What's New in Diabetes Management

A Focus on Transitions of Care

A presentation for HealthTrust Members
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Disclosures

The presenter and her preceptors have no financial relationships with any commercial interests pertinent to this presentation.

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Objectives for Pharmacists and Nurses

- Discuss indications and place in therapy for the new antihyperglycemic agents
- Identify key differences between the glucagon-like peptide 1 receptor agonists (GLP-1 RA) and the sodium-glucose cotransporter 2 inhibitors (SGLT2i)
- Describe the role of the new diabetes agents within a transitions of care plan

Objectives for Pharmacy Technicians

- Identify medications within the same class to ensure there is not duplication of therapies while obtaining medication history
- Outline common lab parameters used to assess the effectiveness of diabetes treatment
- Describe different storage requirements for recommended agents

Presentation Plan

01 Transitions of Care Considerations

02 American Diabetes Association (ADA) Guideline Updates for the management of Type 2 Diabetes

03 Review of SGLT2is

04 Review of GLP-1 RA

05 Utility of once weekly insulin icodec

Transitions of Care

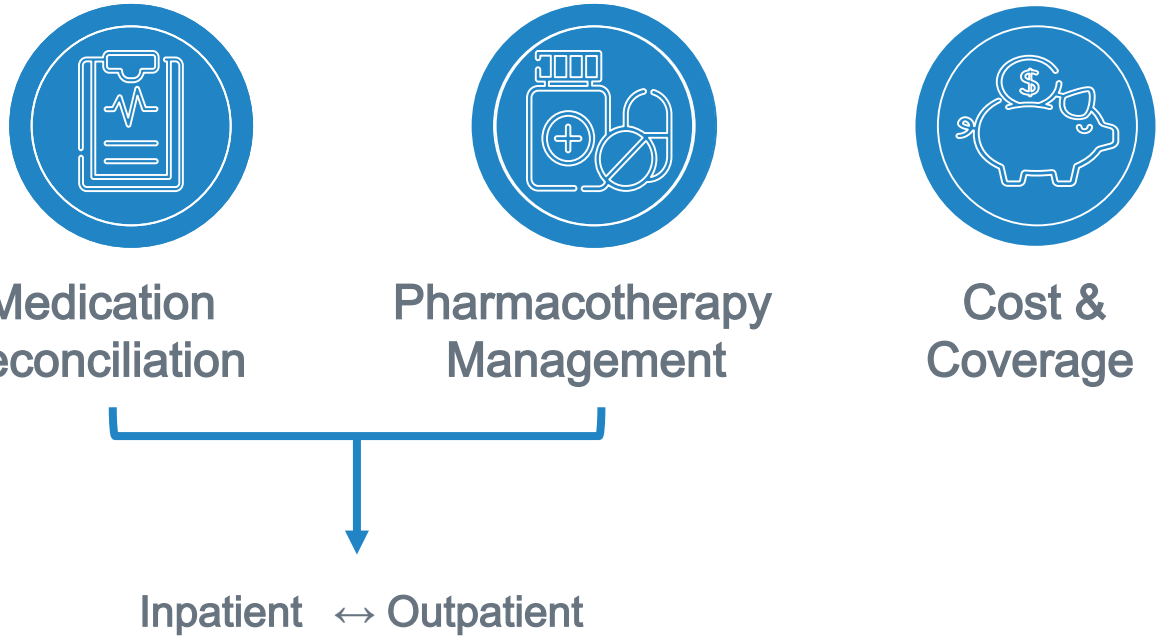
Transitions of Care

- Coordination and continuation of care as patient is transferred between setting
- Effective transitions of care
  - Patient centered
  - Promote interprofessional communication
- Errors most commonly occur in the transfer from inpatient to community setting
  - Inconsistent care coordination ≈ 20% of 30 day readmissions

Medication reconciliation must be performed at all areas of transition!

Source: Kristeller J. *Hosp Pharm* 2014;49(3):215-216.

Aspects of Transitions of Care



Medication Reconciliation

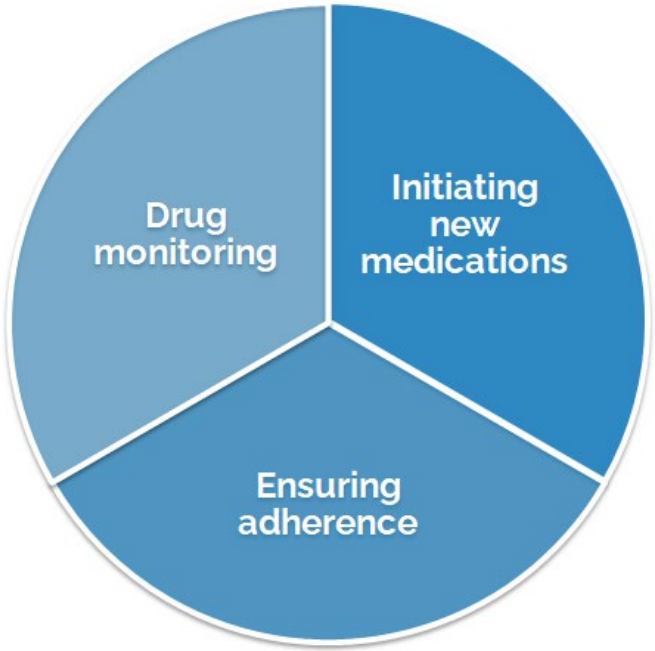
Outpatient to Inpatient

- Confirm the accuracy of prior to admission medication list
- Check the patient has an indication for all medications
- Include over-the-counter and medications taken as needed
- Assess appropriateness for reinitiation inpatient

Inpatient to Outpatient

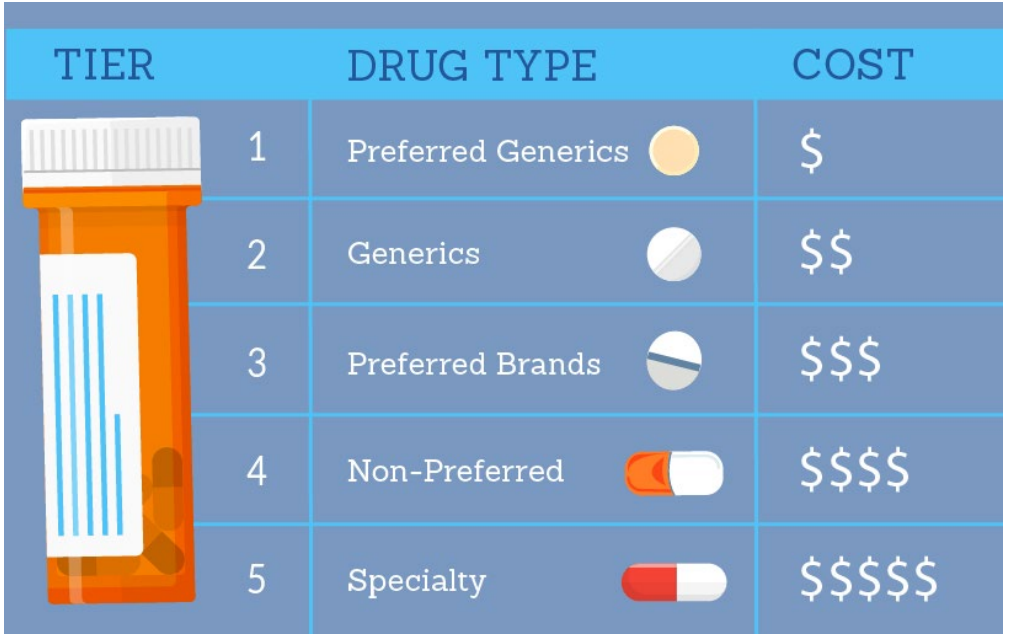
- Assess if each medication should continue upon discharge
- Ensure that the patient has access to medications
- Educate patient on changes to previous medication list

Pharmacotherapy Management



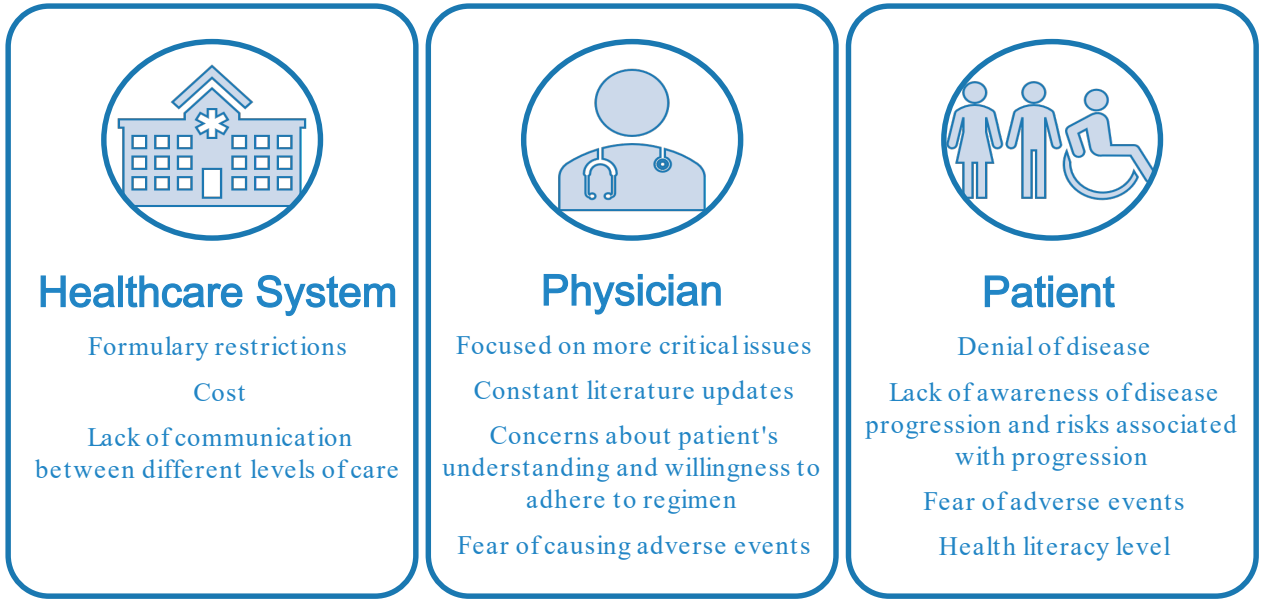
Cost & Coverage

- Insurance coverage
  - Copays
  - Coverage gaps
- Formulary availability
  - Hospital and insurance formularies



Source: Prescription drug formulary: What you need to know. Health Partners website. https://medicarehelp.healthpartners.com/blog/prescription-drug-tiers/. Updated 2021. Accessed April 10, 2021.

