Updates in Type 2 Diabetes Management 2022

Gretchen Ray, PharmD, PhC, CDCES

Associate Professor, UNM COP

gray@salud.unm.edu

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COLLEGE OF PHARMACY

OBJECTIVES

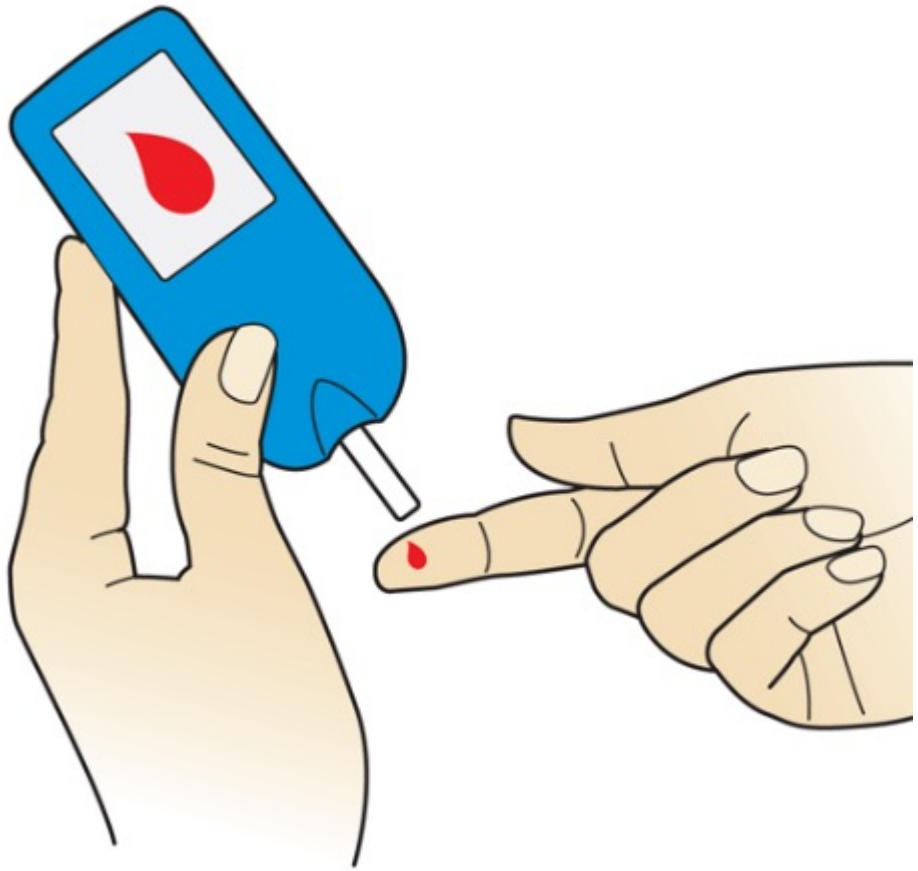
- Describe the SGLT2-inhibitor, GLP-1 receptor agonist, and dual GIP/GLP-1 receptor agonist drug classes and their current outcome studies
- Identify diabetes medications which have additional approved indications for other cardiovascular or renal conditions
- Use the 2022 American Diabetes Association Standards of Medical Care treatment algorithm to provide patient-centered pharmacotherapy for a patient living with type 2 diabetes

GUIDELINES

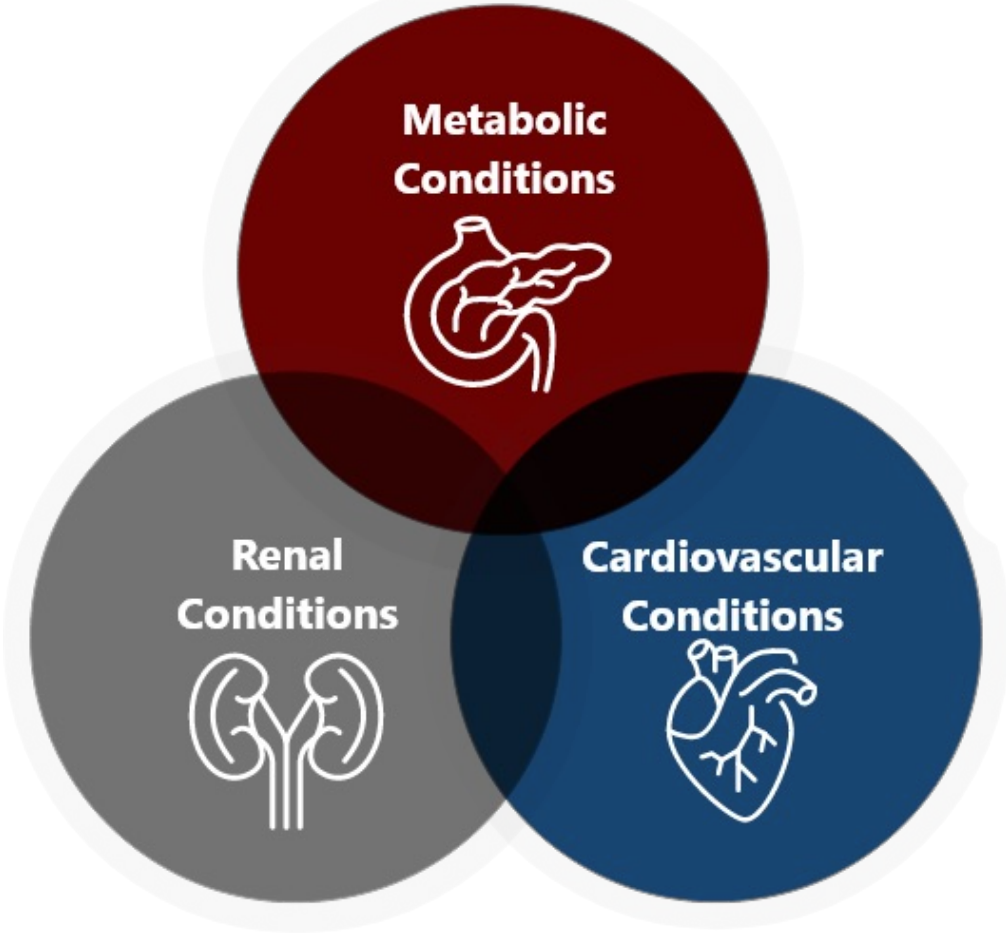
- Standards of Medical Care in Diabetes 2022. *Diabetes Care* 2022;45(Suppl 1)
- professional.diabetes.org

A Shift in Goals When Managing Diabetes

From solely lowering glucose



To considering cardio-renal-metabolic risk factors



CASE

- 60 year-old-male with a 10-year history of type 2 diabetes. A1C 8.2%. eGFR 90 ml/min/m^2
- PMH includes history of a myocardial infarction 5 years ago, hypertension, dyslipidemia
- DM Medications: Metformin 1000 mg BID, Empagliflozin 25 mg once a day
- What would you consider adding to his medication regimen?

A. Pioglitazone

B. glipizide

C. Insulin Degludec once a day

D. Sitagliptin

E. Dulaglutide

CASE

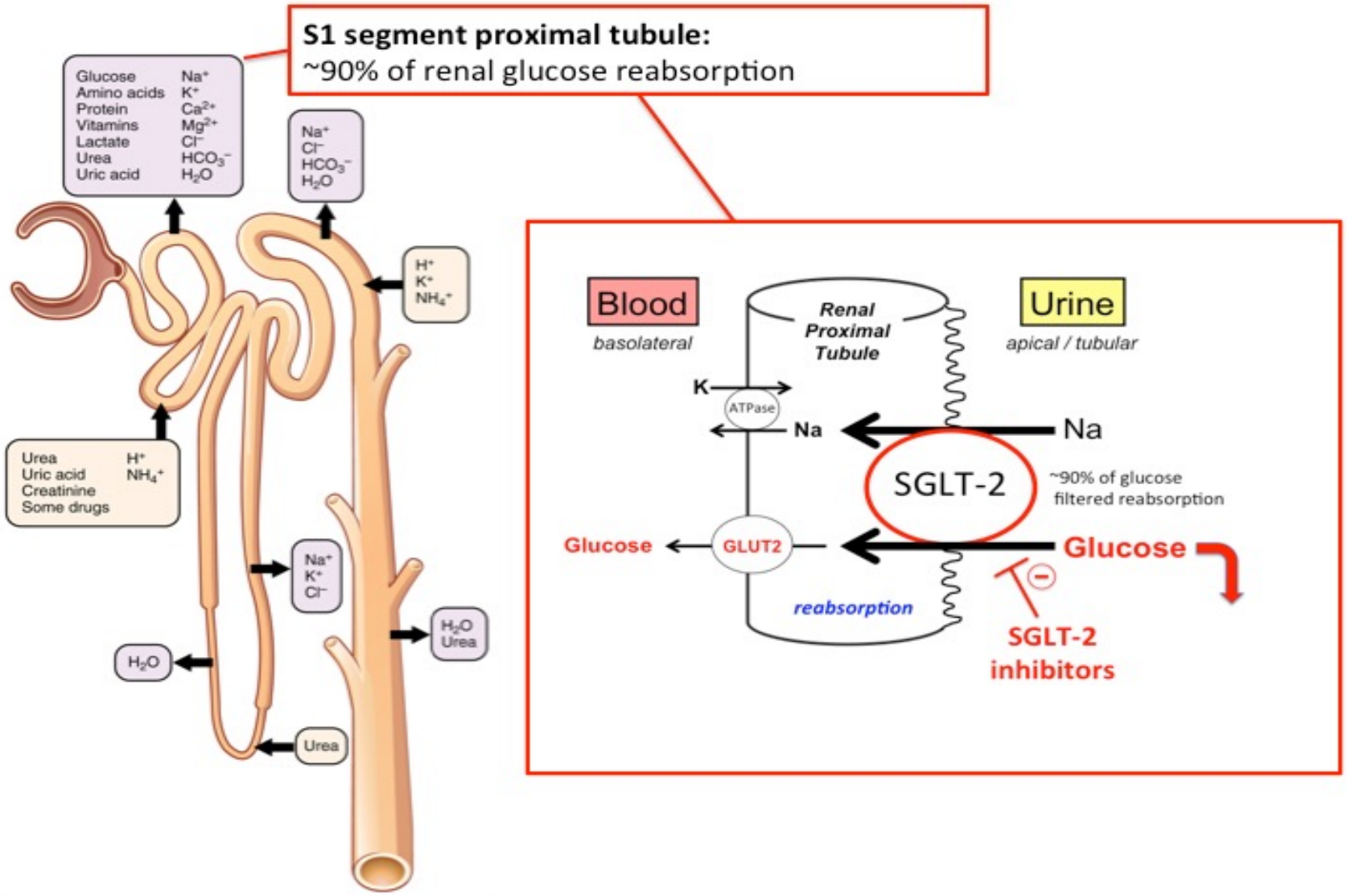
- 56 year old female with PMH of type 2 diabetes x 11 years, dyslipidemia, hypertension, obesity (BMI 33).
- A1C 7% eGFR 50 ml/min/m^2 , urine-albumin-creatinine 326 mg/g
- DM medications: metformin 1000 mg BID, Glipizide XL 20 mg once a day, Insulin glargine 16 units once a day
- What change would you recommend to her diabetes medications?

