

DIABETES MANAGEMENT

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EXPLORE
HEALTHCARE SUMMIT

Disclosures

None to disclose



Objectives

- At the end of this session, learners will be able to:
 - Learn the classification of Diabetes Mellitus
 - Understand the glycemic targets used for management of diabetes mellitus
 - Choose from various insulin and non-insulin drug classes available to treat type1 and type 2 diabetes
 - Make use of technology in management of diabetes
 - Manage diabetes mellitus/hyperglycemia in the hospital



Classification of Diabetes

- **Type 1 Diabetes**
- LADA (Latent autoimmune diabetes of adults)
- **Type 2 Diabetes**
 - Ketosis prone diabetes/ Atypical diabetes
 - Monogenic Diabetes syndromes (neonatal diabetes and MODY)
 - Pancreatic disease (CF and pancreatitis)
 - Drug- or chemical-induced diabetes (GC use, HIV/AIDS, post transplantation)
 - Gestational diabetes
 - Autoimmune diabetes – immunotherapy use

Type 1 Diabetes (T1D)



Diagnosis and Staging for T1D

- **Autoimmune markers:**
 - Autoantibodies to GAD65 (most common)
 - Islet cell autoantibodies
 - ZnT8 antibodies
 - IA2 autoantibodies
- Rate of β -cell destruction is variable
- Children/adolescents mostly present with hyperglycemic crisis/DKA
- Adults may have more insidious onset, eventually becoming insulin dependent
- LADA vs T1D

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 WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

A1C $\geq 6.5\%$ (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

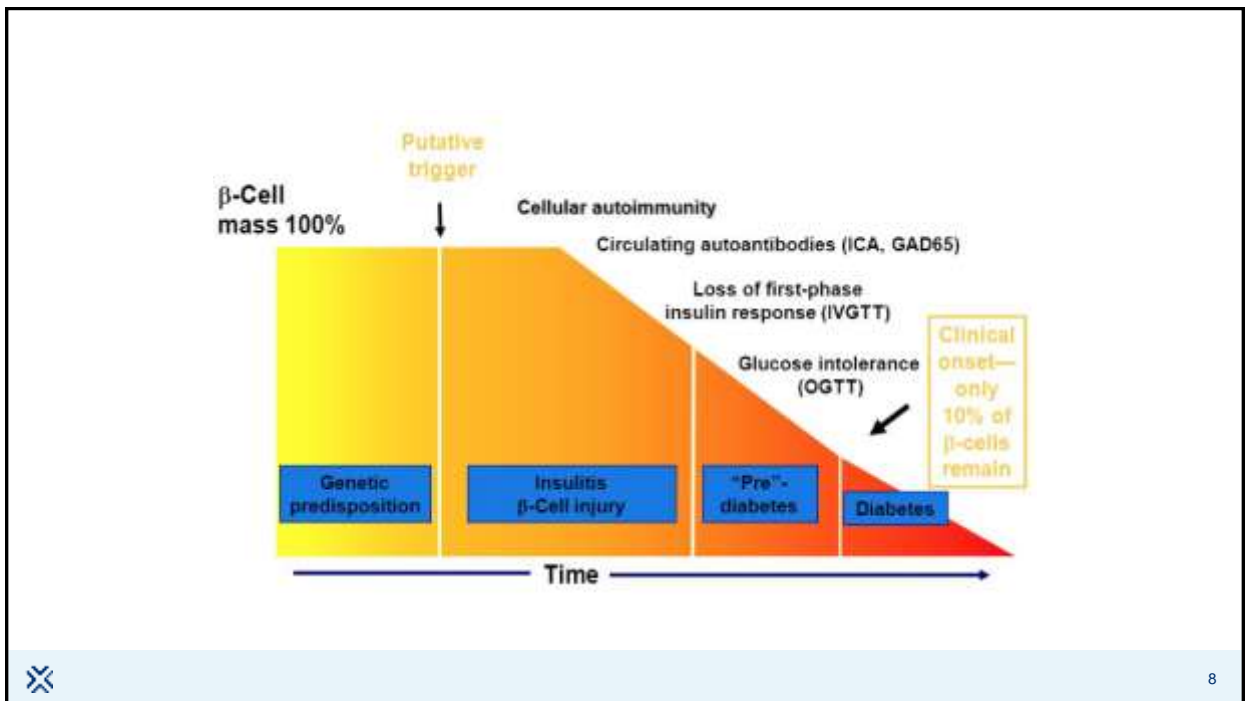
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Table 2.1—Staging of type 1 diabetes (8,10)

	Stage 1	Stage 2	Stage 3
Characteristics	<ul style="list-style-type: none"> • Autoimmunity • Normoglycemia • Presymptomatic 	<ul style="list-style-type: none"> • Autoimmunity • Dysglycemia • Presymptomatic 	<ul style="list-style-type: none"> • New-onset hyperglycemia • Symptomatic
Diagnostic criteria	<ul style="list-style-type: none"> • Multiple autoantibodies • No IGT or IFG 	<ul style="list-style-type: none"> • Multiple autoantibodies • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or $\geq 10\%$ increase in A1C 	<ul style="list-style-type: none"> • Clinical symptoms • Diabetes by standard criteria

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose.