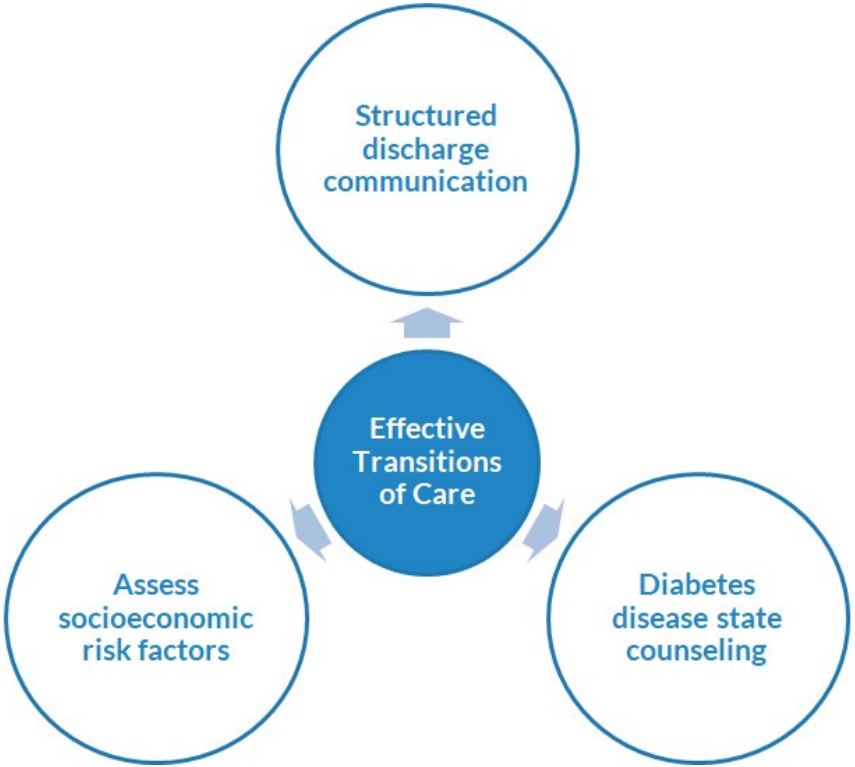
Clinical Inertia in Diabetes



- Prolonged periods of hyperglycemia are associated with…
  - Reduced life expectancy
  - Increased risk for myocardial infarction (MI), heart failure, and stroke

Source: Okemah J, et al. *Adv Ther*. 2018;35(11):1735-1745.

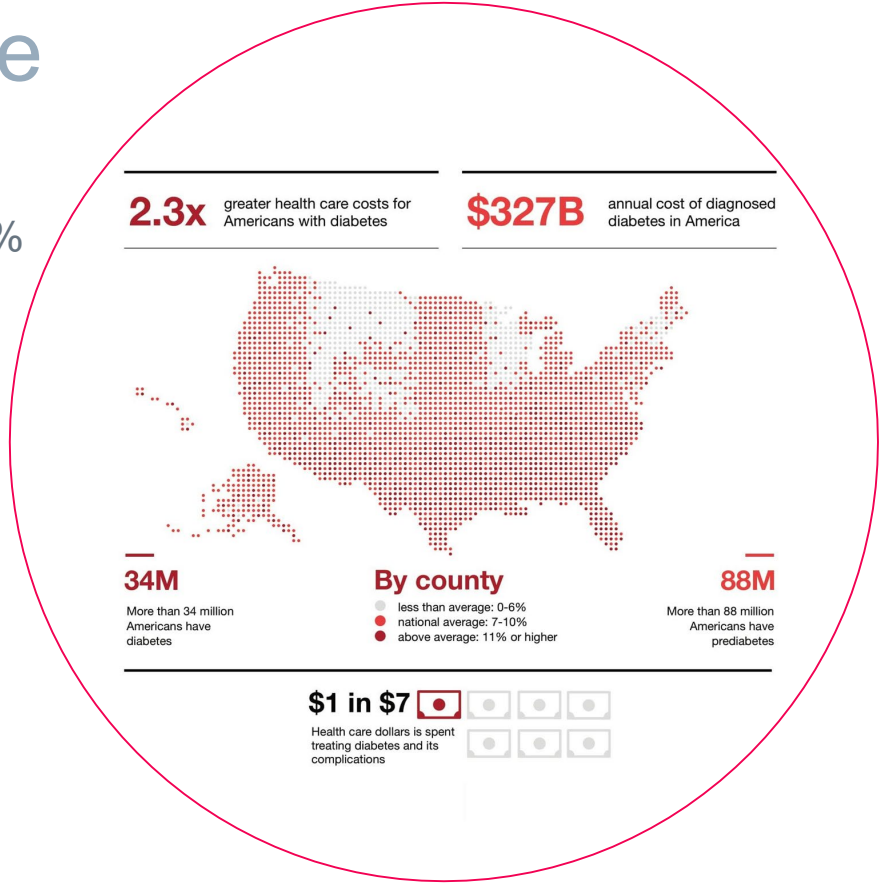
ADA Guideline Recommendations on Transitions of Care



Source: American Diabetes Association. *Diabetes Care* 2021;44(Suppl1):S211-S220.

Type 2 Diabetes in the United States

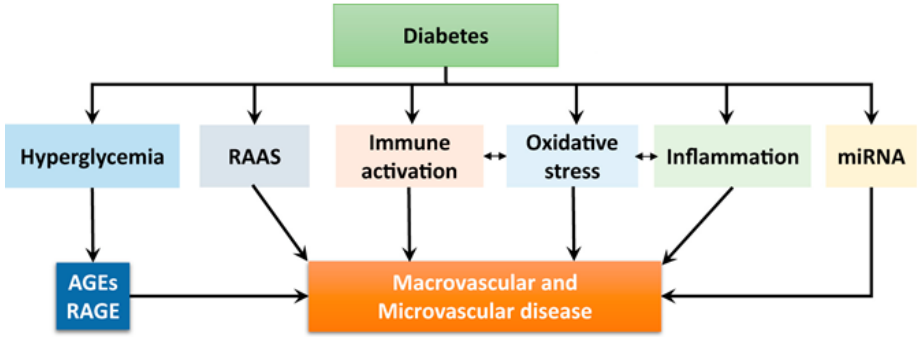
- In 2018, 34.2 million Americans (10.5% of the population) had diabetes
- 1.5 million Americans are diagnosed with diabetes every year
- Microvascular & macrovascular complications
  - Leading cause of morbidity and mortality for individuals with diabetes
  - $37.3 billion in cardiovascular-related spending per year associated with diabetes



Source: American Diabetes Association. *Diabetes Care* 2021;44(Suppl1):S7-S14.
American Diabetes Association. *Diabetes Care* 2021;44(Suppl1):S125-S150.

Management & Complications of Diabetes

- Assessing glycemic control
  - Hemoglobin A1c: < 7%
    - Measured every 3-6 months
  - Preprandial plasma glucose: 80-130 mg/dL
  - Peak postprandial plasma glucose: <180 mg/dL
- Hyperglycemia can accelerate mitochondrial production of reactive oxygen species (ROS)
- ROS interact with DNA to
  - Decrease nitric oxide production
  - Cause endothelial dysfunction
    - Increase inflammatory pathways
    - Stimulate fibrosis
    - Vasoconstriction
    - Platelet aggregation



Source: Petrie JR, et al. *Can J Cardiol* 2018;34(5):575-584.
Burgos-Morón E, et al. *Journal of Clinical Medicine* 2019;8(9):1385.
American Diabetes Association. *Diabetes Care* 2021;44(Suppl 1):S73-S84.

Complications of Diabetes

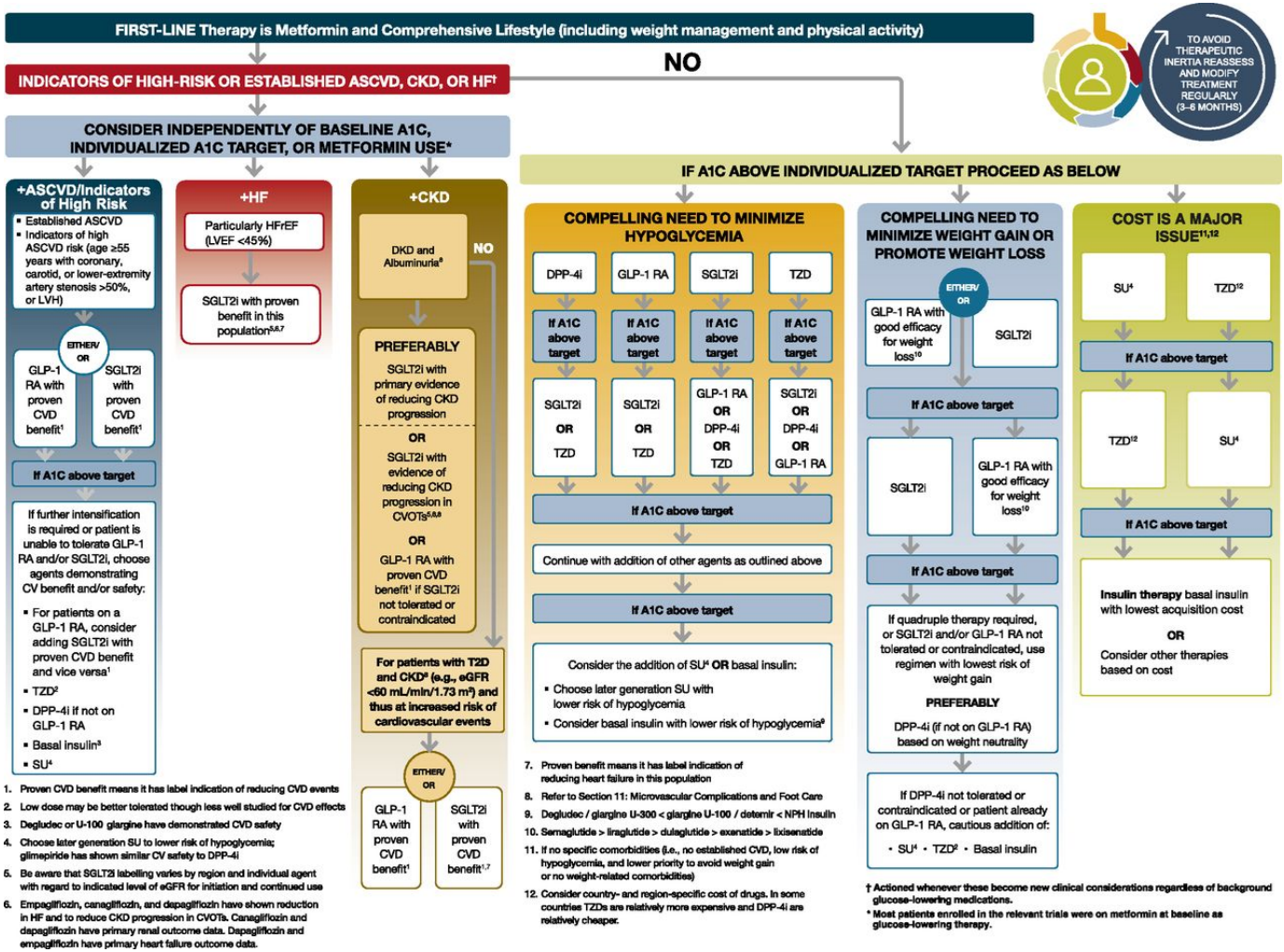
Microvascular	Macrovascular
Retinopathy	Cardiovascular
Nephropathy	Peripheral vascular disease
Neuropathy	Cerebrovascular disease

