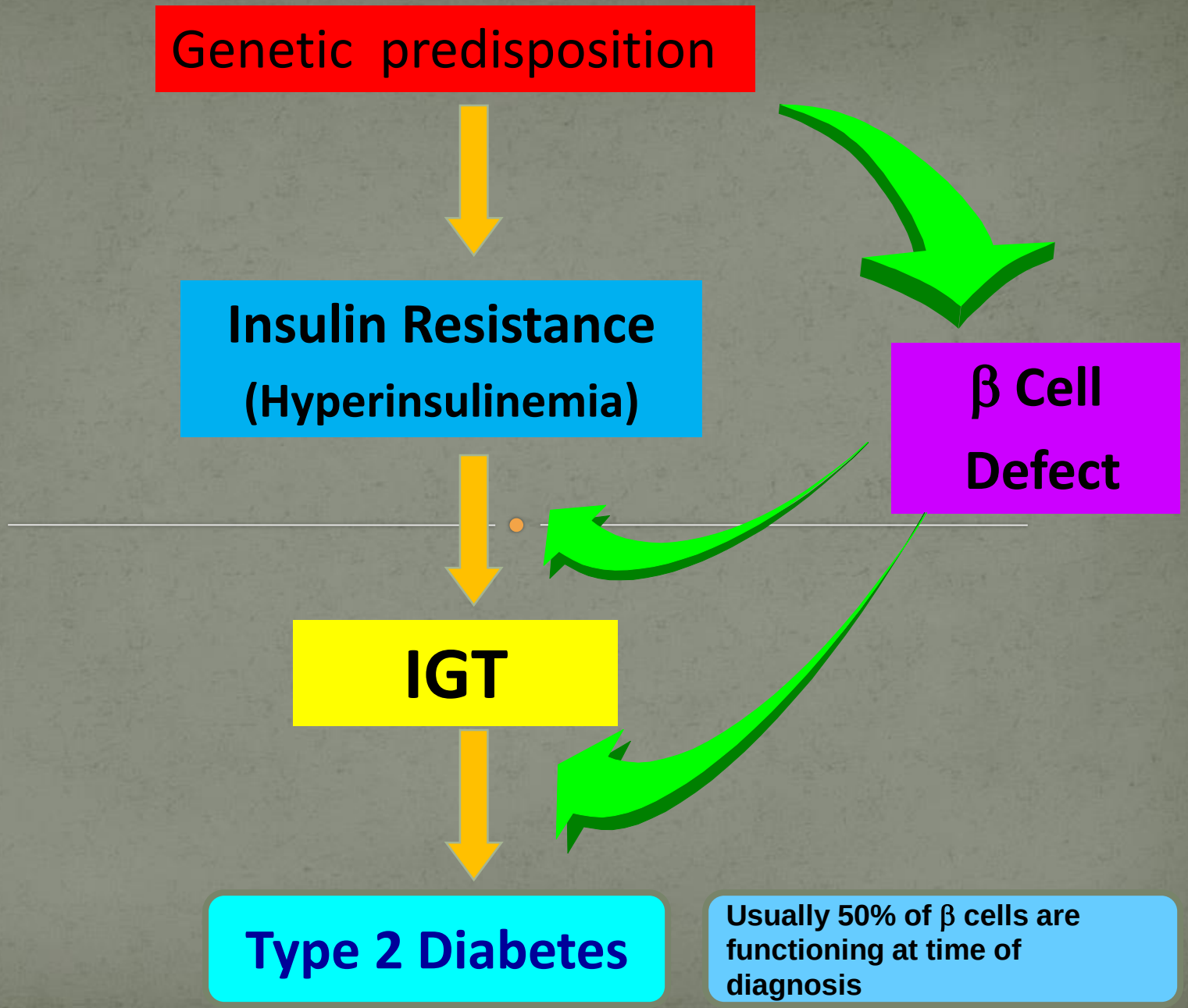
Diabetes Mellitus

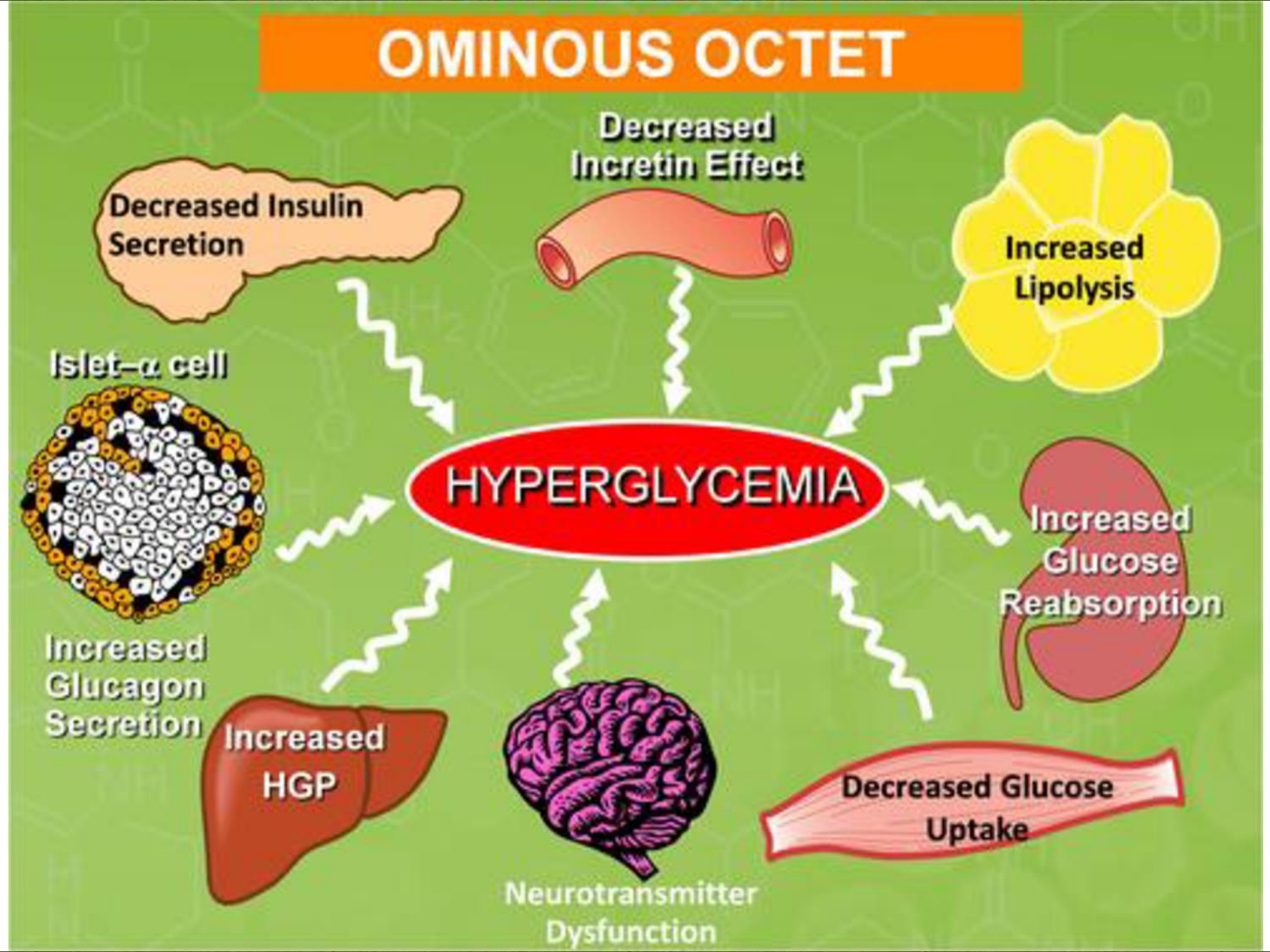
Dr Mohammed Batais

Associate Professor & Consultant , Family Medicine, Diabetes and Chronic Disease Management

King Saud University


Genetic predisposition
Insulin Resistance
(Hyperinsulinemia)
β Cell
Defect
IGT
Type 2 Diabetes
Usually 50% of β cells are functioning at time of diagnosis

OMINOUS OCTET



Prevalence of DM in Saudi Arabia

- A community-based study of 17232 subjects conducted between 1995 and 2000 in KSA.
- The examining age group, 30-70 years of selected households during 5-year period

Mansour M. Al-Nozha et al,The prevalence of CAD among Saudis of both sexes, in rural as well as urban communities, as well as modifiable risk factors for CAD, Saudi Medical Journal 2004; Vol. 25 (9): 1165-1171

Prevalence of DM in Saudi Arabia

- The overall prevalence of DM obtained from this study is 23.7% in KSA.
- The prevalence in males and females were 26.2% and 21.5% respectively ($p<0.00001$).
- A large number of diabetics 1116 (27.9%) were unaware of having DM.

Mansour M. Al-Nozha et al,The prevalence of CAD among Saudis of both sexes, in rural as well as urban communities, as well as modifiable risk factors for CAD. Saudi Medical Journal 2004; Vol. 25 (9): 1165-1171

CLASSIFICATION AND DIAGNOSIS OF DIABETES

- Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency)
- Type 2 diabetes (due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance)

CLASSIFICATION AND DIAGNOSIS OF DIABETES

- Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
- Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug-or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)

Diagnostic Tests for Diabetes

Diagnosis

Table 2.2–Criteria for the diagnosis of diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

OR

2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.*

OR

A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Pre-diabetes

Table 2.3—Categories of increased risk for diabetes (prediabetes)*
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG in the 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
OR
A1C 5.7–6.4% (39–46 mmol/mol)

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

Screening for diabetes

Table 2.3—Criteria for testing for diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in overweight or obese (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans) adults who have one or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension (≥140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Patients with prediabetes (A1C ≥5.7% [39 mmol/mol], IGT, or IFG) should be tested yearly.
3. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.
4. For all other patients, testing should begin at age 45 years.
5. If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

PREVENTION OR DELAY OF TYPE 2 DIABETES

Recommendation

- At least annual monitoring for the development of type 2 diabetes in those with prediabetes is suggested. **E**

1- Lifestyle Interventions

- ***Recommendations***
- Refer patients with prediabetes to an intensive behavioral lifestyle intervention program modeled on the Diabetes Prevention Program to achieve and maintain 7% loss of initial body weight and increase moderate-intensity physical activity (such as brisk walking) to at least 150 min/week. **A**
- Based on patient preference, technology-assisted diabetes prevention interventions may be effective in preventing type 2 diabetes and should be considered. **B**

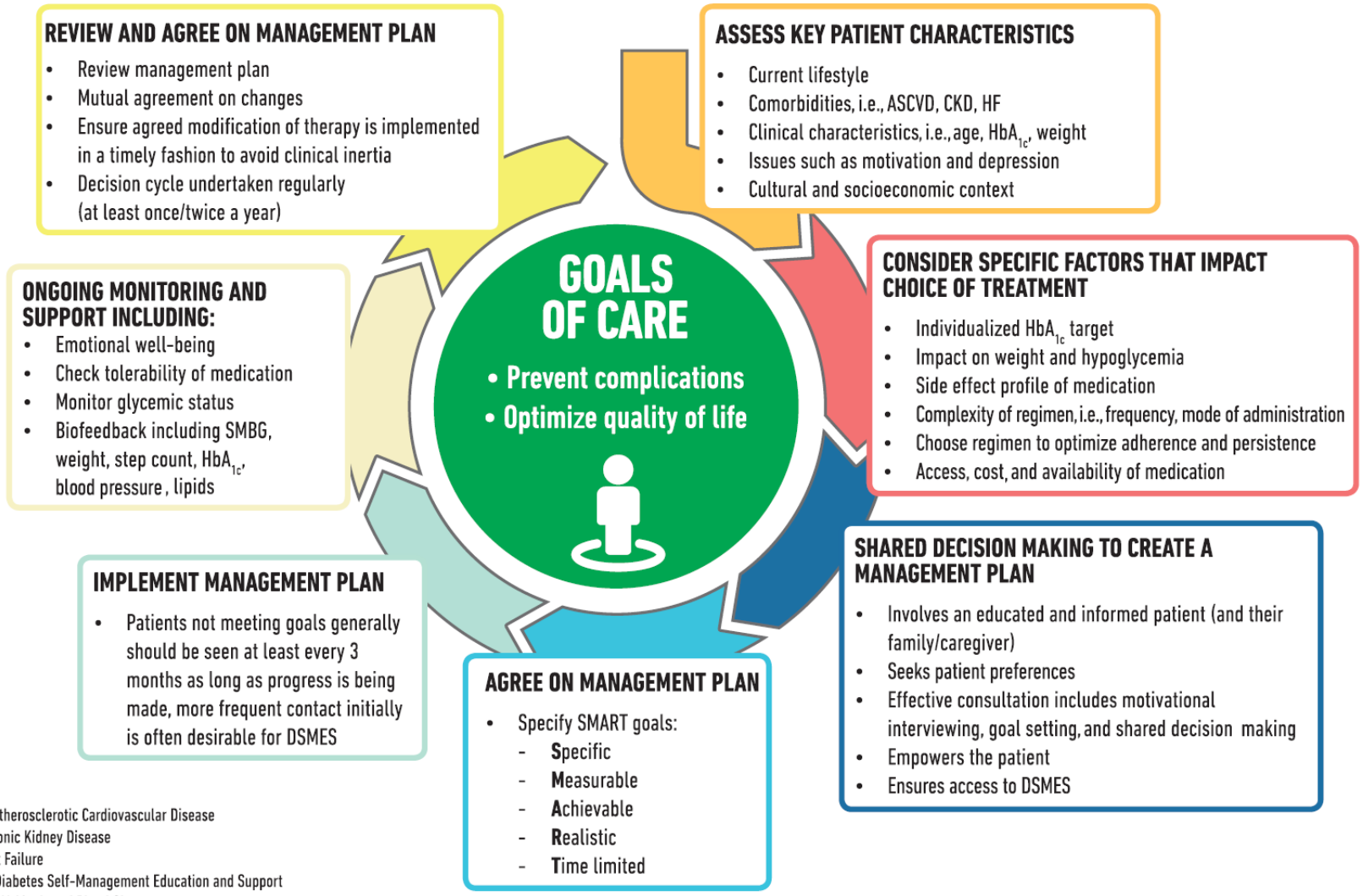
2- Pharmacologic Interventions

- ***Recommendation***
- Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI ≥35 kg/m2, those aged <60 years, and women with prior GDM. **A**