A. Discontinue metformin due to low renal function
B. Add sitagliptin
C. increase Insulin Glargine to 18 units
D. Add canagliflozin
E. No changes are needed

SGLT2 Inhibitors

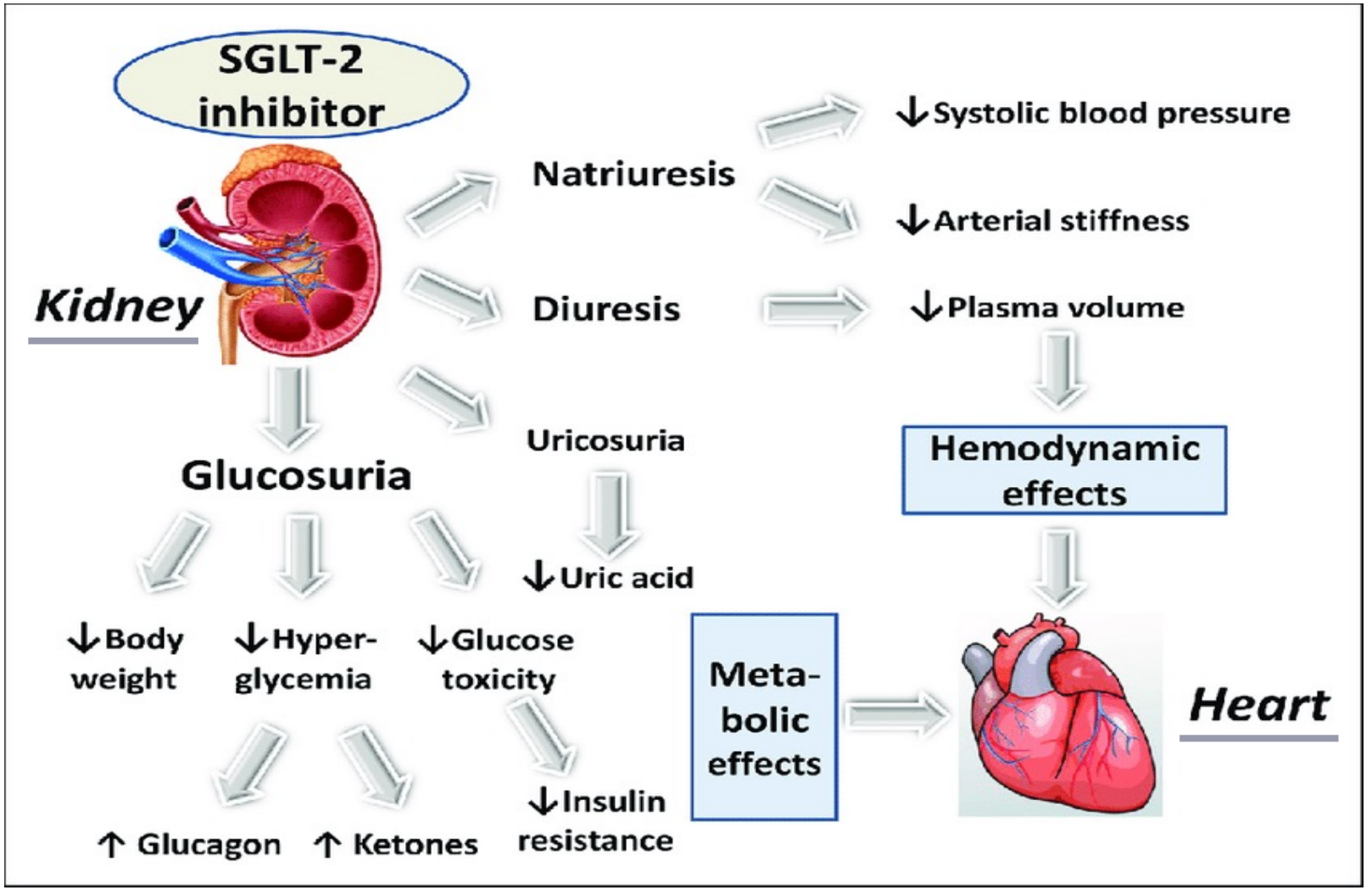
SODIUM-GLUCOSE CO-TRANSPORTER INHIBITORS

Increase urinary glucose excretion



courses.lumenlearning.com

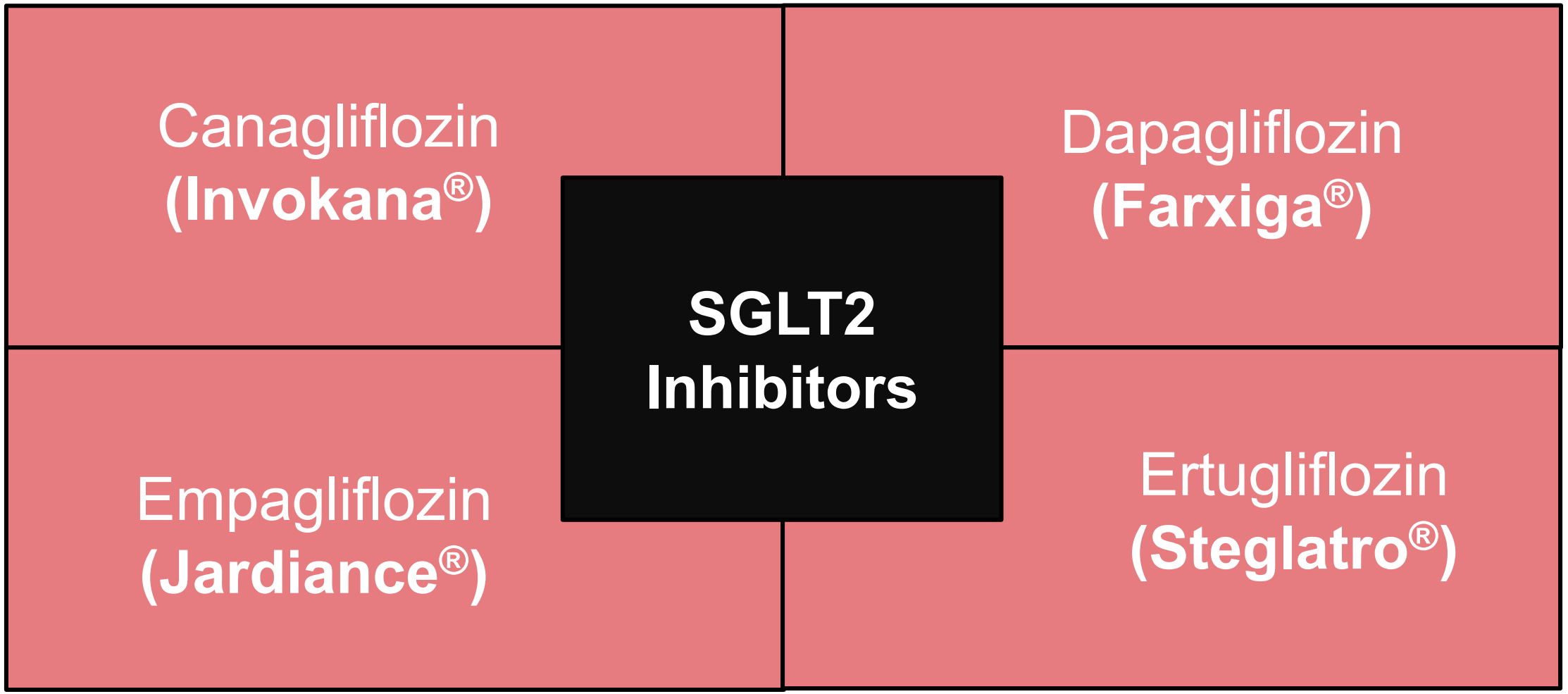
SGLT2I AFFECT THE HEART AND KIDNEYS



Type 2 Diabetes

Heart Failure

Scheen. *Circulation Research.* 2018 May; 122: 1439-1459. doi:10.1161/CIRCRESAHA.117.31158


Canagliflozin
(Invokana®)
Dapagliflozin
(Farxiga®)
SGLT2
Inhibitors
Empagliflozin
(Jardiance®)
Ertugliflozin
(Steglatro®)

LITERATURE- CV MAJOR ADVERSE CARDIAC EVENT **(MACE)** OUTCOMES WITH T2D

2015	**2017**	**2019**	**2020**
EMPA-REG	**CANVAS**	**DECLARE-TIMI 58**	**VERTIS-CV**
Zinman B, et al. NEJM 2015;373:2117-28	Neal B, et al. NEJM 2017:377:644-57	Wiviott, et al. NEJM 2019;380:347-57	Cannon, et al. NEJM 2002;388:1425-35
Empagliflozin	**Canagliflozin**	Dapagliflozin	Ertugliflozin
1° Reduced 3-point MACE **HR 0.86; CI 0.74 - 0.99** p < 0.001 for noninferiority **p = 0.04** for superiority **2° Hospitalization for HF** **HR 0.65; CI 0.50 - 0.85** p < 0.002 **2° CV Death** **HR 0.62; CI 0.49 - 0.77** p < 0.001	**1° Reduced 3-point MACE** **HR 0.86; CI 0.75 - 0.97** p < 0.001 for noninferiority **p = 0.02** for superiority **2° Hospitalization for HF** **HR 0.67; CI 0.52 - 0.87**	**1° Reduced 3-point MACE** HR 0.93; CI 0.84 - 1.03 p < 0.001 for noninferiority p = 0.17 for superiority **1° Composite: CV Death + Hospitalization for HF** **HR 0.83; CI 0.73 - 0.95** p = 0.005 for superiority	**1° Reduced 3-point MACE** HR 0.97; CI 0.85 - 1.11, p < 0.001 for noninferiority **2° Hospitalization for HF** **HR 0.7; CI 0.54 - 0.9**