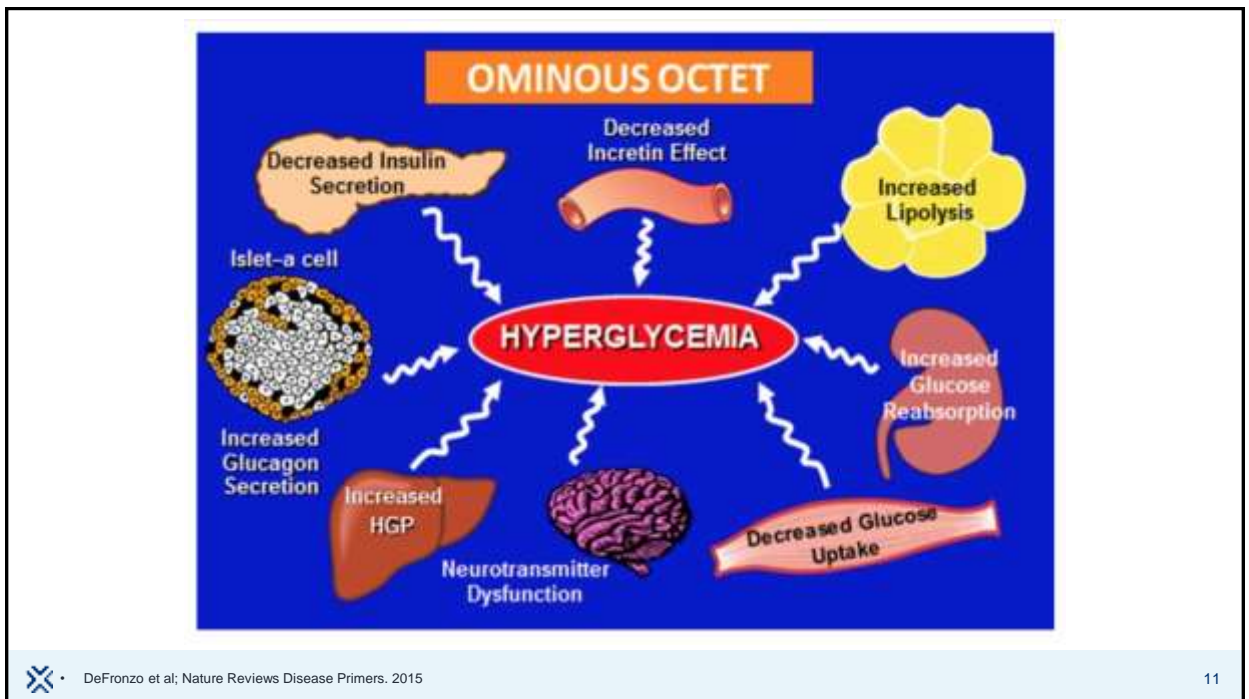
Type 2 Diabetes (T2D)



Metabolic Defect in T2D

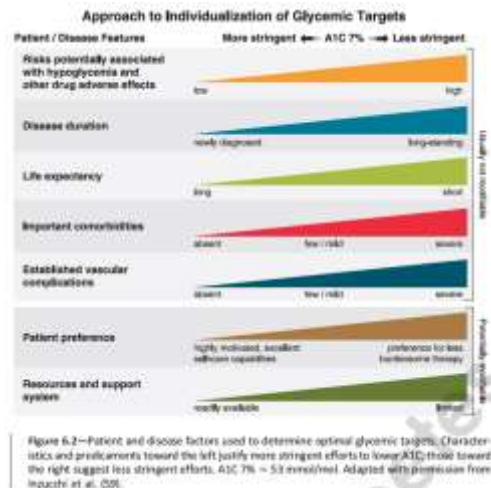
Insulin resistance, not insulin deficiency is the main issue

- Primary defect:
 - Insulin resistance and beta cell dysfunction
- Secondary defect: to ongoing metabolic milieu
 - Hepatic glucose overproduction
 - Glucagon overproduction
 - Incretin defect
 - Renal glucose reabsorption



Glycemic targets

- A1c goal < 7.0% for most nonpregnant patients
- Ambulatory glucose profile from CGM: TIR > 70% and time below range < 4%
- Pre-prandial capillary plasma glucose 80-130 mg/dl
- Peak postprandial capillary plasma glucose < 180 mg/dl



Glycemic Goals in Older Adults (≥ 65 Years Old)

- HbA1c < 7%-7.5%: otherwise healthy and have few coexisting chronic illnesses and intact cognitive and functional status
- HbA1c < 8%-8.5%: multiple coexisting chronic illnesses, cognitive impairment, or functional dependence

Severe comorbidities and limited life expectancy

- HbA1c goal < 8 – 8.5 %

Should be individualized; safety and adherence should be consideration



Assessment of glycemic control

A1c measurements

- 3-month average
- **Limitations**
- Lab error
- Conditions affecting RBC turnover
- Hgb variants
- Does not provide measure for glycemic variability or hypoglycemia

