Pharmacologic Management of Diabetes 2020

Gretchen M. Ray, PharmD, PhC, CDCES
Associate Professor of Pharmacy Practice
UNM COP
gray@salud.unm.edu

COLLEGE OF PHARMACY

1

OBJECTIVES

- Describe available treatment options for type 2 diabetes including drug, dose, advantages and disadvantages of therapy, and contraindications
- Use the 2020 American Diabetes Association Standards of Care treatment algorithm to provide patient-centered glycemic management for a patient with type 2 diabetes

2

RECOMMENDED READING

- Standards of Medical Care in Diabetes 2020. *Diabetes Care* 2020;43(Suppl 1)
  - Download the app!

3

Oral Therapies for Type 2 Diabetes

4

BIGUANIDES- METFORMIN

- ↓ hepatic glucose production, ↓ intestinal glucose absorption, ↑ insulin sensitivity
- Efficacy: ↓ A1C ~1.5%
- **Hypoglycemia: No**
- **Weight: Neutral**
- **Cost: inexpensive**
- Can be used for diabetes prevention in pre-diabetes
- Adverse Effects
  - **Primarily GI (up to 50%)**
    - Titrate dose at weekly intervals to minimize AEs
    - Give with meals
  - **B12 Deficiency**
  - Lactic acidosis- rare

5

CONTRAINDICATIONS/PRECAUTIONS WITH METFORMIN

Contraindications

- Renal impairment
  - **GFR <30 discontinue medication**
- Acute or chronic metabolic acidosis

Precautions

- Radiocontrast studies
- Age >80 unless normal GFR
- Hypoxic states
- Alcoholism

6

SULFONYLUREAS

- ↑ insulin secretion from pancreatic β-cells
- Efficacy: ↓ A1C ~1.5%

- Glyburide
- Glipizide/Glipizide XL (Glucotrol)
- Glimepiride (Amaryl)

7

SULFONYLUREA CONSIDERATIONS

- **Hypoglycemia**: Yes
- **Weight**: gain- due to insulin secretion
- **Cost**: inexpensive

8

THIAZOLIDINEDIONES (TZDS)- INSULIN SENSITIZERS

- TZDs are PPAR- gamma receptor activators: ↑ insulin sensitivity
- **Rosiglitazone** (Avandia®)
- **Pioglitazone** (Actos®)
- **Hypoglycemia**: No
- **Weight**: gain
- **Cost:** *inexpensive*

9

ADVERSE EFFECTS/CONTRAINDICATIONS OF TZDS

Contraindications

- HF NYHA class III or IV

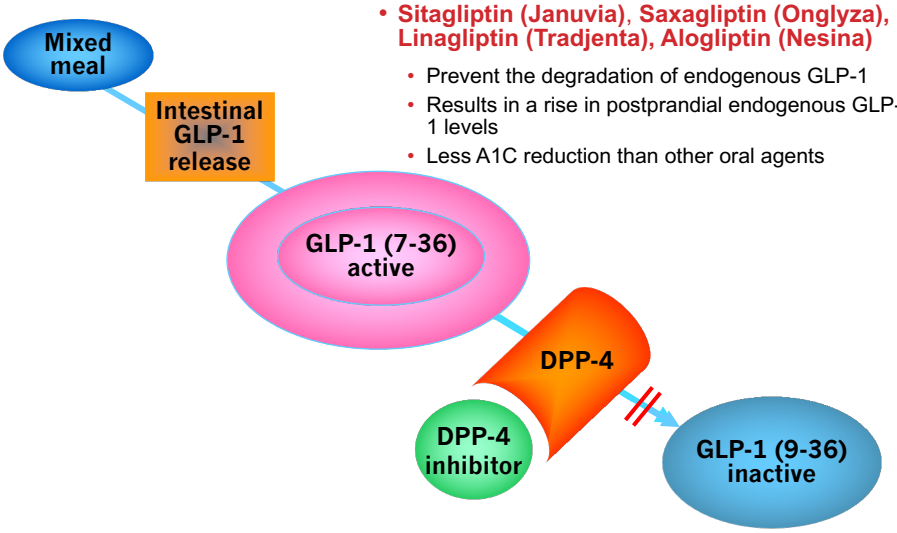
Adverse Effects

- Fluid retention and peripheral edema
- **Weight gain**
  - Fluid retention is a major contributor
  - Redistribution of adipose tissue
- New-onset heart failure
  - < 1%
  - 2-3% when combined with insulin
- Bladder Cancer Risk(pioglitazone)

10

DPP-4 INIBITITORS

- **Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Tradjenta), Alogliptin (Nesina)**
  - Prevent the degradation of endogenous GLP-1
  - Results in a rise in postprandial endogenous GLP-1 levels
  - Less A1C reduction than other oral agents



