Non-Injectable Diabetes Medications/Medication Algorithms

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Disclosures

None to report

Objectives

- Discuss benefits and risks of diabetes medications presented during this course.
- Define the role of newer diabetes medications in therapy.
- Identify patients who may benefit from certain diabetes medications.

Hyperglycemia

Triumvirate

- Beta-cell: Impaired/decreased insulin secretion
- Liver: Increased Hepatic glucose production
- Muscle: Decreased glucose uptake

Ominous Octet

- Same as above PLUS
  - Decreased incretin effect (brain)
  - Increased Lipolysis (adipose)
  - Increased glucose reabsorption (kidney)
  - Neurotransmitter dysfunction (brain)
  - Increased glucagon secretion (islet alpha cell)

DeFronzo RA. Diabetes. 2009 Apr; 58(4): 773–795.

Hyperglycemia

The Egregious Eleven

1. Pancreatic Beta Cells (decreased beta cell function and mass = decreased insulin)
2. Incretin Effect
3. Alpha cell defect: increased glucagon
4. Adipose: Increased lipolysis
5. Muscle: Decreased peripheral muscle uptake
6. Liver: Increased glucose production
7. Brain: Increased appetite, Decreased morning dopamine surge
8. Colon/biome: Abnormal microbiota; possible decreased GLP-1 secretion
9. Immune dysregulation/inflammation: decrease amylin
10. Stomach/small intestine: Increased rate of glucose absorption
11. Kidney: Increased glucose reabsorption

Schwartz SS, et al. Diabetes Care 2016:39(2)

Treating Diabetes

Treating to target blood glucose/A1c

Also need to think pathophysiologically with medication targets

Don't forget the lifestyle changes: diet, physical activity

Pathophysiological Targets

Biguanides (metformin)
- Liver
- Colon (?)

Insulin Secretagogues (Sulfonylureas)
- Pancreas: Beta cell

TZDs
- Peripheral tissue
- Liver
- Fat

DPP4-inhibitors
- Liver
- Pancreas- Alpha and Beta cells

GLP-1 agonists
- GI tract – stomach/small intestine
- Colon (?)
- Liver
- Pancreas – alpha and beta cells

SGLT-2 inhibitors
- Kidney

Alpha Glucosidase Inhibitors*
- GI tract – stomach/small intestine

Dopamine agonists*
- Brain

Cornell S, et al. Postgrad Med. 2012;124:84-94.
Schwartz SS, et al. Diabetes Care 2016:39(2)

* Not commonly used

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

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

*For agentspecific dosing recommendations, please refer to the manufacturers' prescribing information. †FDA approved for CVD benefit. CHF, congestive heart failure; CV, cardiovascular; DPP4, dipeptidyl peptidase 4; DKA, diabetic ketoacidosis; GLP1 RAs, GLP1 receptor agonists; NASH, nonalcoholic steatohepatitis; SQ, subcutaneous; T2DM, type 2 diabetes.

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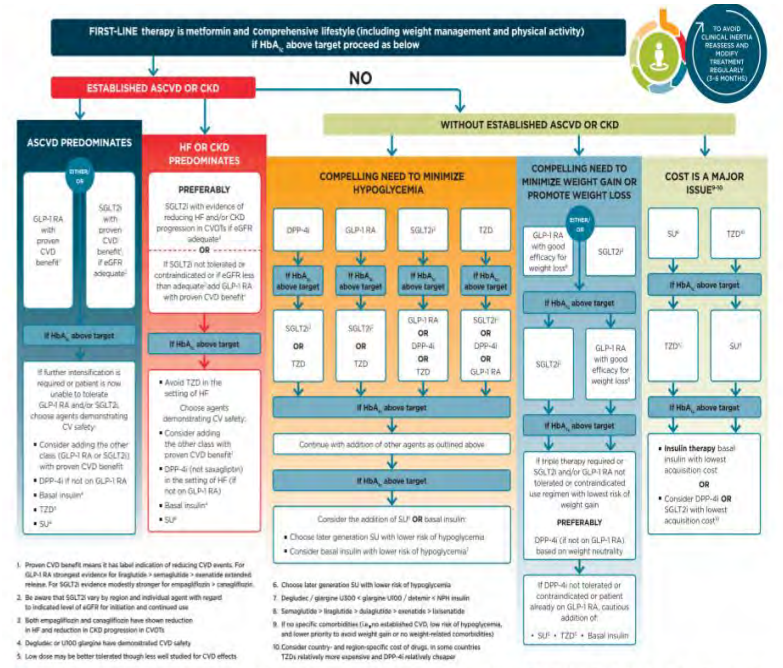

FIGURE 3. Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see Figure 1. CV, cardiovascular; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, GLP-1 receptor agonist; HbA_{1c}, glycated hemoglobin; HF, heart failure; SGLT2i,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

Diabetes Care 2019
Jan; 42(Supplement 1): S1-S2.

