Lecture 6

Editing file

MED438
KING SAUD UNIVERSITY

PRIMARY HEALTHCARE TEAMWORK

Diabetes Mellitus

Objectives:

- ★ Discuss the definition, etiology and classification of diabetes
- ★ Explain the diagnosis and screening criteria for prediabetes and diabetes.
- ★ Discuss comprehensive approach for diabetic patients could be provide in the clinic.
- ★ List the essential Investigations and when should be done.
- ★ Identify the glycemic targets for diabetic patients.
- ★ Enumerate the microvascular and macrovascular complications of diabetes.
- ★ Discuss the management including non-pharmacological and pharmacological for a diabetic patients.

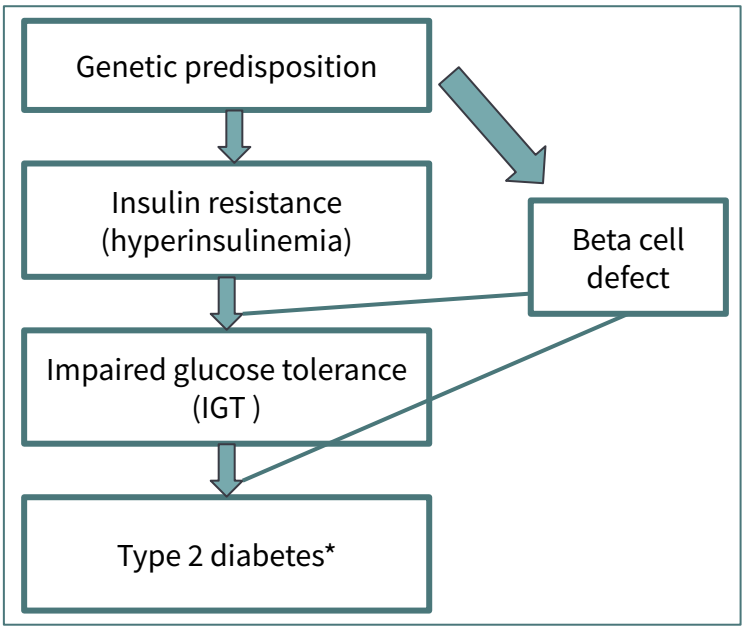
Color index:

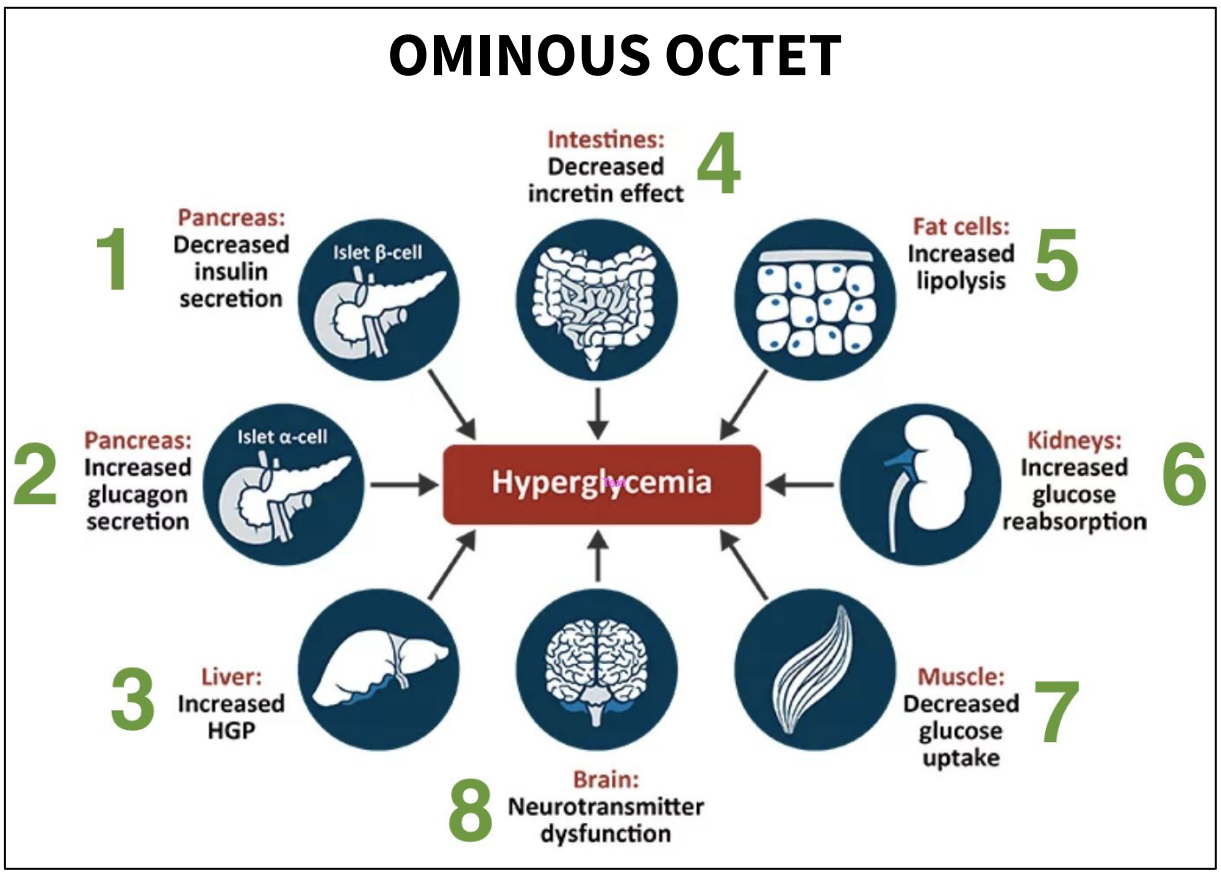
Original text Important Doctor's notes Golden notes Extra

Pathophysiology of DM

Pathophysiology:

- Family history is one of the most important risk factor, if one parent has diabetes the risk is 25% and if both the risk is 50%
- Usually 50% of β cells are functioning at time of diagnosis.





Recently, they found that the pathophysiology of type 2 DM is not limited to insulin resistance and relative reduction of insulin secretion. Other factors such as:
1- increased glucagon secretion
2- incretin system dysfunction (Responsible for 70% of post-prandial insulin)
3- increased intestinal absorption of glucose
4- Brain Neurotransmitters that control satiety and hunger.
So, new drugs are developed to act on these factors.

Prevalence & Classification of DM

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
- 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.
- Meaning that 1 out of 4 are diabetic in SA. That's why screening is essential since most of them are asymptomatic.

Classification diagnosis of diabetes:

- **Type 1 diabetes** (due to autoimmune **β-cell destruction**, usually leading to **absolute insulin deficiency**) (5-10% of all cases & previously called Insulin-dependant DM)
- **Type 2 diabetes** (due to a **progressive loss of β-cell** insulin secretion frequently on the background of **insulin resistance**) (90-95% of all cases & previously called non-Insulin dependant DM)
- Gestational diabetes mellitus (GDM) (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
- Specific Rare types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young (MODY) and LADA (latent autoimmune diabetes in adults)), 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)

An area for your notes

Diagnostic Tests

Diagnostic Tests for Diabetes (IMP)

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

or

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

*in the absence of unequivocal (no symptoms) hyperglycemia, diagnosis requires two abnormal test results from the same sample or in 2 separate test sample.

- If any of the previous tests is abnormal and the patient is symptomatic = Diagnose patient as diabetic.
- If the patient is asymptomatic = **Repeat** abnormal tests to diagnose patient as diabetic.
- Symptoms DM are: Polyuria - polydipsia- weight loss.
- Symptoms usually develop if HbA1c is 9 or above, or random plasma glucose above 250 or 300.

Diagnostic Tests Pre-diabetic (IMP)

- **FPG 100 mg/dL (5.6 mmol/L) to 125 g/dL (6.9 mmol/L)** (Impaired Fasting Glucose '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)** (Impaired Glucose Test '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

- In pre-diabetes, only 3 tests. **No** random plasma glucose as in DM diagnosis .
- You need to **repeat** test even if the patient symptomatic.

Screening Tests

Screening for diabetes (IMP)

1. Testing should be considered in overweight or obese (BMI ≥ 25 kg/m2 or ≥23kg/m2 in Asian Americans) adults who have one or more of the following risk factors:
   A. First-degree relative with diabetes
   B. High-risk race/ethnicity (e.g., African American, Latino, Native American,Asian American, Pacific Islander)
   C. History of CVD
   D. Hypertension (≥ 140/90 mmHg or in therapy for hypertension)
   E. HDL cholesterol level < 35 mg/dL (0.90 mmol/L) and/or a triglyceride level > 250 mg/dL (2.82 mmol/L)
   F. Women with PCOS
   G. Physical inactivity
   H. 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 the **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.