3- **Prevention of Cardiovascular Disease**

- ***Recommendation***
- Prediabetes is associated with heightened cardiovascular risk; therefore, screening for and treatment of modifiable risk factors for cardiovascular disease is suggested. **B**

COMPREHENSIVE MEDICAL EVALUATION AND ASSESSMENT OF COMORBIDITIES



ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose

Comprehensive Medical Evaluation

- ***Recommendations***
- A complete medical evaluation should be performed at the initial visit to: Confirm the diagnosis and classify diabetes. **B**
- Evaluate for diabetes complications and potential comorbid conditions. **B**
- Review previous treatment and risk factor control in patients with established diabetes. **B**
- Begin patient engagement in the formulation of a care management plan. **B**
- Develop a plan for continuing care. **B**

Table 3.1 – Components of the comprehensive diabetes medical evaluation at initial and follow-up visits

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PAST MEDICAL AND FAMILY HISTORY	**Diabetes history**			
	▪ Characteristics at onset (e.g., age, symptoms)	✓		
	▪ Review of previous treatment regimens and response	✓		
	▪ Assess frequency/cause/severity of past hospitalizations	✓		
	Family history			
	▪ Family history of diabetes in a first-degree relative	✓		
	▪ Family history of autoimmune disorder	✓		
	Personal history of complications and common comorbidities			
	▪ Macrovascular and microvascular	✓		
	▪ Common comorbidities	✓		
	▪ Presence of hemoglobinopathies or anemias	✓		
	▪ High blood pressure or abnormal lipids	✓		✓
	▪ Last dental visit	✓		✓
	▪ Last dilated eye exam	✓		
	▪ Visits to specialists	✓	✓	✓
	Interval history			
	▪ Changes in medical/family history since last visit		✓	✓

SOCIAL HISTORY	**Assess lifestyle and behavior patterns** ▪ Eating patterns and weight history ▪ Sleep behaviors and physical activity ▪ Familiarity with carbohydrate counting in type 1 diabetes ▪ Tobacco, alcohol, and substance use ▪ Identify existing social supports	✓ ✓ ✓ ✓ ✓	✓ ✓	✓ ✓
	Interval history ▪ Changes in social history since last visit		✓	✓
MEDICATIONS AND VACCINATIONS	▪ Medication-taking behavior ▪ Medication intolerance or side effects ▪ Complementary and alternative medicine use ▪ Vaccination history and needs	✓ ✓ ✓ ✓	✓ ✓ ✓	✓ ✓ ✓ ✓
TECHNOLOGY USE	▪ Assess use of health apps, online education, patient portals, etc. ▪ Glucose monitoring (meter/CGM): results and data use ▪ Review insulin pump settings	✓ ✓ ✓	 ✓ ✓	✓ ✓ ✓
SCREENING	**Psychosocial conditions** ▪ Screen for depression, anxiety, and disordered eating; refer for further assessment or intervention if warranted ▪ Consider assessment for cognitive impairment*	✓ ✓		✓ ✓
	Diabetes self-management education and support ▪ History of dietitian/diabetes educator visits ▪ Screen for barriers to diabetes self-management ▪ Refer or offer local resources and support as needed	✓ ✓ ✓	✓ ✓	✓ ✓ ✓
	Hypoglycemia ▪ Timing of episodes, awareness, frequency and causes	✓	✓	✓
	Pregnancy planning ▪ For women with childbearing capacity, review contraceptive needs and preconception planning	✓	✓	✓

Table 3.1 – Components of the comprehensive diabetes medical evaluation at initial and follow-up vis

		INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
PHYSICAL EXAMINATION	▪ Height, weight, and BMI; growth/pubertal development in children and adolescents	✓	✓	✓
	▪ Blood pressure determination	✓	✓	✓
	▪ Orthostatic blood pressure measures (when indicated)	✓		
	▪ Fundoscopic examination (refer to eye specialist)	✓		✓
	▪ Thyroid palpation	✓		✓
	▪ Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy)	✓	✓	✓
	▪ Comprehensive foot examination			
	• Visual inspection (e.g., skin integrity, callous formation, foot deformity or ulcer, toenails)	✓	✓	✓
	• Screen for PAD (pedal pulses; refer for ABI if diminished)	✓		✓
	• Determination of temperature, vibration or pinprick sensation, and 10-g monofilament exam	✓		✓
LABORATORY EVALUATION	▪ A1C, if the results are not available within the past 3 months	✓	✓	✓
	▪ If not performed/available within the past year			
	• Lipid profile, including total, LDL, and HDL cholesterol and triglycerides[#]	✓		✓^
	• Liver function tests[#]	✓		✓
	• Spot urinary albumin-to-creatinine ratio	✓		✓
	• Serum creatinine and estimated glomerular filtration rate[†]	✓		✓
	• Thyroid-stimulating hormone in patients with type 1 diabetes[#]	✓		✓
	• Vitamin B12 if on metformin (when indicated)	✓		
	• Serum potassium levels in patients on ACE inhibitors, ARBs, or diuretics[†]	✓		✓

ASSESSMENT AND PLAN	**Goal setting**			
	▪ Set A1C/blood glucose target and monitoring frequency	✓	✓	✓
	▪ If hypertension diagnosed, establish blood pressure goal	✓		✓
	▪ Incorporate new members to the care team as needed	✓	✓	✓
	▪ Diabetes education and self-management support needs	✓	✓	✓
	Cardiovascular risk assessment and staging of CKD			
	▪ History of ASCVD	✓	✓	✓
	▪ Presence of ASCVD risk factors (see Table 9.2)	✓	✓	✓
	▪ Staging of CKD (see Table 10.1)†	✓	✓	✓
	Therapeutic treatment plan			
	▪ Lifestyle management	✓	✓	✓
	▪ Pharmacologic therapy	✓	✓	✓
	▪ Referrals to specialists (including dietitian and diabetes educator) as needed	✓	✓	✓
	▪ Use of glucose monitoring and insulin delivery devices	✓	✓	✓

Table 4.2—Assessment and treatment plan*

Assess risk of diabetes complications

- ASCVD and heart failure history
- ASCVD risk factors (see **Table 10.2**) and 10-year ASCVD risk assessment
- Staging of chronic kidney disease (see **Table 11.1**)
- Hypoglycemia risk (**Table 4.3**)

Goal setting

- Set A1C/blood glucose target
- If hypertension present, establish blood pressure target
- Diabetes self-management goals (e.g., monitoring frequency)

Therapeutic treatment plan

- Lifestyle management
- Pharmacologic therapy (glucose lowering)
- Pharmacologic therapy (cardiovascular disease risk factors and renal)
- Use of glucose monitoring and insulin delivery devices
- Referral to diabetes education and medical specialists (as needed)

ASCVD, atherosclerotic cardiovascular disease. *Assessment and treatment planning is an essential component of initial and all follow-up visits.

Table 4.3—Assessment of hypoglycemia risk

Factors that increase risk of treatment-associated hypoglycemia

- Use of insulin or insulin secretagogues (i.e., sulfonylureas, meglitinides)
- Impaired kidney or hepatic function
- Longer duration of diabetes
- Frailty and older age
- Cognitive impairment
- Impaired counterregulatory response, hypoglycemia unawareness
- Physical or intellectual disability that may impair behavioral response to hypoglycemia
- Alcohol use
- Polypharmacy (especially ACE inhibitors, angiotensin receptor blockers, nonselective β-blockers)

See references 114–118.

Table 4.4—Referrals for initial care management

- Eye care professional for annual dilated eye exam
- Family planning for women of reproductive age
- Registered dietitian for medical nutrition therapy
- Diabetes self-management education and support
- Dentist for comprehensive dental and periodontal examination
- Mental health professional, if indicated

GLYCEMIC TARGETS

A1C Testing

- ***Recommendations***
- Perform the A1C test *at least* two times a year in patients who are meeting treatment goals (and who have stable glycemic control). **E**
- Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. **E**
- Point-of-care testing for A1C provides the opportunity for more timely treatment changes. **E**

A1C Goals

- ***Recommendations***
- A reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol). **A**
- Providers might reasonably suggest more stringent A1C goals (such as <6.5% [48 mmol/mol]) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment (i.e., polypharmacy). Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease. **C**

- Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with a history of level 3 hypoglycemia (altered mental and/or physical state requiring assistance), limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. **B**
- Reassess glycemic targets over time based on the criteria. **E**

TABLE 4. Summary of Glycemic Recommendations for Many Nonpregnant Adults With Diabetes

A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

**More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.*

Hypoglycemia

- Level 1 hypoglycemia is defined as a measurable glucose concentration <70 mg/dL (3.9 mmol/L).
- Level 2 hypoglycemia (defined as a blood glucose concentration <54 mg/dL [3.0 mmol/L]) is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event.
- Level 3 hypoglycemia is defined as a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery.

- ***Recommendations***
- Individuals at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia at each encounter. **C**
- Glucose (15–20 g) is the preferred treatment for the conscious individual with blood glucose <70 mg/dL (3.9 mmol/L), although any form of carbohydrate that contains glucose may be used. Fifteen minutes after treatment, if SMBG shows continued hypoglycemia, the treatment should be repeated. Once SMBG returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia. **E**

- Glucagon should be prescribed for all individuals at increased risk of level 2 hypoglycemia, defined as blood glucose <54 mg/dL (3.0 mmol/L), so it is available should it be needed. Caregivers, school personnel, or family members of these individuals should know where it is and when and how to administer it. Glucagon administration is not limited to health care professionals. **E**
- Hypoglycemia unawareness or one or more episodes of level 3 hypoglycemia should trigger reevaluation of the treatment regimen. **E**

- Insulin-treated patients with hypoglycemia unawareness or an episode of level 2 hypoglycemia should be advised to raise their glycemic targets to strictly avoid hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. **A**
- Ongoing assessment of cognitive function is suggested with increased vigilance for hypoglycemia by the clinician, patient, and caregivers if low cognition or declining cognition is found. **B**

CARDIOVASCULAR DISEASE AND RISK MANAGEMENT

Hypertension/Blood Pressure Control

Recommendations for Screening and Diagnosis

- Blood pressure should be measured at every routine clinical visit. Patients found to have elevated blood pressure (≥140/90 mmHg) should have blood pressure confirmed using multiple readings, including measurements on a separate day, to diagnose hypertension. **B**
- All hypertensive patients with diabetes should monitor their blood pressure at home. **B**

Cardiovascular Disease

- ***Recommendations*** for Screening
- In asymptomatic patients, routine screening for coronary artery disease is not recommended as it does not improve outcomes as long as ASCVD risk factors are treated. **A**
- Consider investigations for coronary artery disease in the presence of any of the following: atypical cardiac symptoms (e.g., unexplained dyspnea, chest discomfort); signs or symptoms of associated vascular disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease; or electrocardiogram abnormalities (e.g., Q waves). **E**

Recommendations: Antiplatelet Agents

Consider aspirin therapy (75–162 mg/day) C

- **As a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk**
- **Includes most men or women with diabetes age ≥50 years who have at least one additional major risk factor, including:**
  - Family history of premature ASCVD
  - Hypertension
  - Smoking
  - Dyslipidemia
  - Albuminuria

Recommendations: Antiplatelet Agents (2)

- **Aspirin is not recommended for ASCVD prevention for adults with DM at low ASCVD risk, since potential adverse effects from bleeding likely offset potential benefits. C**
  - Low risk: such as in men or women with diabetes aged <50 years with no major additional ASCVD risk factors)
- **In patients with diabetes <50 years of age with multiple other risk factors (e.g., 10-year risk 5–10%), clinical judgment is required. E**

Recommendations: Antiplatelet Agents (3)

- Use aspirin therapy (75–162 mg/day) as secondary prevention in those with diabetes and history of ASCVD. A
- For patients w/ ASCVD & aspirin allergy, clopidogrel (75 mg/day) should be used. B
- Dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome. B

Lipid management in diabetic patients

Table 10.2—Recommendations for statin and combination treatment in adults with diabetes

Age	ASCVD or 10-year ASCVD risk >20%	Recommended statin intensity^ and combination treatment*
<40 years	No	None†
	Yes	High • In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)#
≥40 years	No	Moderate‡
	Yes	High • In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

ASCVD, atherosclerotic cardiovascular disease; PCSK9, proprotein convertase subtilisin/kexin type 9. *In addition to lifestyle therapy. ^For patients who do not tolerate the intended intensity of statin, the maximally tolerated statin dose should be used. †Moderate-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. ASCVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, chronic kidney disease, albuminuria, and family history of premature ASCVD. ‡High-intensity statin may be considered based on risk-benefit profile and presence of ASCVD risk factors. #Adults aged <40 years with prevalent ASCVD were not well represented in clinical trials of non-statin–based LDL reduction. Before initiating combination lipid-lowering therapy, consider the potential for further ASCVD risk reduction, drug-specific adverse effects, and patient preferences.