11

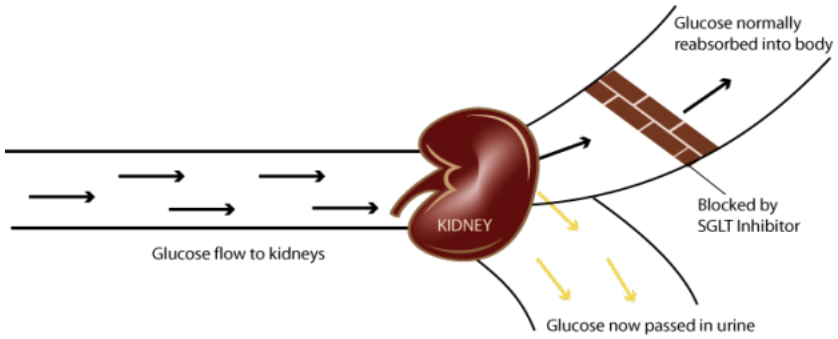
DPP-4 INHIBITORS

- **Side Effects**
  - **Well tolerated**
  - Similar to placebo
  - Few post-marketing reports of hypersensitivity reactions and pancreatitis
  - Saxagliptin and alogliptin have been associated with increased heart failure hospitalizations in large trials

- **Considerations**
- **Weight:** neutral
- **Hypoglycemia**: No
- **Cost**: expensive
- Once daily oral drugs

12

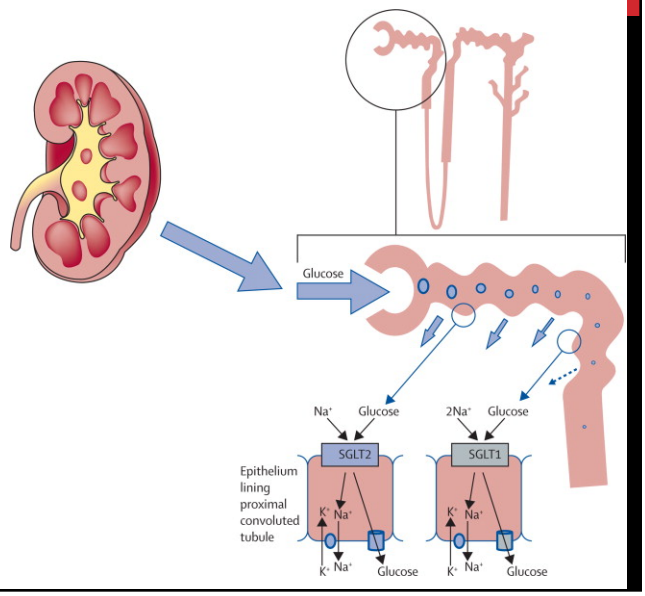
SGLT2 Inhibitors



13

SGLT2 INHIBITORS

- Sodium-glucose co-transporter inhibitors (SGLT2)
- Increase urinary glucose excretion
- **Canagliflozin** (Invokana™)
- **Dapagliflozin** (Farxiga™)
- **Empagliflozin** (Jardiance™)
- **Ertugliflozin** (Steglatro™)



14

SGLT2 INHIBITORS

Side Effects/Precautions

- **Female genital mycotic infections**
- **UTI**
- Increased urination
- Blood pressure reduction
- Not indicated if eGFR<30
- Euglycemic ketoacidosis
  - Rare but recent FDA warning
- Possible fracture risk?

Benefits

- Once daily oral agents
- Insulin independent action
- Weight: loss
- Hypoglycemia: No
- Cost: expensive
- **CV and Renal Benefits (see next slide)**

15

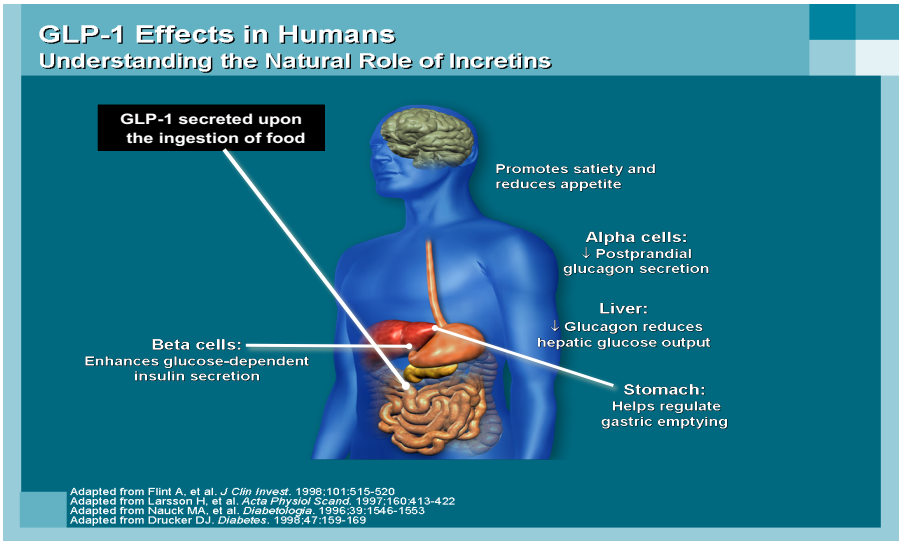
SGLT2 INHIBITORS CV AND RENAL BENEFITS

	Major Adverse CV outcomes	Heart Failure Hospitalizations	Progression of DM Kidney Disease
Empagliflozin	↓	↓	↓
Canagliflozin	↓	↓	↓
Dapagliflozin	-	↓	↓
Ertugliflozin	-	↓	↓

Ertugliflozin CV safety trial presented, but not yet published

16

GLP-1 PHYSIOLOGY



17

GLUCAGON-LIKE PEPTIDE 1 (GLP-1) AGONISTS:

- Exenatide (Byetta®): BID
- Exenatide LAR (Bydureon®): once a week
- Liraglutide (Victoza®): once a day
- Dulaglutide (Trulicity®): once a week
- Semaglutide (Ozempic®): Once a week

Injectable

- Semaglutide (Rybelsus®): **ORAL** once a day
- Glucagon-like-peptide-1 (GLP-1) analogs
  - Incretin mimetic
  - Resistant to degradation by dipeptidyl peptidase-4 (DPP-4)
  - Suppresses high glucagon levels
  - Delays gastric emptying (can affect absorption of other medications)
- ↓ A1C 1-1.6%

18

GLP-1 AGONISTS

Hypoglycemia: No
- Insulin release is glucose dependent

CV and Renal Benefits (see next slide)
- **LEADER and SUSTAIN-6 and REWIND trials**

Weight loss!

