Diabetes Medication Update

Megan Mack, PharmD

Objectives

- Discuss the categories of medications currently available to treat diabetes
- Discriminate the key components of newer diabetes medications, including patient education information

Types of Medications Available

- Agents that Increase Insulin Sensitivity
  - Biguanides
  - Thiazolidinediones
- Insulin Secretagogues
  - Sulfonylureas
  - Meglitinides/Glinides
- Incretin-based Therapies
  - DPP-4 Inhibitors
  - GLP-1 Receptor Agonist
- Other Agents
  - SGLT2 Inhibitors
  - α-Glucosidase Inhibitors
  - Amylin Analog
  - Bile Acid Sequestrant
  - Dopamine Agonist
  - Insulin
  - Combination Agents

Biguanides

Metformin (Glucophage)

- Decreases hepatic glucose production, enhances insulin sensitivity
- 1st line agent
- IR for BID dosing, ER for QD dosing

Advantages

- Lowers A1c by 1.5% - 2%
- Low risk for hypoglycemia
- Weight neutral/loss
- ⇩ CVD risk
- Cost

Disadvantages

- GI side effects- minimize by slowly titrating dose, take with meals
- Vitamin B12 deficiency in long term
- Contraindicated in SCr ≥1.5 mg/dL in men, ≥1.4 mg/dL in women
- Risk of lactic acidosis – Rare
- Must be temporarily discontinued if receiving IV contrast

Biguanide Counseling Points

- Metformin must be temporarily stopped before having a scan with IV contrast.
- Take with meals to minimize stomach discomfort.
- Stop taking the medication if you experience nausea, vomiting, or dehydration.
- Long term use is associated with Vitamin B12 deficiency.
- Swallow XR tablets whole. Breaking the pill causes too much medicine to be released at once.
- Some forms of XR metformin may leave a shell of medicine in your stool. This is normal
- Taking metformin may cause rare, but serious lactic acidosis. Get emergency medical help if you experience any of the following symptoms: weakness, increasing sleepiness, slow heart rate, cold feeling, muscle pain, shortness of breath, stomach pain, feeling light-headed, or fainting.

Thiazolidinediones

- Increase insulin sensitivity in muscle, hepatic & adipose tissues
- Slow progressive deterioration of ß-cell function
- Mixed data on CVD effects (some benefits for pioglitazone)
  - Pioglitazone (Actos) – small increased risk of bladder cancer
  - Rosiglitazone (Avandia) – observational studies showed increased CVD risk

Thiazolidinediones

Advantages

- Lowers A1c by 1% - 1.5%
- Low hypoglycemia risk
- ⇩ triglycerides (pioglitazone)

Disadvantages

- Weight gain
- Edema/heart failure
- Bone fractures
- ⇧ LDL-C with rosiglitazone
- Increased risk of bladder cancer

TZD Counseling Points

- This medicine may take several weeks to lower your blood sugars.
- Contact your doctor right away if you are passing dark-colored urine, have pale stools, feel more tired than usual, or if your skin and/or the whites of your eyes become yellow. These may be signs of liver damage.
- This medicine may cause water retention. This can lead to swollen ankles and difficulty breathing. If this happens, inform your health care provider right away.

Sulfonylureas (2nd generation)

- Stimulate insulin secretion from pancreatic ß-cells
- First agents on the market
- Generally used in combination with other antihyperglycemic agents
  - Glipizide (Glucotrol) – metabolized in liver into inactive metabolites
  - Glyburide (Diabeta, Mirconase) – partially active metabolite accumulates in renal dysfunction, not recommended in patients with CrCl <50, not recommended in elderly due to hypoglycemia risk
  - Glimepiride (Amaryl)

Sulfonylureas

Advantages

- Lowers A1c by 1.5% - 2%
- Rapid onset of action
- Cost

Disadvantages

- High risk of hypoglycemia
- Weight increase
- ß-cell burnout
- Contraindicated in severe renal or liver disease

Sulfonylurea Counseling Points

- Swallow XR tablets whole.
- Take IR tablets 30 minutes prior to first main meal of the day.
- Do not skip meals while taking these medications.
- May cause low blood sugars. Always keep a source of sugar available in case you have symptoms of low blood glucose.
- Make sure you recognize the symptoms of hypoglycemia: shakiness, irritability, headache, confusion, drowsiness, weakness, dizziness, sweating, and fast heartbeat