SMBG/CGM

- More personalized assessment of glycemic control
- Accounts for day to day changes and variability of BG
- Assessment of habits
- TIR: useful metric, correlates well with A1C and risk of complications, acceptable end point for clinical trials
- **Limitations:** more expensive, need to wear sensor or fingerpick daily



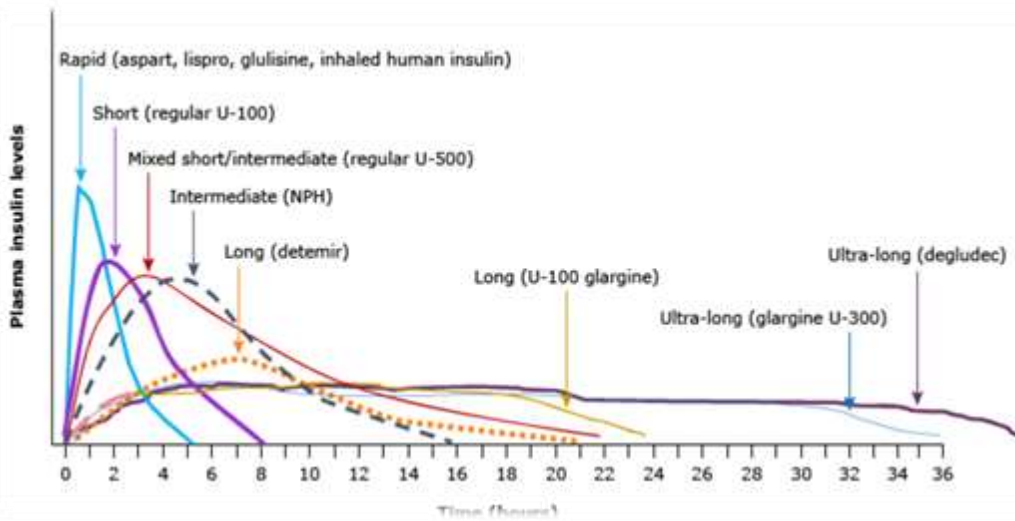
Management of Diabetes



Insulins

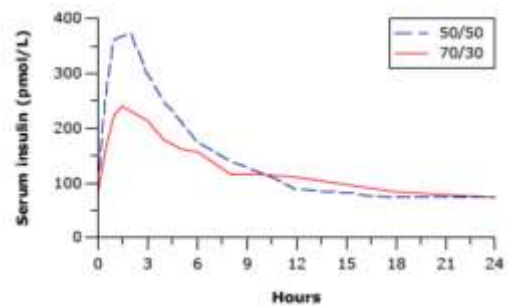
- T1D: essential, life saving, 1st line treatment option
- T2D: not the first line treatment option
 - Added on to oral agents or non-insulin therapies later





Premixed insulins

- Commercially available fixed-ratio pre-mixed insulins (50/50 or 70/30)
- Cheaper than analogs
- Almost never use for treatment in T1D; frequent adjustment for meal time bolus difficult
- Can be used for a type 1 patient non compliant to intensive regimen
- Can be used in T2D with some reasonable effect



Try to avoid if possible



Basal Insulin	Time to onset	Time to peak	Duration of action	Delivery options	Advantages	Disadvantages
NPH	2-4 hr	4-10 hr	12-18 hr	Vial, pen	Cheapest, OTC	Erratic action Marked peak More hypos
Glargine U-100 (LANTUS)	2-4 hr	Flat	20-24 hrs	Vial, pen	Less peak Fewer hypos than NPH in T1D	Expensive
Glargine U-300 (TOUJEO)	N/A	More flat	Upto 36 hrs	Pen only	Flatter and longer than U-100	Expensive Steady state takes 5 days 27% less potent than U-100
Detemir (LEVEMIR)	2-4 hr	Flat	6-24 hrs, mostly 18 hrs	Vial, pen	Flatter than NPH	Expensive Needs twice a day dosing
Degludec U-100 Degludec U-200 (TRESIBA)	N/A	Most flat	> 42 hr	Pen only	Flatter, longer acting Less hypo than glargine U200 pen: 160U/shot	Expensive Steady state takes 3-4 days

Prandial insulin	Time to onset	Time to peak	Duration of action	Delivery options	Advantages	Disadvantages
Human regular U-100	30-45 min	3 hr	6-8 hrs	Vial only	Cheapest, OTC	Doesn't match well More delayed hypos
Lispro U-100 Lispro U-200 (HUMALOG) Aspart (NOVOLOG)	20 min	90-120 min	4-6 hrs	Vial or pen Pen only Vial or pen	Faster than R, matches meal better, less delayed hypo	Expensive
Faster aspart (FIASP)	15-20 min	90-120 min	4-6 hrs	Vial or pen	Less post-meal hyperglycemia	No differences in A1c lowering
Lispro-aabc (Lymjev)	13 min	90-120 min	4.5 hrs	Vial or pen	Less post-meal hyperglycemia	No differences in A1c lowering
Inhaled insulin (AFREZZA)	< 15 min	45-60 min	1.5 hr	Single use cartridges	Faster on and off Matches meal better	Expensive Limited dose intervals C/I - COPD, asthma

