GLP-1 Receptor Agonists for the Management of Type 2 Diabetes: Pharmacist Focus on the Evolving Treatment Landscape

Part 1:

An Overview of GLP-1 Receptor Agonists: What Every Pharmacist Should Know

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Disclosures

Dr. Trujillo has served as a consultant for BD, Sanofi, and Novo Nordisk.

The clinical reviewer, **Joshua J. Neumiller, PharmD, CDE, FAADE, FASCP** has no actual or potential conflicts of interest in relation to this program.

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- **UAN:** 0430-0000-19-116-L01-P
- **Credits:** 1.25 hour (0.125 ceu)
- **Activity Type:** Knowledge

Learning Objectives

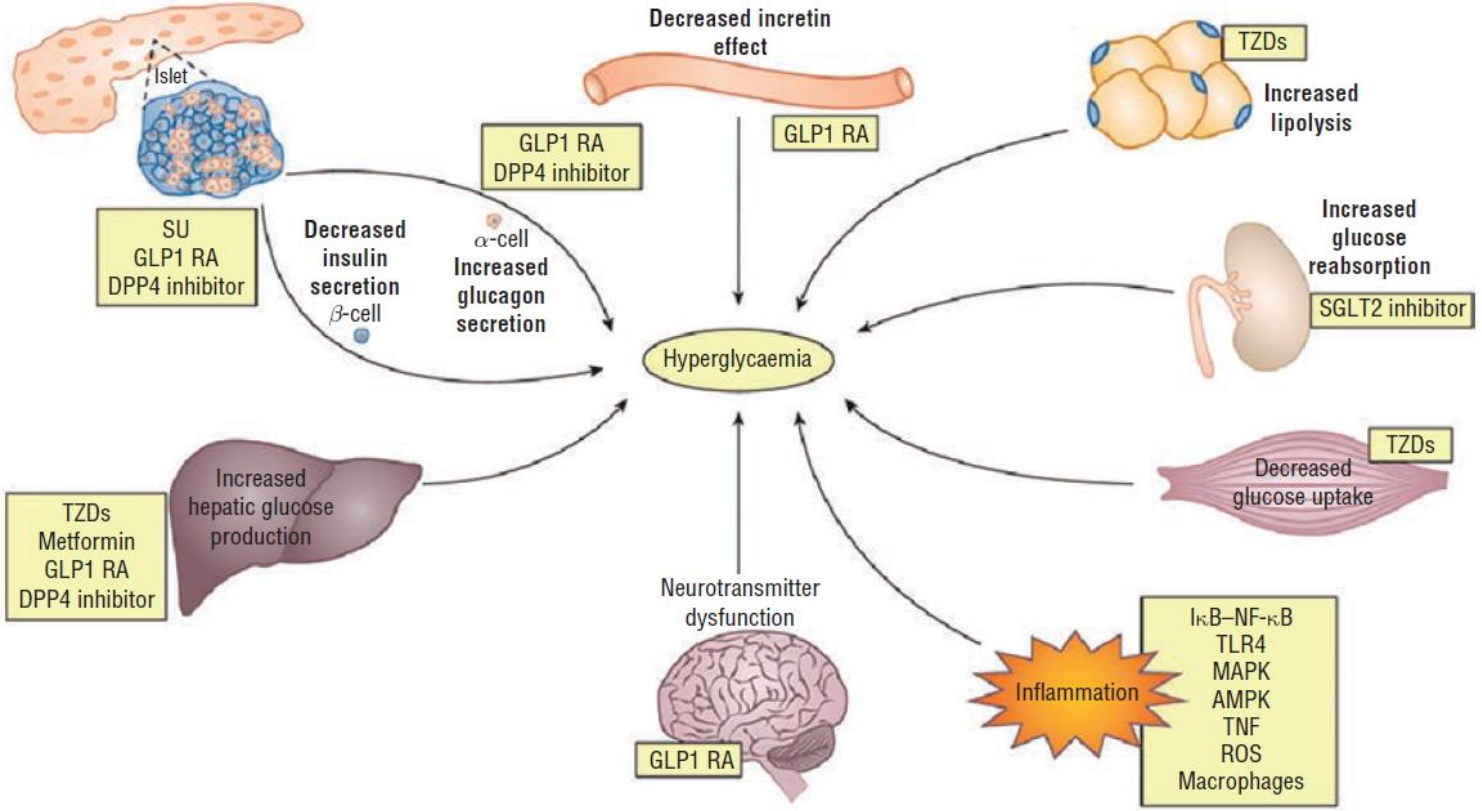
- **Review** the physiologic action, efficacy, safety, advantages, and disadvantages of the glucagon-like peptide (GLP)-1 receptor agonist (RA) medication class
- **Recognize** individual agents within the GLP-1 RA class and understand medication-specific attributes that are important to consider when selecting a GLP-1 RA for use in a specific patient
- **Identify** GLP-1 RAs recently approved or in late-stage development with the potential to impact patient care in the future