Table 10.3—High-intensity and moderate-intensity statin therapy*

High-intensity statin therapy (lowers LDL cholesterol by ≥50%)	Moderate-intensity statin therapy (lowers LDL cholesterol by 30–50%)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg
	Simvastatin 20–40 mg
	Pravastatin 40–80 mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Pitavastatin 2–4 mg

*Once-daily dosing. XL, extended release.

Other Combination Therapy

Recommendations

- Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. **A**
- Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. **A**

MICROVASCULAR COMPLICATIONS AND FOOT CARE

Chronic Kidney Disease

- ***Recommendations*** for Screening
- At least once a year, assess urinary albumin (e.g., spot urinary albumin-to-creatinine ratio) and eGFR in patients with type 1 diabetes with duration of ≥5 years, in all patients with type 2 diabetes, and in all patients with comorbid hypertension. **B**

Diabetic Retinopathy

- ***Recommendations***
- Optimize glycemic control to reduce the risk or slow the progression of diabetic retinopathy. **A**
- Optimize blood pressure and serum lipid control to reduce the risk or slow the progression of diabetic retinopathy. **A**

Screening

- Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. **B**
- Patients with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. **B**
- If there is no evidence of retinopathy for one or more annual eye exam and glycemia is well controlled, then exams every 1–2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations will be required more frequently. **B**

- Telemedicine programs that use validated retinal photography with remote reading by an ophthalmologist or optometrist and timely referral for a comprehensive eye examination when indicated can be an appropriate screening strategy for diabetic retinopathy. **B**
- Women with preexisting type 1 or type 2 diabetes who are planning pregnancy or who are pregnant should be counseled on the risk of development and/or progression of diabetic retinopathy. **B**
- Eye examinations should occur before pregnancy or in the first trimester in patients with preexisting type 1 or type 2 diabetes, and then patients should be monitored every trimester and for 1-year postpartum as indicated by the degree of retinopathy. **B**

Neuropathy

- ***Recommendations*** for Screening
- All patients should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. **B**
- Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All patients should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. **B**
- Symptoms and signs of autonomic neuropathy should be assessed in patients with microvascular complications. **E**

Foot Care

- ***Recommendations***
- Perform a comprehensive foot evaluation at least annually to identify risk factors for ulcers and amputations. **B**
- Patients with evidence of sensory loss or prior ulceration or amputation should have their feet inspected at every visit. **C**
- Obtain a prior history of ulceration, amputation, Charcot foot, angioplasty or vascular surgery, cigarette smoking, retinopathy, and renal disease and assess current symptoms of neuropathy (pain, burning, numbness) and vascular disease (leg fatigue, claudication). **B**
- The examination should include inspection of the skin, assessment of foot deformities, neurological assessment (10-g monofilament testing with at least one other assessment: pinprick, temperature, vibration), and vascular assessment including pulses in the legs and feet. **B**

- Patients with symptoms of claudication or decreased or absent pedal pulses should be referred for ankle-brachial index and for further vascular assessment as appropriate. **C**
- A multidisciplinary approach is recommended for individuals with foot ulcers and high-risk feet (e.g., dialysis patients and those with Charcot foot or prior ulcers or amputation). **B**
- Refer patients who smoke or who have histories of prior lower-extremity complications, loss of protective sensation, structural abnormalities, or peripheral arterial disease to foot care specialists for ongoing preventive care and lifelong surveillance. **C**
- Provide general preventive foot self-care education to all patients with diabetes. **B**
- The use of specialized therapeutic footwear is recommended for high-risk patients with diabetes including those with severe neuropathy, foot deformities, or history of amputation. **B**

Diabetes management:

- **Oral hypoglycemic medication.**
- **Steps for DM treatment.**

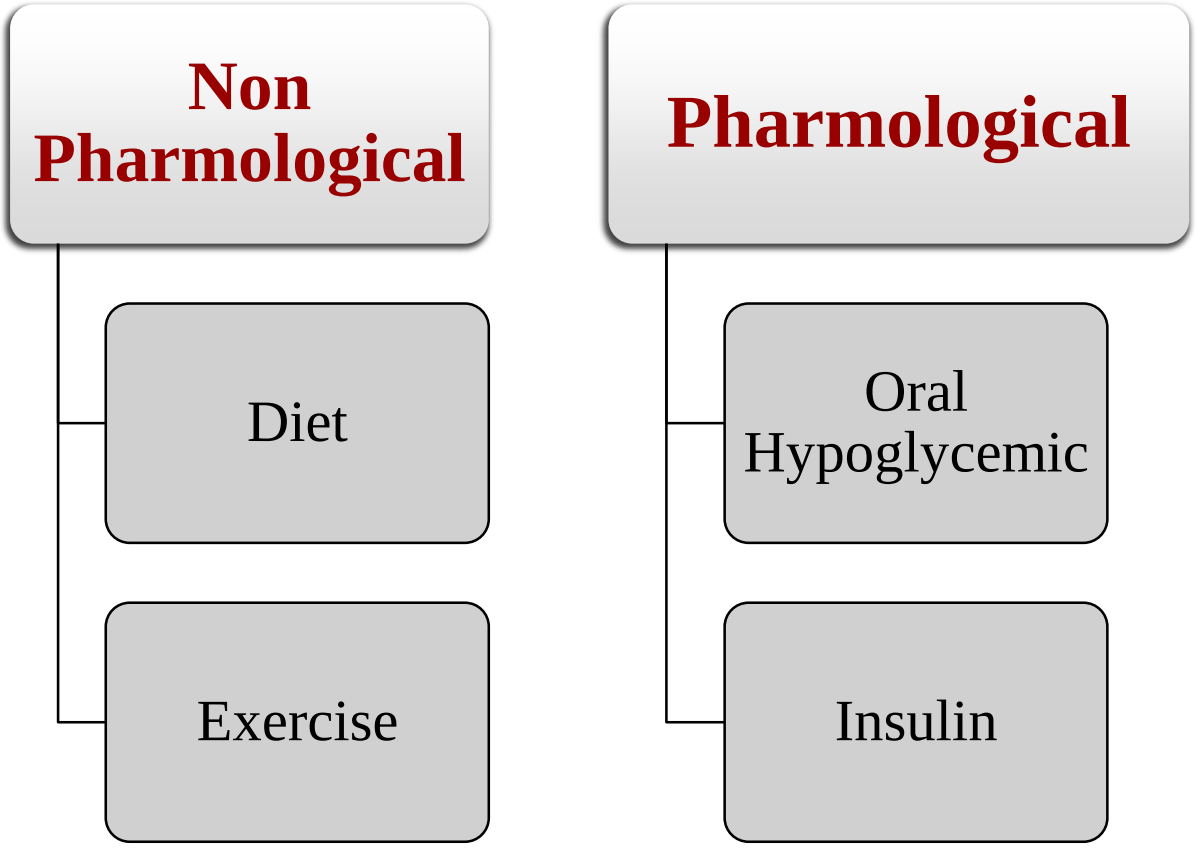

Non Pharmological
Diet
Exercise
Pharmological
Oral Hypoglycemic
Insulin

Table 5.1—Medical nutrition therapy recommendations

Topic	Recommendations	Evidence rating
Effectiveness of nutrition therapy	**5.6** An individualized medical nutrition therapy program as needed to achieve treatment goals, preferably provided by a registered dietitian, is recommended for all people with type 1 or type 2 diabetes, prediabetes, and gestational diabetes mellitus.	**A**
	5.7 A simple and effective approach to glycemia and weight management emphasizing portion control and healthy food choices may be considered for those with type 2 diabetes who are not taking insulin, who have limited health literacy or numeracy, or who are older and prone to hypoglycemia.	**B**
	5.8 Because diabetes nutrition therapy can result in cost savings **B** and improved outcomes (e.g., A1C reduction) **A**, medical nutrition therapy should be adequately reimbursed by insurance and other payers. **E**	**B, A, E**
Energy balance	**5.9** Weight loss (>5%) achievable by the combination of reduction of calorie intake and lifestyle modification benefits overweight or obese adults with type 2 diabetes and also those with prediabetes. Intervention programs to facilitate weight loss are recommended.	**A**
Eating patterns and macronutrient distribution	**5.10** There is no single ideal dietary distribution of calories among carbohydrates, fats, and proteins for people with diabetes; therefore, meal plans should be individualized while keeping total calorie and metabolic goals in mind.	**E**
	5.11 A variety of eating patterns are acceptable for the management of type 2 diabetes and prediabetes.	**B**
Carbohydrates	**5.12** Carbohydrate intake should emphasize nutrient-dense carbohydrate sources that are high in fiber, including vegetables, fruits, legumes, whole grains, as well as dairy products.	**B**
	5.13 For people with type 1 diabetes and those with type 2 diabetes who are prescribed a flexible insulin therapy program, education on how to use carbohydrate counting **A** and in some cases how to consider fat and protein content **B** to determine mealtime insulin dosing is recommended to improve glycemic control.	**A, B**
	5.14 For individuals whose daily insulin dosing is fixed, a consistent pattern of carbohydrate intake with respect to time and amount may be recommended to improve glycemic control and reduce the risk of hypoglycemia.	**B**
	5.15 People with diabetes and those at risk are advised to avoid sugar-sweetened beverages (including fruit juices) in order to control glycemia and weight and reduce their risk for cardiovascular disease and fatty liver **B** and should minimize the consumption of foods with added sugar that have the capacity to displace healthier, more nutrient-dense food choices. **A**	**B, A**

Protein	**5.16** In individuals with type 2 diabetes, ingested protein appears to increase insulin response without increasing plasma glucose concentrations. Therefore, carbohydrate sources high in protein should be avoided when trying to treat or prevent hypoglycemia.	B
Dietary fat	**5.17** Data on the ideal total dietary fat content for people with diabetes are inconclusive, so an eating plan emphasizing elements of a Mediterranean-style diet rich in monounsaturated and polyunsaturated fats may be considered to improve glucose metabolism and lower cardiovascular disease risk and can be an effective alternative to a diet low in total fat but relatively high in carbohydrates.	B
	5.18 Eating foods rich in long-chain n-3 fatty acids, such as fatty fish (EPA and DHA) and nuts and seeds (ALA), is recommended to prevent or treat cardiovascular disease B; however, evidence does not support a beneficial role for the routine use of n-3 dietary supplements. A	B, A
Micronutrients and herbal supplements	**5.19** There is no clear evidence that dietary supplementation with vitamins, minerals (such as chromium and vitamin D), herbs, or spices (such as cinnamon or aloe vera) can improve outcomes in people with diabetes who do not have underlying deficiencies and they are not generally recommended for glycemic control.	C
Alcohol	**5.20** Adults with diabetes who drink alcohol should do so in moderation (no more than one drink per day for adult women and no more than two drinks per day for adult men).	C
	5.21 Alcohol consumption may place people with diabetes at increased risk for hypoglycemia, especially if taking insulin or insulin secretagogues. Education and awareness regarding the recognition and management of delayed hypoglycemia are warranted.	B
Sodium	**5.22** As for the general population, people with diabetes should limit sodium consumption to <2,300 mg/day.	B
Nonnutritive sweeteners	**5.23** The use of nonnutritive sweeteners may have the potential to reduce overall calorie and carbohydrate intake if substituted for caloric (sugar) sweeteners and without compensation by intake of additional calories from other food sources. For those who consume sugar-sweetened beverages regularly, a low-calorie or nonnutritive-sweetened beverage may serve as a short-term replacement strategy, but overall, people are encouraged to decrease both sweetened and nonnutritive-sweetened beverages and use other alternatives, with an emphasis on water intake.	B

PHYSICAL ACTIVITY

- Children and adolescents with type 1 or type 2 diabetes or prediabetes should engage in 60 min/day or more of moderate- or vigorous-intensity aerobic activity, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days/week. **C**