▪ Multiple Daily Insulin (MDI)

- Basal coverage with long-acting insulin once or twice day
- Premeal coverage with rapid-acting insulin used as carb ratio and correctional factor
- Optimal time to dose prandial insulin depends on pharmacokinetics
- Individualized t/t plan and Intensive education of patient on dosing of rapid-acting insulin; account for BG, carb intake and activity levels

▪ Continuous Subcutaneous Insulin Infusion (CSII):

- Via insulin pump, modest lowering of A1c and reduced rates of hypoglycemia
- Pump therapy should be used with CGM whenever possible

Typical insulin doses: 0.4-1.0 U/kg/day, split 50% as basal and 50% as prandial



Insulin injection techniques

- Correct technique important to optimize glucose control
- Appropriate body areas: abdomen, thigh, buttock, upper arm
 - Subcutaneous, not IM
 - IM injection can lead to unpredictable insulin absorption, more frequent and severe hypoglycemia
- Injection site rotation: to avoid lipohypertrophy/atrophy
 - Can contribute to erratic insulin absorption, increased glycemic variability and more hypoglycemia
 - Examination of insulin injection sites should be done each visit
- Assessment of injection device use and injection technique



Lipohypertrophy & Lipoatrophy



Barola et al; BMJ Case Reports 2017
Kadiyala et al; British Journal of Diabetes 2014

Non-insulin therapies

- Metformin
- Sulfonylureas (SU)
- Thiazolidinediones (TZDs)
- Alpha-glucosidase inhibitors
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Glucagon like protein-1 (GLP-1) receptor agonists
- Sodium-glucose transport protein-2 (SGLT-2) inhibitors



METFORMIN

- Can be initiated at the time of diabetes diagnosis
- Longstanding safety record, low cost, high efficacy and reasonable tolerability
- **Glycemic Efficacy:** Typical reduction in A1c is in the range of 1 to 2.0%
- Dose can be started at 500 mg once daily and slowly titrated up (after 1-2 weeks) to avoid gastrointestinal (GI) side effects
- Renal dosing for CKD patients
- Adverse events:
 - GI intolerance
 - Lactic acidosis
 - Vitamin B12 deficiency



SULFONYLUREAS (SU)

- Oldest class of oral antidiabetic medication
- Widely used as they are very inexpensive
- Insulin secretagogues
 - Stimulate insulin secretion in the pancreatic beta-cells
- **Glycemic efficacy:** Reduction in A1c of 0.5-1.5%
 - Those with shorter duration of diabetes and residual beta-cell function are more likely to be responsive
- Adverse effects:
 - Hypoglycemia
 - Weight gain

THIAZOLIDINEDIONES (TZD)

- Improve insulin sensitivity by acting on adipose, muscle and liver to increase glucose utilization and decrease glucose production.
- 2 medications available in this class:
 - Rosiglitazone
 - Pioglitazone
- **Glycemic efficacy:** Expected decrease in A1c is approx. 1.0 to 1.5%
- Effective in improving glycemic control in those with significant insulin resistance.

Adverse effects

- **Weight gain**
 - ~ 2 – 3 kg for every 1 percent decrease in A1c
 - Dose related and can be minimized by using lower doses.
- **Fluid Retention**
 - Dose related
- **Congestive Heart Failure**
 - Risk for CHF development is higher if they have a history of cardiovascular disease.
- **Osteoporosis**
 - Increase in Fracture risk, especially women.

Bladder Cancer

FDA recommends that pioglitazone not be used in diabetic patients with active bladder cancer or a history of bladder cancer



