexplained dyspnea, discomfort in chest).

ii) Abnormal resting ECG.

iii) Prior history or signs and symptoms of vascular disease (TIA, stroke, history of peripheral vascular disease, claudication, carotid artery murmurs, etc.).

iv) Before initiating an intense physical activity program in sedentary people with high CV risk.

v) To detect arrhythmias if palpitation is present.

4. Determining Therapeutic Targets and Lifestyle Interventions

a) Glycemic targets:

i) Target HbA1c,

1) HbA1c levels should be <7% in the overall adult population with diabetes.

2) Relatively less stringent HbA1c targets (e.g. <7.5%) are safer in patients with frequent hypoglycemic episodes.

3) Glycemic control targets in patients with short life expectancy are as follows:

a) A life expectancy of 5-15 years, with moderate comorbidity: HbA1c<7.5-8.0%.

b) A life expectancy of <5 years with a major comorbidity: HbA1c<8.0-8.5%.

c) Complications, comorbid conditions, and other associated risks are considered when determining glycemic targets in older patients with diabetes.

4) During pregnancy, HbA1c concentrations should not exceed the non-diabetic upper limit of normal with 2 standard deviations (ideally <6.0 to 6.5%).

ii) Capillary glucose targets:

1) Fasting plasma glucose (FPG) range is 80-130 mg/dL, and two-hour postprandial glucose (PPG) is <160 mg/dL in the adult population.

2) In pregnant women, FPG should be <95 mg/dL, one-hour PPG should be <140 mg/dL and two-hour PPG should be <120 mg/dL.

b) ABP targets:

i) Primary target <140/90 mmHg.

ii) Secondary target <130/80 mmHg (in young people without risk for hypotension).

iii) Safe lower limit 120/70 mmHg.

c) Lipid targets:

i) LDL cholesterol:

1) Moderate-risk patients <100 mg/dL.

2) High-risk patients <70 mg/dL.

3) Very high-risk patients <55 mg/dL.

ii) Non-high density lipoprotein (HDL) cholesterol (Target LDL cholesterol level+30 mg/dL).

d) Lifestyle interventions:

i) Medical nutrition therapy (MNT)

1) The benefits of MNT are as follows:

a) MNT is crucial for controlling blood glucose levels, ABP, lipid profile, and body weight.

b) MNT could reduce the frequency of complications and facilitate prompt follow-up.

c) MNT should be tailored according to each patient's age, habits, activity levels, and pharmacological treatment of patients with diabetes.

2) Nutrition recommendations to control diabetes-associated complications:

a) Consuming adequate amounts of macronutrients is essential for a balanced diet. The daily diet should consist of 45-60% carbohydrates, 15-20% proteins, and fats should be incorporated into the remaining portion. The upper limit of calorie intake from fats is not clinically relevant, however total calorie intake should be taken into consideration when determining the proportions of macronutrients. Precautions must be taken to keep saturated fats level low (<7%) while avoiding trans fat (<1%).

b) In patients with diabetic kidney disease, high protein intake should be prevented and dietary allowance of protein should be limited to 0.8 g per kg body weight. However, a further reduction (<0.8 g per kg body weight daily) in protein intake is not recommended as it does not offer any benefits regarding glucose control, CV risk factors, or GFR reduction rates.

c) Reduction in daily sodium intake (<2 g/day)

i) In patients with diabetes and CKD effective BP control is recommended to prevent kidney injury and CV complications from occurring.

ii) Sodium reduction may alleviate symptoms in patients with diabetes and symptomatic heart failure.

iii) It may reduce BP in normotensive and hypertensive people.

ii) Exercise counseling

1) Timing of exercise:

a) Exercising during fasting and immediately after a meal is harmful. Ideally, exercise should be performed 1 to 3 hours after the main meal.

b) There is no consensus on the most appropriate time of the day to exercise; however, many reports are indicating that early morning (when the levels of stress hor-

mones are high) physical activity may have unfavorable consequences in people with high CV risk. In this matter health status of the patient should be the decisive.

c) Duration and frequency of exercise: Patients should exercise at least five days a week and the interval between two exercise episodes should not exceed 48 h. Exercise duration should be at least 150 minutes weekly.

d) Exercise intensity: Exercise should be at moderate intensity (60-75% of the maximum heart rate, which, 50-75% in the elderly).

e) Patients with diabetes should have a personalized exercise plan based on their physical capabilities and comorbid conditions. If possible, exercise should be prescribed by a sports medicine practitioner.