ARS Question 1

Which of the following correctly describes one of the physiologic actions of GLP-1 RAs?

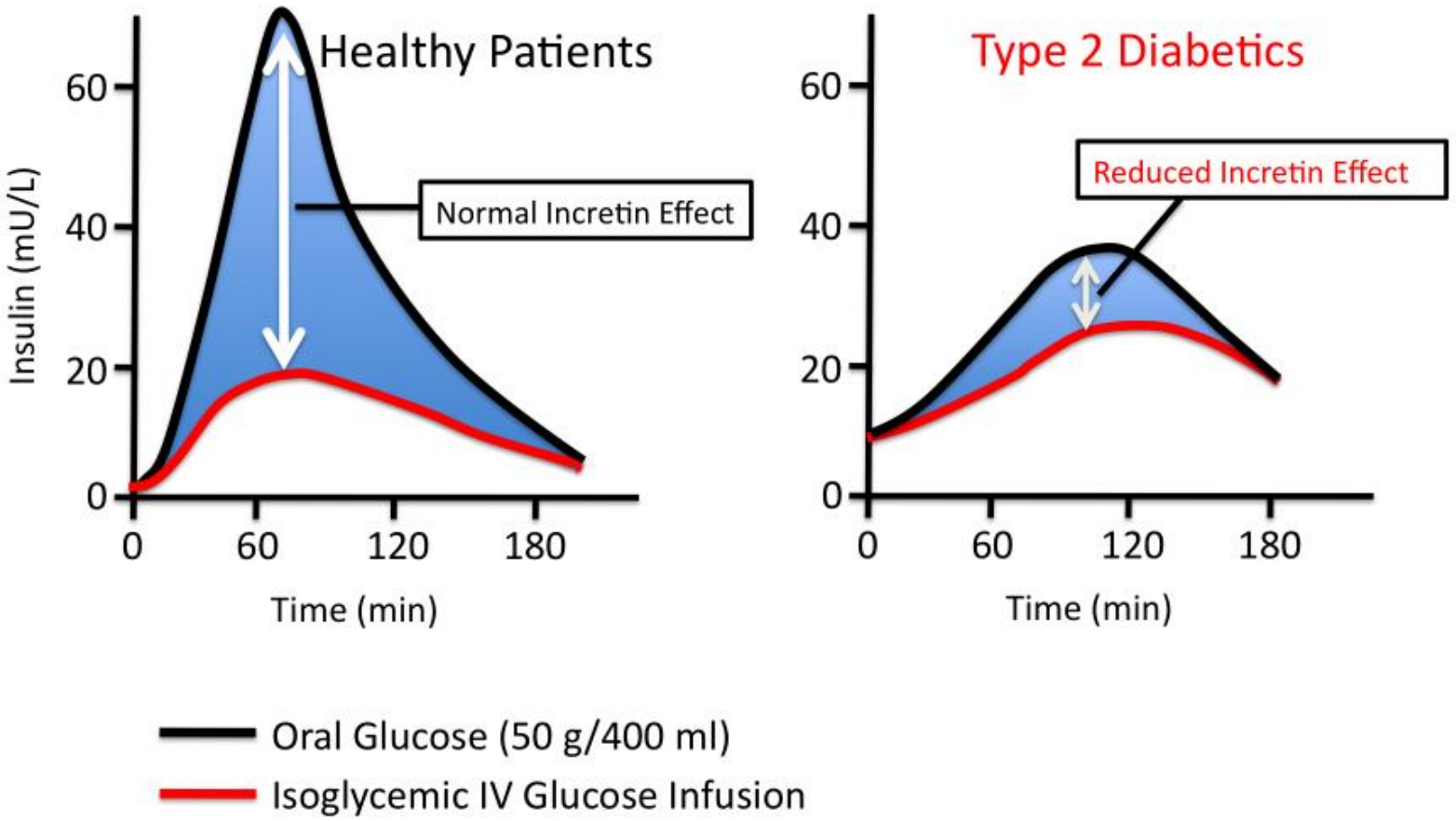
A. Increase glucose-dependent insulin secretion
B. Increase GLP-1 levels back to physiologic levels
C. Inhibit the breakdown of endogenous GLP-1
D. Increase glucose-dependent glucagon secretion