Cost: Expensive

Side Effects
- N/V (slows gastric emptying)
  - Slow dose titration can minimize AEs

Precautions/Contraindications
- Renal impairment (only with exenatide)
- **Gastroparesis**
- **History of pancreatitis**
- History of medullary thyroid carcinoma
- Multiple endocrine neoplasia syndrome 2

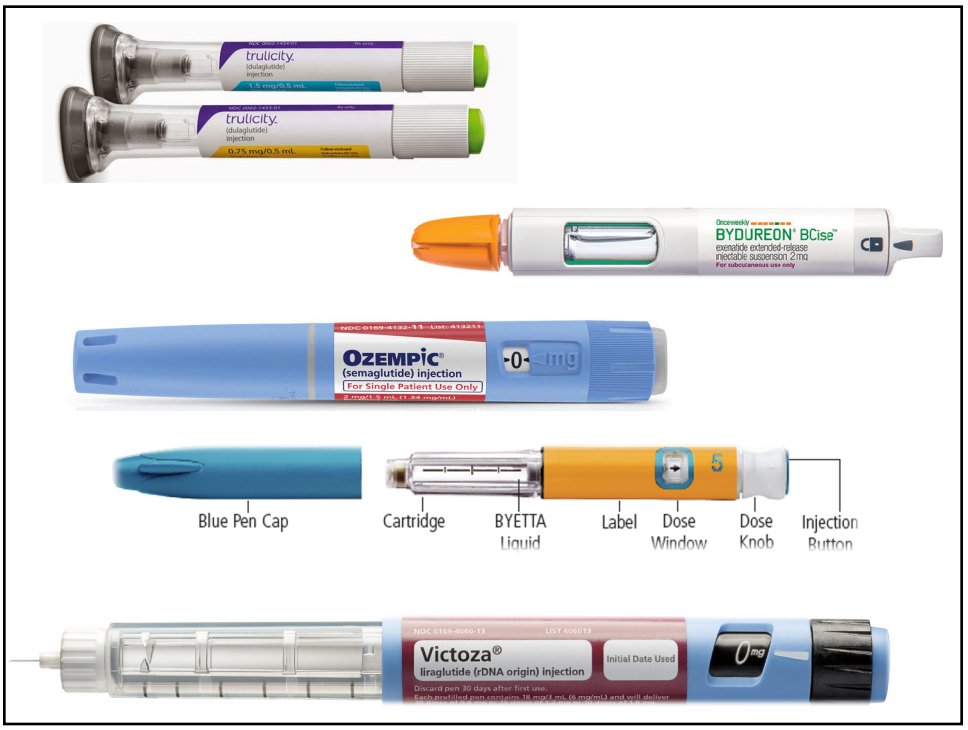
19

GLP-1 RA CV AND RENAL BENEFITS

	Major Adverse CV outcomes	Progression of DM Kidney Disease
Liraglutide	↓	↓
Semaglutide (injection)	↓	↓
Dulaglutide	↓	↓
Exenatide	-	-
Lixisenatide	-	-

Exenatide and Lixisenatide have demonstrated CV safety, but did not provide any protective effects

20



21

ADA Management of Hyperglycemia in Type 2 Diabetes

***Diabetes Care* 2020;43(Suppl 1)**

22

GLYCEMIC CONTROL

ADA Guidelines

- A1C < 7.0%
  - Less stringent A1C goal <8% appropriate for certain patients…see guidelines
- Fasting/premeal glucose 80-130 mg/dl
- Peak postprandial glucose <180 mg/dl
  - 1-2 hours after the start of the meal