Meglitinides

- Increase insulin secretion
- Decrease post-prandial glucose excursions
- Fast onset of action, short duration - must be taken with each meal
- Weight gain
- Contraindicated in diabetic ketoacidosis, co-administration with gemfibrozil, Type 1 Diabetes
  - Nateglinide (Starlix) – targets postprandial blood sugars
  - Repaglinide (Prandin) – considered almost as effective at lowering blood sugars as metformin or sulfonylureas

Meglitinide Counseling Points

- Starlix should not be taken with NPH insulin.
- Take this medication 15 minutes, but no longer than 30 minutes, before a meal.
- Only take this medication when having a meal. Skip or add doses according to your meals as appropriate.
- This medication may cause hypoglycemia. Always keep a source of sugar available in case you have symptoms of low blood glucose

DPP-4 Inhibitors

- Increase insulin secretion & decrease glucagon secretion
- Oral agents typically used in combination with metformin
- ⇩A1c by 0.5% - 0.8%
  - Alogliptin (Nesina) - Renal dose adjustment if CrCl <60 mL/min
  - Saxagliptin (Onglyza) - Renal dose adjustment if CrCl <50 mL/min
  - Linagliptin (Tradjenta) – Do not co-administer with strong CYP3A4 inducers
  - Sitagliptin (Januvia) – Renal dose adjustment if CrCl <50 mL/min

DPP-4 Inhibitors

Advantages

- Low risk of hypoglycemia
- Mild adverse effects
- Weight neutral

Disadvantages

- Angioedema/urticaria
- Potential for acute pancreatitis
- ⇧ heart failure hospitalizations

DPP-4 Inhibitor Counseling Points

- Acute pancreatitis has been reported with use of this medicine. Contact your health care provider if you have nausea, vomiting, swollen and tender abdomen, or severe upper abdominal pain that radiates to your back.
- This medication is unlikely to cause hypoglycemia, but your risk increased when taken with sulfonylureas or insulin. Always keep a source of sugar available in case you have symptoms of low blood glucose.

GLP-1 Receptor Agonists

- Mimic the action of glucagon-like peptide
- Increase insulin secretion & decrease glucagon secretion
- ⇩ A1c by 1% - 1.5%
- Slow gastric emptying
- Increase satiety
- semaglutide (Wegovy), liraglutide (Saxenda) FDA approved for weight loss in patients with a BMI of >30 or >27 with one or more weight associated comorbidity (HTN, dyslipidemia, etc)

GLP-1 Receptor Agonists

Medication	Administration	Comments
Exenatide IR (Byetta)	SubQ Twice Daily	-Administer within 60 min prior to AM and PM meals (at least 6 hours apart) -Not recommended in patients with ESRD or with CrCl <30
Exenatide ER (Bydureon BCise)	SubQ Once Weekly	-Administer without regard to meals on same day each week -Not recommended in patients with ESRD or with CrCl <45 -Injection site reactions more common
Liraglutide (Victoza, Saxenda)	SubQ Once Daily	-Administer without regard to meals -0.6 mg daily dose for 7 days is not effective glycemic control
Lixisenatide (Adlyxin)	SubQ Once Daily	-Administer within 1 hour before first meal of the day -Not recommended in patients with ESRD
Dulaglutide (Trulicity)	SubQ Once Weekly	-Administer without regard to meals
Semaglutide (Ozempic, Wegovy)	SubQ Once Weekly	-Administer without regard to meals on same day each week -0.25 mg weekly dose for 4 weeks is not effective for glycemic control
Semaglutide (Rybelsus)	Orally Daily	-Administer within 30-60 min before first meal of the day with ≤4 oz water. Do not split, crush or chew tablets -3 mg daily dose for 30 days is not effective for glycemic control

GLP-1 Receptor Agonist

- Ozempic (semaglutide) now available as an 8mg/3mL device, allowing the administration of four, 2 mg doses per pen
- In late March, the FDA approved the 2 mg weekly dose of Ozempic
  - 2 mg dose lowers A1c by 2.1%
  - Adjunct to diet/exercise to improve glycemic control in those with T2DM
  - Decrease risk of major CV events in patients with T2DM and known heart disease.
- The 0.25 mg weekly dose for the first 4 weeks is crucial for the patient to tolerate the medication, but they should NOT remain on this dose as it does not result in clinically meaningful reductions in glucose levels.