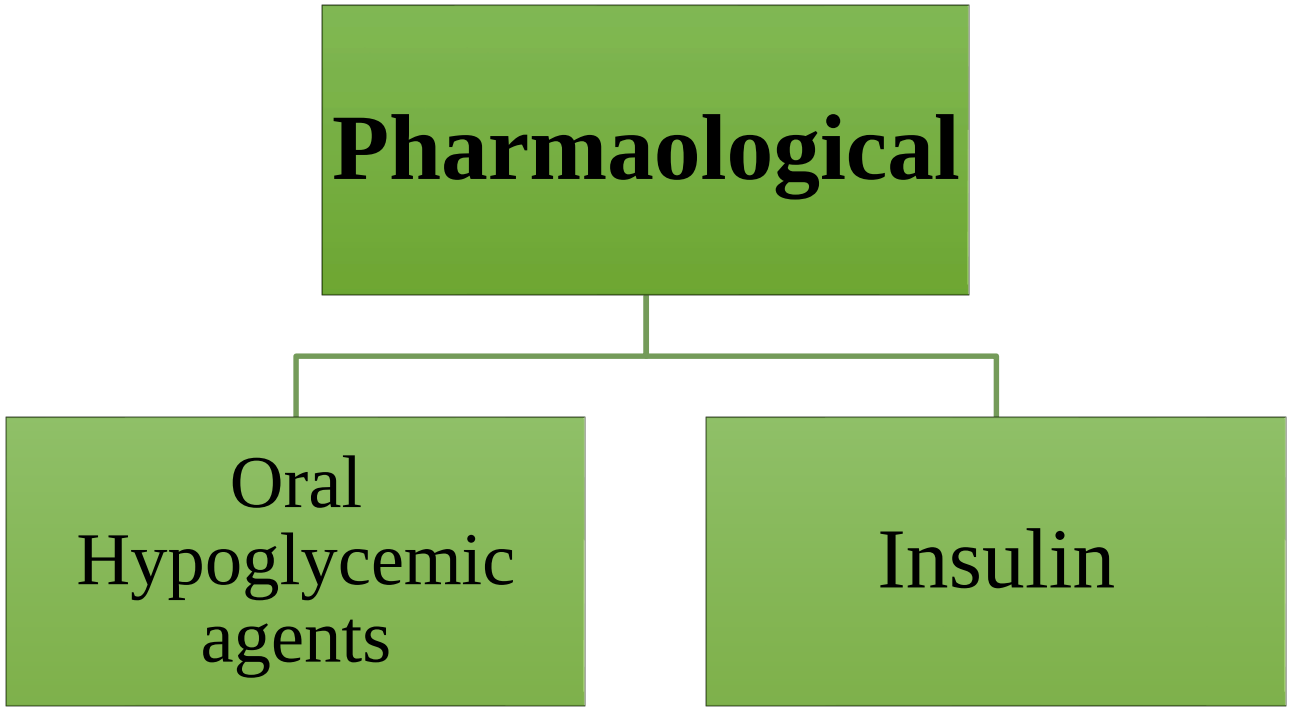
- Most adults with type 1 **C** and type 2 **B** diabetes should engage in 150 min or more of moderate-to-vigorous intensity aerobic activity per week, spread over at least 3 days/week, with no more than 2 consecutive days without activity. Shorter durations (minimum 75 min/week) of vigorous-intensity or interval training may be sufficient for younger and more physically fit individuals.

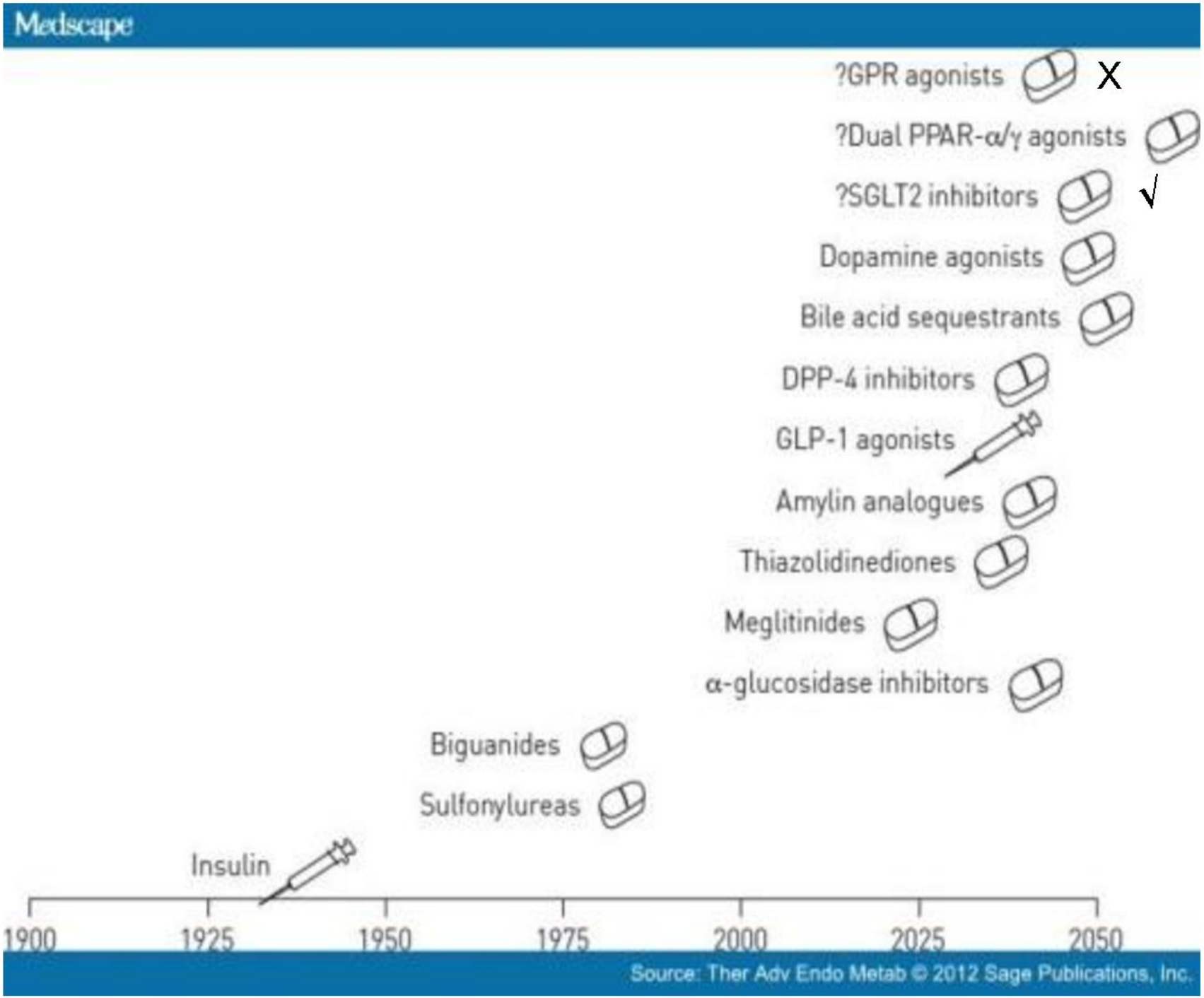
- Adults with type 1 **C** and type 2 **B** diabetes should engage in 2–3 sessions/week of resistance exercise on nonconsecutive days.

- All adults, and particularly those with type 2 diabetes, should decrease the amount of time spent in daily sedentary behavior. **B** Prolonged sitting should be interrupted every 30 min for blood glucose benefits, particularly in adults with type 2 diabetes. **C**

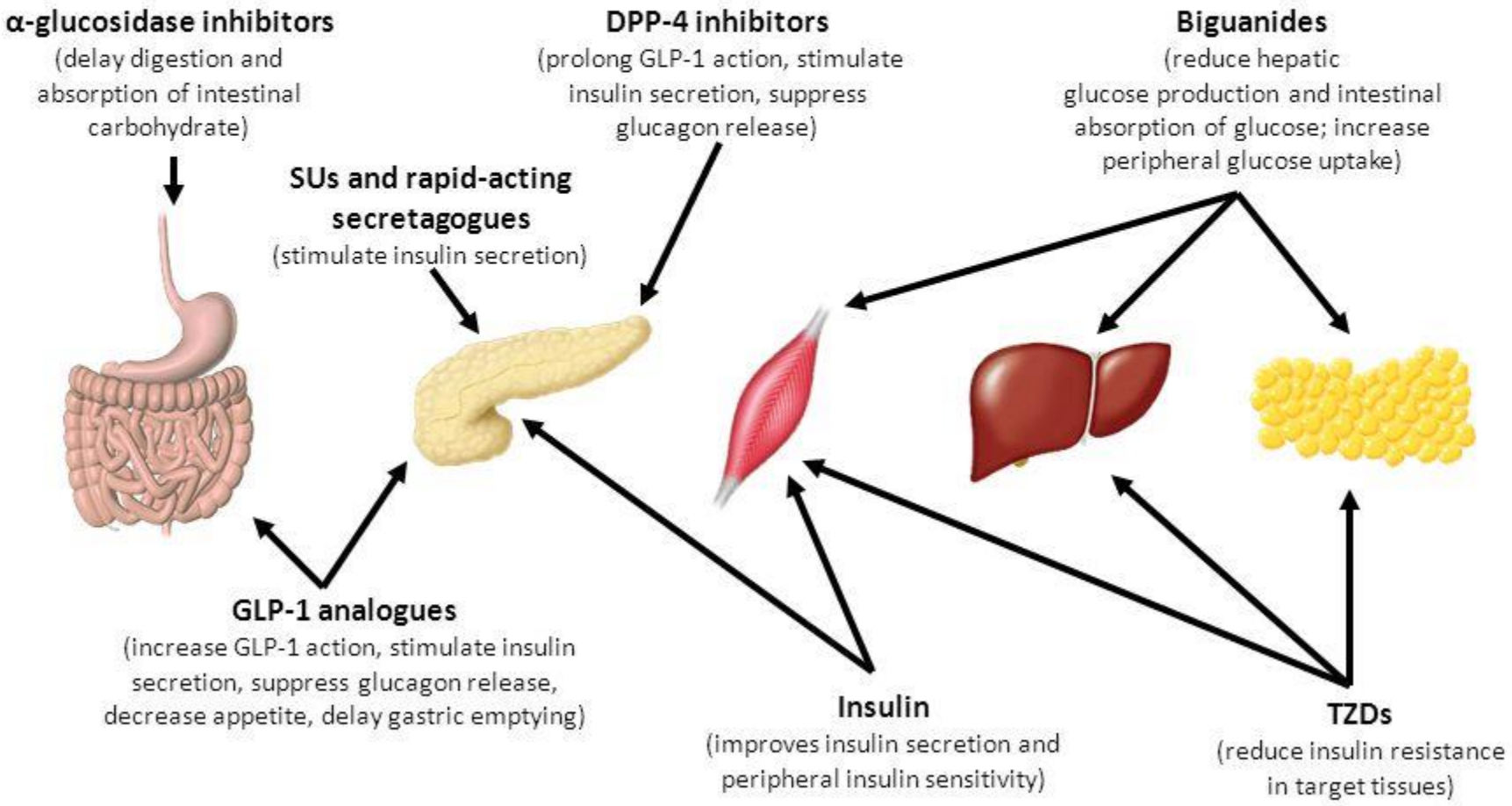
- Flexibility training and balance training are recommended 2–3 times/week for older adults with diabetes. Yoga and tai chi may be included based on individual preferences to increase flexibility, muscular strength, and balance. **C**

Drug therapy of diabetes




Medscape
?GPR agonists
X
?Dual PPAR-α/γ agonists
X
?SGLT2 inhibitors
√
Dopamine agonists
Bile acid sequestrants
DPP-4 inhibitors
GLP-1 agonists
Amylin analogues
Thiazolidinediones
Meglitinides
α-glucosidase inhibitors
Biguanides
Sulfonylureas
Insulin
1900
1925
1950
1975
2000
2025
2050
Source: Ther Adv Endo Metab © 2012 Sage Publications, Inc.