AACE/ACE Guidelines

MONOTHERAPY (ENTRY A1C <7.5%)

- Metformin
  - GLP1-RA
  - SGLT2i
    - DPP4i
    - TZD
      - AGi
        - SU

DUAL THERAPY (ENTRY A1C >7.5% OR IF NOT AT GOAL ON MONOTHERAPY)

Metformin (or other 1st line agent) plus

- GLP1-RA
- SGLT2i
  - DPP4i
  - TZD
    - Basal insulin
      - 3 Other medications
      - SU

AACE/ACE consensus statement. ENDOCRINE PRACTICE Vol 24 No. 1 January 2018

Metformin

Still the GOLD standard

Changes to renal disease/ dysfunction recommendations

- Previously was based on SCr cut off
- Now based on eGFR level

Consider periodic B12 monitoring

eGFR Level (mL/min per 1.73 m^2)	Action
≥ 60	No renal contraindication to Metformin Monitor renal function annually
45 – 59	Continue use Increase monitoring of renal function every 3-6 months
30 – 44	Prescribe Metformin with caution Use lower dose 50% or half of maximum dose Closely monitor renal function every 3 months Do not start new patients on Metformin
< 30	Stop Metformin

Lipska KJ, Bailey CJ, Inzucchi SE. Use of Metformin in the Setting of Mild to Moderate Renal Insufficiency. *Diabetes Care* 2011; 34: 1431-1437

Sulfonylureas

Use if cost concerns

Risk for hypoglycemia

- Increased risk in decreased renal function

Weight gain

AACE/ACE Guidelines

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AACE/ACE consensus statement. ENDOCRINE PRACTICE Vol 24 No. 1 January 2018

TZDs

Remember to avoid in patients with Heart Failure

Weight gain

Moderate fracture risk

Slow onset of action

Good A1c lowering capability

Monitor liver function prior to initiation and every 2 months for first year, periodically there after

Consider for those seeking more affordable options

DPP4 inhibitors

Inhibit breakdown/metabolism of GLP-1

Administer with or without food; Does not need to be timed around meals

Weight neutral

Adverse Effects

- Nasopharyngitis
- Upper Respiratory Tract Infection
- Headache

DPP4 inhibitor Medications

Sitagliptin – renal dose adjustment

Saxagliptin – renal dose adjustment

Linagliptin

Alogliptin – renal dose adjustment

Stop DPP4i if starting GLP-1a

DPP4 inhibitors - FDA safety review

Saxagliptin and Alogliptin

- Not recommended for use in patients with current or prior HF symptoms

"Saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease... As a result, we are adding new warnings to the drug labels about this safety issue."

https://www.fda.gov/drugs/drugsafety/ucm486096.htm

GLP-1 agonists

Mostly Subcutaneous Injections – not in scope of this talk, but...

NEW ORAL GLP-1A SEMAGLUTIDE RECENTLY APPROVED

Better A1c reduction than DPP4i

Endogenous GLP1 in our bodies (broken down by DPP4)

- Promotes satiety, reduces appetite
- Decreases postprandial glucagon secretion
- Decreased glucagon reduces hepatic glucose output
- Slows gastric emptying in the stomach
- Enhances glucose-dependent insulin secretion

GLP1a: mimic endogenous GLP1 and additionally are resistant to DPP4 degradation

GLP-1 agonist oral

Side effects
- Nausea
- Vomiting
- Diarrhea
- Headache
- Weight loss

- Titration
- 3mg po qd x 30 days
- After 30 days on 3mg dose, increase the dose to 7mg qd
- Dose may be increased to 14mg qd if additional glycemic control is needed after at least 30 days on 7mg dose

Administration
- Take at least 30 minutes before first food, beverage, or other oral medications of the day with no more than 4 ounces of plain water only

Black Box Warning
- Medullary Thyroid Cancer

Preferred by AACE/ACE guidelines for add on therapy or as first line if metformin not an option

AACE/ACE consensus statement. ENDOCRINE PRACTICE Vol 24 No. 1 January 2018; FDA package insert for Rybelsus

SGLT-2 inhibitors

Lowers renal threshold of glucose
- insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2