Ozempic

GLP-1 Receptor Agonists

Advantages

- Low risk for hypoglycemia
- ⇩ Weight
- ⇩ Postprandial glucose excursions
- ⇩ Some CVD risk factors
- ⇩ CV event rate and mortality (liraglutide)

Disadvantages

- GI side effects
- ⇧ Heart rate
- Potential for acute pancreatitis
- C-cell hyperplasia/medullary thyroid tumors in animals
- Injectable (except Rybelsus)
- Training requirements

GLP-1 RA Counseling Points

- Common side effects include nausea, vomiting, weight loss, heartburn, dizziness, and headache. Taking with a meal may reduce these symptoms.
- This medicine may cause pancreatitis. Contact your health care provider if you have nausea, vomiting, swollen and tender abdomen, or severe upper abdominal pain that radiates to your back.
- This medicine might be associated with thyroid cancer. Contact your health care provider if you experience swelling or pain in the front of your neck, hoarseness that will not go away, or difficulty swallowing.
- This medicine can increase the risk of hypoglycemia when used in combination with sulfonylureas or insulin. Always keep a source of sugar available in case you have symptoms of low blood glucose.
- Missed dose of:
  - Bydureon – Take within 4 days of missed dose, or wait until next scheduled injection
  - Trulicity – Take within 4 days of missed dose, or wait until next scheduled injection
  - Ozempic -Take within 5 days of missed dose, or wait until next scheduled injection

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SGLT2 Inhibitors

- Blocks glucose reabsorption by the kidney, increasing glucosuria
- Lowers A1c by 0.5% - 0.8%
- Contraindicated in patients with severe renal impairment, end-stage renal disease, or on dialysis
- Should be stopped prior to scheduled surgeries to decrease risk of ketoacidosis
  - Ertugliflozin (Steglatro) – Take in the morning with or without food
  - Dapagliflozin (Farxiga) – Take in the morning with or without food
  - Empagliflozin (Jardiance) - Take in the morning with or without food
  - Canagliflozin (Invokana) – Take before the first meal of the day

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SGLT2 Inhibitors

Medication	Approved Indications
Ertugliflozin (Steglatro)	- Type 2 Diabetes
Dapagliflozin (Farxiga)	- Type 2 Diabetes - Reduce risk of hospitalization for HF in patients with **and** established CV disease or multiple CV risk factors - Reduce risk of CV death and hospitalization for adults with HF with reduced ejection fraction (HFrEF)
Empagliflozin (Jardiance)	- Type 2 Diabetes - Reduce risk of CV mortality in adults with T2DM **and** established CVD
Canagliflozin (Invokana)	- Type 2 Diabetes - Reduce CV risk in those with T2DM - Reduce risk of developing end stage renal disease in those with T2DM

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SGLT2 Inhibitors

Advantages

- Low risk for hypoglycemia
- ⇩ Weight
- ⇩ Blood pressure
- ⇩ CV event rate and mortality

Disadvantages

- Genitourinary infections, cases of urosepsis, pyelonephritis
- Polyuria
- Volume depletion/hypotension/ dizziness
- ⇧ LDL-C
- ⇧ Creatinine (transient)
- Diabetic ketoacidosis

SGLT2 Inhibitors Counseling Points

- Women taking these medications are at increased risk of vaginal fungal infections.
- Men and women are at increased risk of urinary tract infections and nasopharyngitis.
- Keep hydrated while taking these medications. This can help prevent dehydration and hypotension.
- SGLT2 inhibitors may increase LDL levels.
- While taking SGLT2 inhibitors, you will text positive for glucose in your urine.

Alpha Glucosidase Inhibitors

- Delay absorption of dietary carbohydrates
- Reduce post-prandial glucose peaks
- Minimal effect on fasting glucose
- Most effective if diet consists of at least 50% carbohydrates
- Must be taken with first bite of each meal
- Abdominal discomfort, gas, diarrhea are common
  - Acarbose (Precose) - only patients with body weight > 60 kg should be considered for dose titration above 50 mg three times daily – risk of elevated serum transaminases
  - Miglitol (Glyset) – may accumulate in renal impairment

Alpha Glucosidase Inhibitors Counseling Points

- This medicine should be taken with the first bite of every meal.
- Bloating and flatulence are common side effects. GI adverse effects typically improve with time. Low carbohydrate meals are less likely to cause GI upset.
- If hypoglycemia occurs within 2 hours of taking this medication, treat with glucose or lactose.
- Contact your doctor if you experience abdominal pain, diarrhea, mucus discharge, rectal bleeding, or constipation, as this may indicate pneumatosis cystoides intestinalis.