A1C	Mean Plasma glucose mg/dl
6	126
7	154
8	183
9	212
10	240
11	269
12	298

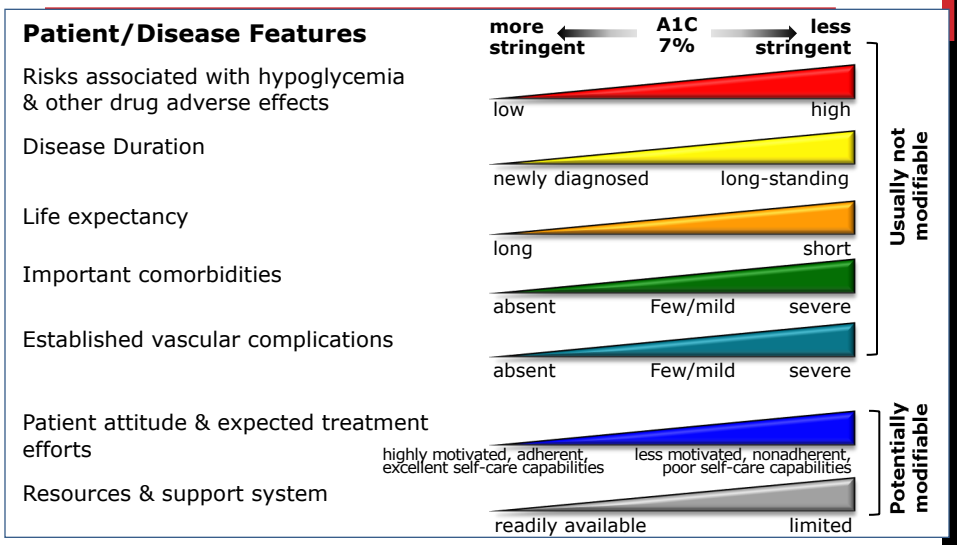
23

MONITORING

- **Self monitoring of blood glucose (SMBG)**
  - At least 3 times/day if on insulin injections
    - Fasting and before or after meals
  - If on orals, just use SMBG to help them achieve their glycemic goals
    - Insurance typically will only allow one test per day if patient not on insulin
  - Use the data to make decisions on what therapy to add
- **A1C**
  - At least twice a year in patients at goal
  - Every 3 months in patients whose therapy has changed or aren't meeting treatment goals

24

APPROACH TO THE MANAGEMENT OF HYPERGLYCEMIA



25

INITIAL THERAPY: METFORMIN

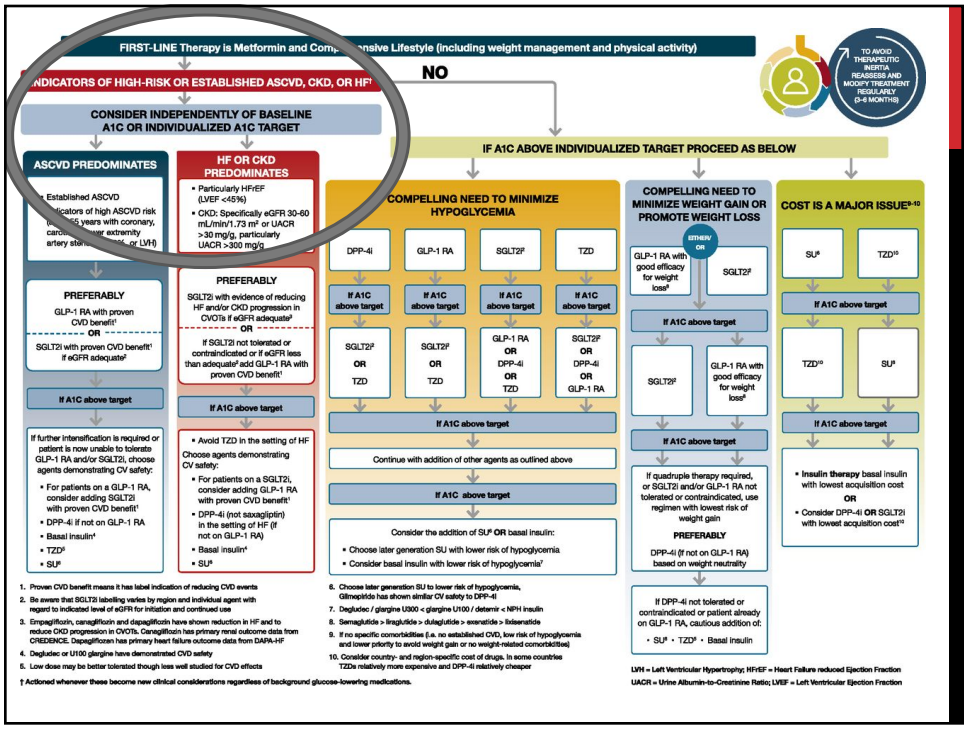
- **Metformin, if not contraindicated, is the preferred 1st line agent**
  - Low risk of hypoglycemia, no weight gain, cheap
- Titrate metformin to max dose over 1-2 months
  - Start with 500 mg once or twice a day
  - After 5-7 days if GI effects haven't occurred, increase to 1000 mg BID
  - If GI effects as dose is increased reduce dose and try to increase again at a later time

26

TYPE 2 DIABETES TREATMENT ALGORITHM IN ADDITION TO METFORMIN

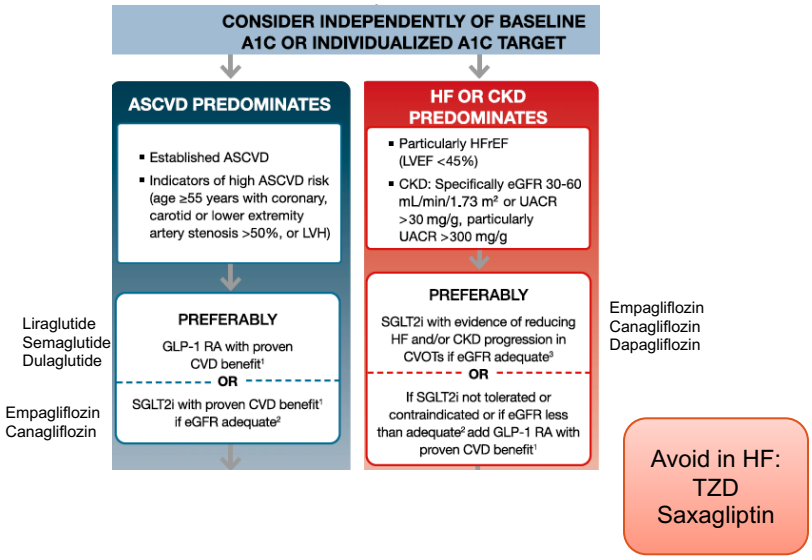
- Pharmacotherapy is determined by:
  - ***1. Presence of atherosclerotic cardiovascular disease (ASCVD)***
  - ***2. Presence of congestive heart failure (CHF)***
  - ***3. Chronic kidney disease (CKD)***
  - 4. Need to minimize hypoglycemia
  - 5. Need to promote weight loss/minimizes weight gain
  - 6. Cost issues