2) Exercise considerations and contraindications to exercise:

a) Diabetes-related risks

i) Patients with risk of hypoglycemia should be advised to measure their blood glucose levels before exercising and between exercise sessions during prolonged workouts and take necessary actions. Additional measures are required if the patient has hypoglycemia unawareness. Patients should avoid exercising if they have experienced a severe hypoglycemia episode during the last 24 h.

ii) Exercise is not recommended in patients with hyperglycemia if they are at risk of ketosis.

iii) Patients with vitreous bleeding and active proliferative retinopathy should avoid intense exercise.

iv) Intense exercise should be avoided in severe peripheral neuropathy leading to sensory loss and severe autonomic neuropathy

b) CV risks

i) Symptoms of stable angina.

ii) Moderate valvular heart disease.

iii) Uncontrolled HTN (Systolic BP>160 mmHg).

5. Rational use of Medicines

a) Glycemic control

i) Major components in diabetes treatment:

1) Education of patients and their caregivers.

2) Healthy diet.

3) Regular physical activity.

4) Age-appropriate pharmacological treatment.

ii) Therapeutic options for controlling glucose levels (in historical order of development)

1) Insulin therapy.

2) Biguanides (metformin).

3) Insulin secretagogues (sulfonylureas and meglitinides).

4) Alpha-glucosidase inhibitors (acarbose and miglitol).

5) Thiazolidinedione group (pioglitazone).

6) Incretin-based drugs [Dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) analogs].

7) Sodium-glucose Co-transporter-2 (SGL T2) inhibitors.

iii) Determinants of pharmacological treatment preferences (Table 1)

1) Glucose-lowering effects

a) Insulin is the most effective agent.

b) Non-insulin therapies' efficacies are close to each other.

2) Side effects

a) Metformin may cause a metallic taste in the mouth, gastrointestinal symptoms, and vitamin B_{12} deficiency. Very rarely, metformin can cause lactic acidosis, so it is recommended to discontinue metformin one or 2 days before major surgical procedures and procedures requiring the use of iodinated contrast media. Metformin is contraindicated in severe hypoxia, decom pensated heart failure, stage 4-5 CKD.

Table 1. Treatment options to be preferred or avoided in glycemic regulation by comorbid conditions.

	Drugs to be preferred	Drugs to be avoided
Hyperglycemic emergencies, acute infections, trauma, perioperative period, pregnancy	Insulin	Other antidiabetics
Obesity	GLP-1 analogs, SGLT2 inhibitors	Insulin secretagogues
Heart failure	SGLT2 inhibitors	Pioglitazone
Atherosclerotic cardiovascular disease	GLP-1 analogs, SGLT2 inhibitors	
Chronic kidney disease	SGLT2 inhibitors, GLP-1 analogs	
Steatohepatitis	Pioglitazone, Liraglutide	

GLP-1: Glucagon-like peptide 1; SGLT2: Sodium-glucose Co-transporter-2.

b) Insulin secretagogues may cause hypoglycemia and weight gain. These agents should not be used in patients susceptible to hypoglycemia or suspected of having Type 1 diabetes.

c) Pioglitazone may cause edema, anemia, and weight gain and may deteriorate preexisting heart failure. Pioglitazone should not be used in patients with heart failure.

d) Acarbose may lead to gastrointestinal symptoms.

e) DPP-4 inhibitors may cause upper respiratory tract infection-like symptoms and arthralgia. Special care should be taken for signs and symptoms of pancreatitis. DPP-4 inhibitors are contraindicated in patients with a history of pancreatitis.

f) GLP-1 analogs may cause gastrointestinal side effects. Special care should be taken for signs and symptoms of pancreatitis. GLP-1 analogs should not be given to patients with a history of pancreatitis.

g) SGLT2 inhibitors may cause genital infections particularly in women. Another rare side effect is euglycemic ketoacidosis.

3) Costs

a) Metformin, acarbose, and sulfonylureas are relatively low-cost agents.