❖ Briefly: When to screen for diabetes.
- Anyone above 45y
- Below 45y and BMI above 25 with any of the above factors: Family history, Hypertension and etc..
- Prediabetic = yearly
- History of gestational diabetes = every 3y
- If testing is normal = repeat after 3y

Prevention Or Delay Of Type 2 Diabetes
(In Prediabetes)

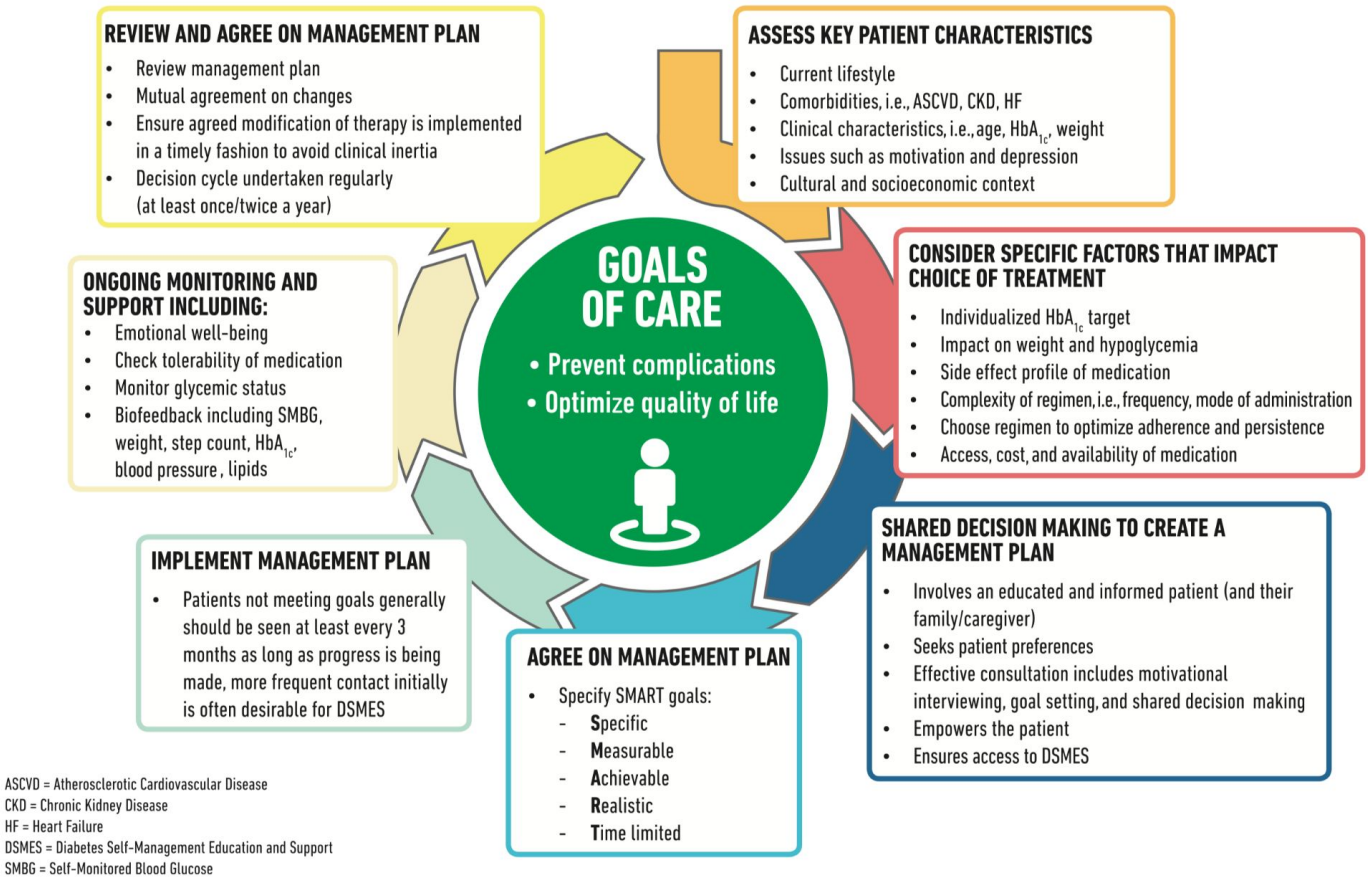
RECOMMENDATIONS:

1. At least annual monitoring for the development of type 2 diabetes in those with prediabetes is suggested. **E**
2. **Lifestyle interventions:**
   A. 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**

   Lifestyle modification:
   - **Physical activity:** brisk walking for 150 min per week. Can be tailored as patient desire (3d with 50 min each or 5d with 30 min each) "brisk walking كأن الواحد بيلحق على الركعة"
   - Weight loss (7-10% of total body weight)

   B. Based on patient preference, technology assisted diabetes prevention interventions may be effective in preventing type 2 diabetes and should be considered. B
3. **Pharmacologic interventions**
   A. **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**
   B. This topic is frequently asked in clinical practice, when to intervene pharmacologically as prevention?
   - Simply, **prediabetic** patients with:
     1. **BMI ≥ 35**
     2. **Age <60y**
     3. **Women with gestational diabetes**
     4. **Failure of life style modification**
   - **Drugs that are proven to reduce progression of pre-diabetes to diabetes are:**
     1. **Metformin**
     2. **Acarbose**
     3. **Pioglitazone (TZD)**
     4. **GLP-1** (Not used , expensive for a prevention method)
4. **Prevention of Cardiovascular disease**
   A. 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



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**

EXTRA: LEVEL OF RECOMMENDATION:

Strength of evidence	Grade of recommendation		
I	Grade A	Strong evidence from one or more systematic review(s) of well-designed RCTs	Highly recommended
II	Grade B	Strong evidence from one or more properly designed RCT(s) of appropriate size	Recommended
III	Grade C	Evidence from well-designed clinical trials without randomization, comparative study in a single group, cohort study, time series study or matched case-control studies	Recommended
IV	Grade D	Evidence from well-designed clinical trials, non-experimental studies from one or more center or research group	The consensus route would have to be adopted
V	Grade D	Opinion of respected authorities, clinical evidence, descriptive studies, or reports of experts committees	The consensus route would have to be adopted

Components Of The Comprehensive Diabetes Medical Evaluation At Initial, Follow-up And Annual Visits.

Table 4.1 – Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual 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 (e.g., obesity, OSA)	✓		
	▪ Hypoglycemia: awareness/frequency/causes/timing of episodes	✓	✓	✓
	▪ 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		✓	✓
LIFESTYLE FACTORS	▪ Eating patterns and weight history	✓	✓	✓
	▪ Physical activity and sleep behaviors	✓	✓	✓
	▪ Tobacco, alcohol, and substance use	✓		✓
MEDICATIONS AND VACCINATIONS	▪ Current medication regimen	✓	✓	✓
	▪ 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 and use	✓	✓	✓
BEHAVIORAL AND DIABETES SELF-MANAGEMENT SKILLS	**Psychosocial conditions**			
	▪ Screen for depression, anxiety, and disordered eating; refer for further assessment or intervention if warranted	✓		✓
	▪ Identify existing social supports	✓		
	▪ Consider assessment for cognitive impairment*	✓		✓
	Diabetes self-management education and support			
	▪ History of dietician/diabetes educator visits/classes	✓	✓	✓
	▪ Assess diabetes self-management skills and barriers	✓		✓
	▪ Assess familiarity with carbohydrate counting (type 1 diabetes)	✓		
	Pregnancy planning HbA1C < 7(Recommended)			
	▪ For women with childbearing capacity, review contraceptive needs and preconception planning	✓	✓	✓

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Components Of The Comprehensive Diabetes Medical Evaluation At Initial, Follow-up And Annual Visits.