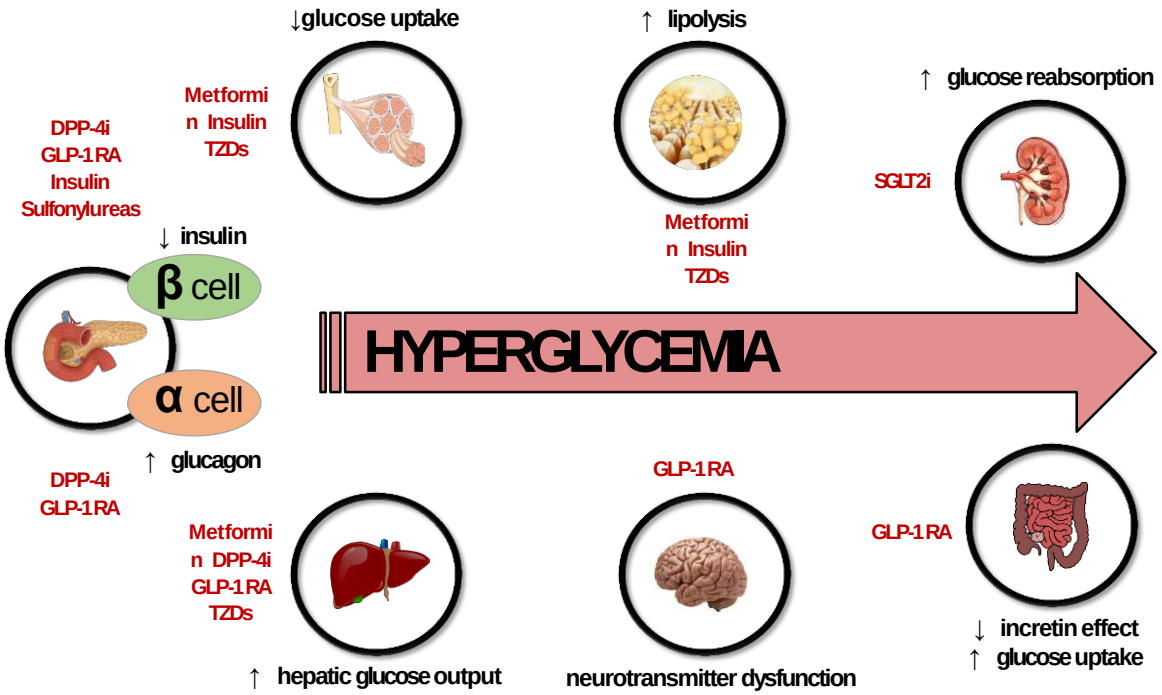
Main Classes of Glucose-Lowering Medications



TZD = thiazolidinedione; DPP = dipeptidyl peptidase; GLP = glucagon-like peptide

Krentz AJ, Bailey CJ. Drugs 2005;65:385-411

Type 2 DM Treatment Targets



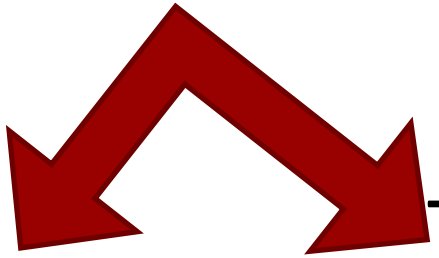
DeFronzo RA. *Diabetes.* 2009;58(4):773-795

(OHA)

1-INSULIN-SENSITIZING AGENTS

reduce blood sugar by making the body's tissues more sensitive to insulin.

Biguanides



Thiazolidinediones (TZD) / glitazone

Biguanides (Metformin)

Glucophage	500, 850, 1000 mg	PO
Glucophage XR	500, 750 mg	PO

DECREASE HGBA1C BY 1.0 to 2.0 %

- The first line for oral treatment of type 2 diabetes
- High efficacy with no hypoglycemia.

Biguanides (Metformin)

Advantages	Disadvantages
Weight neutral	GI side effects
No hypoglycemia	Potential for vitamin B-12 def Lactic acidosis (rare)
lipid-lowering activity	Discontinue during acute illness and before radiographic procedures requiring contrast
Decreased all-cause mortality and a decreased rate of (MI) in overweight and obese patients	Contraindicated in Renal insufficiency (discontinue if eGFR < 30)

Thiazolidinediones (TZD)

- Increase insulin sensitivity by acting on adipose, muscle, and liver to increase glucose utilization and decrease glucose production.
- When used as monotherapy, they reduce hemoglobin (A1C) values by 1.5 %.
- High efficacy with no hypoglycemia.
- Show benefit in NASH
- No dose adjustment

Thiazolidinediones (TZD)

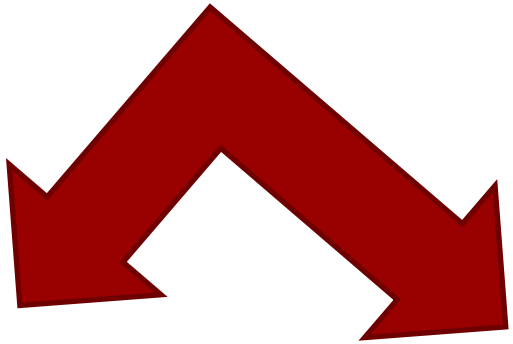
Rosiglitazone(Avandia) **2, 4, 8 mg**	**Pioglitazone (Actos)** 15, 30, 45 mg
increased risk for cardiovascular event.(Progressive ischemia ,MI, HF) Increased LDL	Increase risk for bladder cancer

OTHER ADVERSE EFFECT:

- All thiazolidinediones cause weight gain
- Fluid retention/heart failure (Peripheral edema occurs in 4 to 6 %)
- FDA Black Box: CHF >> pioglitazone & rosiglitazone.
- Decrease bone density and increase fracture risk, particularly in women
- Not recommended in renal impairment due to fluid retention

2- Insulin Secretagogues

- stimulate release of insulin from pancreatic beta cells



Sulfonylureas

Meglitinides

Sulfonylureas

- Lower A1c by 1-2 %
- High efficacy with risk of hypoglycemia.
- Safe in CVD and renal impairment (except glyburide)

Sulfonylureas

Drug	Duration of biologic effect, hour	Usual daily dose, mg	Dosing per day
First-generation sulfonylureas			
Acetohexamide	12 to 18	500 to 750	Once or divided
Chlorpropamide (Diabinese)	24 to 72	250 to 500	Once
Tolbutamide (Orinase)	14 to 16	1000 to 2000	Once or divided

Sulfonylureas

2nd generation Sulfonylureas

Glipizide (minidab)	**Glucotrol (OD or divided)** **Glucotrol XL (OD)**	**(2.5), 5, 10 mg** **(XL)**	**Up to 40 mg** **Up to 20 mg**
Gliclazide	**Diamcrone R (BID) /Glaze** **Diamcrone MR (OD)**	**40,80 mg** **30 , 60 mg**	**Up to 320 mg** **Up to120 mg**
Glibenclamide (Glyburide)	**Doanil** **Diatab**	**2.5 , 5 mg**	**OD or BID** **Up to 10 mg**

3rd generation Sulfonylurea

Glimepiride	**(Amaryl)**	**1, 2, 4 mg**	**OD tablets** **Up to 8 mg**

Side effects:

- Hypoglycemia (most common)
- Nausea, skin reactions (including photosensitivity)
- Weight gain

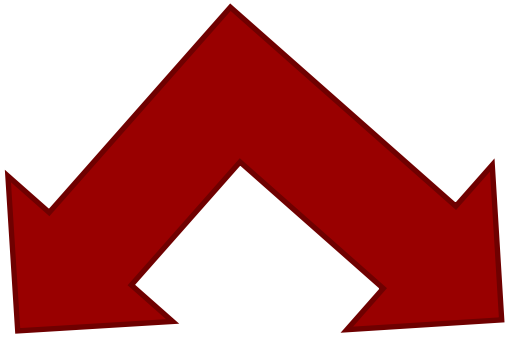
Meglitinides (Glinides)

Repeglinide	0.5 before meal Max 4 mg before each meal
Nateglinide	120 mg immediately before each meal

side effects:

- Hypoglycemia & weight gain (less than sulfa)
- Dosing frequency .
- Repeglinide safe in pt. with decrease GFR or renal failure .

3- Incretin Based Therapy

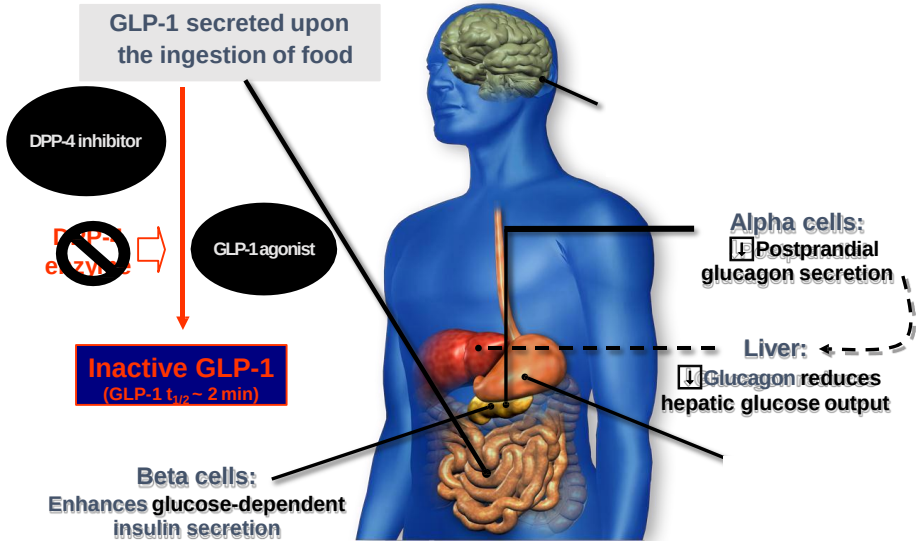


DPP-4 inhibitors

GLP-1 receptor agonists

GLP-1 Effects in Humans

Understanding the Natural Role of Incretins



Adapted from Flint A, et al. *JClin Invest.* 1998;101:515-520
Adapted from Larsson H, et al. *Acta Physiol Scand.* 1997;160:413-422 Adapted from Nauck MA, et al. *Diabetologia*. 1996;39:1546-1553 Adapted from Drucker DJ. *Diabetes*. 1998;47:159-169

DPP-4 inhibitors

- Reduce HbA1c between 0.6- 1.1%
- Intermediate efficacy with no hypoglycemia

1-Sitagliptin	(Januvia)	25, 50, 100 mg	
2-Saxagliptin	(Onglyza)	2.5, 5 mg	
3-Vildagliptin	Galvas	50 mg	OD –BID *
4-linagliptin	Tradjenta	5 mg once daily	
5-Alogliptin	Nesina, Kazano,	25 mg once daily	

DPP-4 inhibitors

- Require dose adjustment except **Linagliptin**
- No effects on body weight or risk of hypoglycemia

Common SE :

- Potential CV risk in saxagliptin and alogliptin.
- Headache, nasopharyngitis, and upper respiratory tract infection
- Joint pain, myalgias, muscle weakness, and muscle spasms.
- Urticaria & angioedema
- Acute pancreatitis

GLP-1 receptor agonists

EXENATIDE **Extended-release:**	**5 mcg subQ** **2 mg subQ**	**BID** **Up to 10 BID** **once /week**
LIRAGLUTIDE	0.6 mg subQ OD	Up to 1.8 mg OD

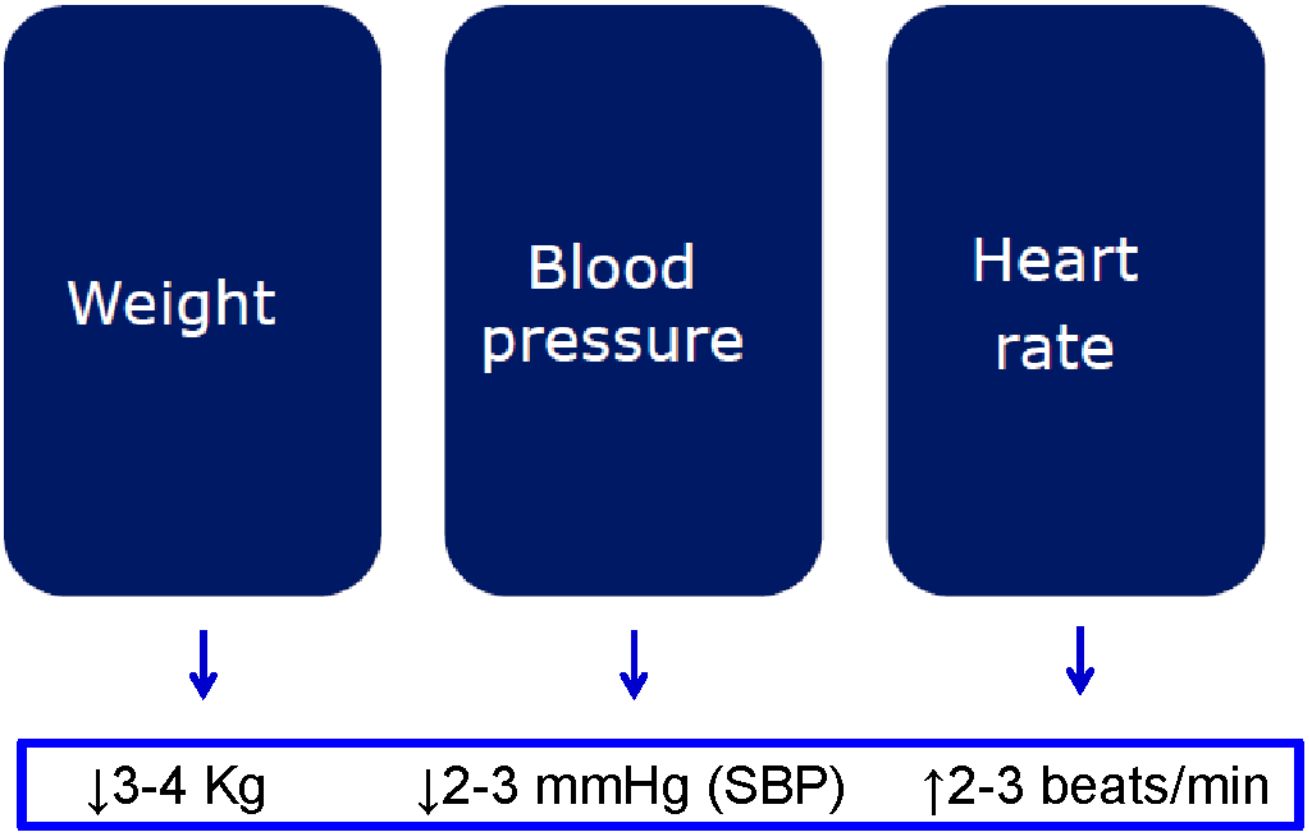
Advantages :