4) Prioritization of medication in comorbidities and diabetic complications:

a) Hyperglycemic emergencies, acute infections, trauma, perioperative period, pregnancy

i) Insulin

b) Obesity

i) GLP-1 analogs

ii) SGLT2 inhibitors

c) Heart failure

i) SGLT2 inhibitors [dapagliflozin (45), empagliflozin (46), canagliflozin (47)] [Particularly in heart failure with reduced EF (i.e., EF<45%)]

d) Atherosclerotic CVD

i) GLP-1 analogs (45,46,48) or SGLT2 inhibitors (47,49)

e) CKD

i) SGLT2 inhibitors (47,50,51)

ii) GLP-1 analogs (45,46,48) [dulaglutide (48), liraglutide (46), semaglutide (45)] Priority should be given to SGLT2 inhibitors particularly in the presence of proteinuria (52). SGLT2 inhibitors are recommended with priority to slow/stop the progression of kidney disease and/or to provide CV protection in patients with a GFR of > 20-25ml/min. (37) Due to the growing information about the SGLT2 inhibitors, the indications and allowable GFR limits are rapidly changing. These agents may not be effective enough for glycemia regulation if GFR<45 mL/min. GLP-1 analogs with nephroprotective effects can be used without dose adjustments until GFR falls to 15 mL/min.

f) Steatohepatitis

i) Pioglitazone (53)

ii) GLP-1 analogs (54)

5) Principles of pharmacological treatment in Type 2 DM

a) Blood sugar levels should be regulated by an appropriate drug after considering its implications on various comorbid conditions along with the probable side effects.

b) Metformin maintains its position as the first treatment of choiceafter considering its cost-effectiveness, glycemic-lowering efficacy, and scarce complications.

c) Many patients require combination therapy with two or three agents to achieve adequate glycemic regulation.

d) Insulin therapy should not be delayed if adequate glycemic regulation cannot be achieved. Health status of the patient should be reassessed, and treatment adjustments should be made after the recovery from glucotoxicity, and non-insulin treatments should be considered, if appropriate.

b) BP control

i) Treatment initiation

1) ABP readings higher than 140/90 mmHg require the initiation of medical treatment. Non-pharmacological treatment should not be omitted in patients on antihypertensive treatment.

ii) Determinants of antihypertensive treatment preferences

1) Any of the following groups of drugs may be preferred in patients without albuminuria.

a) Renin angiotensin aldosterone system (RAAS) Blockers.

b) Calcium channel blockers.

c) Diuretics.

2) RAAS blockers should be preferred with priority in the presence of albuminuria.

iii) BP limit for the initiation of a two-drug combination

1) ABP>150/90 mmHg.

c) Treatment of dyslipidemia

i) LDL cholesterol reduction provided by statins has proven effective in preventing CV events and deaths in patients with diabetes. Therefore, statin therapy is indicated in almost all people with diabetes. Exception for this is patients with diabetes with disease duration of shorter than 10 years who have not developed any macro or microvascular complication, and do not have any other CV risk factor, with LDL cholesterol levels of <100 mg/dL. Apart from people meeting these criteria, all patients should receive lipid-lowering medication.

ii) Target lipid parameters in the treatment of dyslipidemia

1) Lowering LDL cholesterol levels is the highest priority.

2) Lowering the triglyceride levels takes priority in patients with triglyceride levels higher than 500 mg/dL.

3) In very high-risk patients who achieve target LDL cholesterol levels, non-HDL Cholesterol lowering should also be targeted.

iii) Lipid-lowering therapies listed below should be added to statin therapy to further lower LDL Cholesterol levels

1) Ezetimibe.

2) PCSK9 inhibitors.

d) Antiplatelet therapy

i) All adult patients with diabetes and macrovascular disease should use acetylsalicylic acid (ASA) (75-150 mg a day) for secondary prophylaxis.

ii) ASA can also be used for primary prevention at a dose of 75-150 mg a day patients with diabetes at very high CV risk (SCORE>10%) while assessing patients individually for the risk for bleeding.

5) Follow-up visits

a) Patients with diabetes should be monitored at three-month intervals until achieving glycemic control targets.

b) Patients with good glycemic control should be monitored at 6-month intervals.

c) Patients should monitor their BP at home, and additionally, ABP should be measured at every follow-up visit.

d) Lipid profile should be assessed two to three months after treatment initiation, which can be examined annually after completing lipid targets.

Important Considerations in the Management of Diabetic Patients With Chronic Kidney Disease

Purposes and Targets

- To prevent or slow the progression of CKD.
- To alleviate the risk for CV, renal events, or death.

Follow-up Considerations

- Patients diagnosed with CKD should undergo a nephrological evaluation at three to 6-month intervals based on the CKD stage and clinical characteristics of the patient (38,39).
- Glycemic control should be monitored mainly by HbA1c measurements (37). However, HbA1c levels may not fully represent plasma glucose levels in patients with diabetes after developing CKD, which can be interpreted better by using regular capillary glucose measurements (55).
- HbA1c should be measured twice a year in cases of well-controlled diabetes. Measurements should be repeated every 3 months if diabetes is poorly controlled or in case of any change in anti-hyperglycemic medications (37,56).
- Target HbA1c levels should be individualized based on the CKD stage, macrovascular complications, comorbid conditions, life expectancy, and susceptibility to hypoglycemia. In general, the target levels should be ≤7% in the early stages of CKD (GFR≥45 mL/min/1.73 m^2) and 7-8% in intermediate to advanced stages of CKD (GFR<45 mL/min/1.73 m^2) (37,56).