Table 4.1 (cont.)– Components of the comprehensive diabetes medical evaluation at initial, follow-up, and annual visits

		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 Autoimmune Mainly type 1: Thyroid and Celiac Disease	✓		✓
	▪ Skin examination (e.g., acanthosis nigricans, insulin injection or insertion sites, lipodystrophy)	✓	✓	✓
	▪ Comprehensive foot examination Inspection, palpation, vibration and monofilament exam			
	• 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# LFTs & RFT ; As a baseline, beside some diabetic drugs affect liver. Also most of diabetic patients will be on statins	✓		✓
	• 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	✓	✓	✓

Assessment & Treatment Plan/ Hypoglycemia Risk

Table 4.2—assessment And Treatment Plan*

Assess risk of diabetes complications

- ASCVD and heart failure history
- ASCVD risk factors 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 b-blockers)

Table 4.4—referrals For Initial Care Management

Factors that increase risk of treatment-associated hypoglycemia

- 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

HbA1C Testing Recommendation:

- Perform the A1C test at least two times a year (every 6 mo) in patients who are meeting treatment goals (and who have stable glycemic control). **E**
- Perform the A1C test quarterly (every 3 mo) 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**

HbA1C Goals Recommendation: See below*

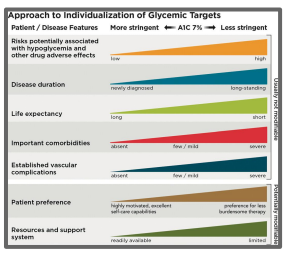
1. A reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol). **A**
2. Providers might reasonably suggest more stringent AIC goals (such as <6.5% [48 mmol/mol]) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment (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.**
3. 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**
4. Reassess glycemic targets over time based on the criteria. **E**

Table 6.2—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.

***HbA1C Goals Recommendation is Based on the patient condition:**
1- Life expectancy
2- DM duration
3- Comorbidities
4- Other factors
85y w/ multiple comorbidities, HbA1c of 8 or 9 can be accepted. In contrary, the target of young healthy may be below 6.5



HbA1c= FPG+OGTT and not alway a reliable test and can be misleading like for example a patient can have <7% and has high variability in the daily readings, also in case of hemoglobinopathies the hemoglobin lifespan is affected (hemolysis: shorter lifespan: less glucose saturation: low HbA1c reading,, and the opposite in iron deficiency anemia longer lifespan: more glucose saturation: high HbA1c reading)

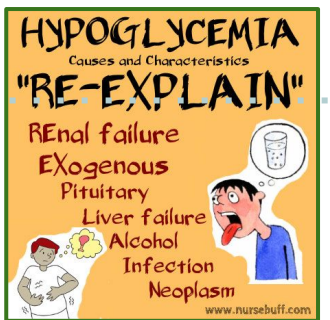
Hypoglycemia

Levels of Hypoglycemia:

- **Level 1 hypoglycemia** is defined as a measurable glucose concentration **<70 mg/ dL** (3.9mmol/L). (Normal glucose level is 70-100 and not more than 140 post-prandial)
- **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 in Hypoglycemia:

- Individuals at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia at each encounter. **C**
- **Glucose (15-20g)** 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 Self-monitoring of blood glucose (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**
    - Hypoglycemia unawareness happens when neuroregulatory mechanisms are adapted to hypoglycemia since patient had several attacks of hypoglycemia. So, the patient will not be aware of hypoglycemia. This is a very serious condition. We usually raise glycemic targets of patient. 200 for pre prandial instead of 80-130.
- 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**
- Hypoglycemia causes in nondiabetic see the picture on the right →



Management of hypoglycemia:

- Remember role of 15
- 1- 15g of simple sugar (juice, honey or soft drinks)
- 2- Reassess after 15 min
- Don't give chocolate because it contains lipids that may delay glucose absorption.

Cardiovascular Disease & 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 and Diagnosis:

- 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) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk. **C**
- 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
- Aspirin is not recommended for ASCVD prevention for adults with DM at low ASCVD risk, since potential adverse effect from bleeding likely offset potential benefits. **C**
  - Low risks 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**
- **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

- Will be studied in details in Dyslipidemia lecture

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 & Foot Care

Chronic Kidney Disease Screening Recommendations:

- 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**

Diabetic Retinopathy Screening Recommendations:

- 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 glycaemia 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**

Microvascular Complications & Foot Care CONT..

Neuropathy Screening Recommendations:

- 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**

Briefly:
DM 1 = screening after 5y of diagnosis
DM 2 = screening at diagnosis (normal > repeat yearly)

Eye > Ophthalmologist
Kidney > Nephrologist
Foot care = Podiatrist

Diabetes Management

Diabetes Management

Non-Pharmacological (LSM):
- **A. Diet**
- **B. Exercise(Physical activity)**

Pharmacological:
- **A. Oral Hypoglycemic Drugs**
- **B. Insulin**

Non-Pharmacological (LSM):

A. Diet therapy and exercise:

- They are the cornerstone for the management of diabetes Their effect appears within 1-4 weeks
- If they did not control hyperglycemia within 3-6 month, start anti-diabetic agent
- **This what you need to know regarding non-pharmacological management:**
  1. Physical activity: brisk walking for 150 min per week. Can be tailored as patient desire (3d with 50 min each or 5d with 30 min each) "brisk walking كأن الواحد بيلحق على الركعة"
  2. Weight loss (7-10% of total body weight)

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**

Diabetes Management

Diabetes Management

Non-Pharmacological (LSM):

A. Diet
B. Exercise(Physical activity)

Pharmacological:

A. Oral Hypoglycemic Drugs
B. Insulin

Diet Recommendations:

- What i need you to know is brisk walking and weight loss mentioned last slide.

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

Diabetes Management

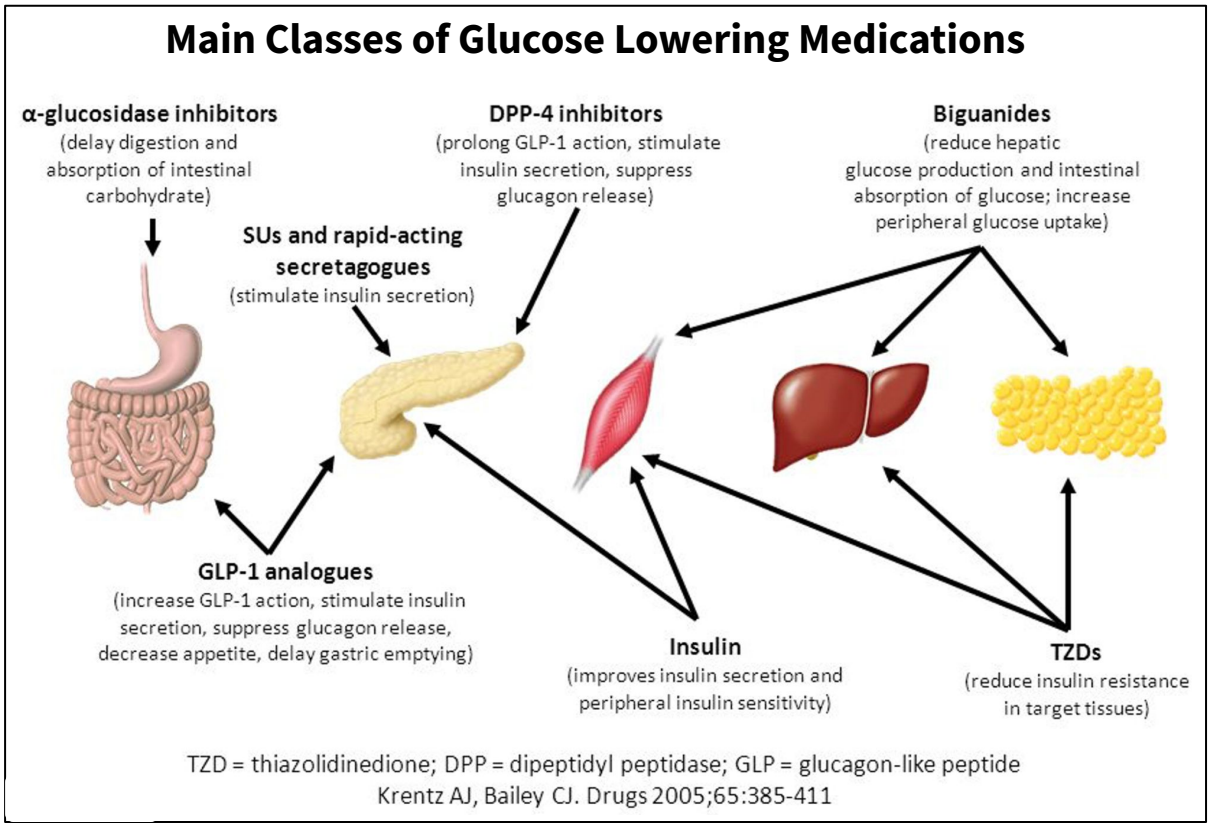
Diabetes Management

Non-Pharmacological (LSM):