Pathophysiology of Type 2 Diabetes



DeFronzo RA. *Diabetes.* 2009;58(4):773-95.

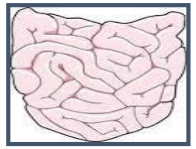
The Incretin Effect



Nauck M, et al. *Diabetologia.* 1986;29(1):46-52.

GLP-1 RAs: Actions on Target Tissues

Food



Gut

GLP-1

$t_{1/2}$ = 1-2 min

DPP-4

Inactive GLP-1

Pancreas

- ↑Glucose-dependent insulin secretion
- ↓Glucose-dependent glucagon secretion

Stomach

- ↓Gastric emptying

Brain

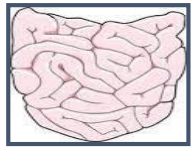
- ↑Satiety

↓Glucose
↓Weight

DPP-4, dipeptidyl peptidase 4.

DPP-4 inhibitors: Actions on Target Tissues

Food



Gut

GLP-1

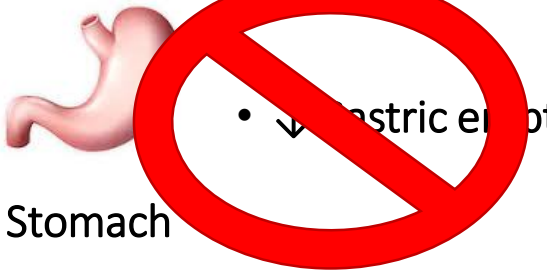
$t_{1/2}$ = 1-2 min

DPP-4

Inactive GLP-1

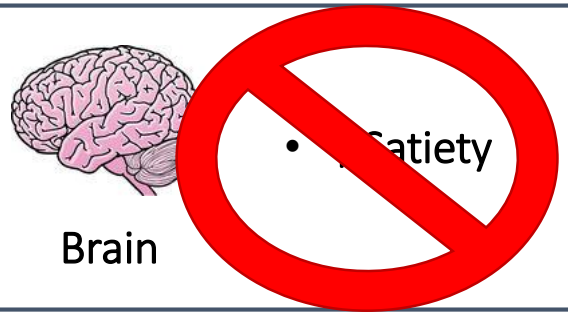
Pancreas

- ↑Glucose-dependent insulin secretion
- ↓Glucose-dependent glucagon secretion



Stomach

- ↓ astric e ptying



Brain

- atiety

↓Glucose

~~↓Weight~~

FDA-Approved GLP-1 RAs

- Exenatide (Byetta): 2005
- Liraglutide (Victoza): 2010
- Exenatide XR (Bydureon): 2012
- Dulaglutide (Trulicity): 2014
- Lixisenatide (Adlyxin): 2016
- Semaglutide (Ozempic): 2017
- Oral semaglutide (Rybelsus): 2019

FDA, United States Food and Drug Administration.

ARS Question 2

Which of the following statements is TRUE about GLP-1 RAs compared to other classes of diabetes medications?

A. GLP-1 RAs are less effective than basal insulin at lowering A1C
B. GLP-1 RAs lower A1C to a similar degree as DPP-4 inhibitors
C. GLP-1 RAs lower weight to a similar degree as thiazolidinediones
D. GLP-1 RAs lower weight while sulfonylureas increase weight

GLP-1 RAs: Pros & Cons

Pros:

- High efficacy
- Low hypoglycemia risk (monotherapy or combination with metformin)
- Cardiovascular & renal benefits
- Weight loss

Potential cons:

- Cost
- Need for renal dose adjustment (some)
- Injectable (most)
- GI intolerance (nausea, vomiting, diarrhea)
- **Rare/serious safety concerns**: thyroid C-cell tumors (long-acting agents), acute pancreatitis

GI, gastrointestinal.