ALPHA-GLUCOSIDASE INHIBITORS

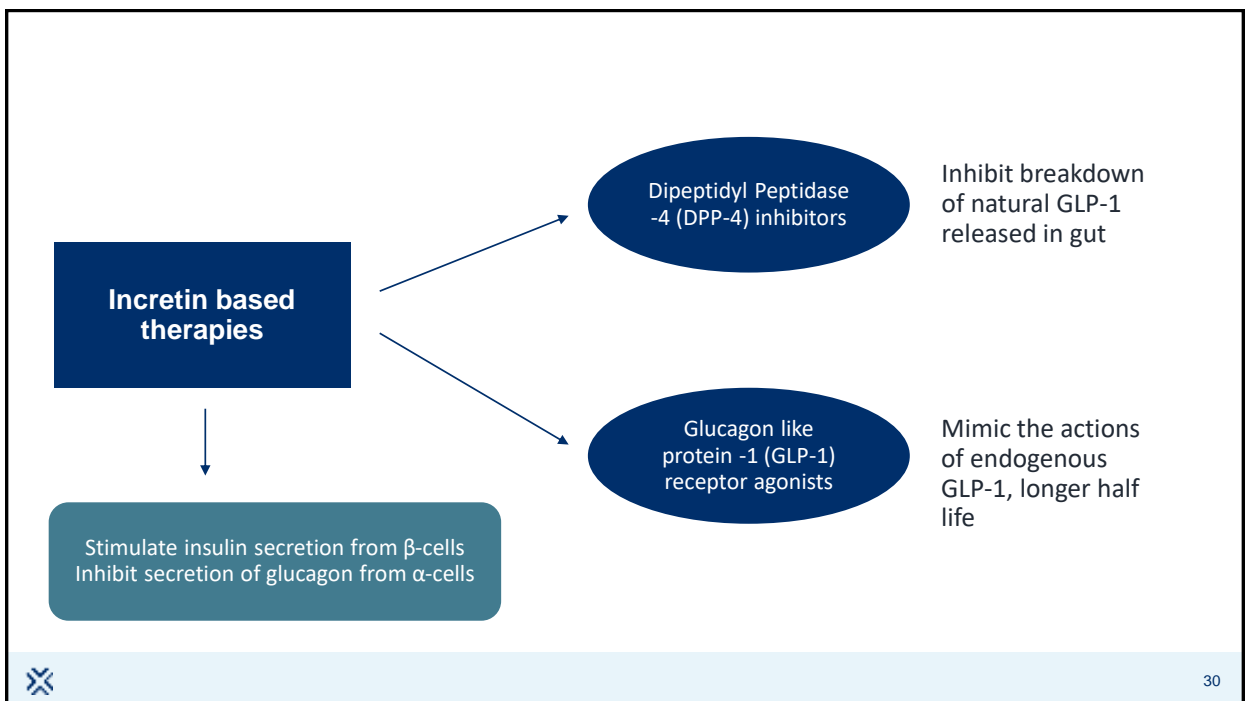
- Inhibit the upper gastrointestinal enzyme (alpha-glucosidase) that convert complex polysaccharide carbohydrates into monosaccharides.
 - Slows the absorption of glucose.

- **Acarbose and Miglitol**
 - Starting dose: 25 mg orally three times daily at start of each meal
 - Maximum dose: 100 mg three times daily with meals.

- Predominant effect on postprandial hyperglycemia.

- **Adverse effects:**
 - **Gastrointestinal**
 - Flatulence, Abdominal discomfort, and/or Diarrhea





Dipeptidyl Peptidase-4 (DPP-4) inhibitors

- Drugs available: Sitagliptin, Saxagliptin, Linagliptin, Alogliptin
- **Glycemic efficacy:** Reduce A1c levels by 0.5 – 1.0 %
 - Effective at lowering post-prandial glucose levels
- **Adverse Effects:**
 - Acute Pancreatitis
 - Increased risk for hospitalization for heart failure: only with *Saxagliptin* in the SAVOR-TIMI 53 study
 - Arthralgias: Discontinue DPP-4 inhibitor if patients develop severe joint pain
- No cardiovascular benefit relative to placebo in CVOTs

	SAVOR TIMI 53	EXAMINE	TECOS	CAROLINA	CARMELINA
Intervention	Saxagliptin/ Placebo	Alogliptin/ Placebo	Sitagliptin/ Placebo	Linagliptin/ Glimepiride	Linagliptin/ Placebo
MACE	Neutral	Neutral	Neutral	Neutral	Neutral
CV Death	N/A				
HF Hospitalization		NS	Neutral	Neutral	NS



Scirica et al; NEJM 2013
White et al; NEJM 2013
Green et al; NEJM 2015

Glucagon like protein-1 (GLP-1) receptor agonists

- GLP-1 analogues with longer half lives to achieve supra-physiological levels:

- Exenatide BID
- Lixisenatide
- Liraglutide
- Dulaglutide
- Albiglutide
- Semaglutide
- Exenatide once weekly
- Tirzepetide (Combined GLP/GIP)

(Approved by the FDA in May 2022 for the treatment of Type 2 Diabetes in adults)

Increasing half-life



Increase insulin secretion
Decrease satiety
Reduce glucagon secretion
Slow gastric emptying

↓ HbA1c (1-2%)
Weight loss



Adverse Effects:

- **Gastrointestinal**
 - Resolve over time
- **Injection site reaction**
 - Rash, erythema
- **Medullary Thyroid cancer**
 - Possible concern in mice studies
 - Not seen with clinical studies in humans
- **Pancreatitis**
- **Retinopathy**
 - Semaglutide in the SUSTAIN 6 trial



GLP-1 RAs Reduce CV risk

	ELIXA Lixisenatide	LEADER Liraglutide	SUSTAIN-6 SQ semaglutide	EXSCEL QW exenatide	HARMONY Albiglutide	REWIND Dulaglutide	PIONEER 6 Oral semaglutide
3P MACE	NS	↓13%	↓26%	NS	↓22%	↓12%	NS
CV Death		↓22%	NS	NS	NS	NS	↓51%
Non fatal stroke		NS	↓39%	NS	NS	↓24%	NS
Non fatal MI		NS	NS	NS		NS	NS
All cause death		↓15%		NS			↓49%
HF Hospitalization		NS		NS			