Amylin Analog

- Pramlintide (Symlin) – synthetic analog of human amylin
- Adjunct treatment in type 1 & 2 diabetes in patients who use mealtime insulin but failed to attain desired glucose control
- Suppresses postprandial glucose secretion, slows gastric emptying & increases satiety
- Lowers A1c by 0.2% - 0.4%
- Increases risk of insulin- induced severe hypoglycemia. May be beneficial to reduce mealtime insulin by 50% when starting pramlintide
- Contraindicated in patients with hypoglycemia unawareness and confirmed gastroparesis

Amylin Analog Counseling Points

- Inject SubQ right before a meal. Do not use if you skip a meal.
- Do not take pramlintide if you plan to eat a meal with less that 250 calories or 30 g of carbohydrates.
- May cause low blood sugars. Always keep a source of sugar available in case you have symptoms of low blood glucose.
- Nausea is most common during the first few weeks of starting this medication. Your doctor may slowly adjust your dose to avoid nausea.

Bile Acid Sequestrant

- Colesevelam (Welchol)
- Lowers blood sugars in Type 2 Diabetes by an unknown mechanism
- Should not be used in patients with serum TG concentration >500 mg/dL or a history of hypertriglyceridemia-induced pancreatitis
- Contraindicated in patients with a history of bowel obstructions
- Counseling Points
  - Should be taken with a meal
  - May decrease absorption of other medications. Take other medications at least 4 hours before colesevelam.

Dopamine 2 Agonist

- Bromocriptine (Cycloset)
- Improves glycemic control by an unknown mechanism
- Adverse effects: nausea, vomiting, fatigue, headache, orthostatic hypotension, syncope,
- Contraindicated in patients with syncopal migraine or patients with severe psychotic disorders
- Should not be administered to women who are breastfeeding as it may inhibit lactation.
- Counseling Points
  - Take this medication within 2 hours after waking in the morning
  - Take with food to minimize GI upset

Insulin

- Rapid-acting
  - May be administered 15 minutes before to 20 minutes after a meal
  - Associated with less hypoglycemia between meals
- Short-acting (regular)
  - May cause delayed hypoglycemia several hours after food is eaten
  - Best administered 30-45 minutes before meals
- Intermediate-acting (NPH)
  - Distinct peak and trough, requires 2 or more injections per day
- Long-acting
  - Once daily dosing in most patients

Rapid Acting Insulin

Insulin	Form	Onset	Peak	Duration
Insulin aspart (Novolog)	Analog	10-20 min	30-90 min	3-5 hours
Insulin aspart (Fiasp)	Analog	16.1 min	1.5-2.2 hours	5-7 hours
Insulin glulisine (Apidra)	Analog	10-20 min	30-90 min	3-5 hours
Insulin human (Afrezza) Inhaled powder	Human	3-7 min	12-15 min	2.5-3 hours
Insulin lispro (Humalog)	Analog	10-20 min	30-90 min	3-5 hours
Insulin lispro U-200 (Humalog U-200)	Analog	15 min	30-90 min	3-5 hours
Insulin lispro (Admelog)	Analog	15 min	2.1 hours	6.9 hours
Insulin lispro-aabc (Lyumjev)	Analog	15-17 min	2-2.9 hours	4.6-7.3 hours

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Regular Insulin

Insulin	Form	Onset	Peak	Duration
Regular (Humulin R)	Human	30-60 min	2-4 hours	5-8 hours
Regular (Novolin R)	Human	30 min	80-120 min	Up to 8 hours
Regular U-500 (Humilin R U-500)	Human	30 min	4-8 hours	Up to 24 hours

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Intermediate Acting

Insulin	Form	Onset	Peak	Duration
NPH (Humulin N)	Human	1-3 hours	8 hours	12-16 hours
NPH (Novolin N)	Human	90 min	4-12 hours	Up to 24 hours

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Long Acting

Insulin	Form	Onset	Peak	Duration
Insulin detemir (Levemir)	Analog	1.6 hours	No peak	Up to 24 hours
Insulin glargine U-100 (Lantus)	Analog	1 hour	No peak	24 hours
Insulin glargine U-100 (Basaglar)	Analog	1 hour	No peak	24 hours
Insulin glargine-yfgn (Semglee) Biosimilar to/interchangeable with Lantus	Analog	1 hours	No peak	24 hours

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Ultra-Long Acting

Insulin	Form	Onset	Peak	Duration
Insulin degludec U-100 and U-200 (Tresiba)	Analog	1 hour	No peak	Up to 24 hours
Insulin glargine U-300 (Toujeo)	Analog	6 hours	No peak	Up to 24 hours