American Diabetes Association. *Diabetes Care.* 2019;42(Suppl 1):S90-S102.

GLP-1 RAs: Clinical Efficacy

- Good effect on A1C
  - Superior or non-inferior to SU, TZD, basal insulin
  - Superior to DPP-4 inhibitors
- Effect on glucose profile
  - Shorter-acting agents: more PPG than FPG
  - Longer-acting agents: PPG and FPG
- Weight loss
  - Major advantage compared to other 2nd-line agents
- Clinical evidence with many combinations and against active comparators
- Some agents have demonstrated CV benefit in CVOTs

CV, cardiovascular; CVOTs, cardiovascular outcomes trials; FPG, fasting plasma glucose; PPG, post-prandial glucose; SU, sulfonylureas; TZD, thiazolidinediones.

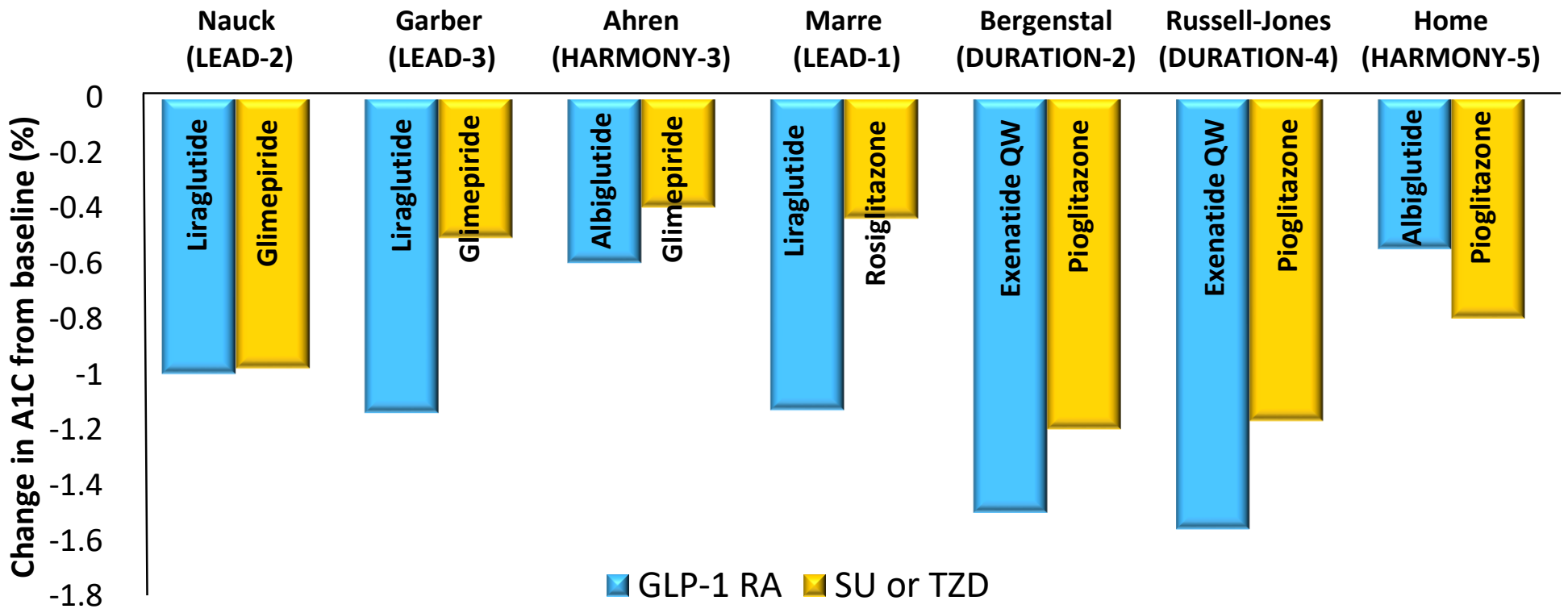
Comparison of Phase 3 Studies of GLP-1 RAs