A. **Diet**
B. **Exercise(Physical activity)**

Pharmacological:

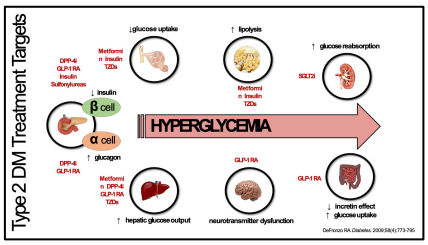
A. **Oral Hypoglycemic Drugs**
B. **Insulin**



Oral Hypoglycemic Drugs:

1. **Insulin Sensitizing Agents:**
   - Reduce blood sugar by making the body tissue more sensitive to insulin.
     - Biguanides (metformin)
     - Thiazolidinediones (TZD)/ glitazone
2. **Insulin Secretagogues:**
   - Stimulate release of insulin from pancreatic beta cells.
     - Sulfonylurea
     - Meglitinides
3. **Incretin Based Therapy:**
   - DPP-4 Inhibitors
   - GLP-1 receptor agonist
4. **α-Glucosidase Inhibitor.**
5. **SGLT-2 Inhibitors:**
   - Inhibit reabsorption of glucose in the distal tubules of the kidney
6. **Insulin.**

- Different classes that act on different targets.



Insulin Sensitizing Agents

Biguanides

- Metformin:
  - First line agent.
  - Glucophage (30% GI side effects)
  - Glucophage XR (Encapsulated Glucophage, 5-6% GI side effect, geven to patients sensitive to it's GI effect)

M.O.A	• Insulin–Sensitizing Agents: Reduce blood sugar by making the body's tissues more sensitive to insulin. • Primary mechanism of action(MOA): Inhibit hepatic gluconeogenesis • Secondary MOA: Increase insulin sensitivity
HbA1C lowering %	• Decrease HgA1C by 1.0 to 2.0%
Advantage	• **The first line for oral treatment of type 2 diabetes** • **High efficacy with no hypoglycemia** • Weight neutral (But some people may have weight loss due to GI upset) • Lipid–lowering activity[1] • Decreased all–cause mortality and a decreased rate of (MI) in overweight and obese patients
Disadvantage	• GI side effects2 • Potential for vitamin B–12 def (Do screening after 4-5 years of use then decide if supplements is needed) • Lactic acidosis (rare) • Discontinue during acute illness and Before radiographic procedures requiring contrast • Contraindicated in Renal insufficiency (discontinue if eGFR ≤ 30)

Adverse Effect	• B12 deficiency is a long term side effect because it reduces intestinal absorption of B12. (الحين يوزعونه توزيع لمرضى السكر وهذا خطأ)
	• Metformin does not cause renal impairment by it self. Drug discontinuation or dose adjustments are required in case of renal impairment to avoid lactic acidosis.
	• Glomerular filtration rate(GFR) based Recommendations:
	  ○ <60 = Observe carefully
	  ○ 30-45 = Half 1/2 dose
	  ○ <30 = Discontinue medication

Doses & Routes	• Glucophage: BID, 500, 850, 1000 mg (PO) • Glucophage XR: Extended Release, QD, 500, 750 mg (PO)

1. lipid-lowering activity, : decrease in serum triglyceride and free fatty acid concentrations, a small decrease in serum low-density-lipoprotein (LDL) cholesterol concentrations, and a very modest increase in serum high-density-lipoprotein (HDL) cholesterol concentrations.
2. GI:metallic taste in the mouth, mild anorexia, nausea, abdominal discomfort, and soft bowel movements or diarrhea.

Insulin Sensitizing Agents

Thiazolidinediones (TZDs) • Pioglitazone • Rosiglitazone	
M.O.A	• Insulin–sensitizing agents: Increase insulin sensitivity by acting on adipose, muscle, and liver to increase glucose utilization and decrease glucose production. • Acts primarily on the peripheral tissue
HbA1C lowering %	• When used as monotherapy, they reduce hemoglobin (A1C) values by 1.5 %
Advantage	• High efficacy with no hypoglycemia • Show benefit in NASH • No dosage adjustment

Disadvantage	• Pioglitazone
	  ○ Increase risk for bladder Cancer
	• Rosiglitazone (Not used any more)
	  ○ Increased risk for cardiovascular event (Progressive ischemia ,MI, HF)
	  ○ Increased LDL
	• Only used in resistance cases

Adverse Effect	• All TZDs cause weight Gain • Fluid retention / Heart failure (Peripheral edema occurs in 4 to 6 %) • Decrease bone density and increase fracture risk , particularly in women • FDA Black Box: CHF >> pioglitazone & rosiglitazone. • Not recommended in renal impairment due to fluid Retention
Doses & Routes	• Pioglitazone (actos): 15, 30, 45 mg • Rosiglitaozone (avandia): 2, 4, 8 mg
Issues With This Group	1. Weight gain 2. Fluid retention = contraindicated in HF or CKD 3. Edema 4. Osteoporosis (fractures) 5. Bladder cancer 6. The drugs need time to show its effects (3-4months)

Insulin Secretagogues

Sulfonylureas

- **(2ND GENERATIONS)**
  - Glipizide (Minidab)
  - Gliclazide (Dimcrone) (Commonly used)
  - Glibenclamide (Glyburide) (Its' old and BID which decrease compliance)
- **(3RD GENERATION)**
  - Glimepiride (Best as its selective only on the pancreas)

M.O.A	• Insulin Secretagogues: stimulate release of insulin from pancreatic beta cells • Stimulate insulin secretion for 24h So, usually is taken once daily.
HbA1C lowering %	• Lower HgA1c by 1- 2%
Advantage	• Safe in CVD and renal impairment (except glyburide) • High efficacy with risk of hypoglycemia (As it stimulates the release of insulin)
Adverse Effect	• Hypoglycemia (most common) • Nausea • Skin reactions (including photo sensitivity) • Weight gain

Sulfonylureas	**2ND GENERATIONS**			**3RD GENERATION**
Name	**Glipizide (Minidab)**	**Gliclazide**	**Glibenclamide (Glyburide)**	**Glimepiride**
Commercial Name	**Glucotrol (OD Or Divided) Glucotrol Xl (OD)**	**Diamcrone R (BID) /Glaze Diamcrone MR (OD)**	**Doanil Diatab**	**(Amaryl)**
Dosage	**(2.5), 5, 10 Mg (Xl)**	**40,80 Mg 30 , 60 Mg**	**2.5 , 5 Mg**	**1, 2, 4 Mg**
Maximum Dose	**Up To 40 Mg Up To 20 Mg**	**Up To 320 Mg Up To 120 Mg**	**OD or BID Up To 10 Mg**	**Od Tablets Up To 8 Mg**