27



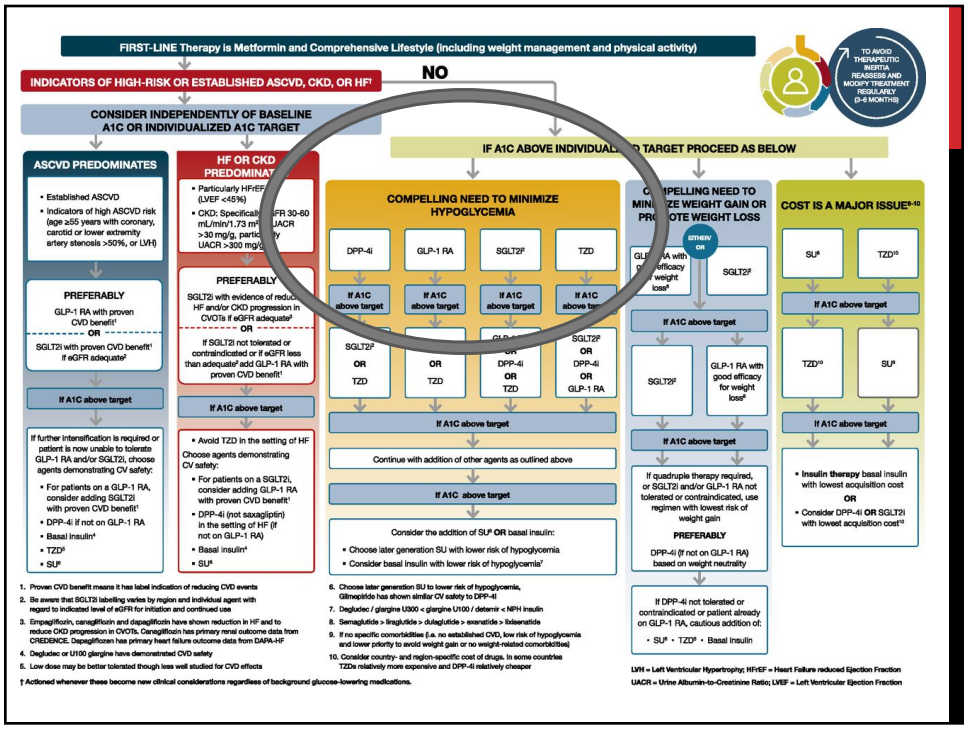
28

ALGORITHM: ASCVD / HF / CKD

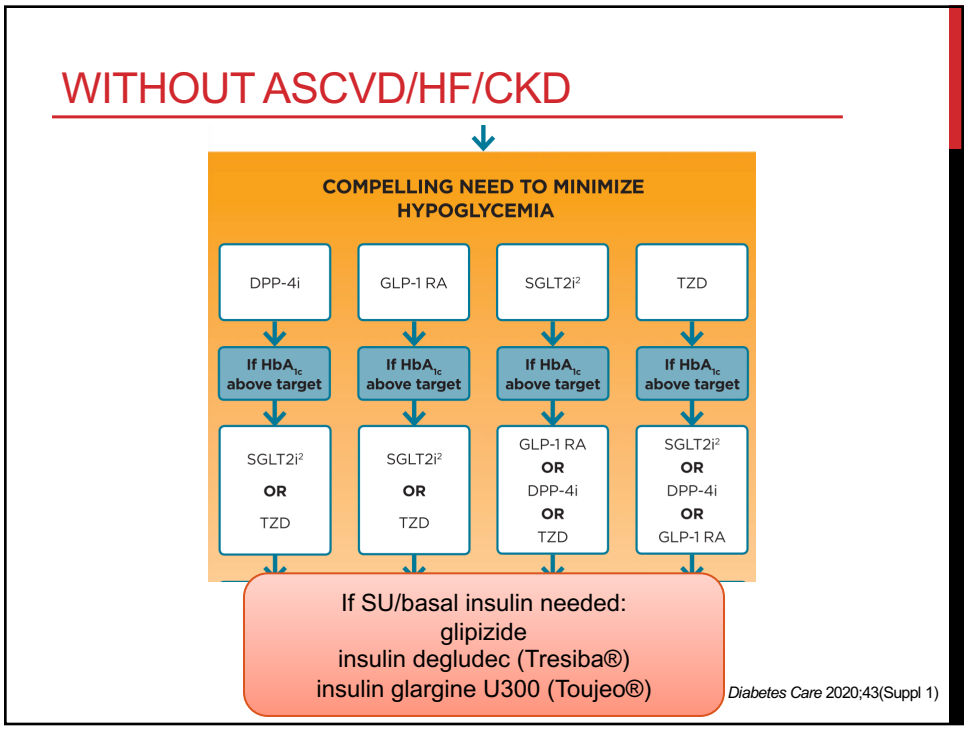


Diabetes Care 2020;43(Suppl 1)