	Exenatide (Byetta)	Lixisenatide (Lyxumia)	Liraglutide (Victoza)	Exenatide XR (Bydureon)	Dulaglutide (Trulicity)	Semaglutide (Ozempic)	Oral semaglutide (Rybelsus)
Phase 3 clinical trial	AMIGO	GetGoal	LEAD	DURATION	AWARD	SUSTAIN	PIONEER
Background therapy	Drug naïve, metformin, SU	Drug naïve, metformin, SU, TZD, basal insulin	Drug naïve, metformin, SU, TZD	Drug naïve, metformin, SU, TZD	Drug naïve metformin, SU, TZD, bolus insulin	Drug naïve, metformin, SU, TZD; basal, bolus, premixed insulin	Drug naïve, metformin, SU, TZD, SGLT2i; basal, bolus, pre-mixed insulin
A1C lowering (%)*	-0.4 to -1.1	-0.46 to -0.99	-0.84 to -1.5	-1.48 to -1.9	-0.71 to -1.64	-1.1 to -2.2	-0.6 to -1.4
Weight lowering (kg)	-0.3 to -2.8	+0.3 to -2.96	+0.3 to -3.24	-2.0 to -4.0	+0.2 to -3.03	-1.4 to -6.5	-1.2 to -4.4

*Includes all doses studied

SGLT2i, sodium-glucose transport protein 2 inhibitor.