Source: Petrie JR, et al. *Can J Cardiol* 2018;34(5):575-584.
Cade WT. *Phys Ther* 2008;88(11):1322-1335.

Updates to Recent ADA Guidelines

- The choice of medication added to metformin is based on the clinical characteristics
  - Established atherosclerotic cardiovascular disease (ASCVD) or indicators of high ASCVD risk
  - Heart failure
  - Chronic kidney disease (CKD)
  - Risk for specific adverse drug effects
- Other considerations include safety, tolerability, and cost of the additional medication
- Guideline recommendations have been updated to include a dedicated decision pathways for patients with **ASCVD/ high risk**, **chronic kidney disease** and **heart failure**
- **GLP-1 RA** have been added to insulin pathway

Source: American Diabetes Association. *Diabetes Care* 2021;44(Suppl1):S111-S124.

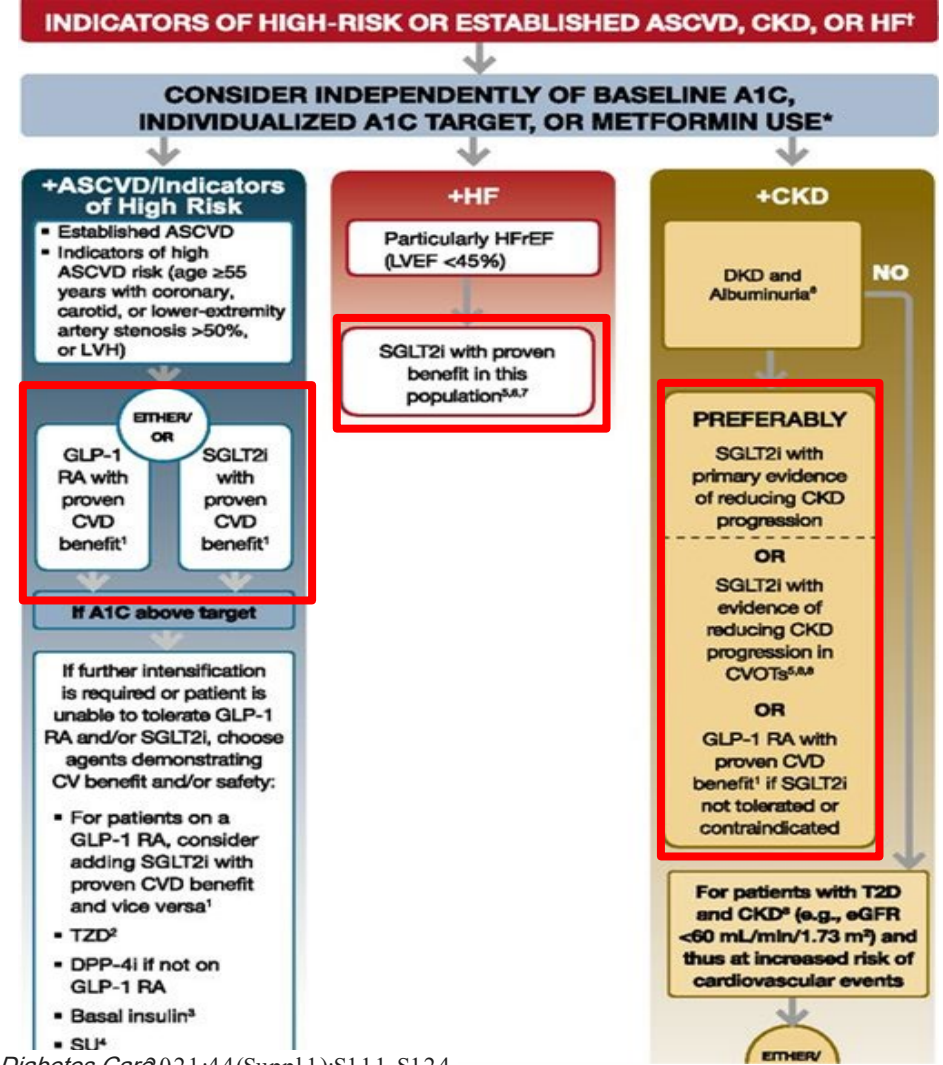


1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. 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)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

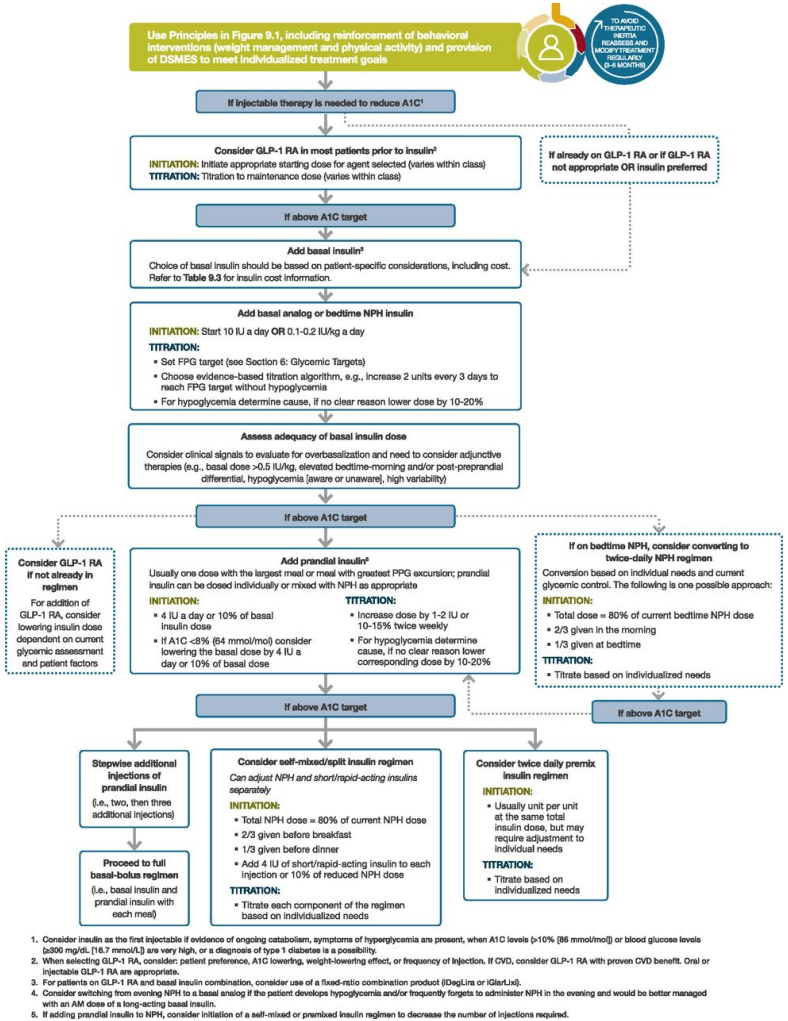
† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

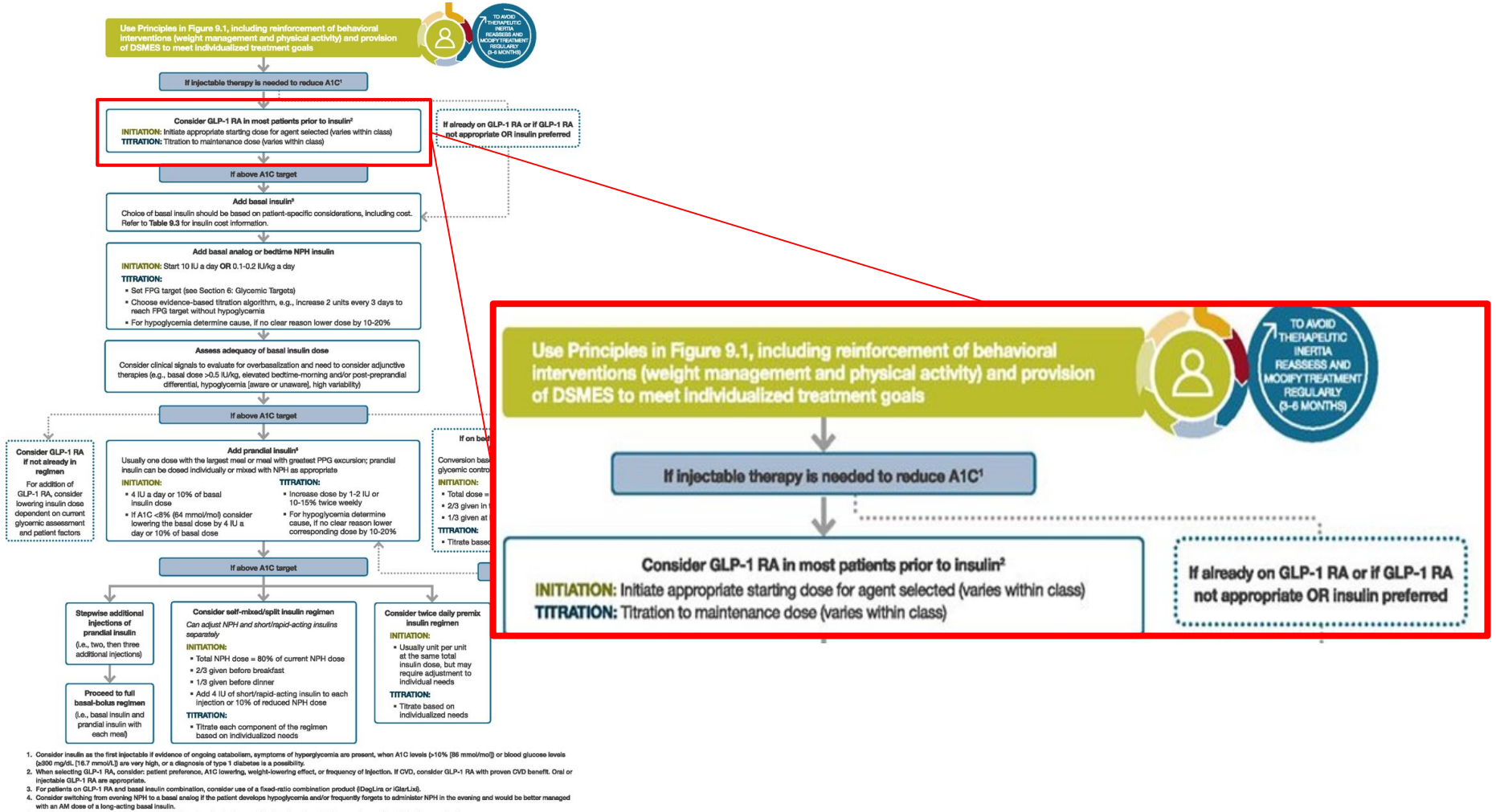
Source: American Diabetes Association *Diabetes Care* 2021;44(Suppl1):S111-S124.