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

Insulin Secretagogues

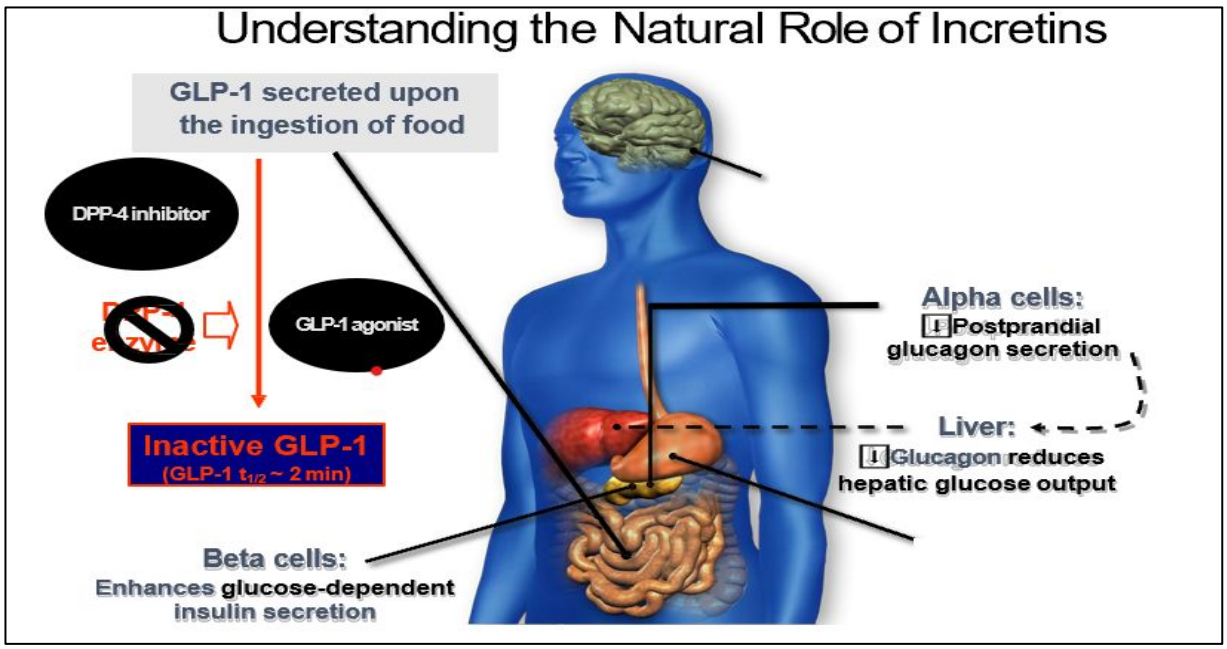
Meglitinides

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

M.O.A	• Insulin secretagogues: stimulate release of insulin from pancreatic beta cells before each meal. • Meglitinides are pharmacologically distinct from sulfonylureas and may be used in patients who have an allergy to sulfonylurea medications. • Stimulate insulin secretion for 3h So, usually is taken before meal.
Advantage	• Repeglinide: ○ Safe in pt. with decrease GFR or renal failure ○ Repeglinide is very safe in renal impairment, we can use it even if the GFR is 15 or 20 with no need for dose adjustment
Disadvantage	• Hypoglycemia • Weight gain(less than sulfa) • Dosing frequency

Incretin Based Therapy:

- **GLP-1 Effects in Humans:**



Incretin Based Therapy

DPP4 Inhibitors

- Sitagliptin
- Saxagliptin
- Vildagliptin
- Alogliptin
- Linagliptin
  - The best for renal impairment, bc it excreted in feces.

M.O.A	• **Incretin Based Therapy:** DDP4 degrades GLP-1
	• Main functions:
	  ○ Intestines: delay gastric emptying
	  ○ Alpha cells inhibit glucagon secretion
	  ○ Beta cells: stimulate insulin secretion
	  ○ Brain : increase satiety

HbA1C lowering %	• Reduce HbA1c between 0.6 – 1.1% less than GLP-1
Advantage	• Intermediate efficacy with no hypoglycemia • No effects on body weight • Safe profile does not cause hypoglycemia" even it stimulates insulin secretion "because it works only when carbs are ingested, and blood glucose is elevated (Glucose dependant).
Disadvantage	• Potential CV risk in saxagliptin and alogliptin (avoided in heart failure) • Require dose adjustment except Linagliptin
Adverse Effect	• Headache, nasopharyngitis ,and upper respiratory tract infection • Joint pain, myalgias , muscle weakness, and muscle spasms • Urticarial & angioedema • Acute pancreatitis in 1 out of 800 • Thyroid carcinoma is only proven in animals. But in practice, if there is a background or family history of thyroid carcinoma, we avoid to prescribe it.

Doses & Frequencies

Name	Sitagliptin	Saxagliptin	Vildagliptin	Alogliptin	Linagliptin
Commercial Name	(Januvia)	(Onglyza)	(Galvas)	(Nesina, Kazano)	(Tradjenta)
Dosage	25, 50, 100 mg	2.5, 5 mg	50 mg OD –BID	25 mg OD	5 mg OD

Incretin Based Therapy

GLP1 receptor Agonists:

- Liraglutide: 0.6mg subQ OD, Up to 1.8mg OD
- Semaglutide
- Dulaglutide
- Exenatide: 5mcg subQ, BID Up to 10 BID
  - Extended-release: 2mg subQ, once /week

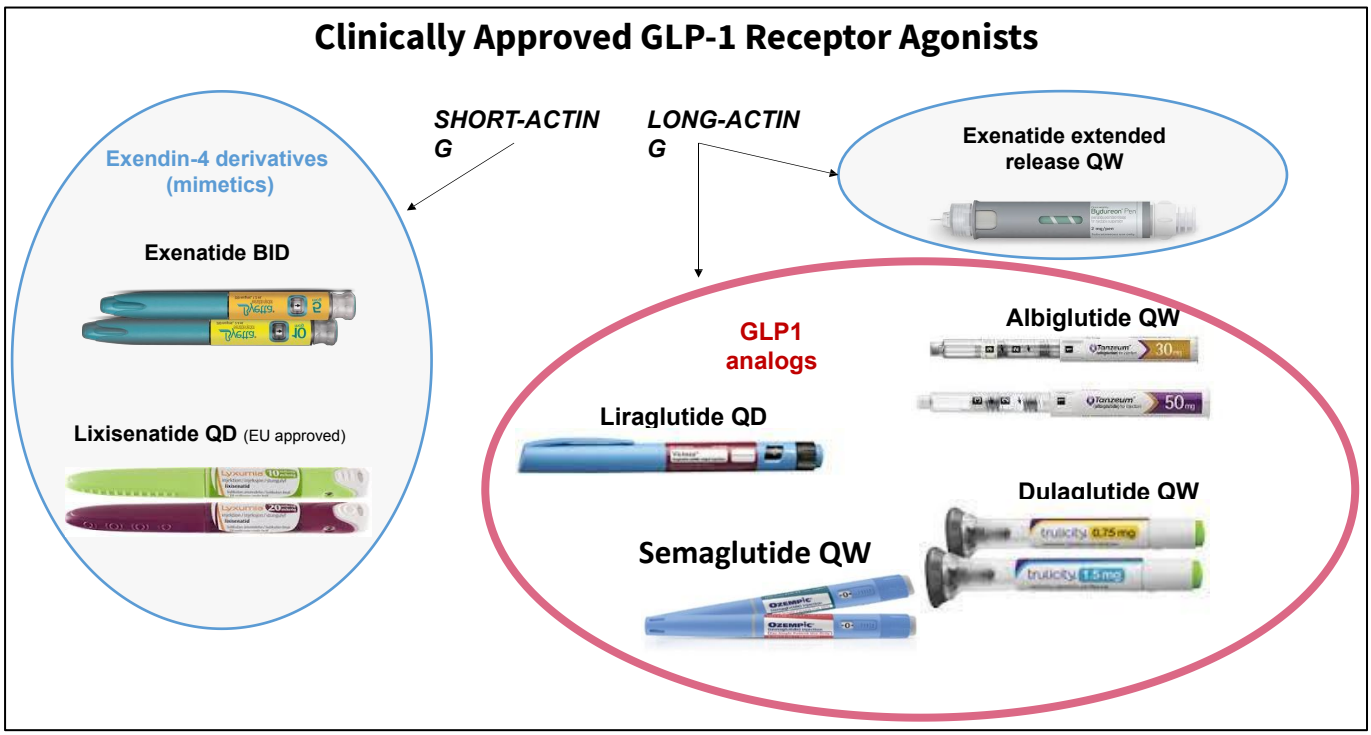
M.O.A	• DPP4 and GLP-1 share similar features since they act on the same target (incretin system)
	• **Incretin Based Therapy:**
	• Main functions:
	  ○ Intestines: delay gastric emptying
	  ○ Alpha cells inhibit glucagon secretion
	  ○ Beta cells: stimulate insulin secretion
	  ○ Brain : increase satiety

HbA1C lowering %	• 1-1.5% above target more than DPP4 • Saxenda is a derivative of Liraglutide which is approved for obesity management.

Advantage	• High efficacy with no hypoglycemia
	• Weight reduction (proven to reduce weight)
	• Decrease ASCVD, Reduce CVD risk (CVD Benefit) in Liraglutide >Semaglutide > Exenatide ER
	• Non glucose effect :
	  ○ ↓ 3-4 kg of weight
	  ○ ↓ 2-3 mmHg of BP
	  ○ ↑ 2-3 beats/min of HR

Disadvantage	• Injectable • Expensive
Adverse Effect	• GI side effect (nausea, vomiting, diarrhea) (30% especially elderly) • Initiating/increasing dose >> Potential risk of AKI (Liraglutide is safe) • FDA Black Box >> cell hyperplasia /medullary thyroid tumors (avoid it only for family or personal history of thyroid cancer) • Pancreatitis(1;800) rare but serious • injection site reaction.