- High efficacy with no hypoglycemia
- Weight reduction .
- Decrease ASCVD in liraglutide > semaglutide > Exenatide ER

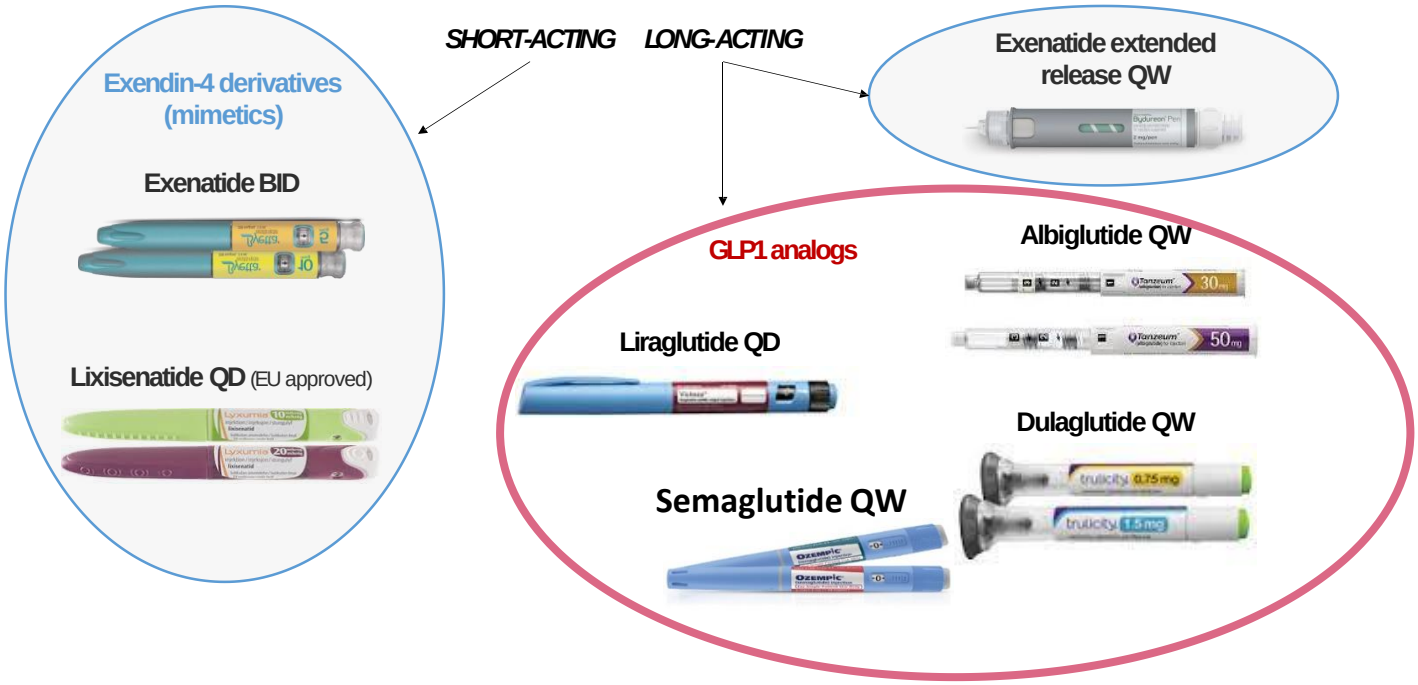
Side Effects:

- GI side effect (nausea, vomiting, diarrhea)
- Initiating / increasing dose >> Potential risk of AKI (liraglutide is safe)
- FDA Black Box >> -cell hyperplasia/medullary thyroid tumors
- Injectable >> injection site reaction.

Non glucose effects of GLP-1 receptor agonists



Clinically Approved GLP-1 Receptor Agonists



Considerations for incretin selection

Clinical variables	DPP-4 inhibitors	GLP1RA
Glycemic effects		
Effective A1C reduction	0.5 – 1.0% above target	1.0 – 1.5% above target
Fasting glucose reduction	0 – 30 mg/dl	20 – 70 mg/dl (long-acting > short-acting)
Post-prandial glucose reduction	<60 mg/dl	60 – 100 mg/dl (short-acting > long-acting)
Non-glycemic effects		
Weight	neutral	1 – 4 kg decrease
Blood pressure	neutral	0 - 3 mmHg decrease
Other		
GI side effects	none	5-20% nausea
Renal insufficiency	Linagliptin no dose adjustments	none indicated in severe renal insufficiency
Cost	$$	$$$

Adapted from Nauck M. Diabetes, Obesity and Metabolism 2016; 18: 203–216

4- α Glucosidase Inhabitors

lowering (A1C) by only 0.4 to 0.9%

1-Acarbose: 50 and 100 mg TID

2-Miglitol

3-Voglibose

- Slow absorption of glucose and reduce postprandial blood glucose concentration.
- Side Effects: flatulence and diarrhea

5- SGLT-2 Inhibitors

- Inhibit the reabsorption of glucose in the distal tubules of the kidney
- Intermediate efficacy with no hypoglycemia
- **FDA Approved SGLT2 Inhibitors**

Agent	Canagliflozin INVOKANA®	Dapagliflozin FARXIGA™	Empagliflozin JARDIANCE®
Dosing	Initial: 100mg daily Max: 300mg daily	Initial: 5mg daily Max: 10mg daily	Initial: 10mg daily Max: 25mg daily
Administration	Before the first meal of the day	In the morning with or without food	In the morning with or without food
Renal Dose Adjustments	Yes	Yes	Yes
Cost	~$350 for 30 tablets	~$350 for 30 tablets	TBD

Advantages	Disadvantages
Weight loss	FDA Black Box: risk of amputation (canagliflozin)
Good CV effect (empagliflozin and canagliflozin)	Risk of bone fracture (canagliflozin)
lipid-lowering activity	DKA risk (all agents, rare in T2DM)
Delay progression of CKD (empagliflozin and canagliflozin)	Genitourinary infections
	Increase LDL cholestrol
	Risk of volume depletion and hypotension

Adverse effects

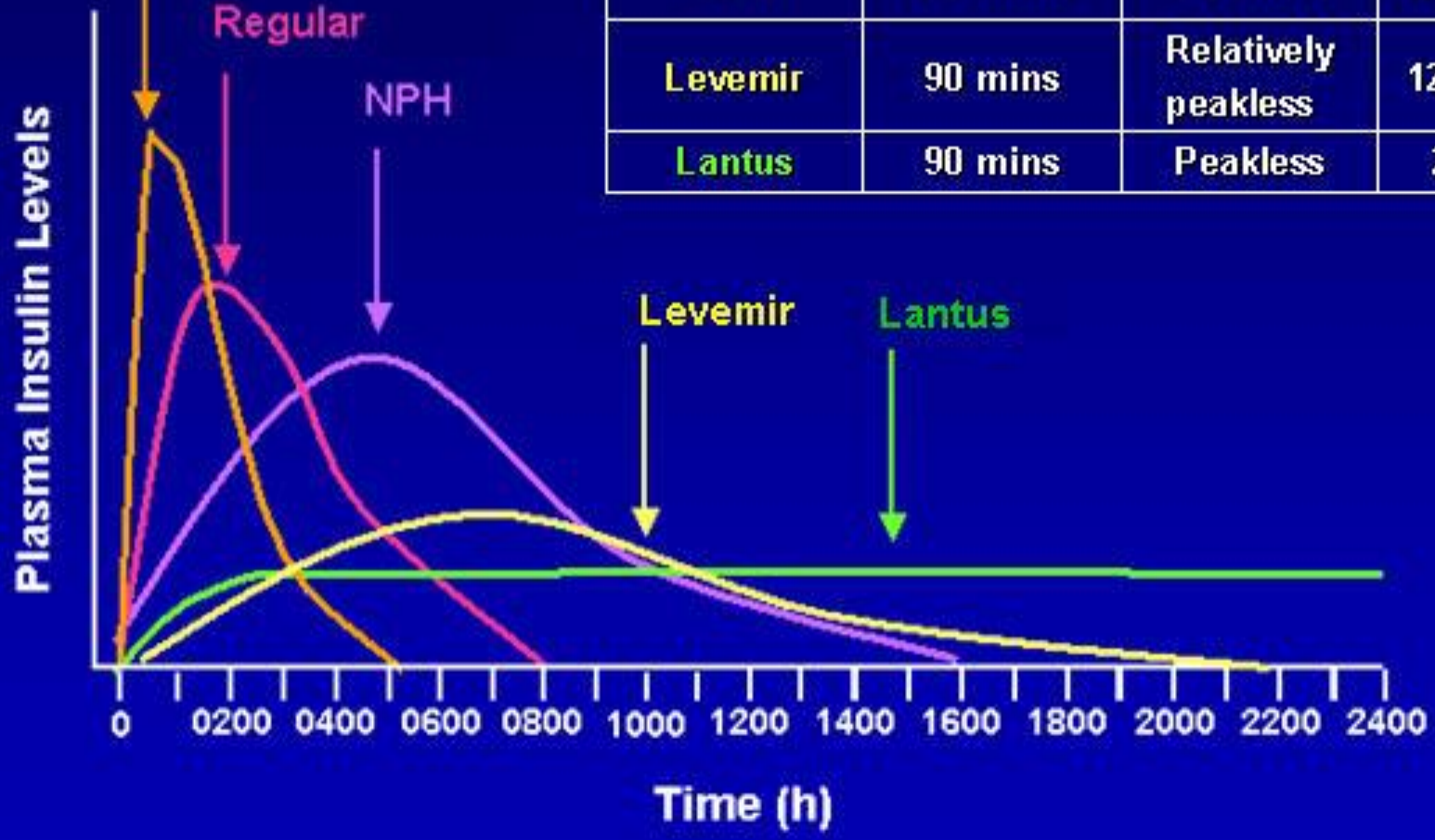
Genitourinary tract	**Hypotension**	**Acute kidney injury**
Bone fracture	**Diabetic ketoacidosis**	**Amputations**

Insulin

- Powerful agent
- Necessary in 20-30%
- Inexpensive

- Weight gain
- Hypoglycaemia
- High level of patient fear

Insulin	Onset	Peak	Duration
Apidra Humalog Novolog	10-15 mins	60-90 mins	4-5 hours
Regular	30-60 mins	2-4 hours	5-8 hours
NPH	1-3 hours	5-8 hours	12- 18 hours
Levemir	90 mins	Relatively peakless	12-24 hours
Lantus	90 mins	Peakless	24 hours



TREATMENT REGIMENS OF TYPE 1 DM

- **Conventional Insulin Therapy**

  Two injections of NPH and Regular Insulin

- **Mixed Insulin**

  Two injections of 70/30 or 60/40 or 50/50

- **Multiple Insulin Injections**

✓ 1 or 2 injections of NPH plus 3 injections of Regular or Rapid Insulin.

✓ One injection of Glargine or Detemir plus 3 injections of rapid insulin(Lispro /Aspart).

TABLE 5. Drug-Specific and Patient Factors to Consider When Selecting Antihyperglycemic Treatment in Adults With Type 2 Diabetes

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	CHF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin	High	Oral	Benefit: canagliflozin, empagliflozin	• Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	• **FDA Black Box:** Risk of amputation (**canagliflozin**) • Risk of bone fractures (canagliflozin) • DKA risk (all agents, rare in T2DM) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL cholesterol • Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide Benefit: liraglutide† > semaglutide > exenatide extended release	Neutral	High	SQ	Benefit: liraglutide	• Renal dose adjustment required (exenatide, lixisenatide) • Caution when initiating or increasing dose due to potential risk of acute kidney injury	• **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) • Gastrointestinal side effects common (nausea, vomiting, diarrhea) • Injection site reactions • ?Acute pancreatitis risk
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin, alogliptin	High	Oral	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	• Potential risk of acute pancreatitis • Joint pain
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Low	Oral	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	• **FDA Black Box:** Congestive heart failure (**pioglitazone, rosiglitazone**) • Fluid retention (edema; heart failure) • Benefit in NASH • Risk of bone fractures • Bladder cancer (pioglitazone) • ↑LDL cholesterol (rosiglitazone)
Sulfonylureas (2nd generation)	High	Yes	Gain	Neutral	Neutral	Low	Oral	Neutral	• Glyburide: not recommended • Glipizide and glimepiride: initiate conservatively to avoid hypoglycemia	• FDA Special Warning on increased risk of cardiovascular mortality based on studies of an older sulfonylurea (tolbutamide)
Insulin: Human insulin	Highest	Yes	Gain	Neutral	Neutral	Low	SQ	Neutral	• Lower insulin doses required with a decrease in eGFR; titrate per clinical response	• Injection site reactions • Higher risk of hypoglycemia with human insulin (NPH or premixed formulations) vs. analogs
Insulin: Analogs						High	SQ			

**For agent-specific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA approved for CVD benefit. CHF, congestive heart failure; CV, cardiovascular; DPP-4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; GLP-1 RAs, GLP-1 receptor agonists; NASH, nonalcoholic steatohepatitis; SQ, subcutaneous; T2DM, type 2 diabetes.*

If you have DM pt on Metformin with HbA1c above target, What to do?