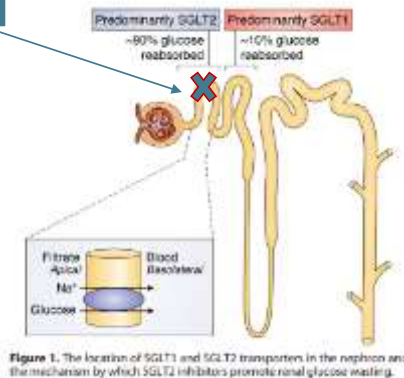
3P MACE = CV death, Non fatal MI, non fatal stroke,



SODIUM-GLUCOSE TRANSPORT PROTEIN 2 (SGLT2) INHIBITORS

SGLT-2 INHIBITORS

- The efficacy of SGLT2 inhibitors is dependent on renal function
 - Ability to lower A1c levels diminishes as renal function declines



Glycemic efficacy

- Decrease A1c by 0.4 – 1.1 %
- Lowers both fasting and postprandial glucose levels

Drugs available

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- Ertugliflozin (Steglatro)

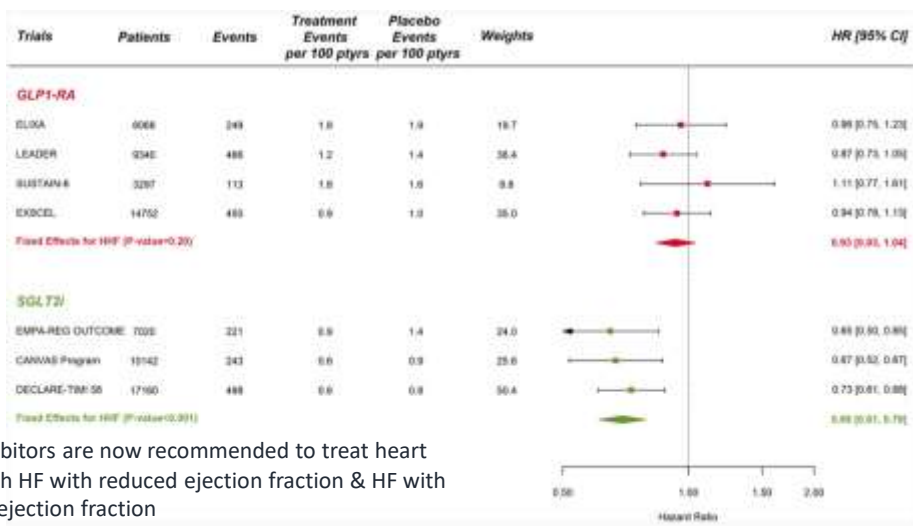


ADVERSE EFFECTS

- **Urinary Tract Infections**
 - Contraindicated in patients with neurogenic bladder and indwelling catheter
- **Genital mycotic infections**
 - Mild and easy to treat
- **Fournier Gangrene: *necrotizing fasciitis of the perineum***
 - Requires immediate surgical intervention and treatment with broad-spectrum antibiotics
- **Euglycemic Diabetic Ketoacidosis**
 - Blood glucose levels at which ketoacidosis develops with SGLT2 inhibitors may be lower (often < 250 mg/dL) than typically expected for cases of diabetic ketoacidosis
 - May result in a delay in diagnosing DKA
- **Amputations**
 - Canagliflozin was associated with an increased risk of amputations in CANVAS study



SODIUM-GLUCOSE TRANSPORT PROTEIN 2 (SGLT2) INHIBITORS and HEART FAILURE



- SGLT-2 inhibitors are now recommended to treat heart failure, both HF with reduced ejection fraction & HF with preserved ejection fraction

WEIGHT LOSS	WEIGHT NEUTRAL	WEIGHT GAIN
GLP-1 Receptor agonists	DDP-4 Inhibitors	Sulfonylureas
SGLT-2 Inhibitors		Thiazolidinediones (TZD)
Metformin		Insulin