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Insulin Mixtures

Insulin	Form	Onset	Peak	Duration
50% lispro protamine (NPL)/50% insulin lispro (Humalog Mix 50/50)	Analog	10-15 min	1-4 hours	16-22 hours
75% lispro protamine (NPL)/25%insulin lispro (Humalog Mix 75/25)	Analog	10-15 min	1-3 hours	16-22 hours
70% aspart protamine/30% insulin lispro (Novolog Mix 70/30)	Analog	10-20 min	1-3 hours	10-16 hours
70% NPH/30% regular (Humulin 70/30)	Human	30-60 min	1-5 hours	12-16 hours
70% NPH/30% regular (Novolin 70/30, ReliOn Novolin)	Human	30 min	4.2 hours	10-16 hours

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Insulin Pens Available - Lilly

Pen Model	Insulins	Dose Delivery	Capacity
Humalog KwikPen, Humalog KwikPen Junior	-Lispro U-100 -Lispro U-200 -Lispro protamine/Lispro, 75/25 -Lispro protamine/Lispro 50/50	-1 unit increments, up to 60 units at a time -Junior: half- unit increments, up to 30 units at a time	-U-200: 600 units -All others: 300 units
HumaPen Luxura HD	-Lispro U-100	-Half-unit increments, up to 20 units at a time	-300 units
Humulin KwikPen	-NPH -NPH/Regular 70/30 -Regular U-500	-U-500: 5 unit increments, up to 300 units at a time -All others: 1 unit increments, up to 60 units at a time	-U-500: 1,500 units -All others: 300 units
Basaglar KwikPen	-Insulin glargine U-100	-1 unit increments, up to 80 units at a time	-300 units

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Insulin Pens Available – Novo Nordisk

Pen Model	Insulins	Dose Delivery	Capacity
FlexPen	-Aspart -Aspart protamine/aspart, 70/30	-1 unit increments, up to 60 units at a time	-300 units
FlexTouch	-Detemir -Degludec U-100 and U-200	-U-100: 1 unit increments, up to 80 units at a time -U-200: 2 unit increments, up to 160 units at a time	-U-100: 300 units -U-200: 600 units
NovoPen Echo, Echo Plus	-Aspart -Detemir	-Half unit increments, up to 30 units at a time	-300 units
NovoPen 5, 6	-Aspart -Detemir	-1 unit increments, up to 60 units at a time	-300 units

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Insulin Pens Available – Owen Mumford

Pen Model	Insulins	Dose Delivery	Capacity
Autopen Classic	-Lispro	-1 unit version, up to 21 units at a time -2 unit version, up to 42 units at a time	300 units
Autopen 24	-Glargine	-1 unit version, up to 21 units at a time -2 unit version, up to 42 units at a time	300 units

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Insulin Pens Available - Sanofi

Pen Model	Insulins	Dose Delivery	Capacity
SoloStar	-Glulisine -Glargine U-100 -Glargine U-300	-1 unit increments, up to 80 units at a time	-U-100: 300 units -U-300: 450 units
Max SoloStar	-Glargine	-2 unit increments, up to 160 units	-900 units

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Insulin Pens Available – Companion Medical

Pen Model	Insulins	Dose Delivery	Capacity
InPen	-Aspart -Lispro	-Half-unit increments, up to 30 units at a time	-300 units

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Combination Oral Agents

	Metformin	Sulfonylureas	TZD	DPP-4
Sulfonylurea	Glucovance (glyburide/metformin) Metaglip (glipizide/metformin)			
TZD	ActoPlus Met IR, XR (metformin/pioglitazone)	Duetact (glimepiride/pioglitazone)		
DPP-4	Jentadueto IR, XR (linagliptin/metformin) Janumet and Janumet XR (metformin/sitagliptin) Kombiglyze XR (metformin/saxagliptin) Kazano (metformin/alogliptin)		Oseni (alogliptin/ pioglitazone)	
SGLT2	Synjardy IR, XR (empagliflozin/ metformin) Xigduo XR (dapagliflozin/metformin) Invokamet XR (canagliflozin/metformin) Segluromet (Ertugliflozin and Metformin)		Glyxambi (Empagliflozin/ Linagliptin) Steglujan (Ertugliflozin and Sitagliptin)	Glyxambi (empagliflozin/ linagliptin) Qtern (dapagliflozin/ saxagliptin)
Other	PrandiMet (Metformin/repaglinide)			Qternmet (dapagliflozin/ saxagliptin, metformin)

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Glyxambi

- Empagliflozin and Linagliptin (oral medication)
  - Adjunct to diet/exercise to improve glycemic control in those with T2DM
  - Decrease risk of CV death in patients with T2DM and known heart disease.
- Lowers A1c by 1% - 1.5%
- Starting dose: Empagliflozin 10 mg/Linagliptin 5 mg once daily in the morning, with or without food
- May increase to Empagliflozin 25 mg/Linagliptin 5 mg once daily
- Not recommended with CrCl <30