- Establieshed ASCVD or CKD.
- Without established ASCVD or CKD:
  - To minimize hypoglycemia
  - To promote weight loss or minimize weight gain
  - Cost is a major issue

CV safety studies

Agents	Saxagliptin	Alogliptin	Sitagliptin	Lixisenatide	Empagliflozin	Liraglutide	Semaglutide
Trial name	SAVOR-TIMI	EXAMINE	TECOS	ELIXA	EMPA-REG	LEADER	SUSTAIN-6
Primary endpoint	Neutral	Neutral	Neutral	Neutral	Benefit	Benefit	Benefit
CV Death	Neutral	Neutral	Neutral	Neutral	Benefit	Benefit	Neutral
Non-fatal AMI	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
Non-fatal Stroke	Neutral	Neutral	Neutral	Neutral	Harm(trend)	Neutral	Benefit
HF	Harm	Harm	Neutral	Neutral	Benefit	Neutral	Neutral
Renal	Neutral	Neutral	Neutral	Neutral	Benefit	Benefit	Benefit

Retinopathy Harm

Large Non-Insulin CV Outcomes Trials in T2D

Study	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
	NEUTRAL	NEUTRAL	NEUTRAL		NEUTRAL
DPP4-I	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	placebo	placebo	placebo	sulfonylurea	placebo
N	16,500	5400	14,000	6000	8300
Results	2013	2013	June 2015	2018	2017

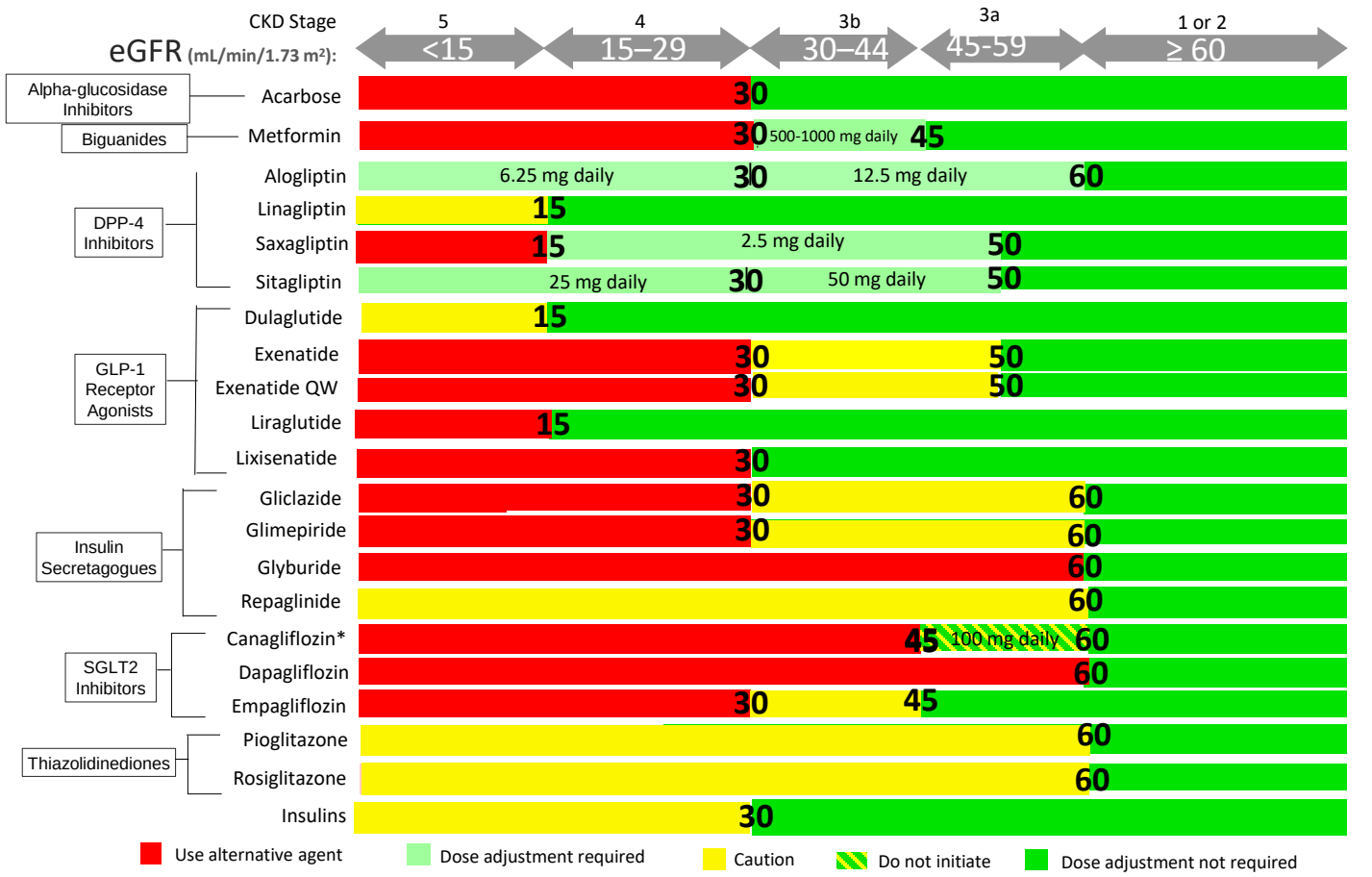
Study	LEADER	ELIXA	SUSTAIN6	EXSCEL	REWIND
	BENEFICIALI	NEUTRAL	BENEFICIALI	NEUTRAL	
GLP1-RA	liraglutide	lixisenatide	semaglutide	exenatide LR	dulaglutide
Comparator	placebo	placebo	placebo	placebo	placebo
N	16,500	14,000	6000	5400	8300
Results	2016	2015	2016	2018	2019

Study	EMPA-REG	CANVAS	DECLARE	NCT01986881
	BENEFICIALI	BENEFICIALI		
SGLT-2-i	empaglifozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	placebo	placebo	placebo	placebo
N	7300	4300	22,200	3900
Results	Sept 2015	2017	2018	2020

Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326.; White WB, et al. *N Engl J Med*. 2013;369:1327-1335.; Green JB, et al. *N Engl J Med*. 2015;373:232-242.; Marx N, et al. *Diab Vasc Dis Res*. 2015;12:164-174.; ClinicalTrials.go (NCT01897532).; Marso SP, et al. *Am J Heart*. 2013;166:823-830.; Pfeffer MA, et al. *N Engl J Med*. 2015;373-2247-

2018 Diabetes Canada CPG – Chapter 13. Pharmacologic Glycemic Management of Type 2 Diabetes

Antihyperglycemic Agents and Renal Function



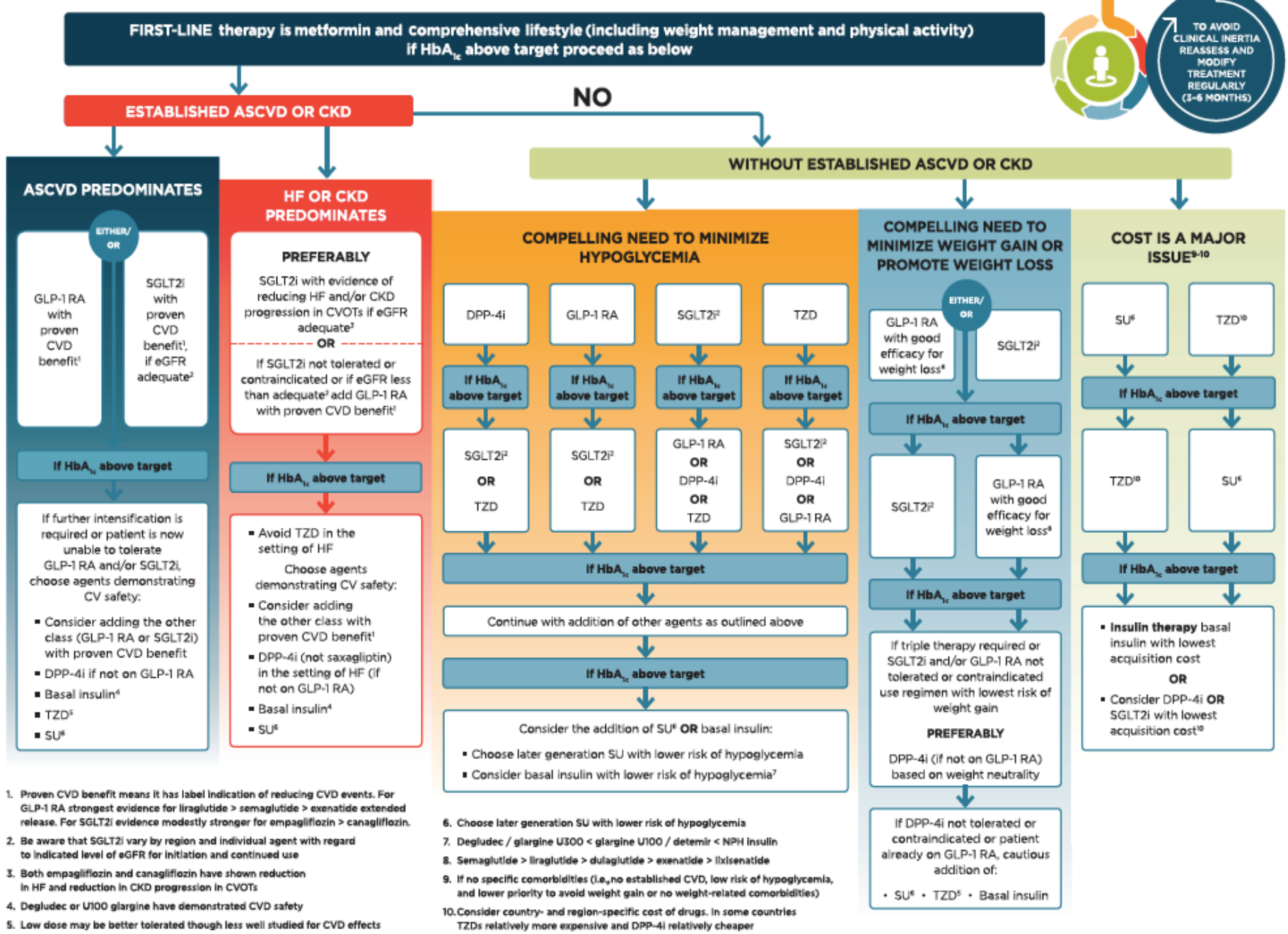
** May be used for cardiorenal benefits in those with clinical CVD, A1C above target and eGFR >30 mL/min/1.73m²*

Efficacy of Non-insulin Anti-diabetes Agents*

Drug	A1c Reduction (%)
Metformin	1.5–2.0
Secretagogue (SFU/Glinide)	1.5–2.0
GLP1RA	1.0-1.5
TZD	1.0–1.5
SGLT2i[1]	0.8-1.5
DPP4i[1]	0.5–1.5
α–GI	0.5–1.0
Bromocriptine IR[2]	0.6-0.9
Amylin[2]	0.4-0.7
Colesevelam[2]	0.3-0.5

Not head to head. Baselines and background therapies differ. Information derived from multiple studies.

[1]http://resources.aace.com. [2]Information taken from manufacturer PI.