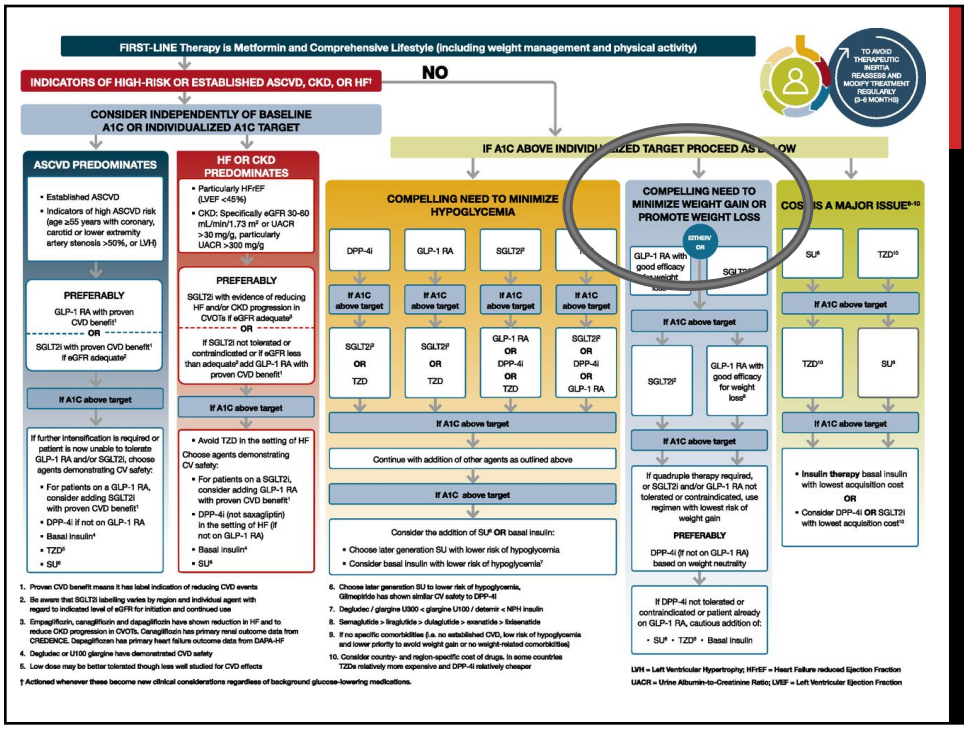
29



30

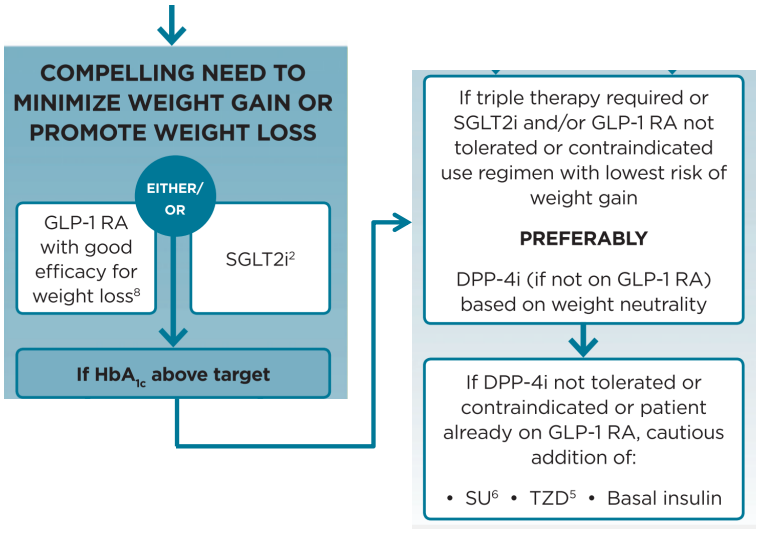

WITHOUT ASCVD/HF/CKD
COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
DPP-4i
GLP-1 RA
SGLT2i²
TZD
If HbA1c above target
If HbA1c above target
If HbA1c above target
If HbA1c above target
SGLT2i² OR TZD
SGLT2i² OR TZD
GLP-1 RA OR DPP-4i OR TZD
SGLT2i² OR DPP-4i OR GLP-1 RA
If SU/basal insulin needed:
glipizide
insulin degludec (Tresiba®)
insulin glargine U300 (Toujeo®)
Diabetes Care 2020;43(Suppl 1)

31


FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)
INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†
NO
CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
ASCVD PREDOMINATES
HF OR CKD PREDOMINATES
COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
If A1C above target
Continue with addition of other agents as outlined above
PREFERABLY
DPP-4i (if not on GLP-1 RA) based on weight neutrality
Proven CVD benefit means it has label indication of reducing CVD events
Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
Degludec or U100 glargine have demonstrated CVD safety
Low dose may be better tolerated though less well studied for CVD effects
† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
Choose later generation SU to lower risk of hypoglycemia, Glimepiride has shown similar CV safety to DPP-4i
Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
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)
Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper
LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