Source: American Diabetes Association *Diabetes Care* 2021;44(Suppl1):S111-S124.



Source: American Diabetes Association *Diabetes Care* 2021;44(Suppl1):S111-S124.



Source: American Diabetes Association *Diabetes Care* 2021;44(Suppl1):S111-S124.

Sodium–glucose cotransporter 2 inhibitors (SGLT2i)

SGLT2 Inhibitors

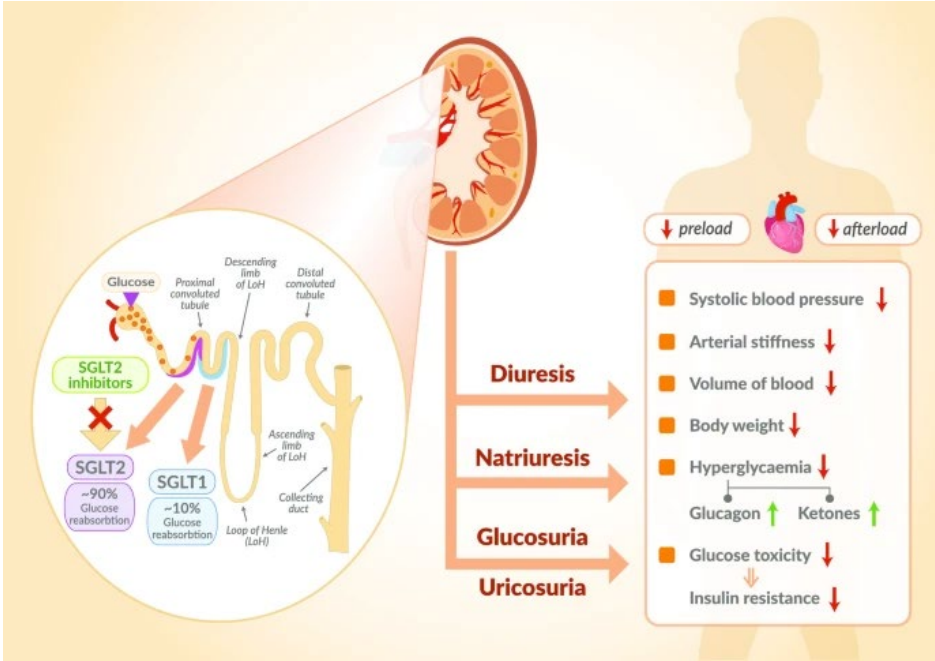
- Common suffix: "-gliflozin"
  - Canagliflozin (Invokanaé)
  - Empagliflozin (Jardianceé)
  - Dapagliflozin (Farxigaé)
  - Ertugliflozin (Steglatroé)
- A1c lowering potential
  - 0.5 - 1%
- Dosing considerations
  - Tablet
  - Dose without regard to meals
  - Renal dose adjustments required
- Storage
  - Room temperature: 25 °C or 77 °F
  - Excursions permitted between 15-30 °C or 59-86 °F

Medication	Dosing	Renal Dose Adjustment	
Canagliflozin	100 - 300 mg PO daily	eGFR 30-60 mL/min	100 mg PO daily
		eGFR < 30 mL/min	Not recommended
Empagliflozin	10 - 25 mg PO daily	eGFR < 30 mL/min	Not recommended
Dapagliflozin	5 - 10 mg PO daily	eGFR < 25 - 30 mL/min	Not recommended
Ertugliflozin	5 - 15 mg PO daily	eGFR < 30 mL/min	Contraindicated

Source: Invokana (canagliflozin) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals; July 2013
Farxiga (dapagliflozin) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; August 2014
Jardiance (empagliflozin) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; December 2016
Steglatro (ertugliflozin) [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; December 2017
American Diabetes Association. *Diabetes Care* 2021;44(Suppl 1):S111-S124.

SGLT2 Inhibitors

- Mechanism of action
  - Proximal convoluted tubule
  - Prevents reabsorption of glucose and sodium
  - Promotes glucose excretion
- Benefits
  - Weight loss
  - Minimal hypoglycemia risk
  - Heart failure, ASCVD, and diabetic kidney disease



Source:Dutka M, et al. *Heart Fail Rev*. 2020;10.1007/s10741-020-10041-1.
American Diabetes Association. *Diabetes Care*. 2021;44(Suppl 1):S111-S124.

SGLT2i: Heart Failure Benefit

Canagliflozin

CANVAS & CANVAS-Renal

10,142 patients
Type 2 diabetes and high cardiovascular risk
Canagliflozin 100 mg daily vs 300 mg vs placebo

Hospitalization for heart failure
5.5 vs 8.7 participants per 1,000 patient-years
(HR 0.67 [95% CI 0.52-0.87])

Canagliflozin

CREDENCE

4,401 patients
Type 2 diabetes and chronic diabetes related kidney disease
Canagliflozin 100 mg daily vs placebo

Hospitalizations for heart failure
15.7 vs 25.3 events per 1000 patient-years
(HR 0.61 [95% CI 0.47–0.80])

Empagliflozin

EMPA-REG OUTCOME

7,020 patients
Type 2 diabetes with established cardiovascular disease
Empagliflozin 10 mg daily vs 25 mg daily vs placebo

Hospitalization for heart failure
2.7% vs 4.1%
(HR 0.65 [95% CI 0.50–0.85])

Empagliflozin

EMPEROR- Reduced

3,730 patients
Class II-IV heart failure with EF≤ 40%
Empagliflozin 10 mg daily vs placebo
• 49.8% of patients in each group had history of diabetes

Composite of cardiovascular death or hospitalization for worsening heart failure:
19.4% vs. 24.7% (HR 0.75 [95% CI 0.65-0.86])
Hospitalizations for heart failure
(HR 0.70 [95% CI, 0.58-0.85])

Source: Neal B, et al *N Engl J Med* 2017;377(7):644-657.
Perkovic V, et al. *N Engl J Med* 2019;380(24):2295-2306.
Zinman B, et al. *N Engl J Med* 2015;373(22):2117-2128.
Packer M, et al. *N Engl J Med* 2020;383(15):1413-1424

SGLT2i: Heart Failure Benefit

Dapagliflozin

DECLARE-TIMI 58

17,160 patients

Type 2 diabetes and established ASCVD or multiple risk factors for atherosclerotic cardiovascular disease

Dapagliflozin 10 mg daily vs placebo

Hospitalization for heart failure

2.5% vs 3.3%

(HR 0.73 [95% CI 0.61–0.88])

Dapagliflozin

DAPA-HF

4,744 patients with class II-IV heart failure with ejection fraction ≤ 40%

Dapagliflozin 10 mg daily vs placebo

- 41.8% of patients had a history of type 2 diabetes in each group

Worsening heart failure

10.0% vs. 13.7%

(HR 0.70 [95% CI 0.59–0.83])