Therapeutic Considerations

Metformin and SGLT2 inhibitors should be preferred for glycemic control if GFR is >30 mL/min/1.73 m^2. Metformin dose should be tapered at GFRs below 45 mL/min and should be discontinued at GFRs below 30 mL/min/1.73 m^2. GLP-1 receptor agonists should be considered in patients who cannot achieve adequate glycemic control and/or cannot tolerate the above-mentioned medications. Risk for hypoglycemia, kidney disease stage as well as potential side effects should be taken into consideration before, including DPP-4 inhibitors, sulfonylureas, meglitinides, glitazone, or alpha-glucosidase inhibitors in the treatment regime. Insulin should be used with frequent dose reductions to control blood sugar levels, particularly in patients with advanced disease or on dialysis (37,56). Conditions for the selection of antihyperglycemic agents in various stages of CKD are outlined in Table 2.

- The frequency of eGFR monitoring should be increased in patients initiated on metformin if eGFR is less than 60 mL/min/1.73 m^2; SGLT2 inhibitors should be used with caution in patients at high risk of ketosis or hypovolemia; GLP-1 receptor agonists and DPP-4 inhibitors should not be used concurrently. A reversible decline may occur in eGFR in patients initiated on an SGLT2 inhibitor. In this case, the SGLT2 inhibitor should not be discontinued, but the frequency of eGFR monitoring should be increased (37,56).
- An ACE-I or ARB should be initiated in patients with diabetes if HTN and albuminuriaare present, and the dose should be increased up to the maximum tolerated dose (37,56).
- In the presence of albuminuria, treatment with an ACE-I or ARB may be considered to preventor slow down the progression of kidney injury in normotensive patients with diabetes (37).
- Alterations in ABP, serum creatinine and potassium levels should be monitored within 2 to 4 weeks of the initiation or dose escalation of ACE-I or ARB (37).
- Treatment should be continued unless a >30% increase occurs at the level of serum creatinine within 4 weeks of the initiation or dose escalation of ACE-I or ARB (37).
- Considering that RAAS inhibitors have significant nephroprotective and cardioprotective effects and these effects are more prominent at the maximum tolerated doses; hyperkalemia associated with ACE-Is or ARBs should be resolved by other potassium lowering measures rather than discontinuing or reducing the doses (37).
- ACE-I and ARB combinations should be avoided due to the risk for severe hyperkalemia and acute kidney injury (37,56).

Table 2. Conditions for the use of antihyperglycemic agents by GFR in various stages of chronic kidney disease.

	Stage 1-2 GFR>60 mL/min	Stage 3a GFR 45-60 mL/min	Stage 3b GFR 30-45 mL/min	Stage 4 GFR 15-30 mL/min	Stage 5 GFR <15 mL/min
Insulin*					
Metformin			500-1,000 mg/day		
Sulfonylureas*		Gliclazide, Glimepiride			
Glinide*				Repaglinide	
Acarbose					
Pioglitazone**					
DPP-4 inhibitor			Sitagliptin (25 mg) Linagliptin		
GLP-1 Agonist				Liraglutide, Dulaglutide	
SGLT2 inhibitor			**Reduced glycemic efficacy**	Empagliflosin (GFR>20ml/min) and Dapagliflosin (GFR>25ml/min) for Heart Failure	

	Can be used
	Use with caution. Dose adjustments are required
	Not recommended

The risk for *hypoglycemia and **edema increases as GFR decreases. The doses and potential side effects of every group of drugs should be considered with caution in advanced stages; GFR: Glomerular filtration rate; DPP-4: Dipeptidyl peptidase 4; GLP-1: Glucagon-like peptide 1; SGLT2: Sodium-glucose Co-transporter-2.

- Mineralocorticoid receptor antagonists are effective in the treatment of resistant HTN; however, these medications should be used with caution due to the risk for hyperkalemia (37,56).
- Lipid-lowering therapy with statin+ezetimibe combination should be initiated before initiating dialysis in patients with diabetes to reduce CV risk. These therapies are not recommended in patients on dialysis as the efficacy has not been established yet in patients on dialysis. However, patients who have been on-lipid lowering therapy at the onset of dialysis should continue the same medications (57).
- Patients should be supported for lifestyle interventions (regular physical activity, healthy eating, weight management in overweight and obese patients, smoking cessation, etc.) (37).
- Salt intake should be limited to <2 g/day (37).
- Dietary allowance of protein should be limited to 0.8 g/kg/day in patients who are not on dialysis (37).