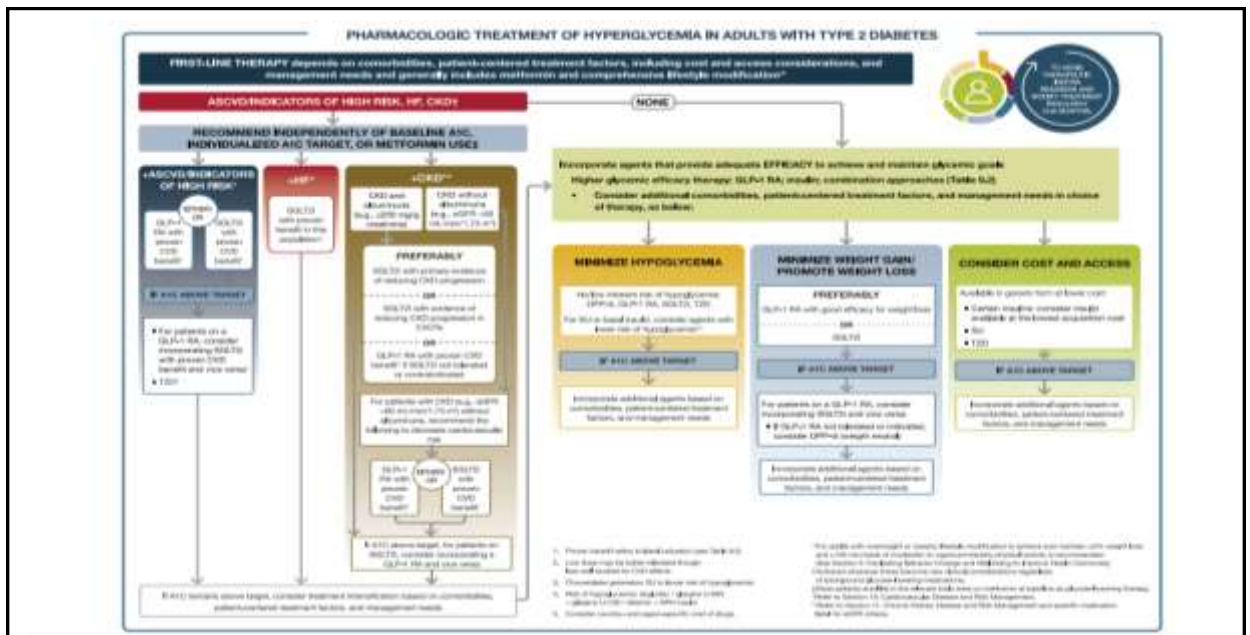


TYPE 2 DM DIABETES: INITIATING PHARMACOTHERAPY

Standards of Medical Care in Diabetes – 2022 Guideline update

- First medication that should be prescribed should **usually** be Metformin in addition to comprehensive lifestyle changes.
 - allows for more flexibility than the 2021 ADA recommendation:
“all people should be prescribed metformin”
- Alternative initial treatment approaches to Metformin is now acceptable depending on several factors, such as:
 - 1) **Co-morbidities:** atherosclerotic cardiovascular disease (ASCVD) and indications for high ASCVD risk; chronic kidney disease (CKD) and heart failure (HF)
 - 2) **Hypoglycemia risk**
 - 3) **Effects on body weight**
 - 4) **Side effects**
 - 5) **Cost**
 - 6) **Patient preference**





Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S125-S143. doi: 10.2337/dc22-S009. PMID: 34964831



Use of technology in diabetes

- Technology is rapidly changing, but there is no “one-size-fits-all” approach to technology use in people with diabetes
- Use of technology should be individualized based on a patient’s needs, desires, skill level, and availability of devices



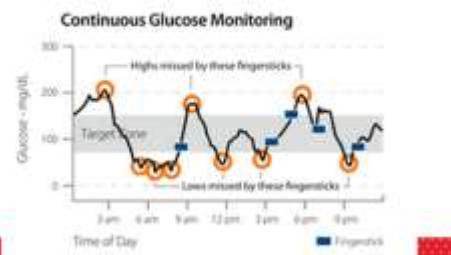
- Traditional “fingerstick” glucose testing



- Continuous glucose monitoring (CGM)



- A. Sensor
- B. Transmitter
- C. Display device



CGM devices



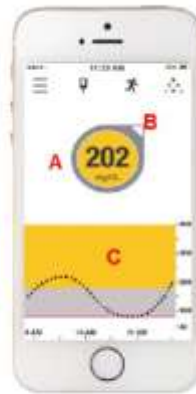
FreeStyle Libre



Guardian
Connect



Eversense



G6

ABBOTT FREESTYLE LIBRE

- Flash Glucose Monitor (FGM)
 - Factory Calibrated
 - 14-day wear following 12-hr warm-up
- No alarms (except libre 2 has alarms for low BG)
 - Sensor worn on back of upper arm
 - Must scan every 8 hours to maintain a constant stream of data
 - Can use receiver or smart phone with Libre View app to scan sensor



Freestyle Libre 3 CGM



Real-time glucose readings are sent every minute to the smartphone app and can be viewed with a quick glance



<https://www.freestyle.abbott/us-en/products>

DEXCOM G6

Does not need calibration, warm up period of 2 hrs
 Has Tylenol blocking, no false low BGs
 Data can be uploaded to clarity app (like an icloud)
 10 day wear