Ertugliflozin

VERTIS CV

8,246 patients

Established atherosclerotic cardiovascular disease

Ertugliflozin 5 mg daily vs 15 mg daily vs placebo

Hospitalization for heart failure

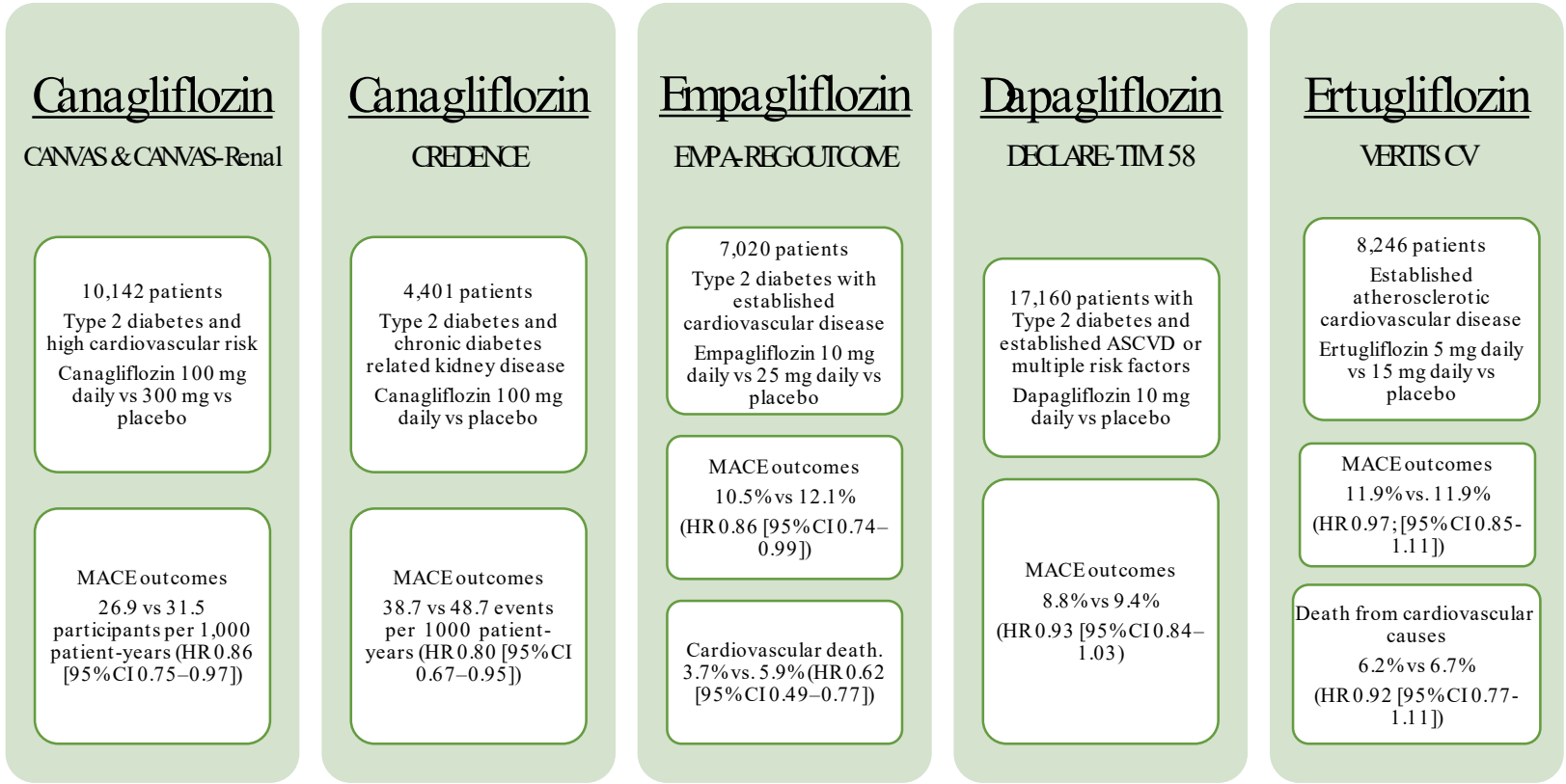
2.5% vs 3.6%

(HR 0.70; [95% CI 0.54- 0.90])

not included in statistical hierarchy

Source: Wiviott SD, et al. *N Engl J Med* 2019;380(4):347-357.
McMurray JJV, et al. *N Engl J Med* 2019;381(21):1995-2008.
Cannon CP, et al. *N Engl J Med* 2020;383(15):1425-1435.

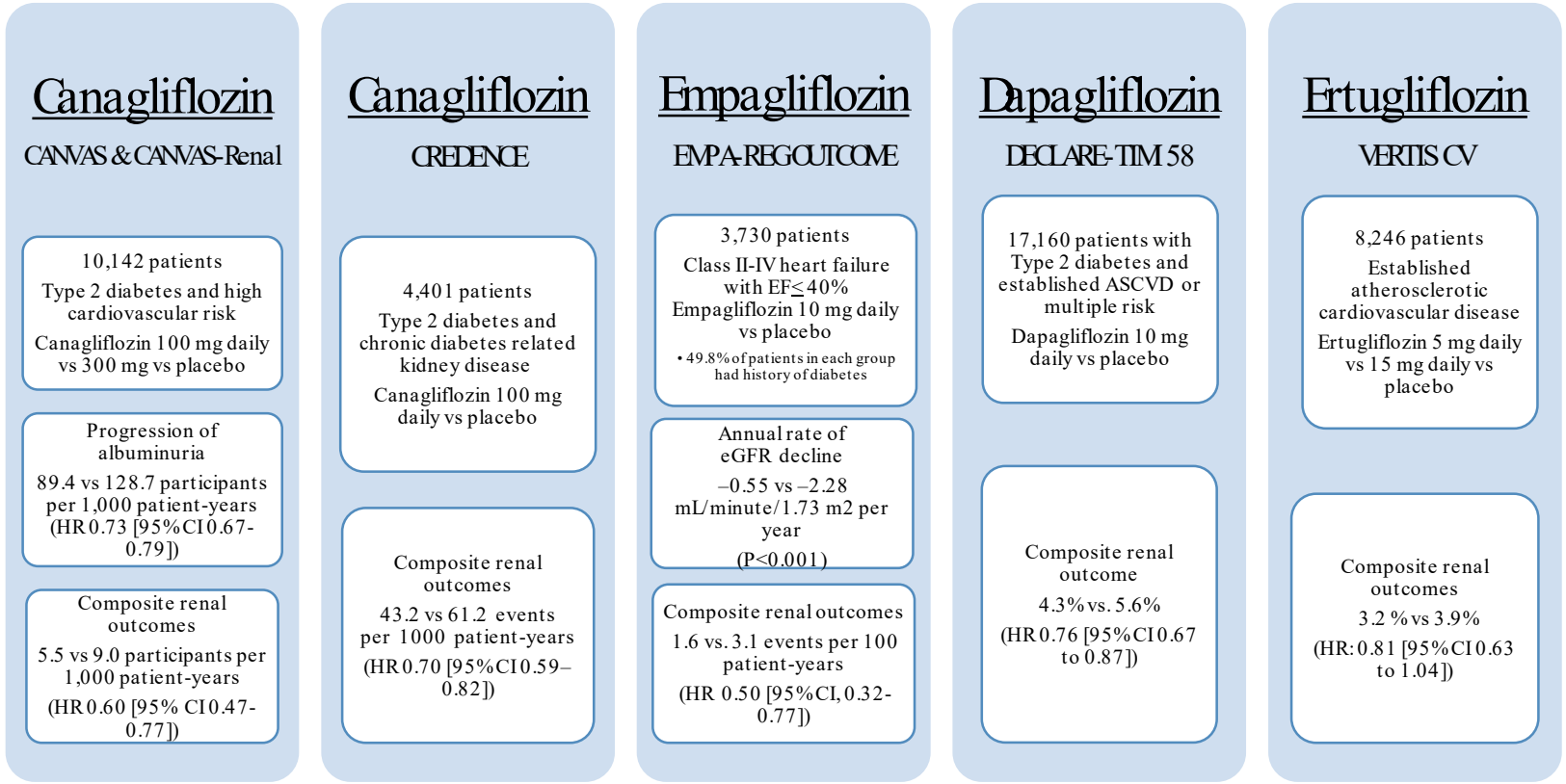
SGLT2i: ASCVD Benefit



MACE outcomes : composite endpoint including cardiovascular death, myocardial infarction, or stroke

Source: Neal B, et al. *N Engl J Med* 2017;377(7):644-657.
Perkovic V, et al. *N Engl J Med* 2019;380(24):2295-2306.
Zinman B, et al. *N Engl J Med* 2015;373(22):2117-2128.
Wiviott SD, et al. *N Engl J Med* 2019;380(4):347-357.
Cannon CP, et al. *N Engl J Med* 2020;383(15):1425-1435.

SGLT2i: Diabetic Kidney Disease Benefit



Composite renal outcome : sustained 40% reduction in eGFR, need for renal replacement therapy, doubling of serum creatine, or death from renal causes

Source: Neal B, et al. *N Engl J Med* 2017;377(7):644-657.
Perkovic V, et al. *N Engl J Med* 2019;380(24):2295-2306.
Zinman B, et al. *N Engl J Med* 2015;373(22):2117-2128.
Wiviott SD, et al. *N Engl J Med* 2019;380(4):347-357.
Cannon CP, et al. *N Engl J Med* 2020;383(15):1425-1435.

SGLT2i: Adverse Events cont.

Genitourinary infections (8-12%)

- Mechanism: glucosuria
- Genital mycotic infections and bacterial urinary tract infections
- Five-fold increase in genital mycotic infections compared to other medications

Fournier's gangrene (<1%)

- Mechanism: excess glucose in the urine allows bacteria to grow and infect the tissue under the skin that surrounds muscles, nerves, fat, and blood vessels of the perineum

Acute kidney injury (1-3%)

- Mechanism: proximal tubular natriuresis
- Risk factors: use with other renin-angiotensin-aldosterone system antagonists and traditional diuretics
    - Potential risk of AKI with canagliflozin and dapagliflozin is likely attributable to the high-risk population and not related to any inherent nephrotoxicity of these agents

Source: Lupsa BC, et al. *Diabetologia* 2018;61(10):2118-2125.
Nadkarni GN, et al. *Diabetes Care* 2017;40(11):1479-1485.

SGLT2i: Adverse Events cont.

Volume depletion (1-4%)

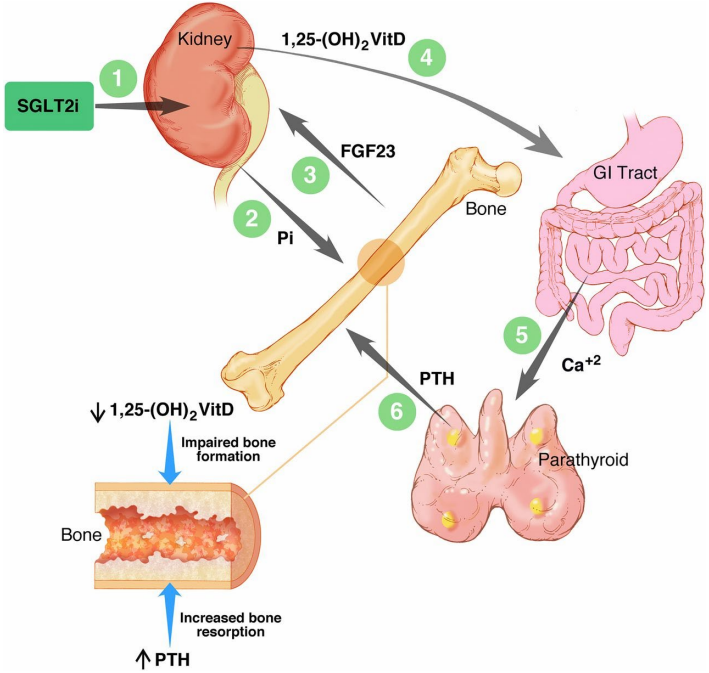
- Mechanism: osmotic diuresis
- CANVAS trial showed significant increase in canagliflozin group
- Can lead to other complications