Important Considerations in the Management of Diabetic Patients With Cardiovascular Disease

Purposes and Targets

- To prevent or slow the progression of heart failure.
- To alleviate the risk for CV events or death.

Follow-up Considerations

- The respiratory system and CV system should be thoroughly investigated and peripheral pulses, heart rate, ABP, and body weight should be evaluated in physical examination at every visit.
- In patients with CAD an ECG should be recorded, symptoms and *New York Heart Association* functional class should be determined at every outpatient visit.
- In patients with heart failure symptoms suggesting volume overload such as peripheral edema and jugular vein distention should be assessed.
- In patients describing a worsening in their exercise capacity or new-onset or acceler-

ated chest pain, ECG findings and clinical patterns of angina (stable or unstable angina) should be assessed.

- In the presence of unstable angina or crescendo-like anginal symptoms at rest, previous assessment of revascularization images may lead to a coronary invasive intervention if necessary.
- Every patient presenting with acute coronary syndrome should be investigated for Type 2 diabetes. In patients with known diabetes, treatment should be reviewed, and proper follow-up visits should be scheduled. An Oral Glucose Tolerance Test should be performed in patients experiencing a transient blood glucose elevation at the time of admission.

Considerations for revascularisation

- A coronary artery bypass grafting (CABG) is preferred over percutaneous revascularization if coronary artery anatomy is suitable and estimated surgical mortality is low in diabetic patients with multivascular diseases.
- Usage of the left internal mammary artery is recommended for CABG, and a drug-eluting stent is recommended for percutaneous revascularization.
- Renal function should be assessed before percutaneous coronary interventions. The use of metformin should be avoided in hemodynamically unstable, hypotensive patients with reduced renal perfusion.
- Patients presenting with stable angina symptoms who do not require revascularization or patients with symptoms suggesting microvascular angina should be considered for anti-anginal therapeutic approaches (nitrates, calcium antagonists, ranolazine, ivabradine).

Considerations for heart failure assesment

- Natriuretic peptides should be measured in patients presenting with symptoms suggesting a worsening in exercise capacity and volume overload.
- An echocardiogram should be requested in patients who have not undergone an echocardiography over the last year or who present with new cardiac symptoms, in order to assess left ventricular wall motion, left ventricular mass and left atrial size, left and right ventricular EF, valvular heart disease and to assess diastolic dysfunction using Doppler parameters and if needed vena cava index.
- Attention should be paid to the possible development of heart failure with low or preserved EF in patients with diabetes. These patients should be carefully assessed for other predictors of heart failure [history of CAD, HTN, CKD, peripheral vascular disease, advanced age, poor glycemic control (HbA1c>9.0%), elevated BMI, etc.].

Disease Management in the Presence of Heart Failure and Atherosclerotic Cardiovascular Disease

- SGLT2 inhibitors should be used in the presence of heart failure with reduced EF independently of glycemic regulation while avoiding the use of Pioglitazone.
- In diabetic patients with atherosclerotic CVD or multiple CV risk factors, GLP-1 analogs or SGLT2 inhibitors with proven benefits are recommended to reduce CV events and ensure glycemic regulation (See section: rational use of medicines).
- SGLT2 inhibitors with proven benefits may prevent heart failure from occurring in this patient population.
- Beta-blocker, RAAS blocker and statin therapies should be reviewed in order to check if patients are receiving optimal doses.
- If left ventricular hypertrophy and proteinuria are present, priority should be given to RAAS blockers for the treatment of elevated BP, and fixed dose combination therapy should be started earlier. Further information on BP control can be found in sections (Rational Use of Medicines and Important Considerations in the Management of Diabetic Patient with Chronic Kidney Disease).
- High-intensity statins (atorvastatin 40-80 mg, rosuvastatin 20-40 mg) should be used and ezetimibe should be added to the regimen if the target LDL cholesterol level cannot be achieved in people with diabetes. Please see details in the section: Rational Use of Medicines.
- The effectiveness and side effects of medical therapy should be periodically evaluated by relevant laboratory tests.
- Patients should be well informed about the importance of lifestyle modifications, optimum calorie intake, the utility of a Mediter-

ranean diet as well as moderate-intensity physical activity.

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