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Segluromet

- Ertugliflozin and Metformin (2.5/500 mg, 7.5/500 mg, 2.5/1000mg, 7.5/1000mg)
- Adjunct to diet/exercise to improve glycemic control in those with T2DM
- Lowers A1c by 0.7%
- May increase risk of lactic acidosis
- Contraindicated in patients with CrCl <30, ESRD, or on dialysis
- Already on Metformin: Ertugliflozin 5 mg/day plus a similar total daily dose of Metformin, in 2 divided doses
- Already on Ertugliflozin: Metformin 1 g/day plus a similar total daily dose of Ertugliflozin, in 2 divided doses
- Max dose: Ertugliflozin 15 mg/Metformin 2 g per day

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Steglujan

- Ertugliflozin and Sitagliptin (5/100 mg, 15/100 mg)
- Adjunct to diet/exercise to improve glycemic control in adults with T2DM
- Lowers A1c by 1.4%
- Starting dose: ertugliflozin 5 mg/sitagliptin 100 mg once daily
- May increase to ertugliflozin 25 mg/sitagliptin 100 mg once daily if tolerated
- Contraindicated in CrCl < 30

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Synjardy

- Empagliflozin and Metformin
- Lowers A1c up to 2.1%
- Immediate release: 5/500 mg, 5/1000 mg, 12.5/500 mg, 12.5/1000 mg
- Extended release: 5/1000 mg, 10/1000 mg, 12.5/1000 mg, 25/1000 mg
- Administered twice daily for IR and once daily for XR
- Max dose: Empagliflozin 25 mg/Metformin 2 g per day
- May increase risk of lactic acidosis
- Contraindicated in patients with CrCl <30, ESRD, or on dialysis

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Xigduo XR

- Dapagliflozin IR and Metformin ER (5,500 mg, 10/500 mg, 2.5/1000 mg, 5/1000 mg, 10/1000 mg)
- Lowers A1c by up to 2%
- For glycemic control: start at dapagliflozin 5 mg/Metformin 500 mg daily and increase as tolerated
- For risk reductions for heart failure: dapagliflozin 10 mg plus appropriate dose of Metformin
- Max dose: dapagliflozin 10 mg/Metformin 2000 g daily
- Contraindicated in patients with CrCl <30, ESRD, or on dialysis

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Combination Injectable Agents

- Soliqua (Insulin glargine/lixisenatide)
- Xultophy (Insulin degludec/liraglutide)

Soliqua

- Insulin glargine 100 U/lixisenatide 33 mcg per mL
- Lowers A1c by 0.5%
- Uncontrolled on <30 units daily of basal insulin (with or without a GLP-1 agonist): Start with 15 units (insulin glargine) SQ once daily.
- Uncontrolled on 30-60 units/day of basal insulin: Start with 30 units (insulin glargine) SQ once daily.
- Adjust dose by 2-4 units each week.
- Maximum daily dose is 60 units insulin glargine/ 20 mcg lixisenatide per day.
- Administer within one hour before the first meal of the day.

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Xultophy

- Insulin degludec 100 U/liraglutide 3.6 mg per mL
- Lowers A1c by 1%
- Administer SQ once daily at the same time each day, without regard to meals
- Naive to basal insulin or GLP-1 therapy: start with 10 units insulin degludec/ 0.36 mg liraglutide.
- Patients currently on basal insulin or GLP-1 therapy: start with 16 units insulin degludec/ 0.58 mg liraglutide.
- Adjust dose by 2 units (insulin degludec) every three to four days
- Maximum daily dose is 50 units insulin degludec/ 1.8 mg liraglutide
- If it has been >3 days since the last dose, restart at the recommended starting dose to reduce GI symptoms.