Amputation

- Mechanism: potentially due to decreased organ perfusion in the setting of volume depletion
- Risk factors: history of amputation or peripheral vascular disease
  - CANVAS trial odd ratio = 1.97

Skeletal Fractures

- Mechanism: weight loss, impaired calcium excretion, or falls
- CANVAS trial showed significant increase in fractures
  - Odds ratio = 1.26

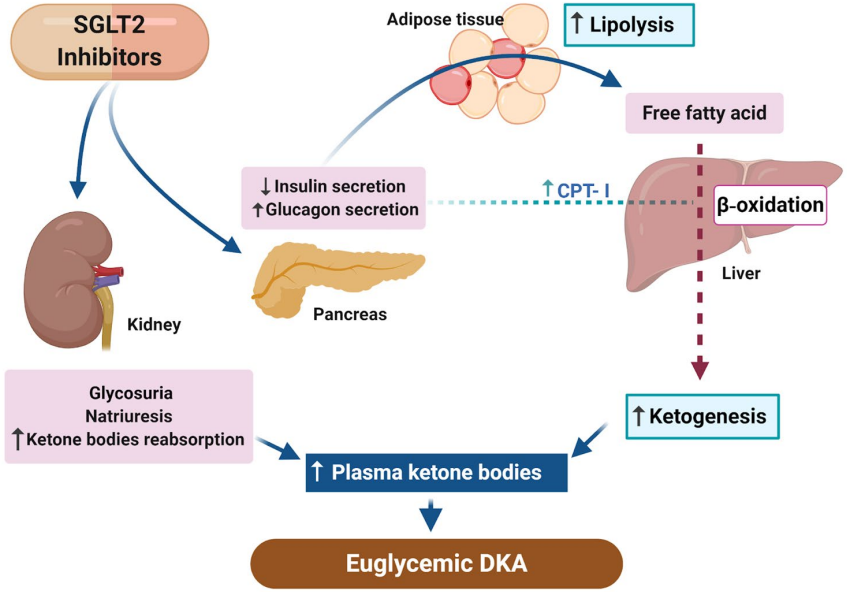


Source:LupsaBC, et al.*Diabetologia*2018;61(10):2118-2125.
Beitelshees AL, et al. *Diabetes*2019;68(6):1109-1120

SGLT2i: Adverse Events

Euglycemic diabetic ketoacidosis (<1%)

- Presentation
  - Nausea, vomiting, malaise
  - Blood glucose level: <250 mg/dL
  - Ketones in blood and urine
  - Anion-gap metabolic acidosis
    - pH <7.3, serum bicarbonate of <18mEq/L
- Exacerbated by illness, surgery, increase ethanol intake, or decreased food intake



Source:LupsaBC, et al.*Diabetologia*2018;61(10):2118-2125.
Meena P. SGLT2 Inhibitor-induced Euglycemic Diabetic Ketoacidosis. Renal Fellow Network website. https://www.renalfellow.org/2020/09/08/sglt2-inhibitor-induced-euglycemic-diabetic-ketoacidosis/. updated September 8, 2020. Accessed April 10, 2021.

SGLT2i Transitions of Care

Medication reconciliation

- Check for class duplication within combination products
- Continuation of medication
  - Assess risk for euglycemic DKA
    - Experiencing nausea, vomiting, malaise
    - Severe infection
    - Planned surgery within 3 days
    - Decreased oral intake (NPO, malnutrition)
  - Consider re-starting 1-2 days prior to discharge

Brand name	Ingredients
Invokameté	Canagliflozin and metformin
Invokamet XRé	Canagliflozin and metformin extended-release
Xigduo XRé	Dapagliflozin and metformin extended-release
Qterné	Canagliflozin and sitagliptin
Glyxambié	Empagliflozin and linagliptin
Synjardyé	Empagliflozin and metformin
Synjardy XRé	Empagliflozin and metformin extended-release
Seglurometé	Ertugliflozin and metformin
Steglujan é	Ertugliflozin and sitagliptin

SGLT2i Transitions of Care

Pharmacotherapy management

- Initiation of new medication
  - Assess for contraindications
    - History of euglycemic DKA, Fournier's gangrene
  - Consider starting 1-2 days prior to discharge if on hospital formulary
- Monitoring
  - Renal function
  - Volume status
    - Systolic blood pressure >100 mmHg
  - Weight changes
  - Adverse events
- Ensuring adherence
  - Providing education
  - Utilizing teach back

SGLT2i Transitions of Care

Cost & Coverage

- Brand only products
- Formulary coverage
  - Preferred agent
- Patient assistance program
  - Different criteria for insured patients, Medicare/ Medicaid, and uninsured patients

Compound(s)	Dosage strength/product	Median 30 day AWP	Median 30 day NADAC
Ertugliflozin	15 mg	$354	$284
Dapagliflozin	10 mg	$621	$496
Empagliflozin	25 mg	$627	$501
Canagliflozin	300 mg	$622	$499

AWP: average wholesale price
NADAC: National Average Drug Acquisition Cost

Source: American Diabetes Association *Diabetes Care* 2021;44(Suppl1):S111-S124.

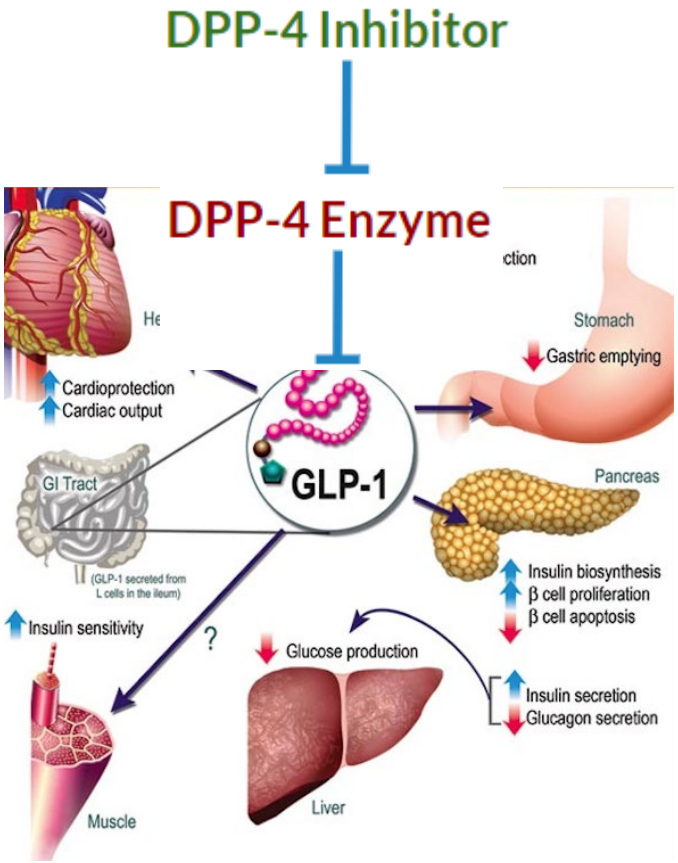
Glucagon-like peptide 1 receptor agonists (GLP-1 RA)

GLP-1 Receptor Agonists

- Common suffix: "-tide"
  - Exenatide (Byettaé, Bydureoné)
  - Liraglutide (Victozaé)
  - Dulaglutide (Trulicityé)
  - Semaglutide (Ozempicé, Rybelsusé)
  - Lixisenatide (Adlyxiné)

- A1c lowering potential
  - 0.8-1.7 %

- Mechanism of action
  - Analog of glucagon-like peptide-1
  - Increases glucose-dependent insulin secretion
  - Decreases inappropriate glucagon secretion
  - Increases B-cell growth/replication
  - Slows gastric emptying and decreases food intake



Source: Hinnen D. *Diabetes Spectr* 2017;30(3):202-210.

GLP-1 Receptor Agonists

- Dosing considerations
  - Oral tablet or subcutaneous injection
  - Twice daily, daily or weekly administration
  - Renal dose adjustment

Medication	Starting Dose	Maximum Dose	Titration	Renal Dose Adjustment
Exenatide	IR: 5 mcg SC BID prior to meal	10 mcg SC BID prior to meal	Increase to 10 mcg BID after 1 month	CrCl < 30 mL/min Not recommended
	ER: 2 mg SC once weekly			eGFR <45 mL/min Not recommended
Liraglutide	0.6 mg SC daily	1.8 mg SC daily	Increase 1.2 mg after one week, may increase to 1.8 mg if needed for glycemic control	No adjustments necessary
Dulaglutide	0.75 mg SC once weekly	4.5 mg SC once weekly	Increase to 1.5 mg after 4 to 8 weeks if needed to achieve glycemic goals. If additional glycemic control is needed, may further increase to 3 mg after at least 4 weeks and then to a maximum of 4.5 mg after at least 4 weeks	No adjustments necessary
Semaglutide	3 mg PO daily	14 mg PO daily	Increase to 7 mg after 30 days, then to 14 mg after another 30 days if needed for glycemic control	No adjustments necessary
	0.25 mg SC once weekly	1 mg SC once weekly	Increase to 0.5 mg after 4 weeks, may increase to 1 mg after an additional 4 weeks if needed to achieve glycemic goals	
Lixisenatide	10 mcg SC daily	20 mcg SC daily	Increase to 20 mcg after 14 days	eGFR < 15 mL/min Not recommended

Source: Bydureon(exenatide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2017.
Byetta (exenatide) [prescribing information]. San Diego, CA: Amylin Pharmaceuticals, Inc.; October 2009.
Victoza (liraglutide) [prescribing information]. Bagsvaerd, Denmark: Novo Nordisk Inc.; August 2017.
Trulicity (dulaglutide) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; January 2017.
Rybelsus(semaglutide) [prescribing information]. Bagsvaerd, Denmark: Novo Nordisk Inc;. September 2019.
Ozempic(semaglutide) [prescribing information]. Bagsvaerd, Denmark: Novo Nordisk Inc.; December 2017.
Adlyxin (lixisenatide) [prescribing information]. Bridgewater, NJ: Sanofi-aventis U.S. LLC; July 2016.