LITERATURE- HEART FAILURE **WITH & WITHOUT T2D**

2019
DAPA-HF
McMurray, et al. NEJM 2019;381:1995-08

2020
EMPEROR-Reduced
Packer, et al. NEJM 2020;383:1413-24

2021
EMPEROR-Preserved
Anker, et al. NEJM 2021;385:1451-61

DELIVER (HFpEF), DETERMINE-Preserved

Dapagliflozin	Empagliflozin	Empagliflozin	Dapagliflozin
1° Worsening HF or CV Death HR 0.74; CI 0.65 - 0.85 p < 0.001 **2° Hospitalizations for HF** HR 0.71; CI 0.61 - 0.82 p < 0.001	**1° Composite: Hospitalization for HF or CV Death** HR 0.75; CI 0.65 - 0.86 p < 0.001 **2° Hospitalizations for HF** HR 0.70; CI 0.58 - 0.85 p < 0.001	**1° Composite: Hospitalization for HF or CV Death** HR 0.79; CI 0.69 - 0.9 p < 0.001 **2° Hospitalizations for HF** HR 0.73; CI 0.61 - 0.88 p < 0.001	Not yet published

LITERATURE- CKD **WITH AND WITHOUT T2D**

2018
CREDENCE
Perkovic, et al. NEJM 2019;380:2295-06

2020
DAPA-CKD
Heerspink, et al. NEJM 2020;383:1436-46

2022
EMPA-KIDNEY
Presented, but not yet published

Canagliflozin

1° ESRD, doubling Scr, renal morality or CV morality
HR 0.70; CO 0.59 - 0.82
p = 0.00001

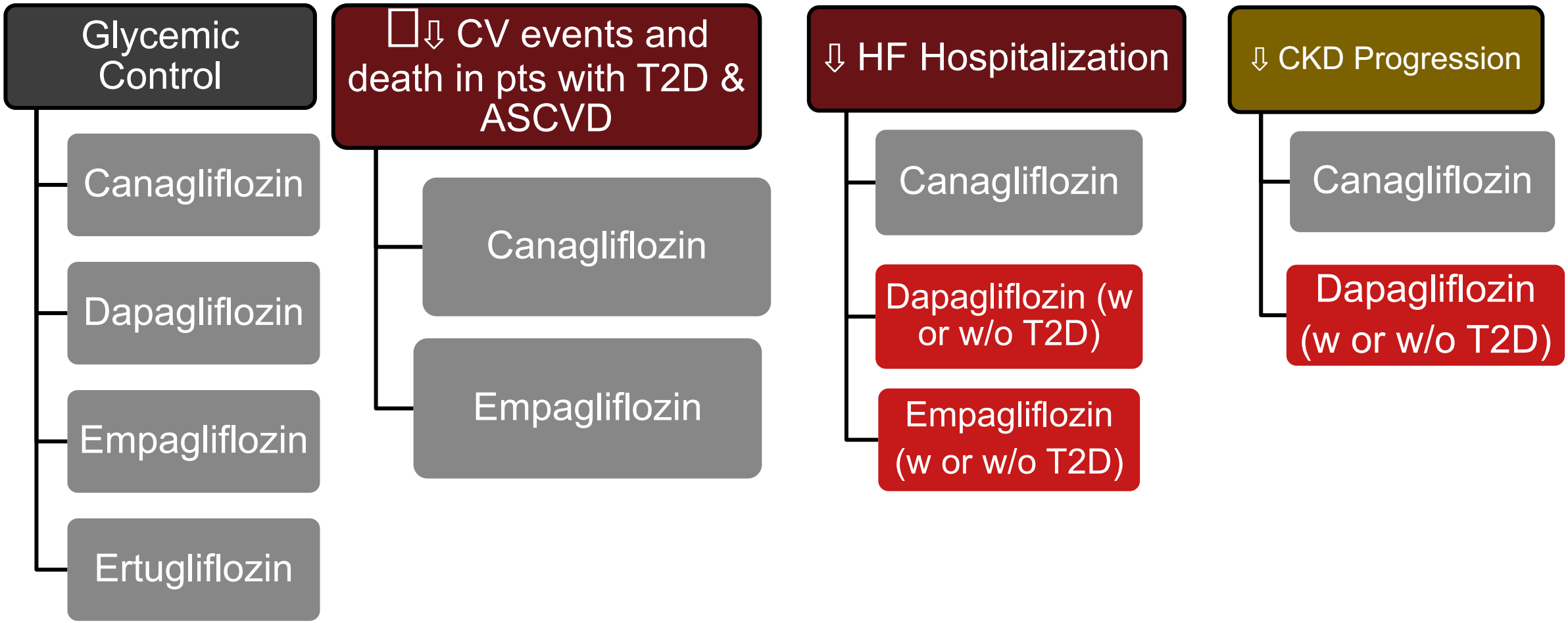
Dapagliflozin

1° Decline of >50% in eGFR, new ESRD, renal morality, or CV morality
HR 0.61; CI 0.51 - 0.72
p<0.001

Empagliflozin

Trial ended early March 2022 due to positive results

SGLT2I FDA APPROVED INDICATIONS

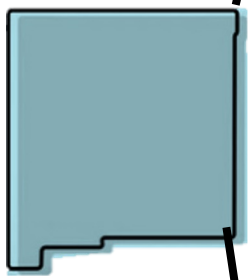


SGLT2I ADVERSE EFFECTS

- Initial slight worsening of eGFR (similar to ACE-I or ARB effects)
- Increased urination
- Hypotension due to volume depletion
  - Risk factors: advanced age, low BP, use of diuretics
- Euglycemic DKA: specific risk factors
  - Surgery (Hold 72 hours prior)
  - Dehydration
  - Alcohol intake
  - Acute illness/infection
  - Extended Fasting
  - Patients with T1D
- **Urinary tract infection (UTI)**
- **Genital mycotic infections**
  - Encourage personal hygiene
- Fournier's gangrene
  - post-marketing case reports

Neal et al. NEJM. 2017; 377:644-657. doi: 10.1056/nejmoa1611925
Ryan et al. Diabetes Obes Metab. 2018 Nov;20(11):2585-2597. doi: 10.1111/dom.13424.

NEW MEXICO STATEWIDE COVERAGE (SGLT2I)



Common Coverage Plans	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Steglatro (ertugliflozin)
BCBS	X	X	X	X
Express Scripts	X			X
BCBS Centennial	NC*PA	NC*PA	NC*PA	X
Western Sky	NC*PA	NC*PA	NC*PA	X
Pres Centennial	NC*PA	NC*PA	NC*PA	X
Humana	X	X	X	X
UnitedHealthcare	X	NC	X	NC
CVS Caremark	X	X	X	X
UNM Care	X		X	

Table Legend

- Commercial
- Medicaid
- Medicare
- Assistance

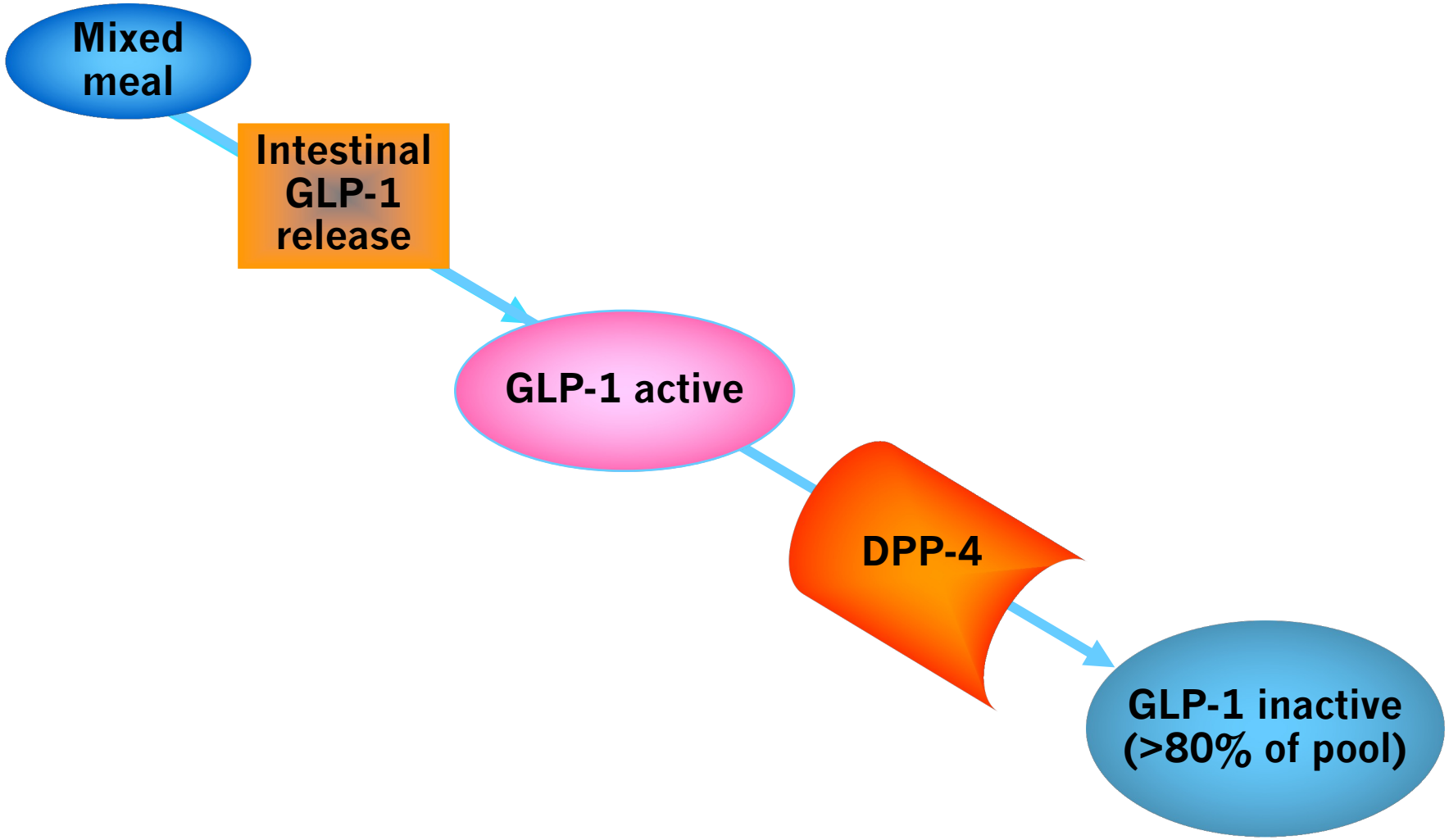
NC = not covered
PA = Prior authorization