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	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	▪ Contraindicated with eGFR <30 mL/min/1.73 m^2	▪ Gastrointestinal side effects common (diarrhea, nausea) ▪ Potential for B12 deficiency
SGLT2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin†	Benefit: empagliflozin‡, canagliflozin, dapagliflozin‡, ertugliflozin	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin§	▪ See labels for renal dose considerations of individual agents ▪ Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	▪ Should be discontinued before any scheduled surgery to avoid potential risk for DKA ▪ DKA risk (all agents, rare in T2D) ▪ Risk of bone fractures (canagliflozin) ▪ Genitourinary infections ▪ Risk of volume depletion, hypotension ▪ ↑LDL cholesterol ▪ Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Benefit: dulaglutide†, liraglutide†, semaglutide (SQ)† Neutral: exenatide once weekly, lixisenatide	Neutral	High	SQ; oral (semaglutide)	Benefit on renal end points in CVOTs, driven by albuminuria outcomes: liraglutide, semaglutide (SQ), dulaglutide	▪ See labels for renal dose considerations of individual agents ▪ No dose adjustment for dulaglutide, liraglutide, semaglutide ▪ Caution when initiating or increasing dose due to potential risk of nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting severe adverse GI reactions when initiating or increasing dose of therapy.	▪ **FDA Black Box:** Risk of thyroid C-cell tumors in rodents; human relevance not determined **(liraglutide, dulaglutide, exenatide extended release, semaglutide)** ▪ GI side effects common (nausea, vomiting, diarrhea) ▪ Injection site reactions ▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected.
DPP-4 inhibitors	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	High	Oral	Neutral	▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment ▪ No dose adjustment required for linagliptin	▪ Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected. ▪ 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: generally not recommended in chronic kidney disease ▪ 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**	High	Yes	Gain	Neutral	Neutral	Low (SQ)	SQ; inhaled	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			