Incretin Based Therapy



GLP-1 are divided into long acting and short acting:

- Short acting
  - **Lixisenatide** taken 45 Min before meal (First generation).
- Long acting:
  - **Liraglutide** (Victoza) good for blood sugar & dcrease weight up to 5kg.
  - **Liraglutide** (Saxenda) (higher dose of liraglutide) decrease weight up to 8 kg. Approved to treat obesity.
  - **Dulaglutide** (Trulicity) has the best for cardiovascular benefits.
  - **Semaglutide** (Ozempic) made for obesity and has cardiovascular benefits it's cool it's decrease weight up to 13 kg.
- As a general rule we always start using GLP-1 analogues gradually to avoid strong GI upset.

Considerations For Incretin Selection:

Clinical variables	DPP-4 inhibitors	GLP1 RA
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	$$	$$$

Alpha Glucosidase Inhibitors

Alpha Glucosidase Inhibitors • Acarbose (50 and 100 mg TID) • Miglitol • Voglibose	
M.O.A	• Slow absorption of glucose and reduce postprandial Blood glucose concentration • Inhibit intestinal absorption of glucose • Need to be taken 10-15 min before meal
HbA1C lowering %	• lowering (A1C) By only 0.4 to 0.9%
Advantage	• if the HbA1c is not high and the post prandial is the main problem, those drugs are very effective • Safe drugs but GI upset is really irritating to patients (Flatulence)
Disadvantage	• Need to be given before each meal.
Adverse Effect	• Flatulence • Diarrhea • Like GLP 1, patient may stop it due to GI upset.

An area for your notes

SGLT2 Inhibitors

SGLT2 Inhibitors • Canagliflozin • Dapagliflozin • Empagliflozin	
M.O.A	• Inhibit the reabsorption of glucose in the distal tubules of the kidney • Inhibit renal absorption of glucose = losing glucose in urine beside calories (weight loss)
HbA1C lowering %	• Up to 1%
Advantage	• Weight loss • Intermediate efficacy with no Hypoglycemia • lipid–lowering activity • Good CV effect **Reduce CVD risk(CVD Benefit)** and specifically heart failure patient (Empagliflozin And Canagliflozin) • Delay progression of CKD (Empagliflozin And Canagliflozin) • Diuretic effect, so it can be used in case of HF glucose will drag water
Disadvantage	• FDA Black Box: Risk Of amputation (Canagliflozin) • It needs GFR > 45 to initiate the treatment • In General, safe drugs
Adverse Effect	• Genitourinary infections (10%) • Risk of bone • Fracture (Canagliflozin) • DKA risk (all agents, rare in T2DM) • Increase LDL Cholesterol • Risk of volume depletion and hypotension, so we advise the patient to drink lots of water • Acute kidney injury

FDA Approved SGLT2 Inhibitors

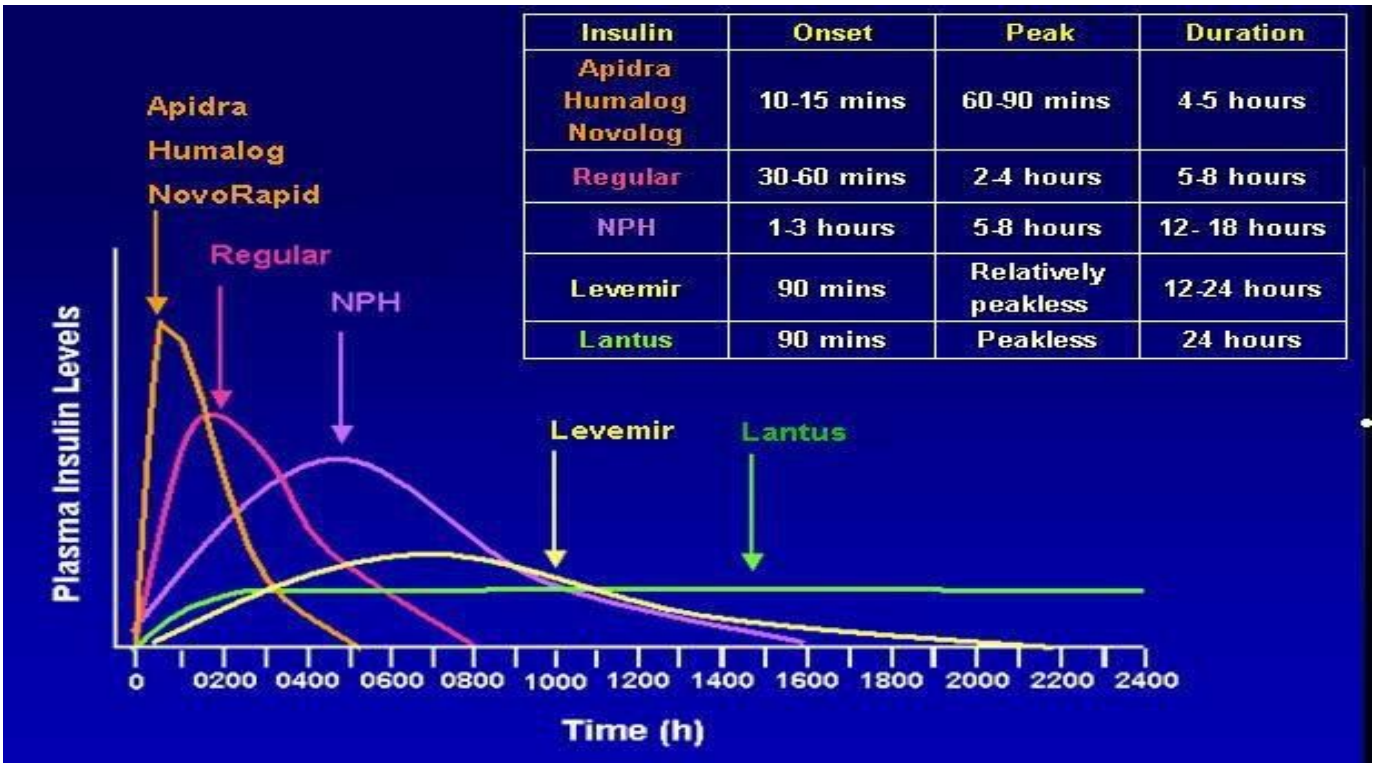
Agent	Canagliflozin INVOKANA®	Dapagliflozin FARXIGA™	Empagliflozin JARDIANCE®
Dosing	Initial: 100mg daily Max: 300mg daily	Initial: 5mg daily Max: 10mg daily	Initial: 10mg daily Max: 25mg daily
Administration	Before the first meal of the day	In the morning with or without food	In the morning with or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

INSULIN

Insulin	
Advantage	• Powerful agent • Necessary in 20-30% • Inexpensive
Disadvantage	• Hypoglycemia • Weight gain • High level of patient fear

Treatment Regimens Of Type 1 DM

- **Conventional Insulin Therapy:**
  - Two injections of NPH and Regular Insulin
- **Mixed Insulin:** (basal(24h)/prandial(4-5h))
  - 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)



Diabetes Management

If You Have DM Pt On Metformin With HbA1C Above Target, What To Do As A Second Line medication?

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

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:
  1. HbA1C very high > 11% (9 or above)
  2. Symptoms or evidence of catabolism:
     - Sever weight loss, Polyuria & Polydipsia which suggest insulin deficiency
     - Glucose toxicity
  3. If type−1 diabetes is a possibility.
  4. If already on GLP−1 RA or if GLP−1 RA not appropriate or Insulin preferred

How to manage type 2 DM:

1. We start usually with LSM & Metformin if fails to reach target →
2. Then add other OHGs and/or Injectable agents (especially if obese) and monitor FPG it should be 80-130 if failing to reach the target →
3. Then start basal insulin -best for controlling FPG- with the OHGs -to control postprandial-, we start the basal insulin at 10 units then increasing the dose until the FPG is between 80-130 when achieved start monitoring the HbA1C If still high →
4. Then this means a problem in the prandial insulin here you start prandial insulin when you start the prandial stop all the medications except metformin to avoid hypoglycemia.
5. We give mixed (Basal & Prandial) to control both FPG & HA1C and to decrease dosing on the patient.

If HbA1c still above target despite adequately titrated basal insulin OR once basal insulin > 0.7 – 1.0 IU/kg OR FPG at target, What to do?