PATIENT ASSISTANCE PROGRAMS

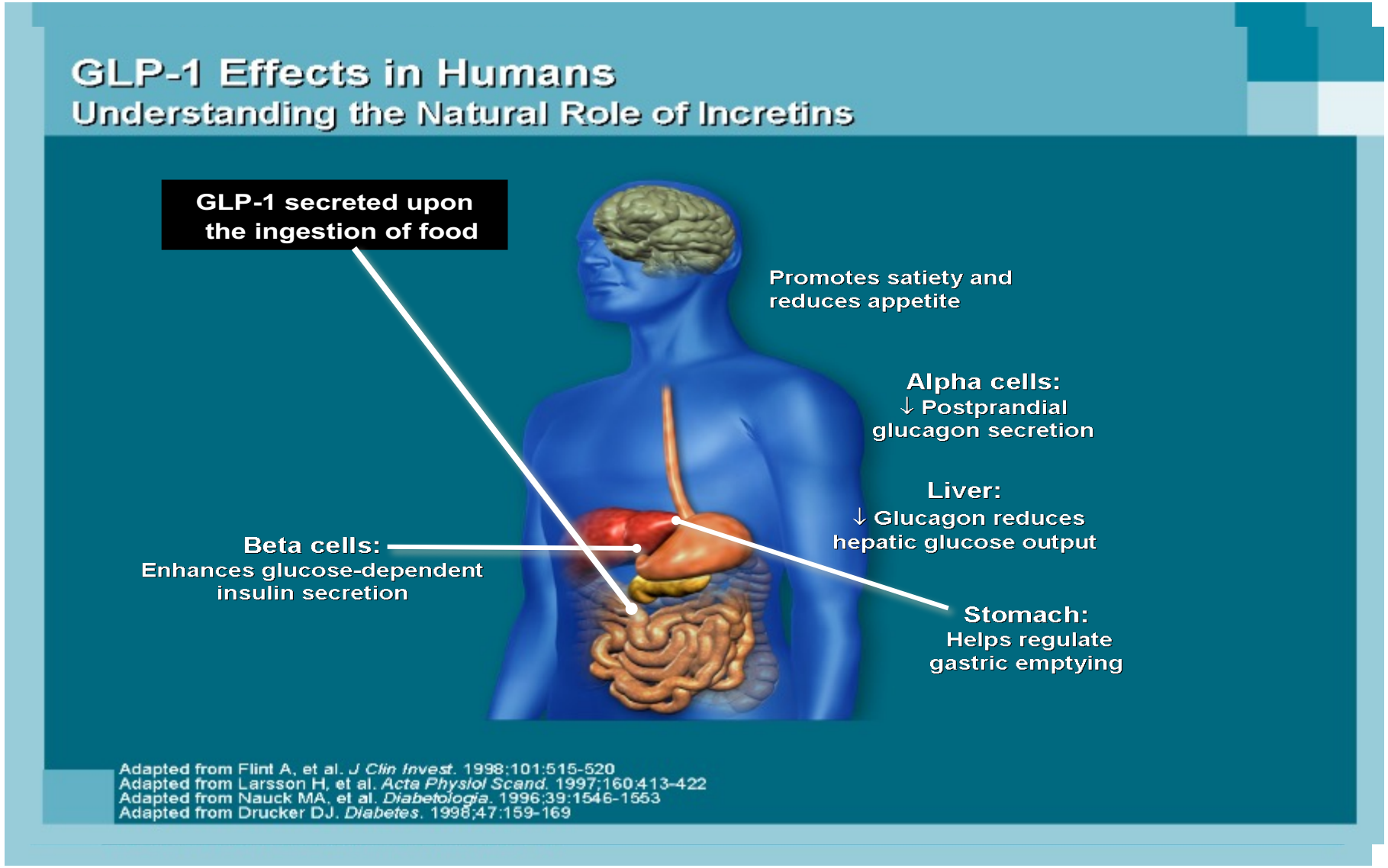
Medication	Farxiga (dapagliflozin)	Jardiance (empagliflozin)	Invokana (canagliflozin) Invokamet (canagliflozin/metformin)
Website	**AstraZeneca's AZ&Me**	**Boehringer-Ingelheim Cares**	**J&J Patient Assistance Foundation**
PAP Benefits	**1 year of enrollment** **90-day supply**	**1 year of enrollment** **90-day supply** **No proof of income needed**	**Up to 120-day supple, sent to healthcare provider's office** **12 months of enrollment or end of calendar year (Medicare)** **Refills coordinated by HCP**
PAP Criteria	**Must be resident of US** **Must not have prescription drug coverage through private insurance or government insurance** **If enrolled in Part D,** *(must have spent at least 3% of household income on prescription medications since the start of the calendar year at time of application)* **Must meet household income guidelines**	**Must be a resident of the US with physical address** **Must either have no health insurance or not enough coverage to pay for the medication (meaning you cannot afford the out-of-pocket expense)** **Meet household income guidelines**	**Must live in US or US territory** **Must not have private insurance or prescription coverage** **If enrolled in Part D (**must have spent at least 4% of your annual income on prescription medications) **Must meet household income guidelines**

GLP-1 Receptor Agonists

GLP-1 Secretion and Inactivation



GLP-1 PHYSIOLOGY



AVAILABLE GLP-1RA AGENTS

Twice a day

Exenatide
(Byetta®)
5 & 10 mcg

Once a day

Liraglutide
(Victoza®)
0.6, 1.2, 1.8 mg

Lixisenatide
(Adlyxin®)
10, 20 mcg

Once a day Oral

Semaglutide
(Rybelsus®)
3, 7, 14 mg

Once a WEEK

Semaglutide
(Ozempic®)
0.25, 0.5, 1, 2 mg

Dulaglutide
(Trulicity®)
0.75, 1.5, 3, 4.5 mg

Exenatide ER
(Bydureon®)
2 mg

Resistant to degradation by dipeptidyl peptidase-4 (DPP-4)

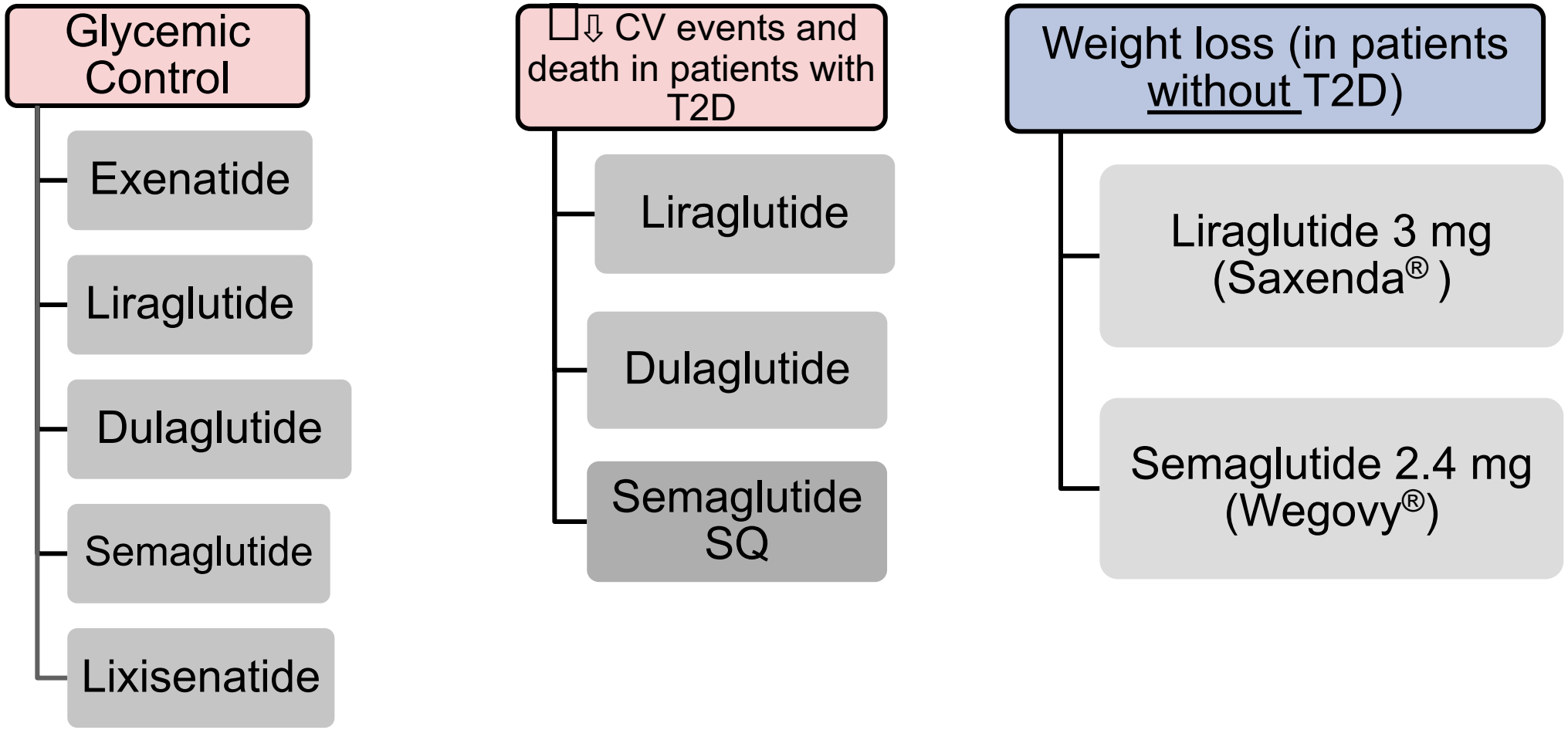
CV OUTCOMES IN T2D: GLP-1 RA STUDIES

GLP-1 RA: Study Name	N	Med F/u, Yrs	CV Disease,* %	Statin Use, %	BL Age	BL A1C	BL BMI	Primary Composite CV Outcome HR (95% CI)	*P* Value
Lixisenatide: ELIXA	6068	2.1	100	93	60.3	7.7	30.1	1.02 (0.89-1.17)	.81
Liraglutide: LEADER	9340	3.8	81	72	64.3	8.7	32.5	0.87 (0.78-0.97)	.01
Semaglutide: SUSTAIN-6	3297	2.1	60	73	64.6	8.7	32.8	0.74 (0.58-0.95)	.02
Exenatide QW: EXSCEL	14,752	3.2	73.1	74	62.0	8.0	31.8	0.91 (0.83-1.00)	.06
Albiglutide: HARMONY	9463	1.6	100	84	64.1	8.7	32.3	0.78 (0.68-0.90)	.0006
Dulaglutide: REWIND	9901	5.4	31.5	66	66.2	7.2	32.3	0.88 (0.79-0.99)	.026
Oral semaglutide: PIONEER 6	3183	1.3	84.7	85	66.0	8.2	32.3	0.79 (0.57-1.11)	.17

*Remaining participants with CV risk factors.