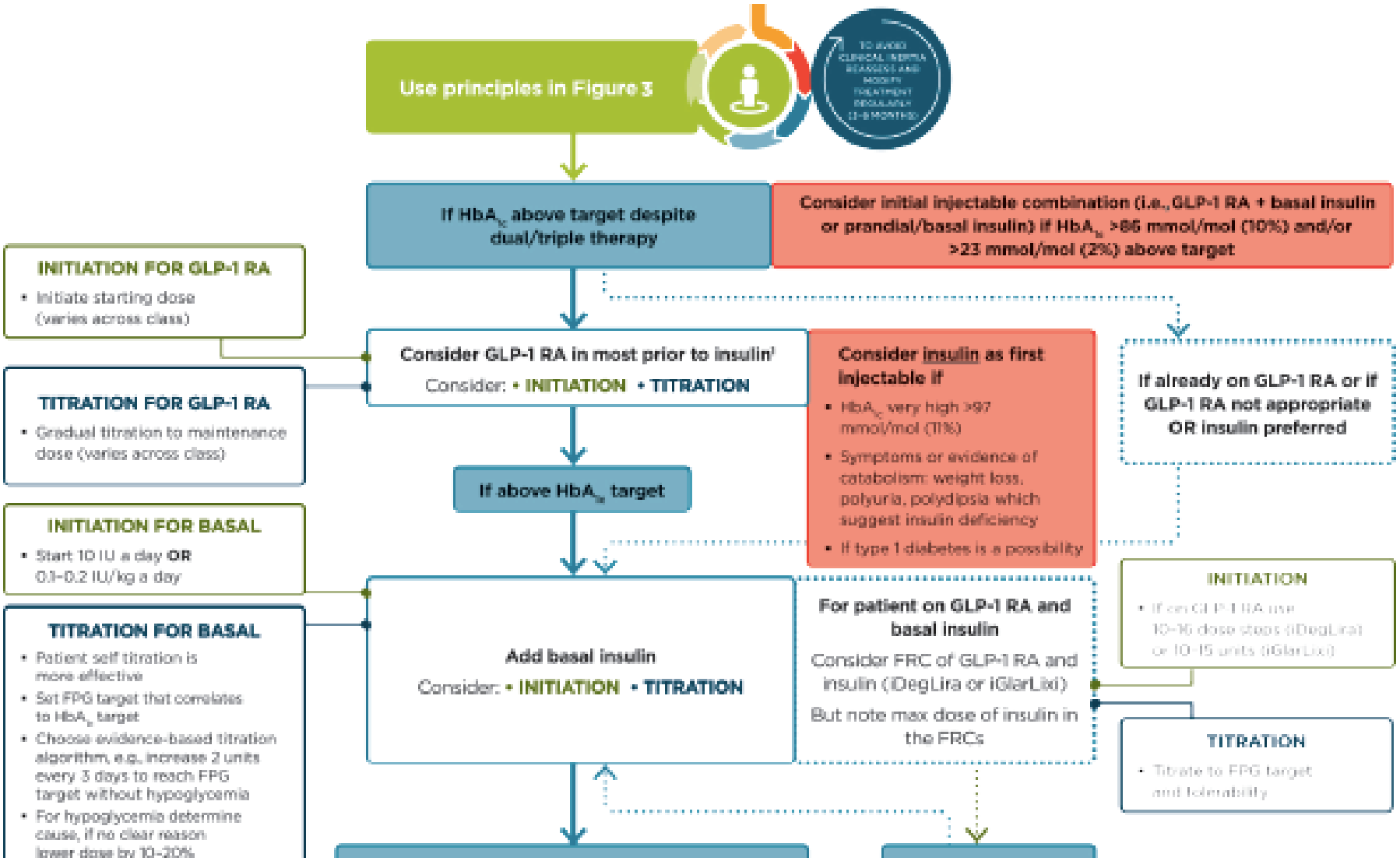


1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

FIGURE 3. Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see Figure 1. CV, cardiovascular; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, GLP-1 receptor agonist; HbA_{1c}, glycated hemoglobin; HF, heart failure; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Adapted from Davies MJ, D'Alessio DA, Fradkin J, et al. Diabetes Care 2018;41:2669–2701.

If HbA1c still above target despite dual/triple therapy, What to do?

- Consider GLP-1 RA in most prior to insulin.
- Consider insulin as first injectable if:
  - HbA1c very high > 11%
  - Symptoms or evidence of catabolism: Wt loss, polyurea, polydispsia which suggest insulin deficiency.
  - If type-1 diabetes is a possibility.
  - If already on GLP-1 RA or if GLP-1 RA not appropriate or Insulin preferred.


Use principles in Figure 3
If HbA1c above target despite dual/triple therapy
Consider initial injectable combination (i.e., GLP-1 RA + basal insulin or prandial/basal insulin) if HbA1c >86 mmol/mol (10%) and/or >23 mmol/mol (2%) above target
INITIATION FOR GLP-1 RA
• Initiate starting dose (varies across class)
TITRATION FOR GLP-1 RA
• Gradual titration to maintenance dose (varies across class)
Consider GLP-1 RA in most prior to insulin†
Consider: • INITIATION • TITRATION
Consider insulin as first injectable if
• HbA1c very high >97 mmol/mol (11%)
• Symptoms or evidence of catabolism: weight loss, polyuria, polydipsia which suggest insulin deficiency
• If type 1 diabetes is a possibility
If already on GLP-1 RA or if GLP-1 RA not appropriate OR insulin preferred
If above HbA1c target
INITIATION FOR BASAL
• Start 10 IU a day OR 0.1–0.2 IU/kg a day
TITRATION FOR BASAL
• Patient self titration is more effective
• Set FPG target that correlates to HbA1c target
• Choose evidence-based titration algorithm, e.g. increase 2 units every 3 days to reach FPG target without hypoglycemia
• For hypoglycemia determine cause, if no clear reason lower dose by 10–20%
Add basal insulin
Consider: • INITIATION • TITRATION
For patient on GLP-1 RA and basal insulin
Consider FRC of GLP-1 RA and insulin (iDegLira or iGlarLixi)
But note max dose of insulin in the FRCs
INITIATION
• If on GLP-1 RA use 10–16 dose steps (iDegLira) or 10–15 units (iGlarLixi)
TITRATION
• Titrate to FPG target and tolerability

If HbA1c still above target despite adequately titrated basal insulin

OR once basal insulin > .7 – 1.0 IU/kg OR FPG at target, What to do?

- Add prandial insulin (one dose with the largest meal).
- If HbA1c still above target:
  Stepwise additional injections of prandial insulin (ex. two, then three additional injections).
- If HbA1c still above target:
  Proceed to full basal-bolus regimen.

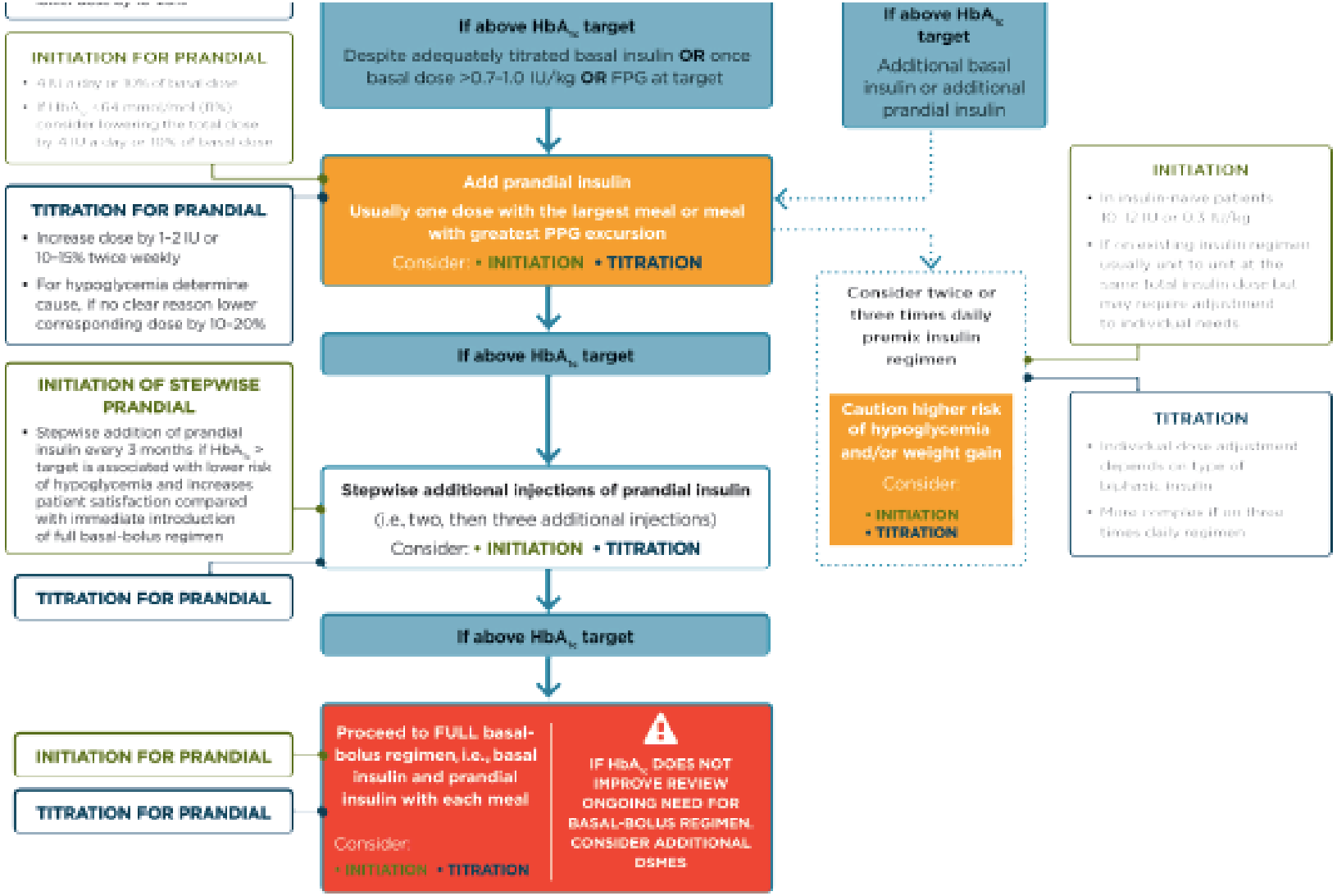
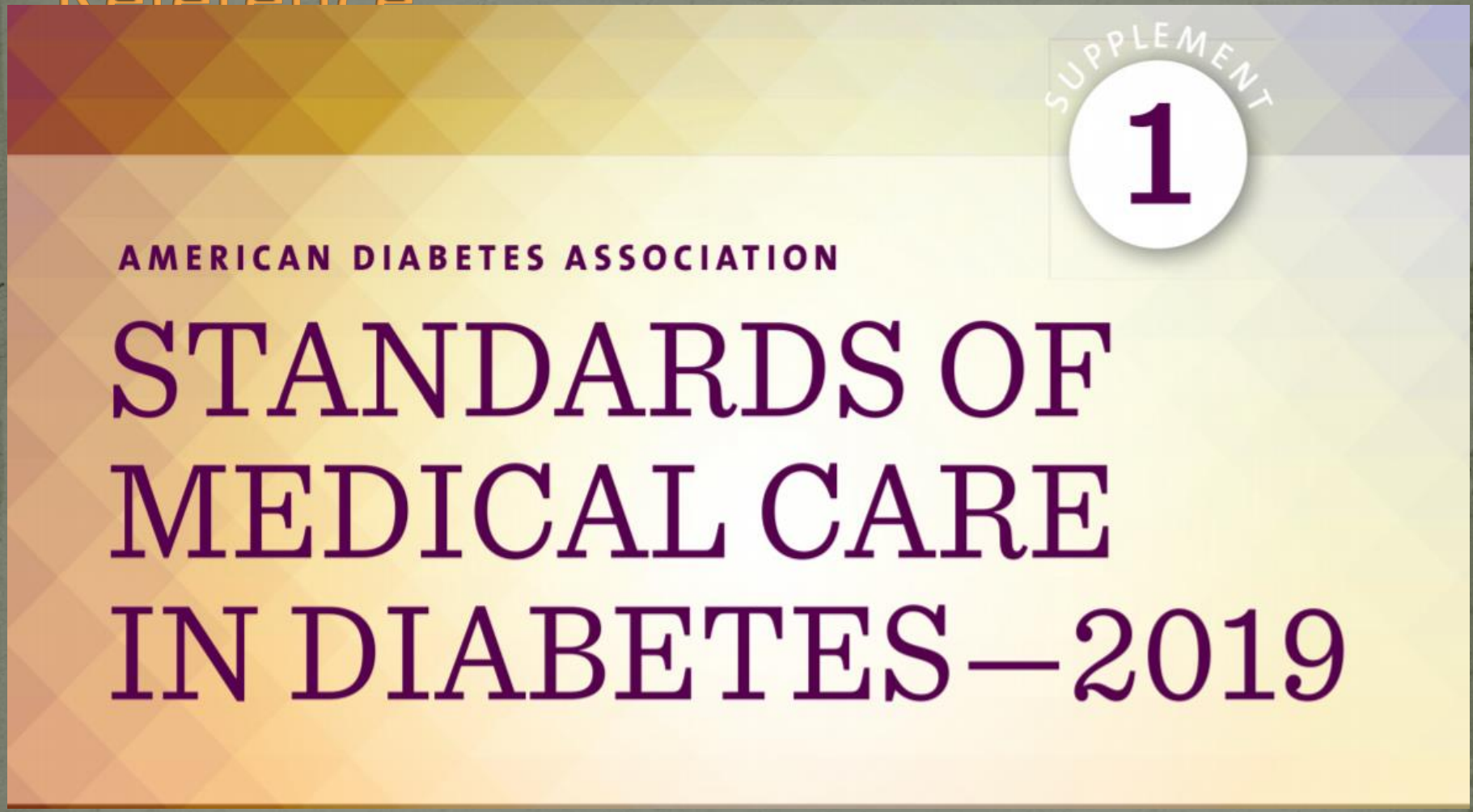


FIGURE 4. Intensifying to injectable therapies. FRC, fixed-ratio combination; GLP-1 RA, GLP-1 receptor agonist; Hba_{1c}, glycated hemoglobin; iDegLira, insulin degludec/liraglutide; iGlarLixi; insulin glargine/lixsenatide; max, maximum; PPG, postprandial glucose. Adapted from Davies MJ, D'Alessio DA, Fradkin J, et al. *Diabetes Care* 2018;41:2669–2701.

Reference


SUPPLEMENT
1
AMERICAN DIABETES ASSOCIATION
STANDARDS OF MEDICAL CARE IN DIABETES—2019

Thank You