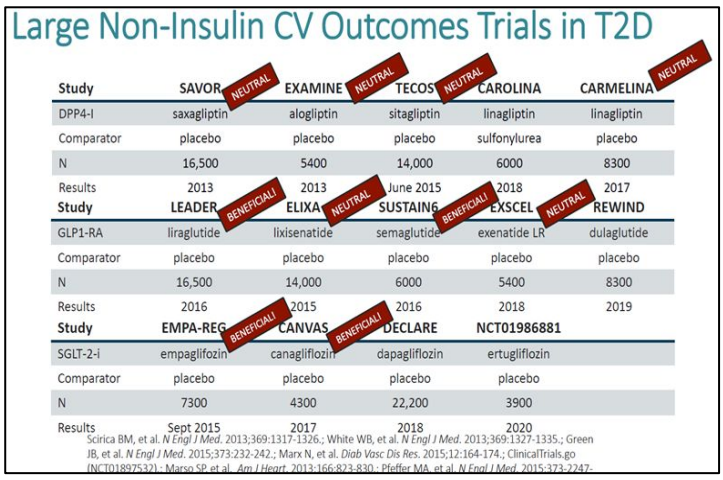
- Add prandial insulin (one dose with the largest meal).
- If HbA1c still above target:
  - Stepwise additional injections of prandial insulin (ex. two, then three additional injections).
- If HbA1c still above target: Proceed to full basal-bolus regimen.

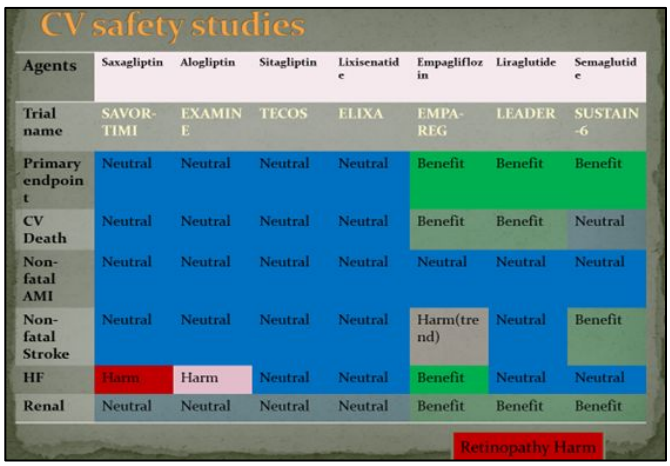
Suammary Of Treatment

Table 9.1—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
	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; DKD, diabetic kidney disease; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; NASH, nonalcoholic steatohepatitis; SGLT2, sodium–glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes.





Diabetes Management

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.

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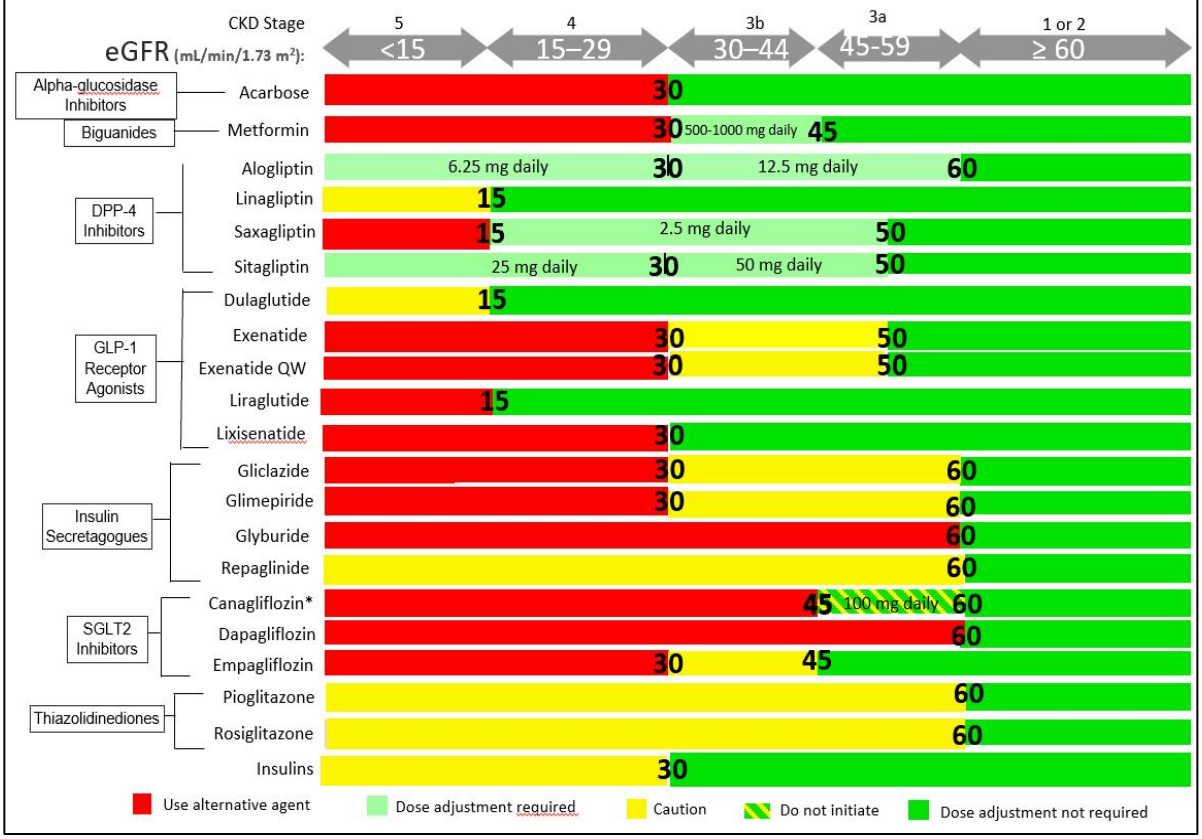
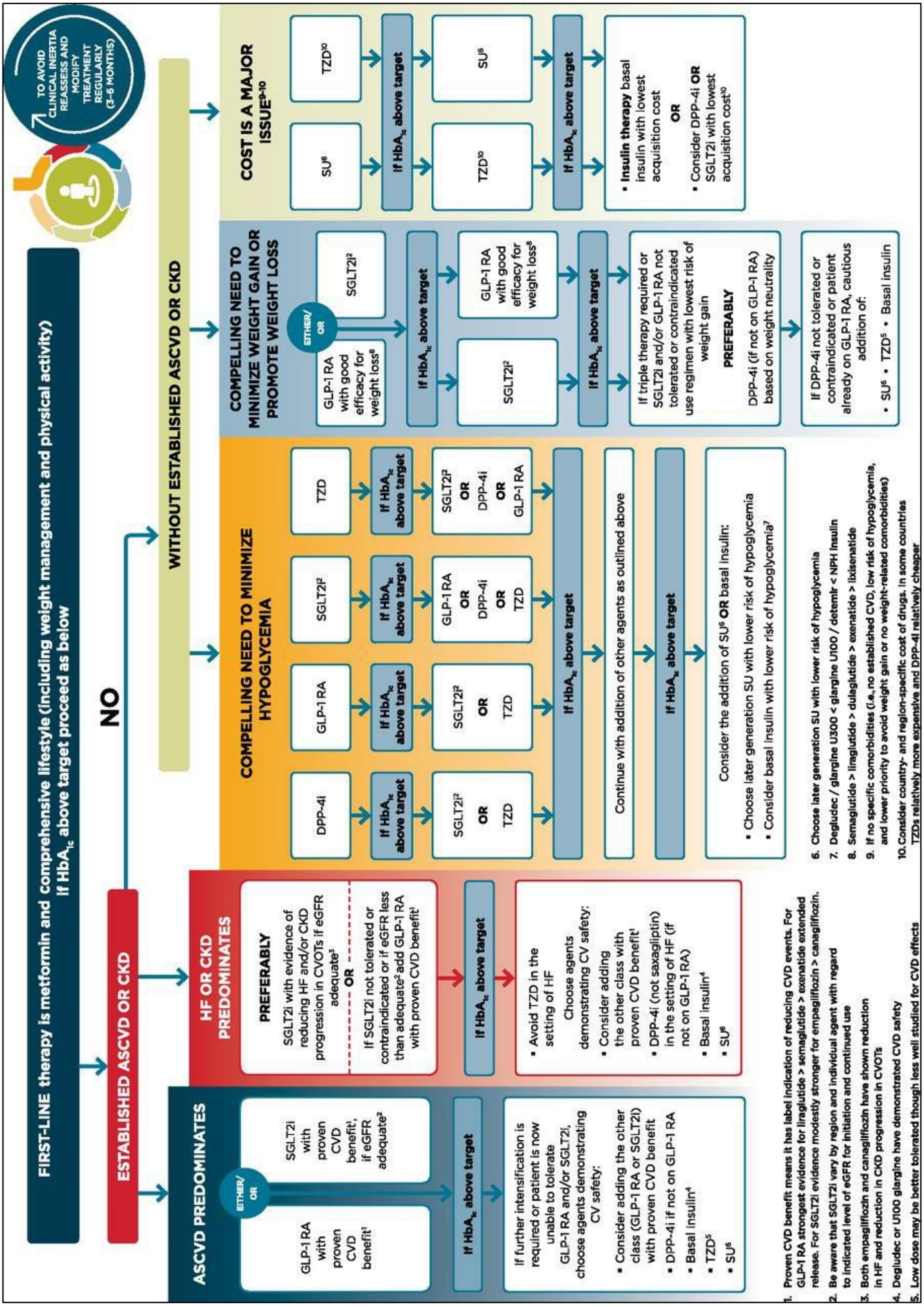
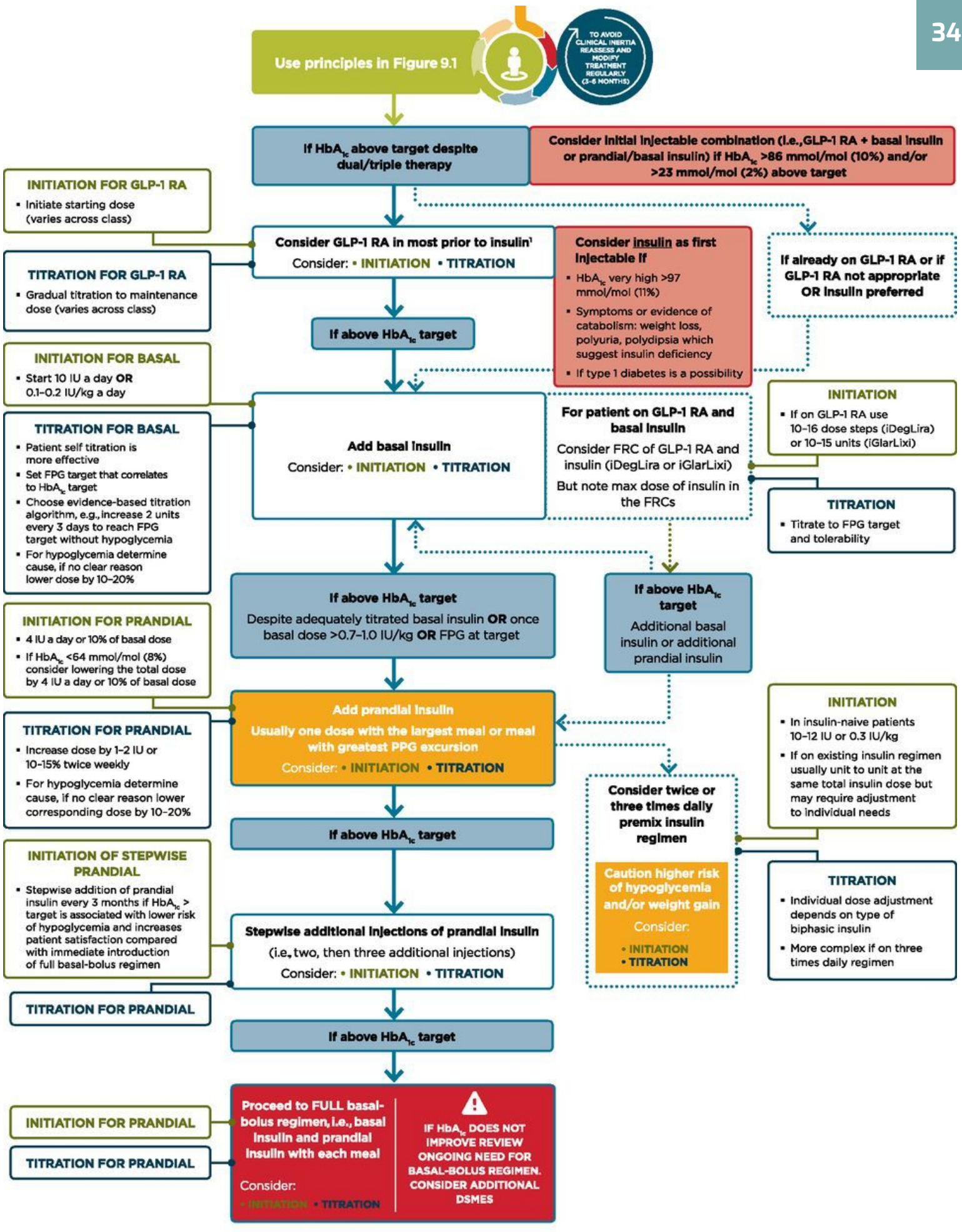
Antihyperglycemic Agents and Renal Function