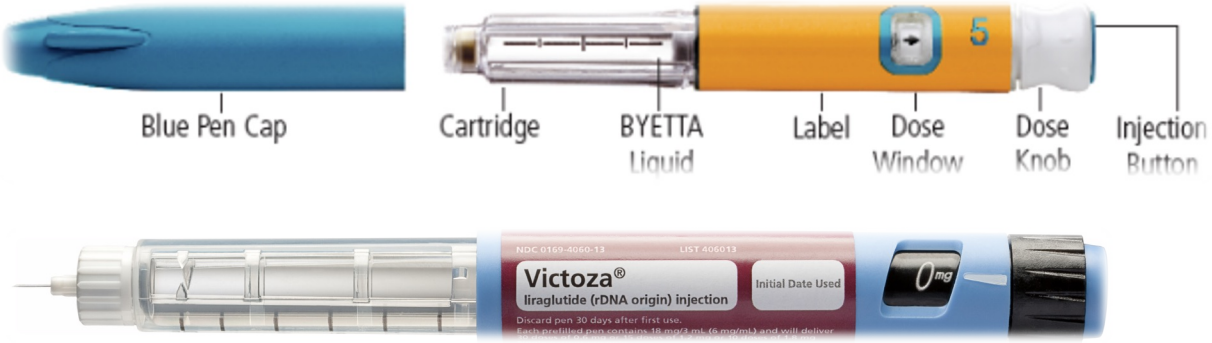
Postgrad Med J. 2020;96:156.

GLP-1RA FDA Approved Indications



Dulaglutide (Trulicity®) and Exenatide ER (Bydureon® BCise)
-No needle is attached. Already self contained
-patient does not see the needle.
-Each pen only injects one dose, must re-prescribe for next dose

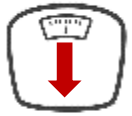
Semaglutide (Ozempic®)
-Functions like an insulin pen- dials up a dose.
-Comes with its own needles



Exenatide IR (Byetta®) & Liraglutide (Victoza®)
-similar to insulin pens however Exenatide pen only contains one dose- Liraglutide pens dial to each available dose
-*prescribe pen needles separately*

GLP-1 RA CONSIDERATIONS

Benefits

- Low Risk of Hypoglycemia
  - Insulin release is glucose dependent
- Weight Loss! 
- CV Indications 
- Slowed progression of renal disease (no FDA indication, but positive outcomes in the CV trials) 

Cost: Expensive $$$

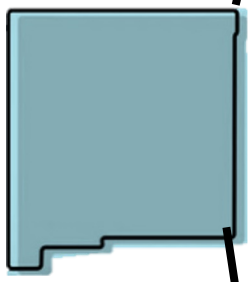
Adverse Effects

- N/V or diarrhea
  - Slow dose titration can minimize AEs

Contraindications

- Gastroparesis
- History of pancreatitis
- History of medullary thyroid carcinoma
- Multiple endocrine neoplasia syndrome 2

NEW MEXICO STATEWIDE COVERAGE (GLP-1 AGONISTS)



Common Coverage Plans	Byetta (exenatide)	Bydueron (exenatide)	Victoza (Liraglutide)	Trulicity (dulaglutide)	Ozempic (semaglutide)	Rybelsus (semaglutide)
BCBS	X	X	X	X	X	X
Express Scripts	X	X	NC	X	X	X
BCBS Centennial	NC*PA	NC*PA	NC*PA	X	NC*PA	NC*PA
Western Sky	X	X	NC*PA	X	X	NC*PA
Pres Centennial	NC*PA	NC*PA	X	X	NC*PA	NC*PA
Humana	X	X	X	X	X	X
UnitedHealthcare	X	X	X	X	X	X
CVS Caremark	X	X	X	X	X	X
UNM Care	X		X			

Table Legend

- Commercial
- Medicaid
- Medicare
- Assistance

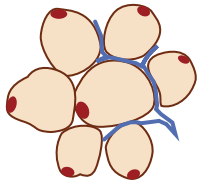
NC = not covered
PA = Prior authorization

Patient Assistance Programs (GLP-1 agonists)

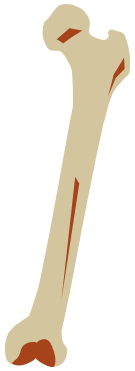
Medication	Bydueron (exenatide) Byetta (exenatide)	Trulicity (dulaglutide)	Ozempic (semaglutide) Rybelsus (semaglutide) Victoza (Liraglutide)
Website	AstraZeneca's AZ&Me	LilyCares	Novo Nordisk
PAP Benefits	1 year of enrollment 90-day supply	Repeated up to a 120-day (3-month) supply for up to one year. 12 months of enrollment or end of calendar year (Medicare) Must reapply each year	Up to 120-day supple, sent to healthcare provider's office 12 months of enrollment or end of calendar year (Medicare) Refills coordinated by HCP
PAP Criteria	Must be resident of US Must not have prescription drug coverage through private insurance or government insurance If enrolled in Part D, *(must have spent at least 3% of household income on prescription medications since the start of the calendar year at time of application)* Must meet household income guidelines	Must be a resident of the US or Puerto Rico. Must have no health insurance, have Medicare Part D, or no coverage for the Lilly medication. Must not be enrolled in federal, state, government programs (VA, Low Income Subsidy) Meet household income guidelines	Must be US citizen or resident Must be uninsured or have Medicare Not enrolled in or qualify for federal, state, government programs (VA, Low Income Subsidy) Meet household income guidelines

Dual **Glucose-dependent insulinotropic polypeptide (GIP) and GLP-1** Receptor Agonist

GIP & GLP-1 ROLES IN METABOLISM

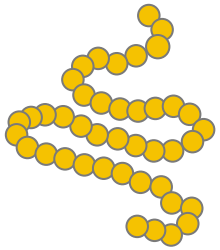


↑ LPL activity
↑ Adipose tissue accretion

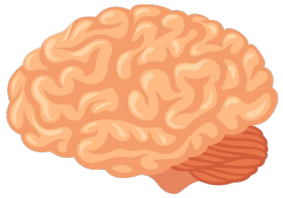


↓ Bone resorption

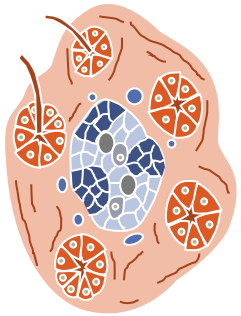
GIP



↑↓ Glucagon secretion

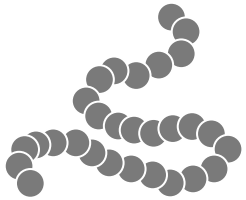


↓ Food intake
↑ Weight loss

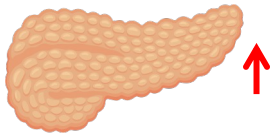


↑ Insulin secretion

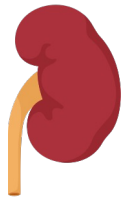
GLP-1



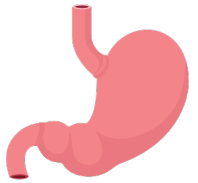
↓ Glucagon secretion



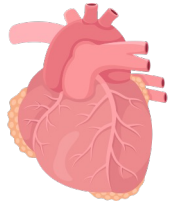
↑ Enzyme secretion



↑ Natriuresis
↑ Diuresis



↓ Gastric emptying



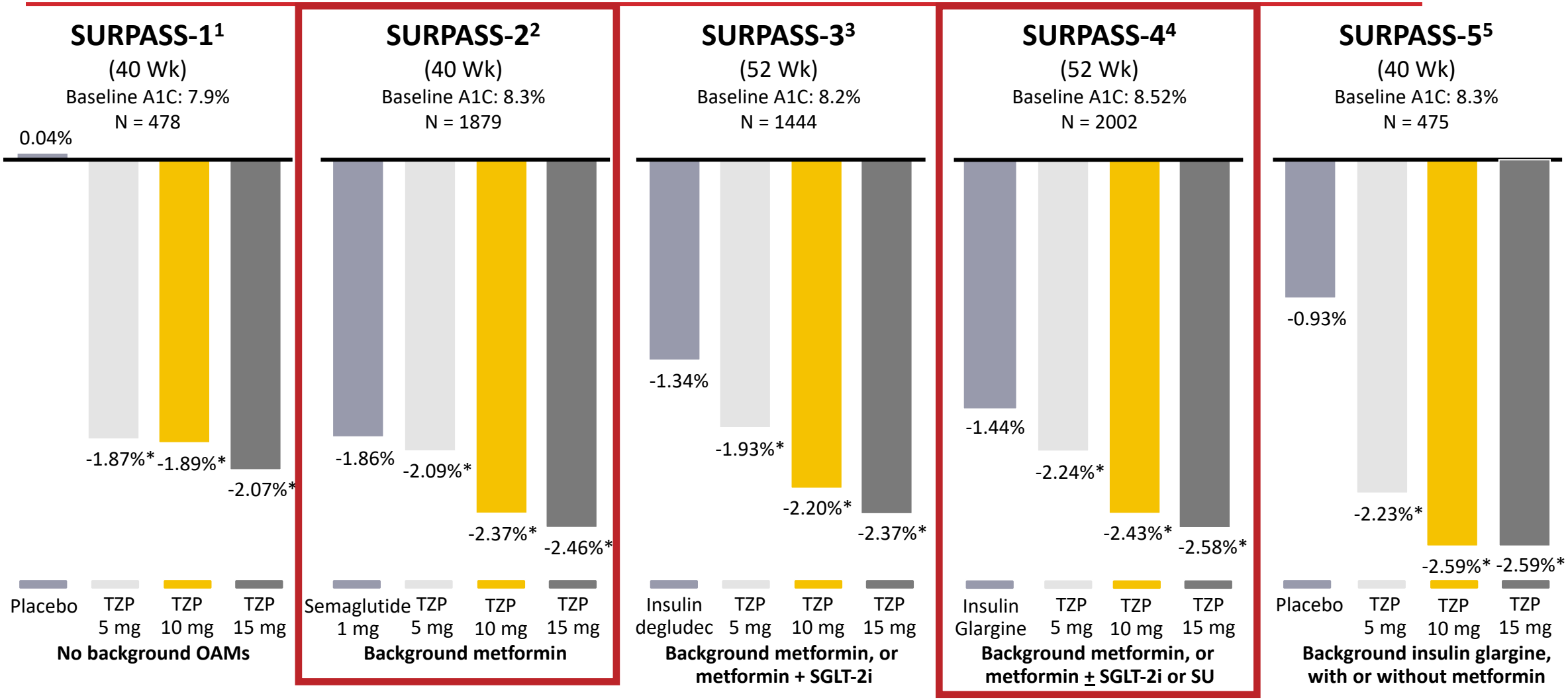
↑ Cardioprotection

Baggio. J Mol Metabolism. 2020;46:101090.