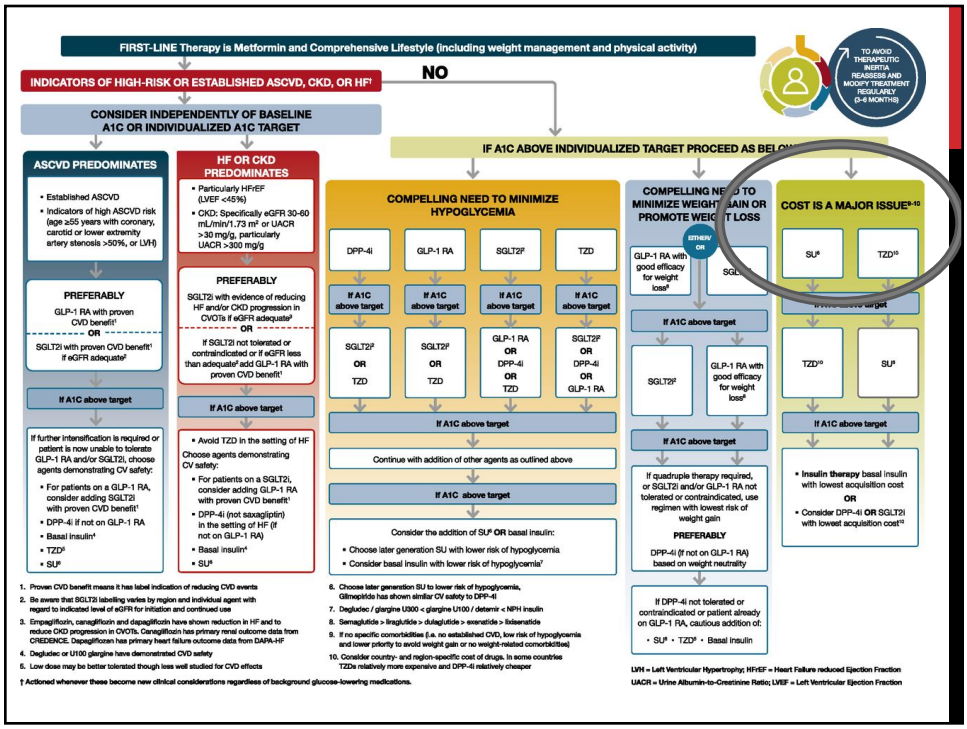
32

ALGORITHM: WEIGHT LOSS



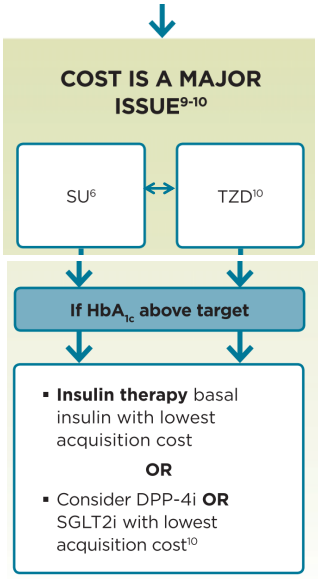
Adapted from *Diabetes Care* 2020;43(Suppl 1)

33



34

ALGORITHM: COST



Adapted from *Diabetes Care* 2019;42(Suppl 1)

35

COST CONCERNS

- Commercially Insured Patients- Download copay cards from manufacturer websites to reduce brand name copay
  - SGLT2i $0 copay card
  - GLP1-RA $25 per month copay card
- Medicaid
  - Most plans cover ONE formulary SGLT2i and GLP1-RA
    - BCBS & Pres: *Steglatro (ertugliflozin)*, Victoza (Liraglutide), Trulicity (dulaglutide)
    - Western Sky: covers a few from each drug class
  - **Try prior auth for patients with ASCVD, HF, or CKD**
- Medicare part D
  - Dual Medicare/Medicaid covered with low copay
  - Medicare part D plans alone cover at least one drug from each class
    - Highly variable copays and Donut Hole/coverage gap is the concern

36

Insulin

When to start??

37

TYPES OF INSULIN

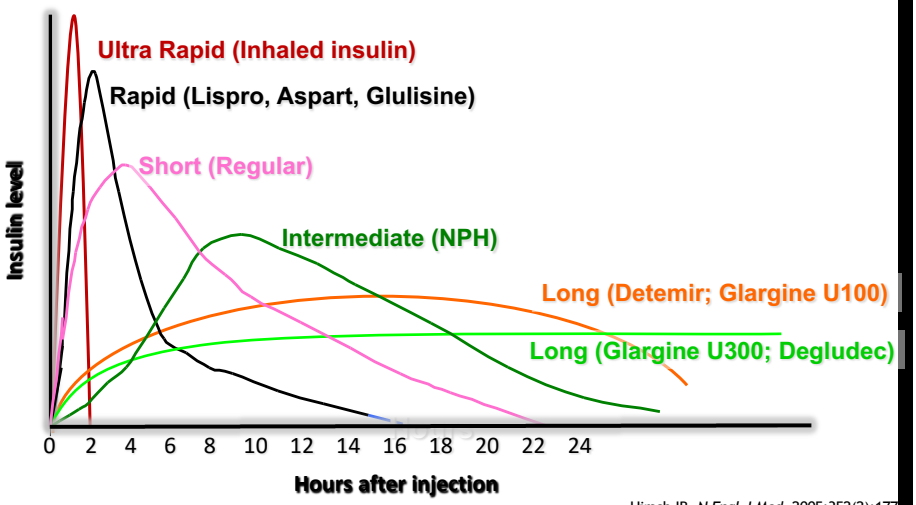
- Rapid Acting
  - Humalog®, Admelog® (lispro)
  - Novolog ® (aspart)
  - Apidra ® (glulisine)
- Short Acting-Regular Insulin (R)
  - Novolin® R
  - Humulin® R
- Intermediate Acting-NPH (N)
  - Novolin® N
  - Humulin ® N
- Long Acting – Basal Insulin
  - Levemir® (detemir)
  - Lantus®, Basaglar® (glargine)
  - Toujeo® (U-300 glargine)
  - Tresiba®(Degludec)