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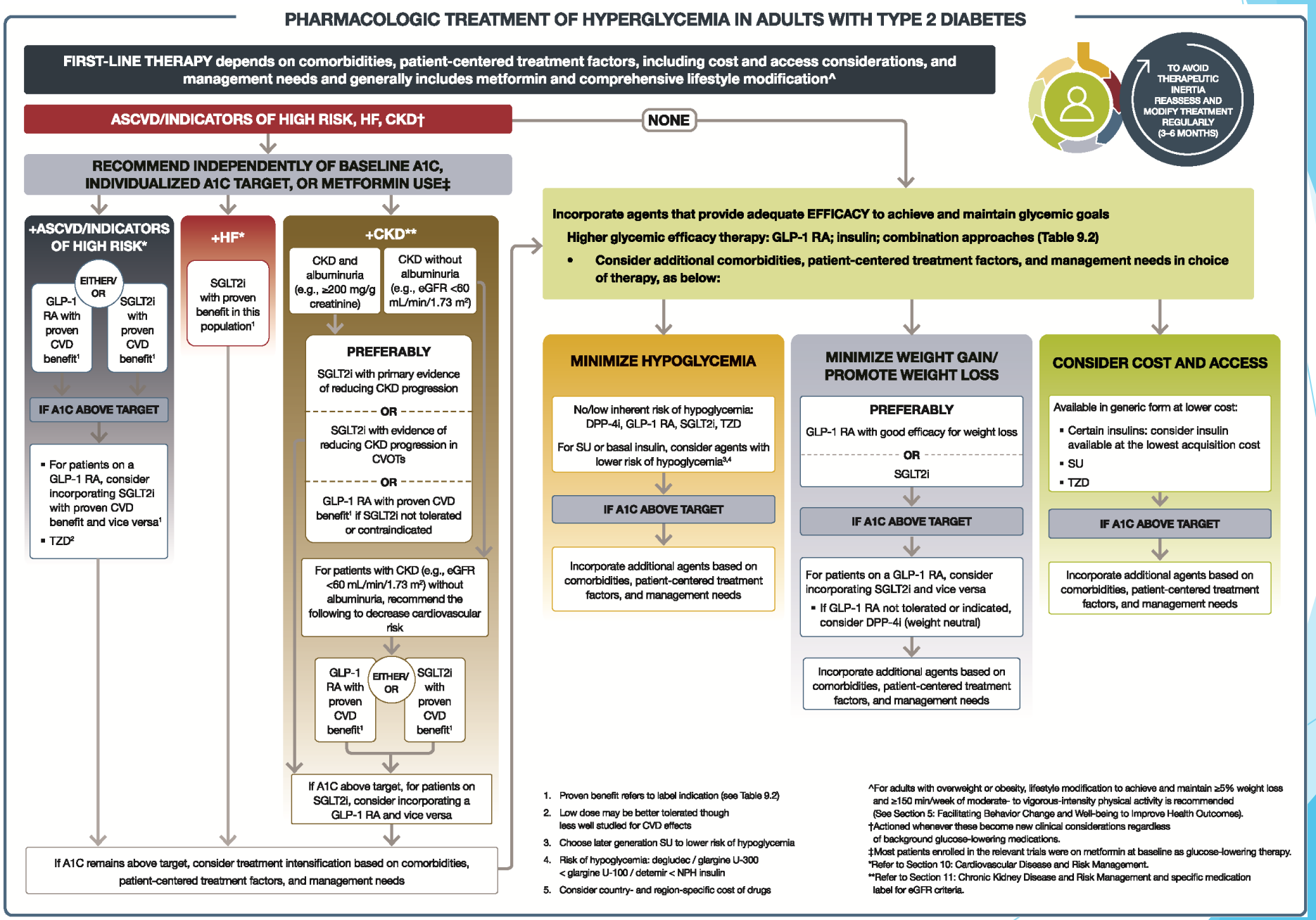
PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN ADULTS WITH TYPE 2 DIABETES
FIRST-LINE THERAPY depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and management needs and generally includes metformin and comprehensive lifestyle modification^
TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
ASCVD/INDICATORS OF HIGH RISK, HF, CKD†
NONE
RECOMMEND INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE‡
+ASCVD/INDICATORS OF HIGH RISK*
EITHER/ OR
GLP-1 RA with proven CVD benefit[1]
SGLT2i with proven CVD benefit[1]
IF A1C ABOVE TARGET
▪ For patients on a GLP-1 RA, consider incorporating SGLT2i with proven CVD benefit and vice versa[1]
▪ TZD[2]
+HF*
SGLT2i with proven benefit in this population[1]
+CKD**
CKD and albuminuria (e.g., ≥200 mg/g creatinine)
CKD without albuminuria (e.g., eGFR <60 mL/min/1.73 m²)
PREFERABLY
SGLT2i with primary evidence of reducing CKD progression
OR
SGLT2i with evidence of reducing CKD progression in CVOTs
OR
GLP-1 RA with proven CVD benefit[1] if SGLT2i not tolerated or contraindicated
For patients with CKD (e.g., eGFR <60 mL/min/1.73 m²) without albuminuria, recommend the following to decrease cardiovascular risk
GLP-1 RA with proven CVD benefit[1]
EITHER/ OR
SGLT2i with proven CVD benefit[1]
If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA and vice versa
If A1C remains above target, consider treatment intensification based on comorbidities, patient-centered treatment factors, and management needs
Incorporate agents that provide adequate EFFICACY to achieve and maintain glycemic goals
Higher glycemic efficacy therapy: GLP-1 RA; insulin; combination approaches (Table 9.2)
• Consider additional comorbidities, patient-centered treatment factors, and management needs in choice of therapy, as below:
MINIMIZE HYPOGLYCEMIA
No/low inherent risk of hypoglycemia: DPP-4i, GLP-1 RA, SGLT2i, TZD
For SU or basal insulin, consider agents with lower risk of hypoglycemia[3,4]
IF A1C ABOVE TARGET
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
MINIMIZE WEIGHT GAIN/ PROMOTE WEIGHT LOSS
PREFERABLY
GLP-1 RA with good efficacy for weight loss
OR
SGLT2i
IF A1C ABOVE TARGET
For patients on a GLP-1 RA, consider incorporating SGLT2i and vice versa
▪ If GLP-1 RA not tolerated or indicated, consider DPP-4i (weight neutral)
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
CONSIDER COST AND ACCESS
Available in generic form at lower cost:
▪ Certain insulins: consider insulin available at the lowest acquisition cost
▪ SU
▪ TZD
IF A1C ABOVE TARGET
Incorporate additional agents based on comorbidities, patient-centered treatment factors, and management needs
1. Proven benefit refers to label indication (see Table 9.2)
2. Low dose may be better tolerated though less well studied for CVD effects
3. Choose later generation SU to lower risk of hypoglycemia
4. Risk of hypoglycemia: degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
5. Consider country- and region-specific cost of drugs
^For adults with overweight or obesity, lifestyle modification to achieve and maintain ≥5% weight loss and ≥150 min/week of moderate- to vigorous-intensity physical activity is recommended (See Section 5: Facilitating Behavior Change and Well-being to Improve Health Outcomes).
†Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
‡Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.
*Refer to Section 10: Cardiovascular Disease and Risk Management.
**Refer to Section 11: Chronic Kidney Disease and Risk Management and specific medication label for eGFR criteria.

References

- American Diabetes Association. Introduction: *Standards of Medical Care in Diabetes—2022*. *Diabetes Care* 1 January 2022.
- American Pharmacists Association; Pharmacotherapy of Diabetes. The Pharmacist and Patient-Centered Diabetes Care. 2017.
- Clinical Resource. Comparison of GLP-1 Agonists. Pharmacist's Letter/Prescriber's Letter. August 2019.
- Companion Medical. InPen System Instructions for Use. 2022
- Lexi-Comp. 2022.
- Ozempic. How to Take: Ozempic Dosing. April 2022.

Questions?