GLP-1 Receptor Agonists

- Storage considerations

Medication	Formulation	Prior to first use	After first use
Exenatide (IR)	Pre-filled, multi -dose pen	Refrigerated at 36ºF to 46ºF (2ºC to 8ºC)	Do not to exceed 77ºF (25ºC) Discard after 30 days
Exenatide (ER)	Single dose vial with diluent or pen	Refrigerated at 36ºF to 46ºF (2ºC to 8ºC) until expiration date on package or room temperature 77ºF (25ºC) for 4 weeks	N/A
Liraglutide	Pre-filled, multi -dose pen	Refrigerated at 36 °F to 46 °F (2°C to 8 °C)	Room Temperature 59 °F to 86 °F (15°C to 30 °C) or Refrigerated at 36 °F to 46 °F (2°C to 8 °C) Discard after 30 days
Dulaglutide	Single use pen or syringe	Refrigerated at 36 °F to 46 °F (2°C to 8 °C)	N/A
Semaglutide (tablet)	Blister packed tablets	Store at 68° to 77°F (20 to 25°C); excursions permitted to 59° to 86°F (15° to 30°C)	
Semaglutide (injection)	Pre-filled, multi -use pen injector	Refrigerated at 36 °F to 46 °F (2°C to 8 °C)	Room temperature 59 °F to 86 °F (15°C to 30 °C) or refrigerated at 36 °F to 46 °F (2°C to 8 °C) Discard after 56 days
Lixisenatide	Pre-filled, multi -use pen	Refrigerated at 36 °F to 46 °F (2°C to 8 °C)	Store below 86 °F (30°C) Discard after 14 days

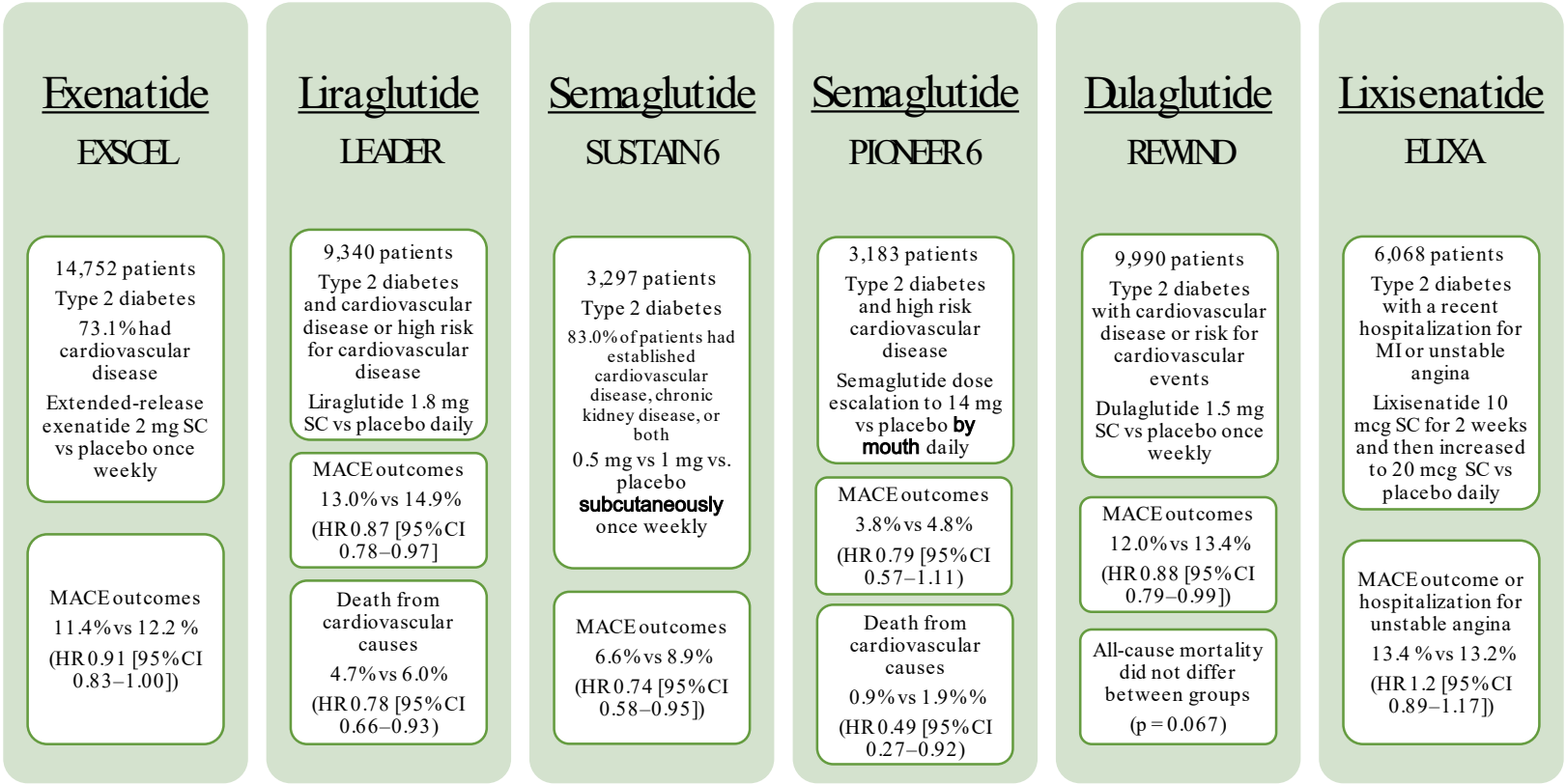
Source:Bydureon(exenatide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2017.
Byetta (exenatide) [prescribing information]. San Diego, CA: Amylin Pharmaceuticals, Inc.; October 2009.
Victoza (liraglutide) [prescribing information]. Bagsvaerd, Denmark: Novo Nordisk Inc.; August 2017.
Trulicity (dulaglutide) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; January 2017.
Rybelsus(semaglutide) [prescribing information]. Bagsvaerd, Denmark: Novo Nordisk Inc;. September 2019.
Ozempic(semaglutide) [prescribing information]. Bagsvaerd, Denmark: Novo Nordisk Inc.; December 2017.
Adlyxin (lixisenatide) [prescribing information]. Bridgewater, NJ:Sanofi-aventis U.S. LLC; July 2016.

GLP-1 Receptor Agonists

- Benefits
  - Weight loss
  - Minimal hypoglycemia risk
  - ASCVD and diabetic kidney disease
- Adverse Events
  - Gastrointestinal effects
  - Pancreatitis
  - Injection site reactions
- Black Box Warning
  - Risk of thyroid C-cell tumors

Source: American Diabetes Association *Diabetes Care* 2021;44(Suppl1):S111-S124.

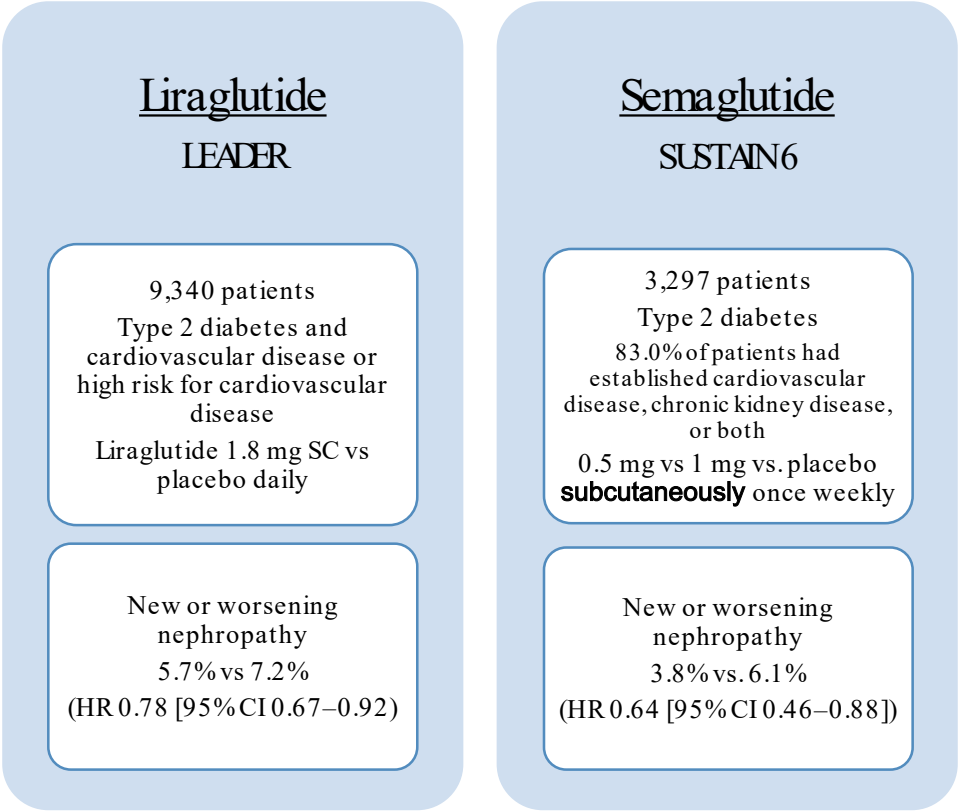
GLP-1 RA: ASCVD Benefit



MACE outcomes : composite endpoint including cardiovascular death, myocardial infarction, or stroke

Source: Holman RR, et al. *N Engl J Med* 2017;377(13):1228-1239.
Marso SP, et al. *N Engl J Med* 2016;375(4):311-322.
Marso SP, et al. *N Engl J Med* 2016;375(19):1834-1844.
Husain M, et al. *N Engl J Med* 2019;381(9):841-851.
Gerstein HC, et al. *Lancet* 2019;394(10193):121-130.
Muskiet MHA, et al. *Lancet Diabetes Endocrinol* 2018;6(11):859-869.

GLP-1RA: Diabetic Kidney Disease Benefit



Composite renal outcome : sustained 40% reduction in eGFR, need for renal replacement therapy, doubling of serum creatines, or death from renal causes

Source: Marso SP, et al *N Engl J Med* 2016;375(4):311-322.
Marso SP, et al. *N Engl J Med* 2016;375(19):1834-1844.

GLP-1 RA Transitions of Care

Admission medication reconciliation

- Check for class duplication
  - Combination products
  - DPP-4 inhibitors (-gliptins)
- Confirm dosing schedule for weekly formulations
- Continuation of medication inpatient
  - Typically not on hospital formularies
  - Combination GLP-1 RA and insulin products
    - Need to adjust insulin dose based in GLP-1 RA requirements
    - Recommended increasing basal insulin by 10% with removal of GLP-1 RA

Brand name	Ingredients
Soliqua®	Lixisenatide and insulin glargine
Xultophy®	Liraglutide and insulin degludec

Source: Pasquel FJ, et al. *Diabetes Obes Metab*. 2021;10.1111/dom.14347.