Controls Post-prandial glucose

Controls Fasting Glucose

38

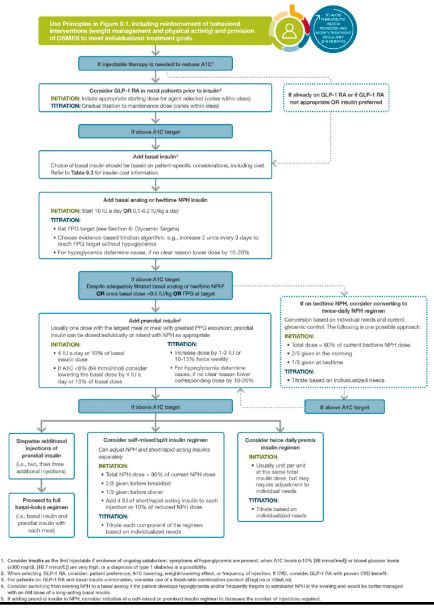
INSULIN PHARMACOKINETIC PROFILES



Hirsch IB. *N Engl J Med*. 2005;352(2):177
Afrezza (insulin human) inhalation powder PI. MannKind Corporation; 2014
Riddle MC et al. Diabetes Care. 2014 Oct;37(10):2755-62
Zinman B et al. Diabetes Care. 2012 Dec;35(12):2464-71

39

INTENSIFYING TO INJECTABLE THERAPY



1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RA, consider: patient preference, A1C lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit.
3. For patients on GLP-1 RA and basal insulin combination, consider use of a fixed-ratio combination product (iDegLira or IGlarLixi).
4. Consider switching from evening NPH to a basal analog if the patient develops hypoglycemia and/or frequently forgets to administer NPH in the evening and would be better managed with an AM dose of a long-acting basal insulin.
5. If adding prandial insulin to NPH, consider initiation of a self-mixed or premixed insulin regimen to decrease the number of injections required.

Diabetes Care 2020;43(Suppl 1)

40

INTENSIFYING TO INJECTABLE THERAPY

- *USE INJECTABLE THERAPIES FLOWCHART*
- GLP-1 RA are preferred over insulin in most situations
- If already on GLP-1RA or if GLP-1RA not appropriate, consider insulin
- **Insulin is preferred as first injectable *if* A1C ≥ 10%, glucose >300 mg/dL or symptomatic from hyperglycemia**
  - **Start basal first**
    - 10 units once a day or 0.1-0.2 units/kg once a day
      - Increase 2 units every 3 days until fasting <130 mg/dL
  - **Start mealtime insulin *if*:**
    - *A1C still above goal despite adequate basal dose*
    - *Basal dose is >0.5unit/kg/day*
    - *Or fasting glucose at target, but high A1C*
    - Initiate 4 units or 10% of basal dose at largest meal
      - Increase 1-2 units or 10% twice a week targeting post prandial levels <180 mg/dL
    - **Stop sulfonylureas when starting mealtime insulin**

41

INSULIN COST CASE

- You receive a call from your patient who has been on Insulin Glargine U-300 (Toujeo®) 65 units once a day + metformin. She has fallen into the Medicare part D coverage gap for the rest of the year and her copay is now $200/month for her insulin. What can you do?

A. Switch Toujeo to Novolin® N BID

B. Switch Toujeo® to Novolin® 70/30 BID

C. Switch Toujeo to insulin glargine (Basaglar®)

D. Discontinue insulin until January 1st of the next year when her insurance rolls over

42

INSULIN COST CONCERNS

- Cash price can vary significantly between pharmacies
- Basaglar® box of 5 pens (1500 units) = ~$250
- Tresiba® U-200 box of 3 pens (1800 units) =~$630
- Humalog® Box of 5 pens (1500 units) = ~$330
- Admelog® Box of 5 pens (1500 units) = ~$469
- Novolin® N or R one 10 mL vial (1000 units)= $25 at Walmart
- Patients with insurance will pay similar copays regardless of the insulin
- Insulin manufacturers have increased availability of patient assistance programs for un-insured patients and caps on copays for commercially insured patients
  - Medicare part D patients will enter into the donut hole early in the year and their % copay may be unaffordable
    - Can switch to NPH or Regular during that time of the year

43

INSULIN PATIENT ASSISTANCE PROGRAMS

- http://www.sanofipatientconnection.com
- https://www.lillycares.com
- https://www.novocare.com/diabetes-overview/let-us-help/pap.html

44