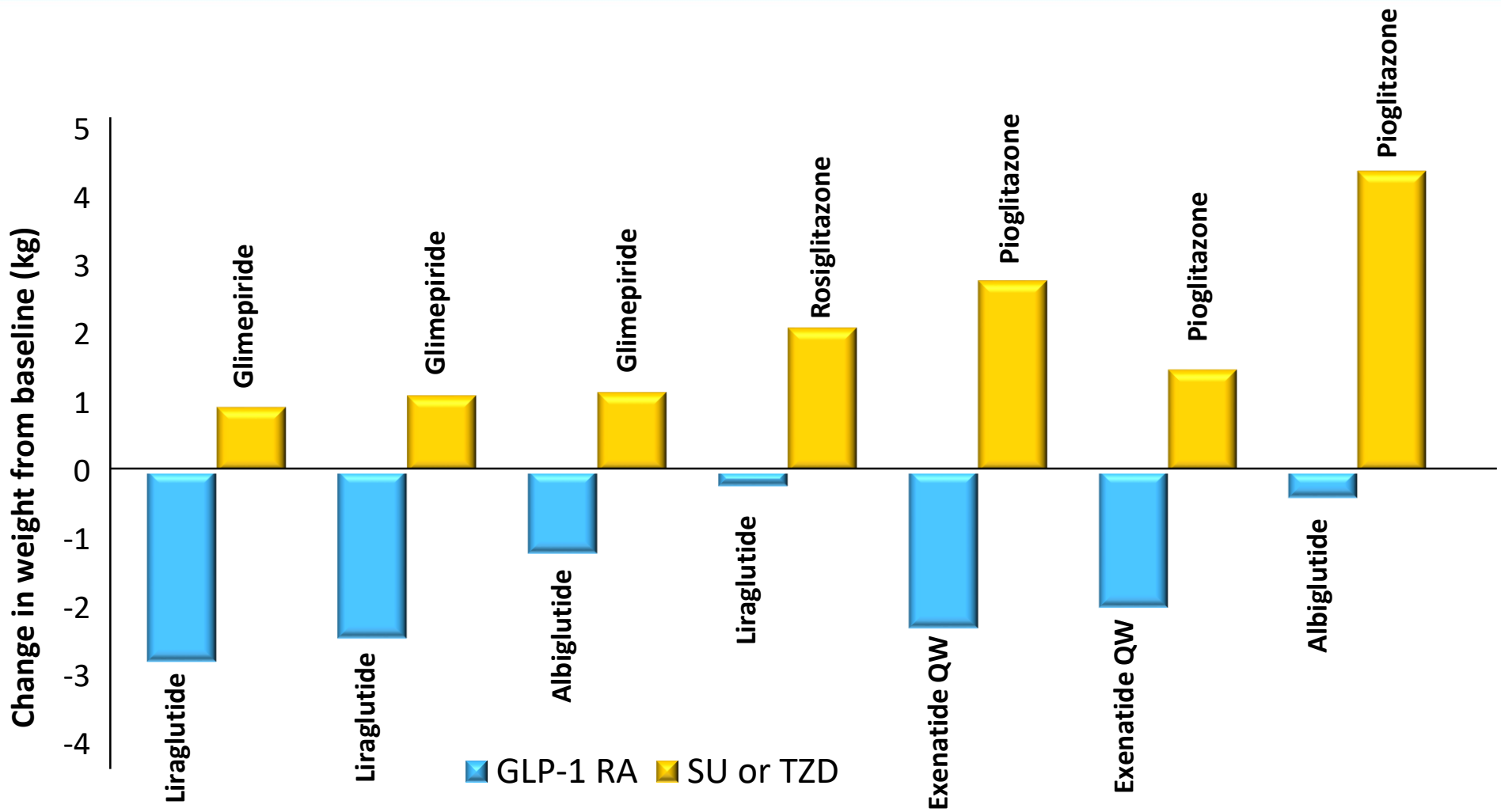
A1C: GLP-1 RAs vs. SU or TZD



QW, every week.

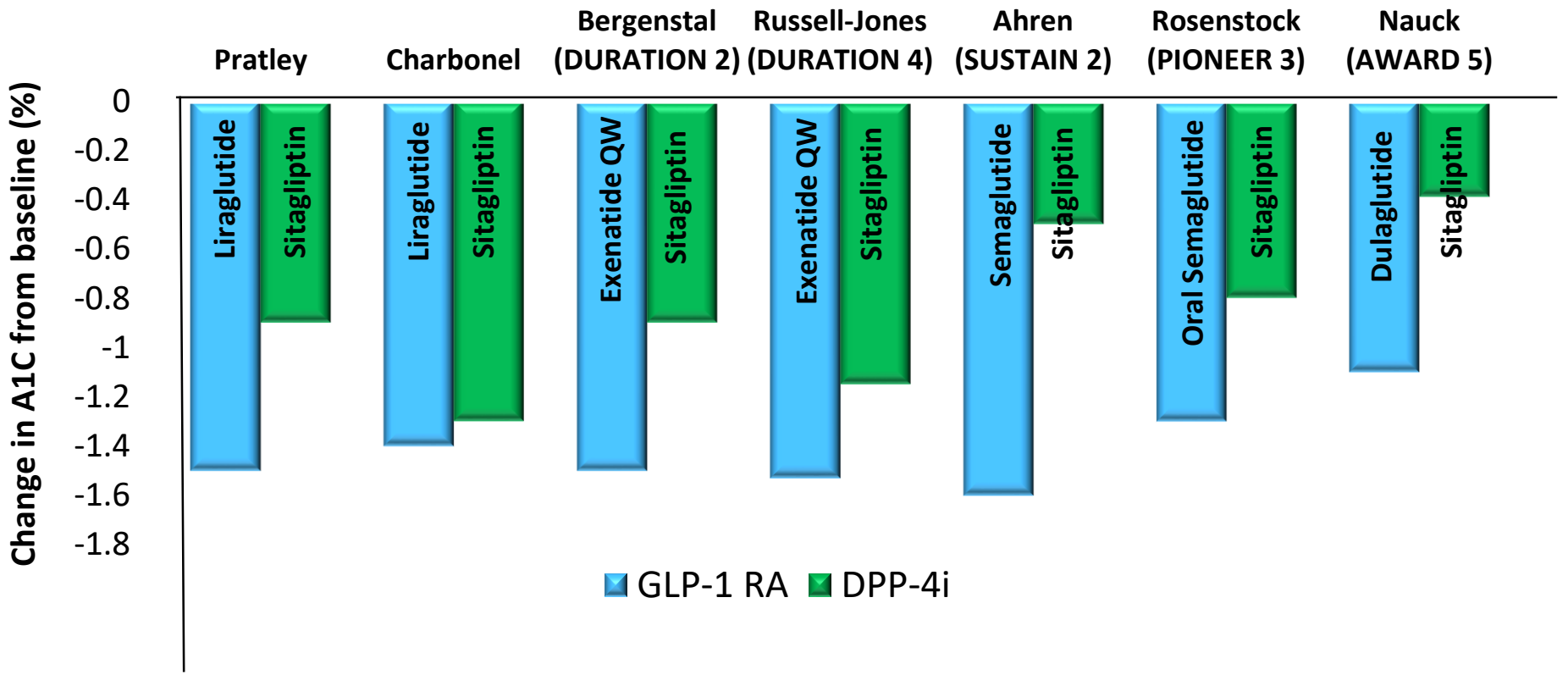
Ahrén B, et al. *Diabetes Care*. 2014;37(8):2141-8.; Bergenstal RM, et al. *Lancet*. 2010;376(9739):431-9.; Garber A, et al. *Lancet*. 2009;373(9662):473-81.; Home PD, et al. *Diabetes Obes Metab.* 2015;17(2):179-87.; Marre M, et al. *Diabet Med*. 2009;26(3):268-78.; Nauck MA, et al. *Diabetes Care*. 2009;32(1):84-90.; Russell-Jones D, et al. *Diabetes Care*. 2012;35(2):252-8.