1ST DUAL GIP/GLP-1 RA APPROVED MAY 2022

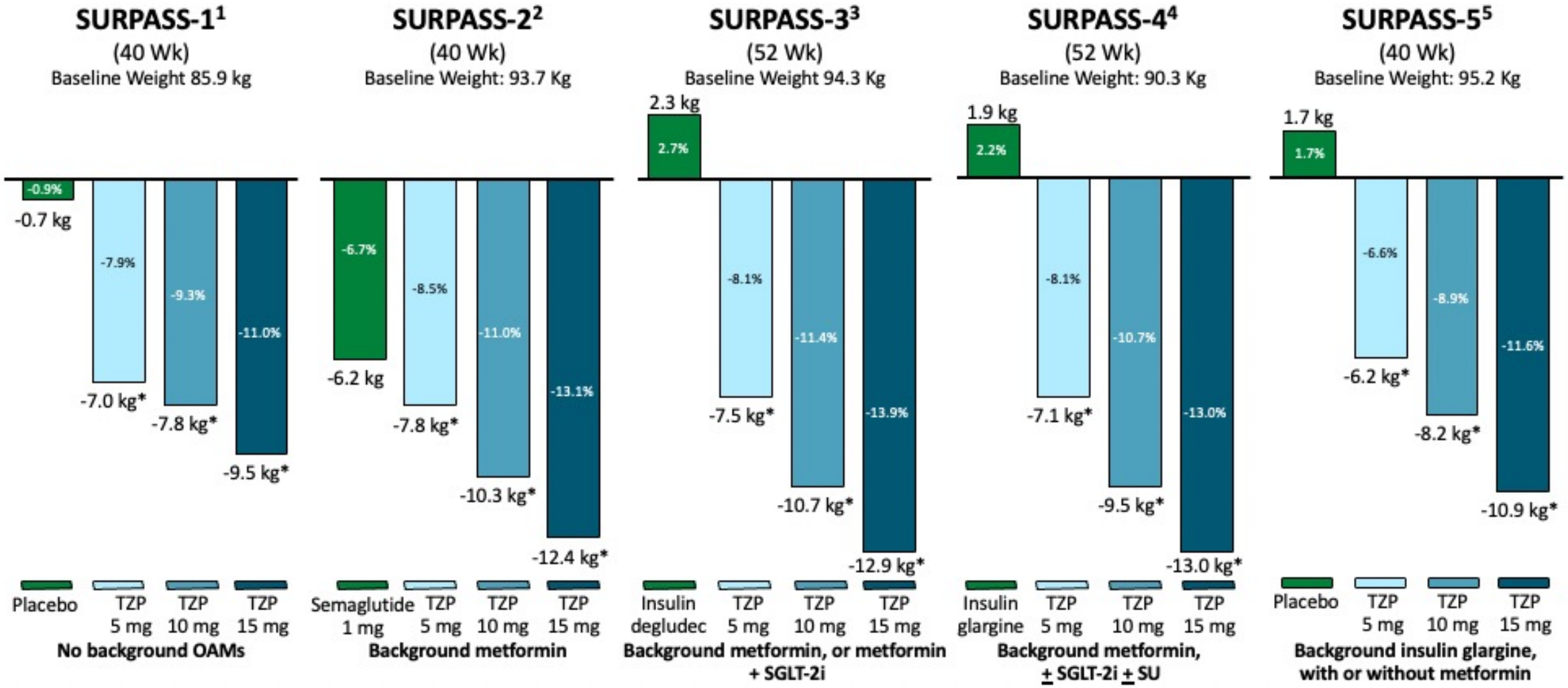
- **Tirzepatide** (Mounjaro®) once weekly injection
  - 2.5, 5, 7.5, 10, 12.5, 15 mg doses
- Most A1C reduction in clinical trials
- Greatest amount of weight loss observed to date in clinical trials (see next slides)

SURPASS TRIALS : TIRZEPATIDE A1C REDUCTION



1. Lancet 2021;398:143-55
2. NEJM 2021;385(6):503-15
3. Lancet 2021;398:583-98
4. Lancet 2021;398:1811-24
5. JAMA 2022;327:534-45

SURPASS: Weight Loss With Tirzepatide in T2D



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3. Lancet 2021;398:583-98
4. Lancet 2021;398:1811-24
5. JAMA 2022;327:534-45

American Diabetes Association Standards of Medical Care Treatment Recommendations

Diabetes Care 2022;45(Suppl 1)

TYPE 2 DIABETES TREATMENT ALGORITHM IN ADDITION TO METFORMIN

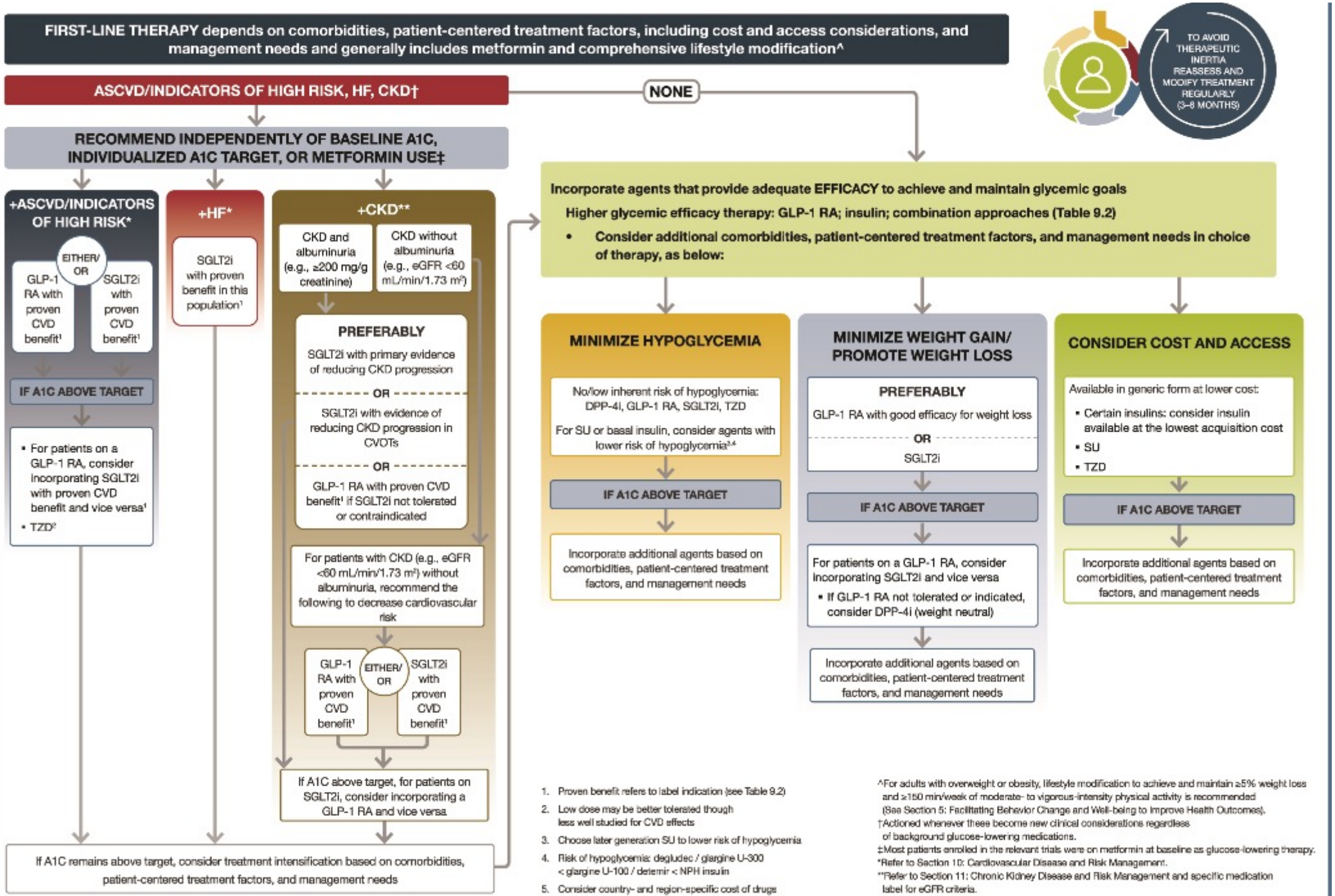
- Pharmacotherapy is determined by:

1. Presence of atherosclerotic cardiovascular disease (ASCVD)

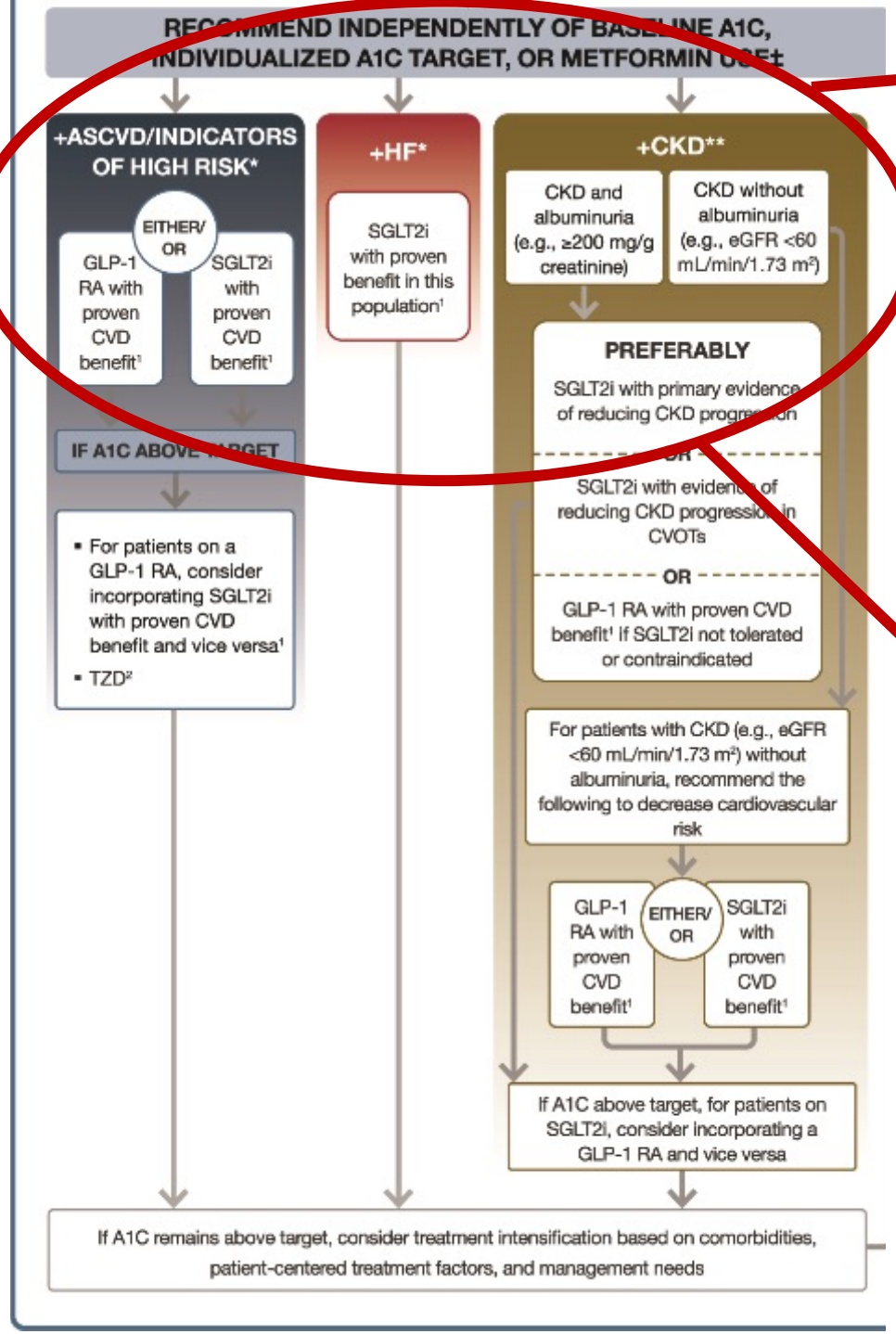
2. Presence of congestive heart failure (CHF)

3. Chronic kidney disease (CKD)

4. Need to minimize hypoglycemia
5. Need to promote weight loss/minimizes weight gain
6. Cost issues



Diabetes Care 2022;45(Suppl 1)



ASCVD or Indicators of High Risk

- Established ASCVD
- Indicators of High ASCVD Risk
  - age ≥55 with coronary, carotid, or lower extremity artery stenosis >50%
  - Left Ventricular Hypertrophy

1st line:
Liraglutide
Dulaglutide
Semaglutide (inj)

OR

Empagliflozin
Canagliflozin

Heart Failure

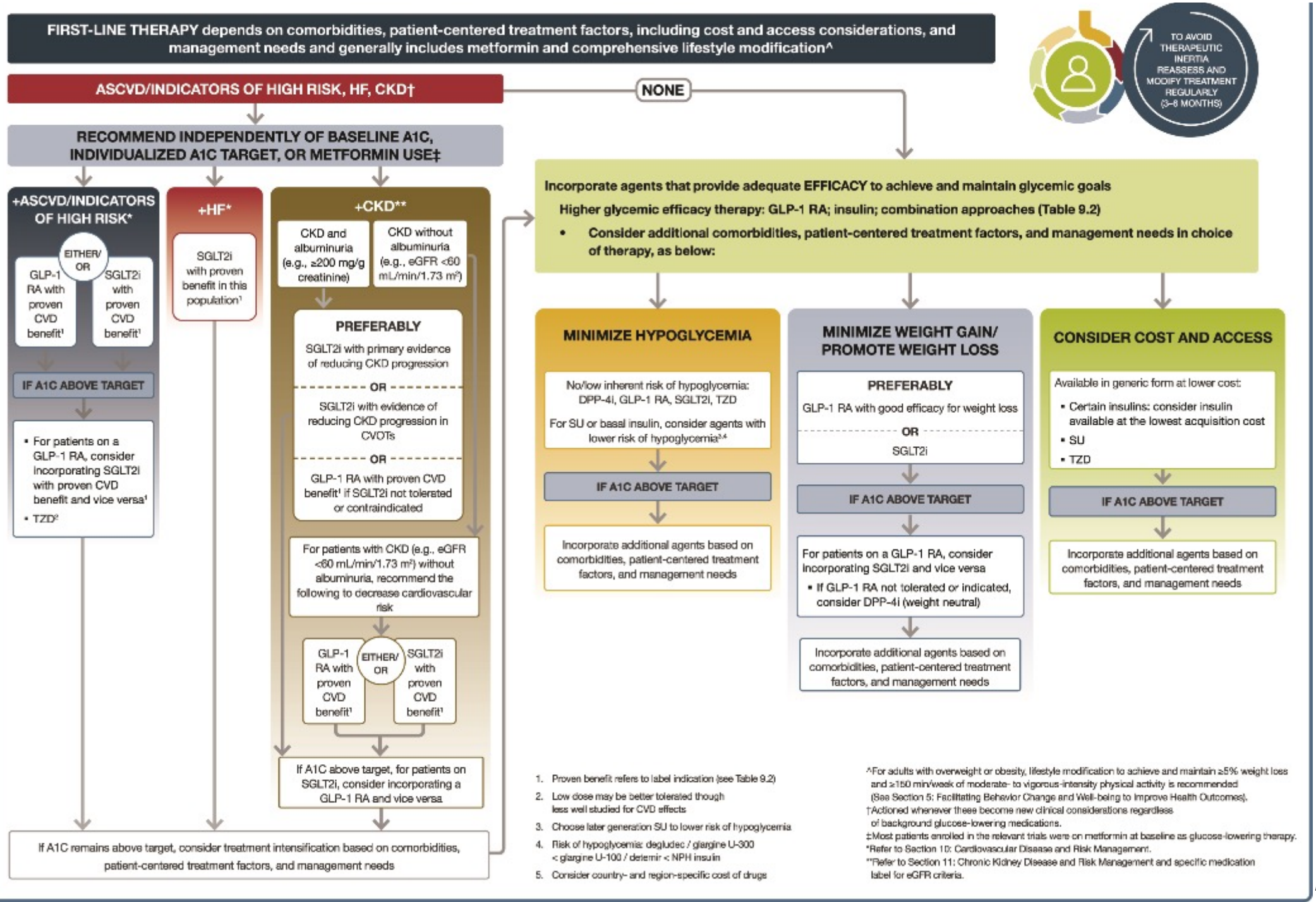
Chronic Kidney Disease

- Kidney Disease + Albuminuria
- T2DM + CKD (eGFR <60 ml/min/1.73m^2) and thus at increased risk of CV events

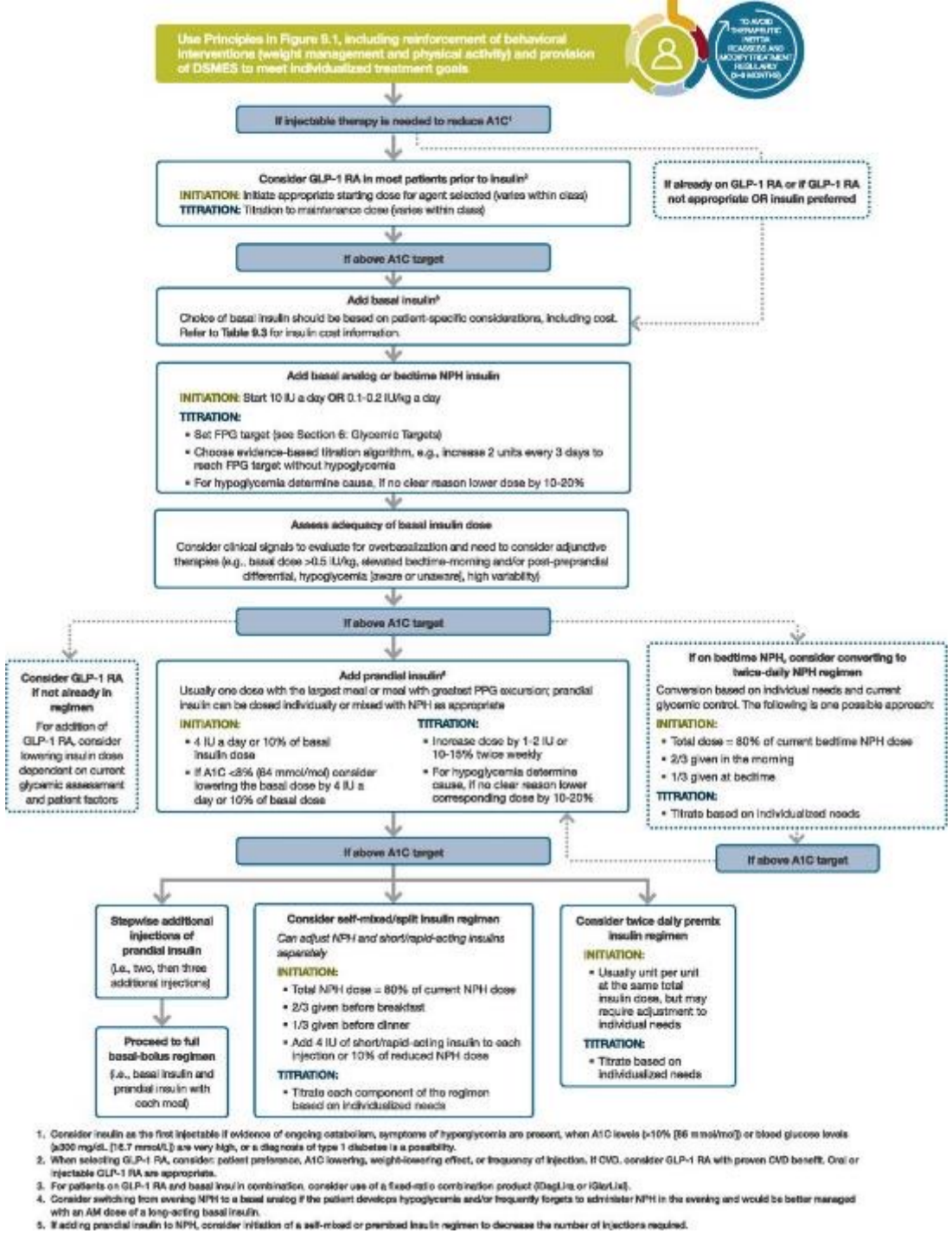
1st line:
Empagliflozin
Dapagliflozin
Canagliflozin