Important Summary Of The Criteria





1. When selecting GLP-1 RA, consider: patient preference, HbA_{1c} lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit

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.

Management Summary (Doctor's Notes)

A patient w/ glycemic picture (Abnormal HbA1C, etc)

A. **Lifestyle modification + metformin (first line).** If the patient is still **not controlled** (abnormal HbA1c, etc)

B. Ask yourself **two questions**:

1. Has the patient have **clinical ASCVD** (MI,stroke, aneurysm or etc.)?, Then prescribe drugs that are proven to **reduce ASCVD** (**GLP-1 and SGLT2**)
2. Has the patient have **heart failure(HF) or chronic kidney disease (CKD)**?, Then prescribe drugs that are proven to **reduce HF or CKD** (**SGLT2** b/c it acts as diuretic)

C. If the two questions **does not fit** your patient, then selection can be **categorized into 3**:

- **Hypoglycemia** represent a major issue so, prescribe drugs **that don't cause hypoglycemia (TZD, DPP4, GLP1 or SGLT2)**
- **Weight loss** represent a major issue so, prescribe drugs that **promote weight loss (GLP1 or SGLT2)**
- **Cost** represent a major issue so, prescribe **cheap drugs (SU or TZD)**

D. If the patient is **still not controlled with dual or triple medications** then you can **prescribe insulin**

E. **Don't give B12 with metformin immediately, just screen for B12 deficiency after 3-4 years then give supplement if needed.**

Important clues or features of DM drugs:

- Drugs that cause **Hypoglycemia (SU, Meglitinides or insulin)**
- Drugs that cause **Weight gain (SU, Meglitinides ,insulin & TZD)**
- Drugs that are **Weight neutral (Metformin, Acarbose or DPP4)**
- Drugs that cause **Weight loss (GLP-1 or SGLT2)**
- Drugs that posses **CVD benefit (GLP-1 or SGLT2)**
- Drugs that are **Safe in renal impairment (Meglitinides or linagliptin"DPP4")**
- Drugs that are **Contraindicated in HF or CKD(TZD)**
- Drugs that are **Beneficial in HF or CKD (SGLT2)**

Lecture Quiz

Q1: A 48-year-old man with type 2 diabetes currently takes Metformin 2gm per day. BMI 34 and HbA1C is 8.4%. You decided to start him on Liraglutide (GLP-1). Which one of the following explains its mechanism of action?

A. Delays absorption of glucose by small intestine
B. Increase the sensitivity of the muscle to insulin
C. Inhibits the hepatic gluconeogenesis
D. Stimulates the secretion of insulin

Q2: 54 years old patient known case of diabetes on metformin and Gliclazide came to the ER with chest pain and diagnosed with heart failure his HBA1C is 8% what you will do?

A. Dapagliflozin
B. Increase metformin dose
C. Liraglutide
D. Sitagliptin

Q3: A female patient with controlled hypertension and dyslipidemia came for a follow up. Her previous doctor advised her to lose weight since her BMI is 38 but she didn't show interest. She also noted that she has slight DM but she didn't appear concerned. Her lab results are shown (HbA1c is 8%). Which of the following responses are you going to use to tell her about her results?

A. She must lose 10 Kg, exercise, and stop using added sugar
B. Tell her that she has diabetes and assess her readiness for management.
C. Tell her that diabetes can lead to kidney failure.
D.Reassurance

Q4: A male patient came to the clinic for the first time when we check his blood sugar reveals as following (FPG 7.1) (Hb1ac 5) / (Fasting was abnormal 1Ac was normal).

A.He is a diabetic
B.Repeat the FPG
C.Repeat Hba1c
D.Start him on metformin

Answers: Q1:D | Q2:A | Q3:B | Q4:B

THANKS!!

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Send us your feedback:
We are all ears!