Sensor + Algorithm

Factory calibrated
 10 Day Session
 Acetaminophen blocking



Applicator

Push Button
 Sensor Applicator



Transmitter

BLE - 20 Foot Range
 3 Month Life



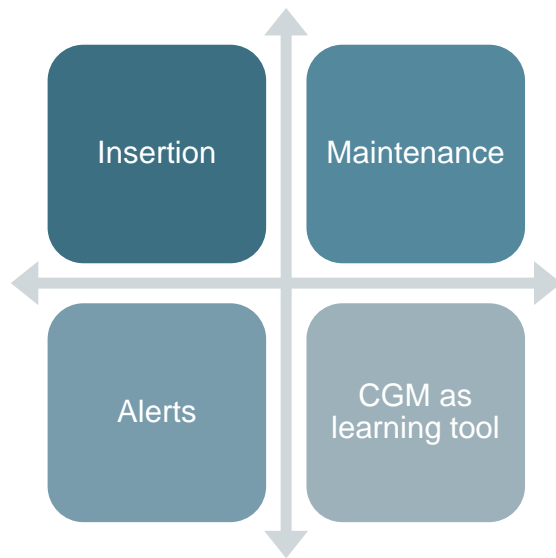
Apps  

Dexcom G6 App
 Urgent Low Soon Alert
 Remote Monitoring



<https://www.dexcom.com/products>

CGM Patient Training



Management of Hyperglycemia in the Hospital



GLYCEMIC TARGETS IN THE HOSPITAL

- NICE-SUGAR trial
 - Higher rates of hypoglycemia and mortality in intensive glycemic control group (80-110) compared to moderate glycemic targets (140-180)
- BG target **140-180** for both critically and non critically ill patients
- BG goal 110-140; for cardiac surgery patients, critically ill post surgical patients (as long as without hypoglycemia)
- BG 180-250; severe comorbidities, frequent hypoglycemia
- BG > 250; terminally ill patients with short life expectancy



BEDSIDE BLOOD GLUCOSE MONITORING

Frequency of BG testing

- Patients who are eating: before meals AND bedtime
- Patient not eating: every 4-6 hours
- Patients on IV insulin – every 30 min – 2 hours

Hospitalized for noncritical illness who are at high risk of hypoglycemia, use of real-time continuous glucose monitoring (CGM) with confirmatory bedside point-of-care blood glucose (POC-BG) monitoring is recommended

This does not apply to situations in which CGM may not be accurate:

- Patients with extensive skin infections
- Hypoperfusion
- Hypovolemia
- Those receiving vasoactive or pressor therapy



TREATMENT

Critical care setting

- Continuous insulin infusions per validated computerized protocols
- Adjustment of infusion rate per BG value

Non critical care setting

- Insulin is the preferred treatment
- Scheduled insulin regimens should be used
- Non insulin therapies should not be used (with certain exceptions)

Enteral nutrition

- Enteral nutrition with diabetes-specific or nonspecific formulations, neutral protamine Hagedorn (NPH)-based or basal bolus regimens are recommended

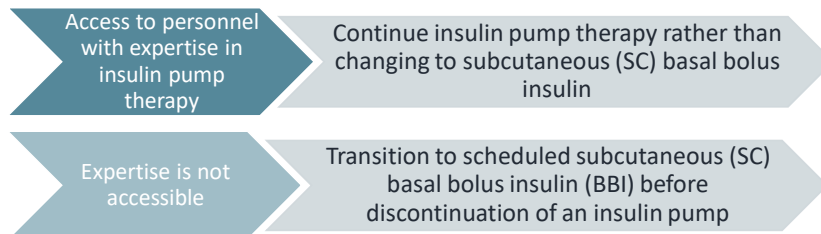


Insulin therapy - basics

- In adults with no prior history of diabetes hospitalized for noncritical illness with hyperglycemia
 - Initial therapy with correctional insulin over scheduled insulin therapy (defined as basal or basal/bolus insulin) to maintain glucose targets in the range of 100 to 180 mg
 - For patients with persistent hyperglycemia [POC-BG measurements \geq 180 mg/dL in a 24-hour period on correctional insulin alone], we suggest the addition of scheduled insulin therapy
- In adults with insulin-treated diabetes prior to admission who are hospitalized for noncritical illness, we recommend continuation of the scheduled insulin regimen (basal/bolus regimen) modified for nutritional status and severity of illness to maintain glucose targets in the range of 100 to 180 mg/dL
- Correctional insulin should be AC/HS or q4-6 hrs (**NOT AS DIRECTED PRN**)
- POC testing and insulin injections should align with meals
- *Reactive/sliding scale insulin regimens should not be used*



PATIENTS WITH INSULIN PUMP



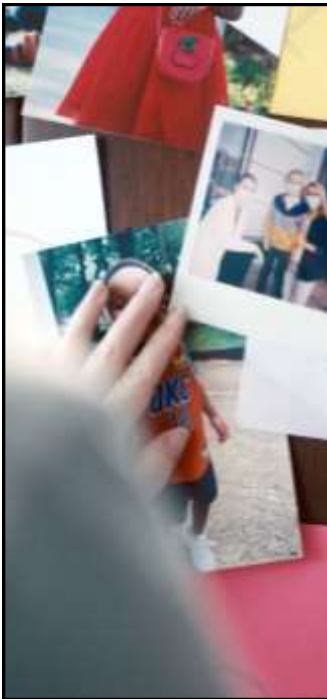
Who are not candidates for inpt use of insulin pump:

- Impaired level of consciousness
- Inability to appropriately adjust pump settings
- Critical illness (intensive care unit care)
- Diabetic ketoacidosis or hyperosmolar hyperglycemic state



QUESTIONS??





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