GLP-1 RA Transitions of Care

Pharmacotherapy management/ discharge medication reconciliation

- Ensuring adherence
  - Slow titration schedule
  - Education on injection technique
  - Once weekly formulations
- Monitoring
  - Renal function (for specific agents)
  - Weight changes
  - Adverse events
- Initiation of new medication upon discharge
  - Benefits of adding liraglutide vs insulin upon discharge
    - Pasquel et al. showed significant reduction in A1c, hypoglycemia events, and body weight at 26 weeks
    - Significant increase in GI side effects leading to discontinuation in 10% of patients
- Transitioning from GLP-1RA monotherapy to combination
  - Different concentrations of GLP-1 RA in combination formulations compared to single agent formula

Brand name	Monotherapy Dose (per mL)	Combination Dose (per mL)
Soliquaé	Lixisenatide: 50- 100 mcg	Lixisenatide: 33 mcg Insulin glargine: 100 units
Xultophyé	Liraglutide: 6 mg	Liraglutide: 3.6 mg Insulin degludec: 100 units

Source: Yang T, et al. *J Pharm Pract* 2019;32(4):447-449.
Artigas CF, et al. *Expert Opin Pharmacother* 2015;16(10):1417-1421.
Pasquel FJ, et al. *Diabetes Obes Metab*. 2021;10.1111/dom.14347.

GLP-1 RA Transitions of Care

Cost & Coverage

- Brand only products
- Formulary coverage
- Patient assistance programs
  - Different criteria for insured patients, Medicare/ Medicaid, and uninsured patients

Compound(s)	Dosage strength/product	Median 30 day AWP	Median 30 day NADAC	Maximum daily dose
Exenatide (extended release)	2 mg powder for suspension or pen	$882	$706	2 mg
Exenatide	10 µg pen	$752	$720	20 µg
Dulaglutide	4.5/0.5 mL pen	$957	$766	4.5 mg
Semaglutide	1 mg pen	$973	$779	1 mg
	14 mg tablet	$927	$738	14 mg
Liraglutide	18 mg/3 mL pen	$1,161	$930	1.8 mg
Lixisenatide	300 µg/3 mL pen	$774	N/A	20 µg

AWP: average wholesale price
NADAC: National Average Drug Acquisition Cost

Source: American Diabetes Association *Diabetes Care* 2021;44(Suppl1):S111-S124.

Comparing SGLT2i & GLP-1 RA

	SGLT2i	GLP-1 RA
Route	Oral	Oral & subcutaneous
Adherence	+	++
HF benefit	✓ (except ertugliflozin)	X
ASCVD benefit	✓	✓
DKD benefit	✓	✓ (only liraglutide & SQ semaglutide)
Cost	$$	$$$
Hospital availability	~✓	X
Insurance coverage	++	+
Storage	Room temp	Refrigerated or room temp

Insulin Icodec

Insulin icodec Literature Review

Phase 2 Study					
Population	N = 247 patients Type 2 diabetes • Diagnosed in last 180 days • A1c = 7.0 – 9.0% • Receiving stable daily doses of metformin ± DPP-4 inhibitor • Not previously on long-term insulin				
Intervention	Once-weekly insulin icodec (196 hours (8.1 days)) 70 units SC + once–daily placebo vs. once-daily insulin glargine SC 10 units + once-weekly placebo for 26 weeks 1:1 randomization Stratified based on dipeptidyl peptidase 4 (DPP-4) inhibitor use (~46% in each group) Insulin doses were adjusted weekly to achieve fasting blood glucose of 70-108 mg/dL				
Outcomes	Primary		**Icodec**	**Glargine**	**Difference or ratio (95% CI)**
		Change in A1c (mean)	-1.33	-1.15	-0.18 [-0.38 - 0.02]
	Secondary	Mean weekly insulin dose	229.06 (~33 units/day)	284.05 (~41 units/day)	0.81 [0.69 – 0.94]
	Safety	Hypoglycemia alert (%)	67 (53.6)	46 (37.7)	OR: **1.84** [1.10 – 3.07]
		Clinically significant or severe hypoglycemia (%)	20 (16.0)	12 (9.8)	OR: 1.70 [0.79 – 3.66]

Source: Rosenstock J, et al. *N Engl J Med* 2020;383(22):2107-2116.

Insulin Icodec: Study Considerations

Population

- Diabetes diagnosis in last 6 months with A1c below 10%
- Excluded if taking GLP-1 RA

Real world application

- All glucose levels were measured using continuous glucose monitoring device (Freestyle Libre Pro)
- Rapid dose adjustments
- Weekly follow up

Statistical Analysis

- Study not powered
- Patients included in statistical analysis for efficacy endpoints were limited to those who
  - Did not receive ancillary therapy (other than metformin or DPP-4 inhibitors)
  - Had at least 70% flash glucose monitoring in last 2 weeks

Source: Rosenstock J, et al. *N Engl J Med* 2020;383(22):2107-2116.

Insulin Icodec: Transitions of Care Considerations

Potential Benefits

Reduce number of injections and increase compliance

Similar A1c and fasting blood glucose reduction compared to daily administration

Potential Pitfalls

Study showed increased risk for hypoglycemia

First product of its kind = $$

References

- Kristeller J. Transition of care: pharmacist help needed. Hosp Pharm. 2014;49(3):212-216.
- Prescription drug formulary: What you need to know. Health Partners website. https://medicarehelp.healthpartners.com/blog/prescription-drug-tiers/. Updated 2021. Accessed April 10, 2021.
- Okemah J, Peng J, Quiñones M. Addressing Clinical Inertia in Type 2 Diabetes Mellitus: A Review. Adv Ther. 2018;35(11):1735-1745.
- American Diabetes Association. 15. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S211-S220.
- American Diabetes Association. 1. Improving Care and Promoting Health in Populations: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S7-S14.
- American Diabetes Association. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S125-S150.
- American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S111-S124.
- Petrie JR, Guzik TJ, Touyz RM. Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms. Can J Cardiol. 2018;34(5):575-584.
- Burgos-Morón E, Abad-Jiménez Z, Martínez de Marañón A, et al. Relationship between Oxidative Stress, ER Stress, and Inflammation in Type 2 Diabetes: The Battle Continues. Journal of Clinical Medicine. 2019; 8(9):1385.
- Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. Phys Ther. 2008;88(11):1322-1335.

References

- American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes—2021. Diabetes Care. 2021;44(Suppl 1):S73-S84.
- Invokana (canagliflozin) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals; July 2013
- Farxiga (dapagliflozin) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; August 2014
- Jardiance (empagliflozin) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; December 2016.
- Steglatro (ertugliflozin) [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; December 2017
- Dutka M, Bobiński R, Ulman-Włodarz I, et al. Sodium glucose cotransporter 2 inhibitors: mechanisms of action in heart failure [published online ahead of print, 2020 Nov 4]. Heart Fail Rev. 2020;10.1007/s10741-020-10041-1.
- Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017;377(7):644-657.
- Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019;380(24):2295-2306.
- Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-2128.
- Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-1424
- Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019;380(4):347-357.
- McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019;381(21):1995-2008.

References

- Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. N Engl J Med. 2020;383(15):1425-1435.
- Lupsa BC, Inzucchi SE. Use of SGLT2 inhibitors in type 2 diabetes: weighing the risks and benefits. Diabetologia. 2018;61(10):2118-2125.
- Nadkarni GN, Ferrandino R, Chang A, et al. Acute Kidney Injury in Patients on SGLT2 Inhibitors: A Propensity-Matched Analysis. Diabetes Care. 2017;40(11):1479-1485.
- Beitelshees AL, Leslie BR, Taylor SI. Sodium-Glucose Cotransporter 2 Inhibitors: A Case Study in Translational Research. Diabetes. 2019;68(6):1109-1120.
- Meena P. SGLT2 Inhibitor-induced Euglycemic Diabetic Ketoacidosis. Renal Fellow Network website. https://www.renalfellow.org/2020/09/08/sglt2-inhibitor-induced-euglycemic-diabetic-ketoacidosis/. Updated September 8, 2020. Accessed April 10, 2021.
- Hinnen D. Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. Diabetes Spectr. 2017;30(3):202-210.
- Bydureon (exenatide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; October 2017.
- Byetta (exenatide) [prescribing information]. San Diego, CA: Amylin Pharmaceuticals, Inc.; October 2009.
- Victoza (liraglutide) [prescribing information]. Bagsvaerd, Denmark: Novo Nordisk Inc.; August 2017.
- Trulicity (dulaglutide) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; January 2017.
- Rybelsus (semaglutide) [prescribing information]. Bagsvaerd, Denmark: Novo Nordisk Inc;. September 2019.
- Ozempic (semaglutide) [prescribing information]. Bagsvaerd, Denmark: Novo Nordisk Inc.; December 2017.
- Adlyxin (lixisenatide) [prescribing information]. Bridgewater, NJ: Sanofi-aventis U.S. LLC; July 2016.

References

- Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2017;377(13):1228-1239.
- Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016;375(4):311-322.
- Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016;375(19):1834-1844.
- Husain M, Birkenfeld AL, Donsmark M, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2019;381(9):841-851.
- Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394(10193):121-130.
- Muskiet MHA, Tonneijck L, Huang Y, et al. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2018;6(11):859-869.
- Pasquel FJ, Urrutia MA, Cardona S, et al. Liraglutide hospital discharge trial: A randomized controlled trial comparing the safety and efficacy of liraglutide versus insulin glargine for the management of patients with type 2 diabetes after hospital discharge [published online ahead of print, 2021 Feb 16]. Diabetes Obes Metab. 2021;10.1111/dom.14347.
- Yang T, Cutshall BT, Tatara A, Rueger M. Combined Insulin and GLP-1 Receptor Agonists: Simplifying Treatment or Adding Obstacles?. J Pharm Pract. 2019;32(4):447-449.
- Artigas CF, Stokes V, Tan GD, Theodorakis MJ. Insulin dose adjustments with add-on glucagon-like peptide-1 receptor (GLP-1R) agonists in clinical practice. Expert Opin Pharmacother. 2015;16(10):1417-1421.
- Rosenstock J, Bajaj HS, Janež A, et al. Once-Weekly Insulin for Type 2 Diabetes without Previous Insulin Treatment. N Engl J Med. 2020;383(22):2107-2116.

Thank you!

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