OR GLP-1RA if SGLT2i not tolerated

***Diabetes Care* 2022;45(Suppl 1)**

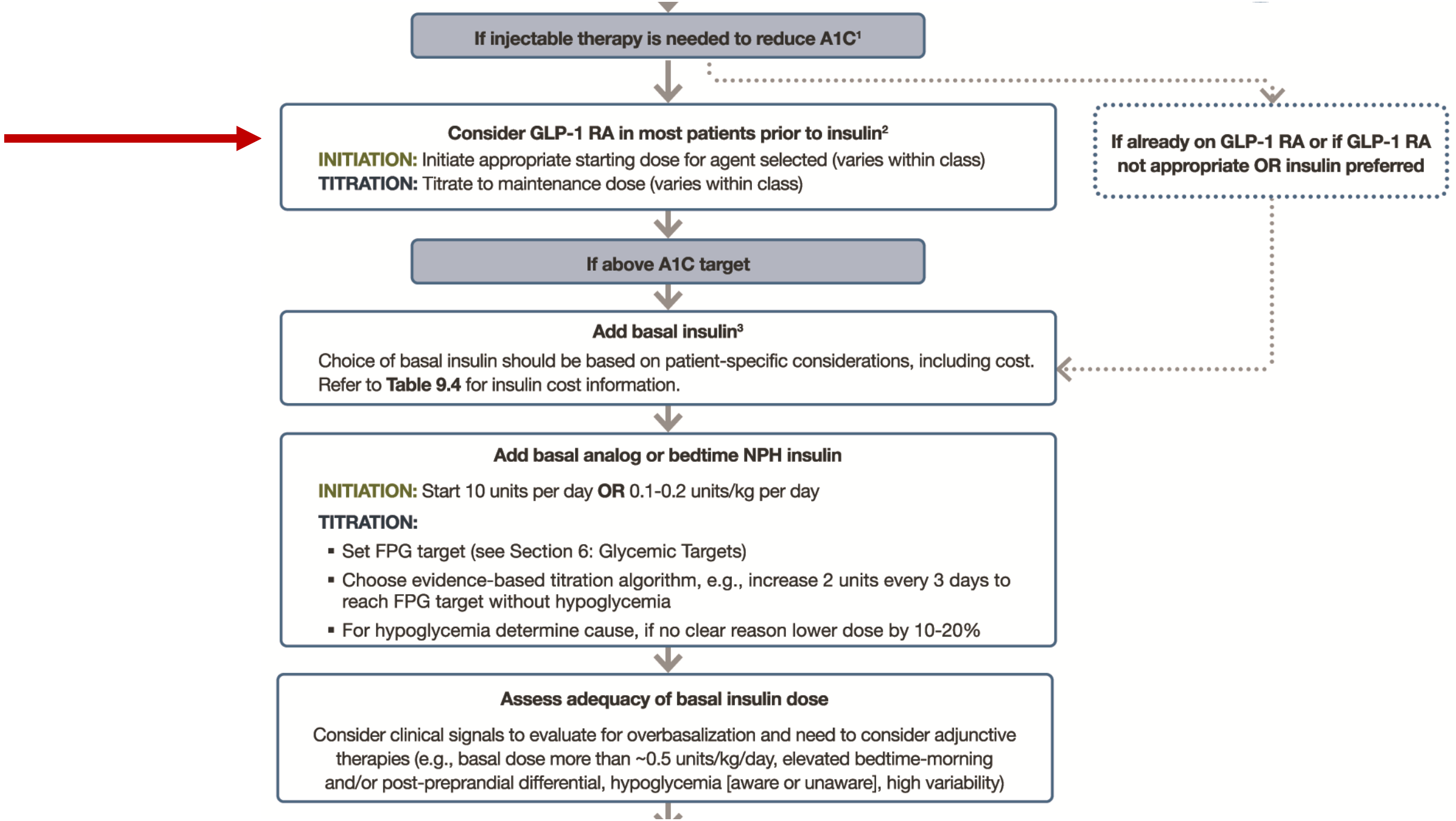


Diabetes Care 2022;45(Suppl 1)

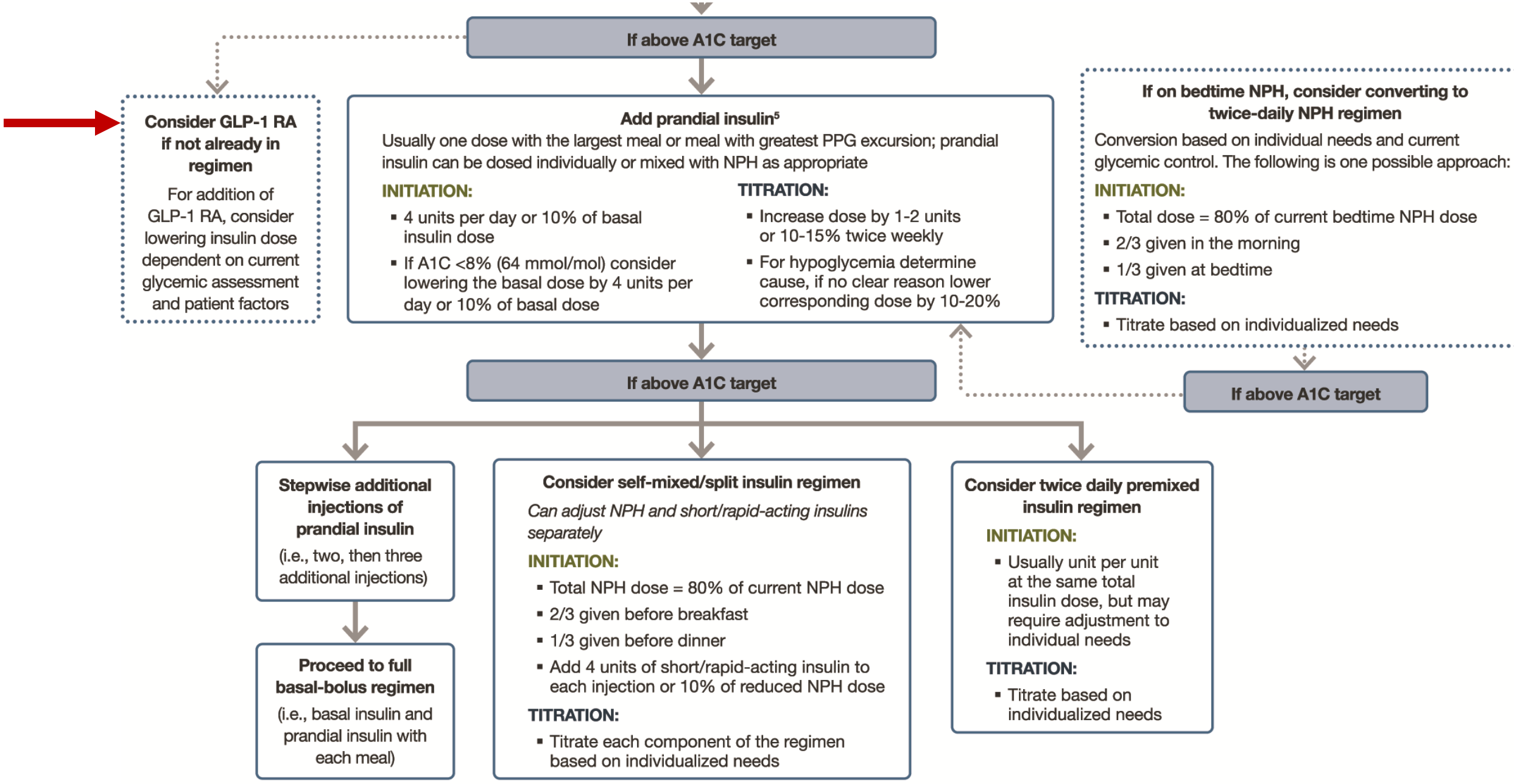


1. Consider insulin as the first injectable if evidence of ongoing catabolism, symptoms of hyperglycemia are present, when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high, or a diagnosis of type 1 diabetes is a possibility.
2. When selecting GLP-1 RA, consider: patient preference, A1C lowering, weight-lowering effect, or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit. Oral or injectable GLP-1 RA are appropriate.
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 2022;44(Suppl 1)



Diabetes Care 2022;45(Suppl 1)



Diabetes Care 2022;45(Suppl 1)

T2D Drug Regimen Adjustments when Adding a GLP-1RA or SGLT2i

CASE: 49 Y/O MALE WITH T2D

- PMH:
  - Neuropathy, obesity (BMI 44), HTN, hyperlipidemia,
- Medications:
  - Metformin 1000 mg BID, **insulin glargine 54 units once a day, insulin lispro 20 units before meals**, atorvastatin 20 mg, losartan 100 mg
- Labs: A1C 7.3%, eGFR 65
- Subjective: he works variable shifts at work alternating between days/nights. Always brings insulin to work, and is consistent with its use. His goal is to improve his A1C and interested in weight loss

HOW TO ADD A GLP-1RA OR SGLT2I?

- #1 verify no contraindications to therapy
- Long-acting GLP-1RA provide both fasting and post-prandial effects
  - GLP-1RA can achieve equivalent glycemic reduction compared to both fasting and prandial insulin
- If on insulin, addition of the GLP-1RA or SGLT2i will reduce their insulin need and can increase their risk of hypoglycemia if not adjusted

ADDING NON-INSULIN THERAPY TO AN INSULIN REGIMEN

- No clear guidance, need to consider the baseline A1C and individual risks for hypoglycemia
  - If A1C is <8% greater insulin dose reductions are warranted

- At GLP-1RA initiation: consider reducing dose of one or both insulins by at least 20% (even up to 50% reduction)
  - Very close follow-up is needed. Continue to reduce insulin doses by 10-20% per week to determine the lowest necessary dose of insulin needed
  - Suggest tapering off the mealtime insulin first
  - Insulin requirement will continue to decline over time after weight loss from the GLP-1RA

- At SGLT2i initiation: **DO NOT** suddenly discontinue insulin therapy especially if they are on higher doses or basal + bolus insulin
  - Can increase risk of euDKA
  - If A1C <8%, reasonable to proactively reduce insulin dose by ~20%
  - Slowly taper the insulin according to their home readings

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Questions

Gretchen Ray, PharmD, PhC, CDCES

gray@salud.unm.edu

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