Weight loss

Decreased blood pressure

Cardiovascular Benefits

Renal Benefits

SGLT-2 inhibitors

Adverse Effects

- Urinary Tract Infections
- Yeast infections, genital mycotic infections
- Hypovolemia/Decreased blood pressure
- Hyperkalemia
- Increased LDL cholesterol
- Hypoglycemia with Empagliflozin
- FDA Safety Announcement: may lead to ketoacidosis (05-15-2015)
- August 2018: FDA Warns of Serious Genital Infection With SGLT2 Inhibitors: necrotizing fasciitis of the perineum in patients taking SGLT2i

https://www.fda.gov/downloads/drugs/drugsafety/ucm446954.pdf
https://www.fda.gov/Drugs/DrugSafety/ucm617360.htm

SGLT-2 inhibitors: Canagliflozin

- 100 mg once daily
- May increase to 300 mg once daily in patients who require additional glycemic control

Renal dose adjustments

- Do not use if eGFR is persistently less than 45 mL/min/1.73 m2
- Do not use 300mg dose if eGFR 45-60

Increased risk of leg and foot amputations: FDA warning

As of October 2018: FDA approved canagliflozin to reduce the risk of heart attack, stroke or cardiovascular death in adults with Type 2 Diabetes and established cardiovascular disease

FDA approved to treat diabetic kidney disease and reduce risk of hospitalization for heart failure in patients with T2D and diabetic kidney disease

https://www.fda.gov/downloads/drugs/drugsafety/ucm558427.pdf
https://www.janssen.com/us-fda-approves-invokanar-canagliflozin-reduce-risk-heart-attack-stroke-or-cardiovascular-death

SGLT-2 inhibitors: Dapaglifozin

5 mg once daily

- May increase to 10 mg once daily in patients who require additional glycemic control
- No dosage adjustment is needed in patients with eGFR ≥45mL/min/1.73m2
- Use is not recommended in patients with eGFR <45mL/min/1.73m2 and is contraindicated in those with eGFR <30mL/min/1.73m2

Slow progression of kidney failure and prevent cardiovascular and renal death in patients with CKD

DECLARE-TIMI 58 Trial

- Dapagliflozin significantly reduced hospitalization for heart failure or CV Death in a broad patient population with Type 2 Diabetes in the Landmark DECLARE-TIMI 58 Trial
  - Fewer MACE events observed with dapagliflozin vs. placebo, but this finding did not reach statistical significance
  - No imbalance in amputations, fractures, bladder cancer or Fournier's gangrene with dapagliflozin vs. placebo

FDA approved to cut risk of hospitalization for heart failure in T2D

Wiviott S et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019; 380:347-357

SGLT-2 inhibitors: Empagliflozin

10mg daily

- May increase to 25mg daily

If eGFR is less than 45 mL/minute/1.73 m2: Do not use

FDA approved indication to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease

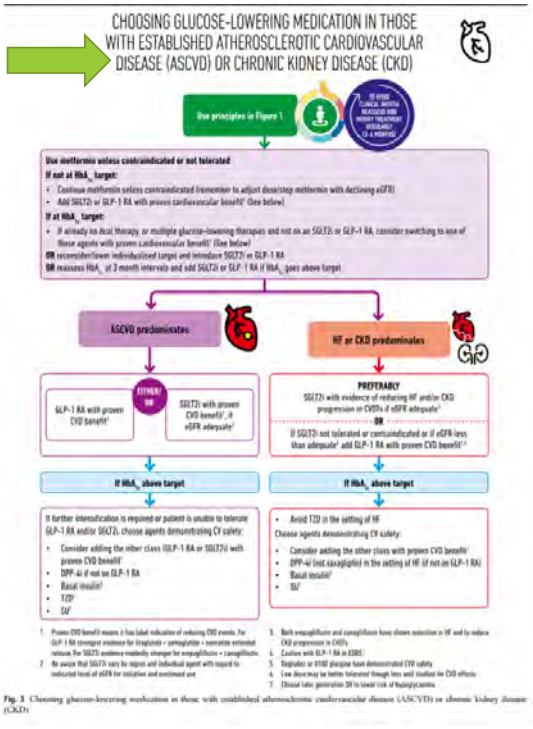
Improved renal outcomes

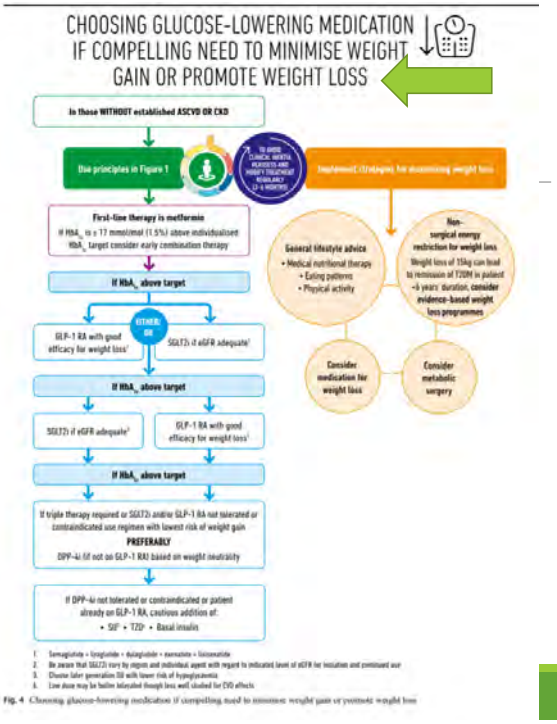
https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm531517.htm

SGLT-2 inhibitors: Ertugliflozin

Steglatro

- 5 mg once daily
  - May increase to 15 mg once daily
- Not recommended: eGFR <30 mL/minute/1.73 m2





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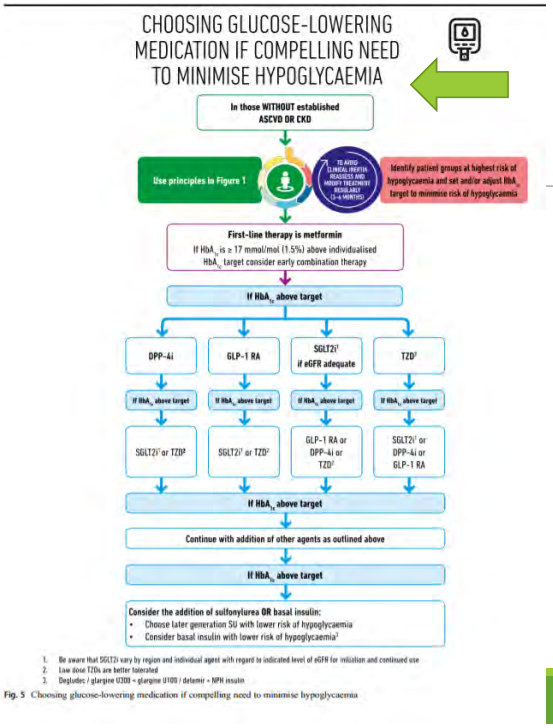

Fig. 5 Choosing glucose-lowering medication if compelling need to minimise hypoglycaemia

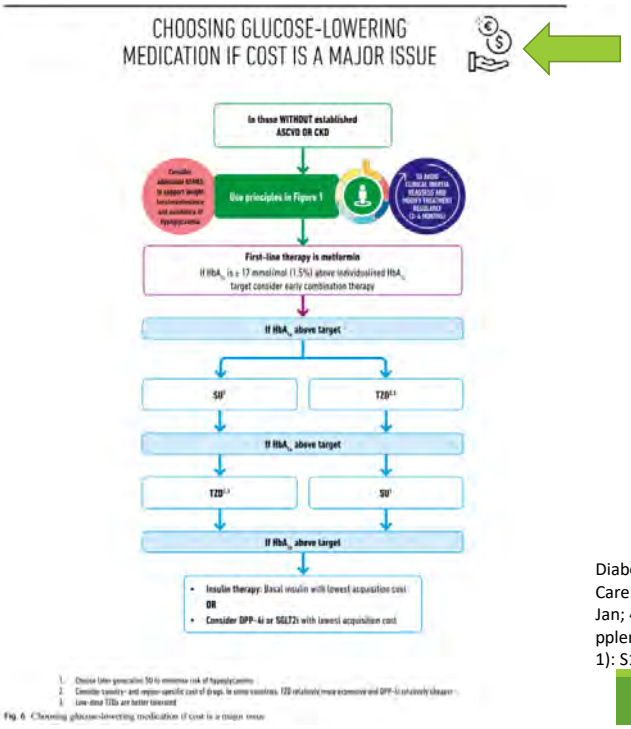

Fig. 6 Choosing glucose-lowering medication if cost is a major issue

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Take home points

New therapies coming out frequently

New guidelines yearly

- Also consider patient preference and characteristics (age, co-morbidities, etc)

Medications plus lifestyle modifications

Newer medications can address other conditions (cardiovascular, obesity)

Limited use for sulfonylureas (cost)

Try to minimize risk of hypoglycemia, weight gain, drug interactions, side effects

We can recommend what we think is the best medication, but truly the best medication is one that the patient will take correctly

Thank you!

Any questions?