Weight: GLP-1 RAs vs. SU or TZD



Ahrén B, et al. *Diabetes Care*. 2014;37(8):2141-8.; Bergenstal RM, et al. *Lancet*. 2010;376(9739):431-9.; Garber A, et al. *Lancet*. 2009;373(9662):473-81.; Home PD, et al. *Diabetes Obes Metab*. 2015;17(2):179-87.; Marre M, et al. *Diabet Med*. 2009;26(3):268-78.; Nauck MA, et al. *Diabetes Care*. 2009;32(1):84-90.; Russell-Jones D, et al. *Diabetes Care*. 2012;35(2):252-8.

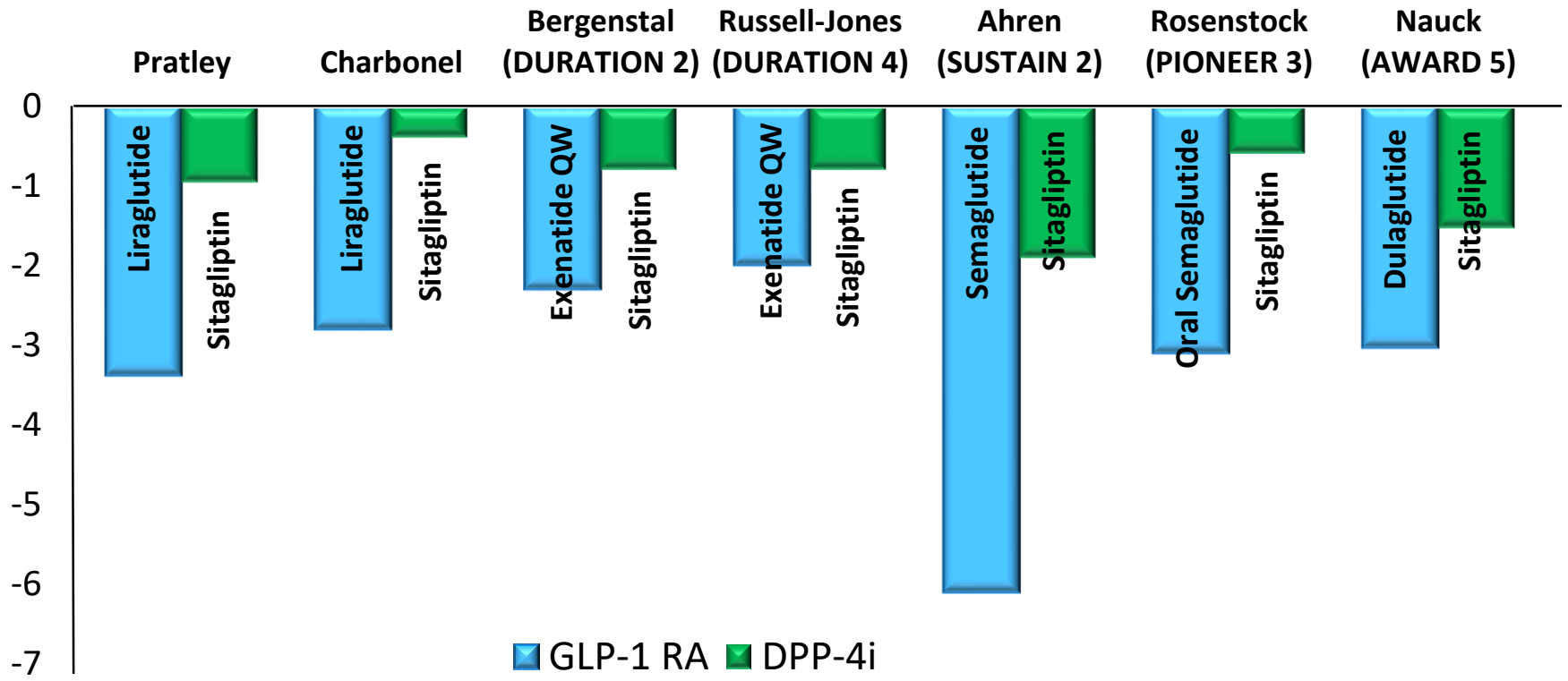
A1C: GLP-1 RAs vs. DPP-4 Inhibitors



DPP-4i, dipeptidyl peptidase 4 inhibitor.

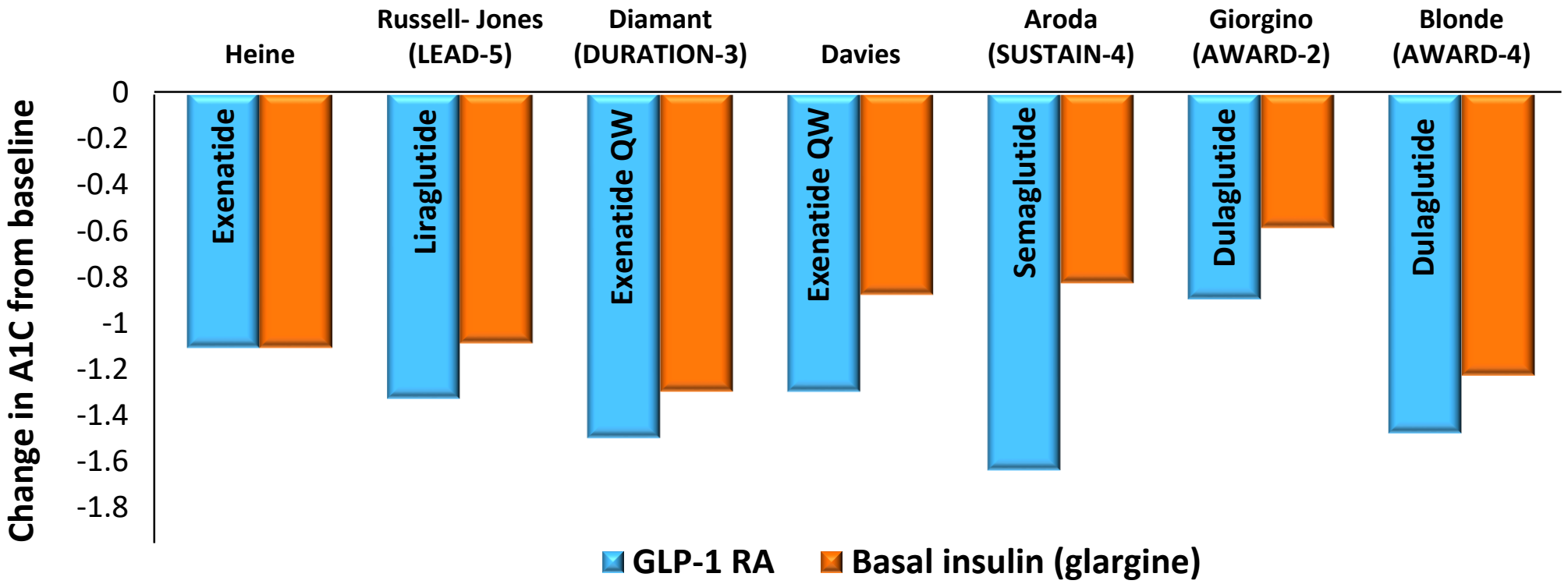
Ahrén B, et al. *Lancet Diab Endocrinol.* 2017;5(5):341-54.; Bergenstal RM, et al. *Lancet.* 2010;376(9739):431-9.; Charbonnel B, et al. *Diabetologia.* 2013;56(7):1503-11.; Nauck M, et al. *Diabetes Care.* 2014;37(8):2149-58.;Pratley RE, et al. *Lancet.* 2010;375(9724):1447-56.; Rosenstock J, et al. *JAMA*. 2019;321(15):1466-80.; Russell-Jones D, et al. *Diabetes Care.* 2012;35(2):252-8.

Weight: GLP-1 RAs vs. DPP-4 Inhibitors



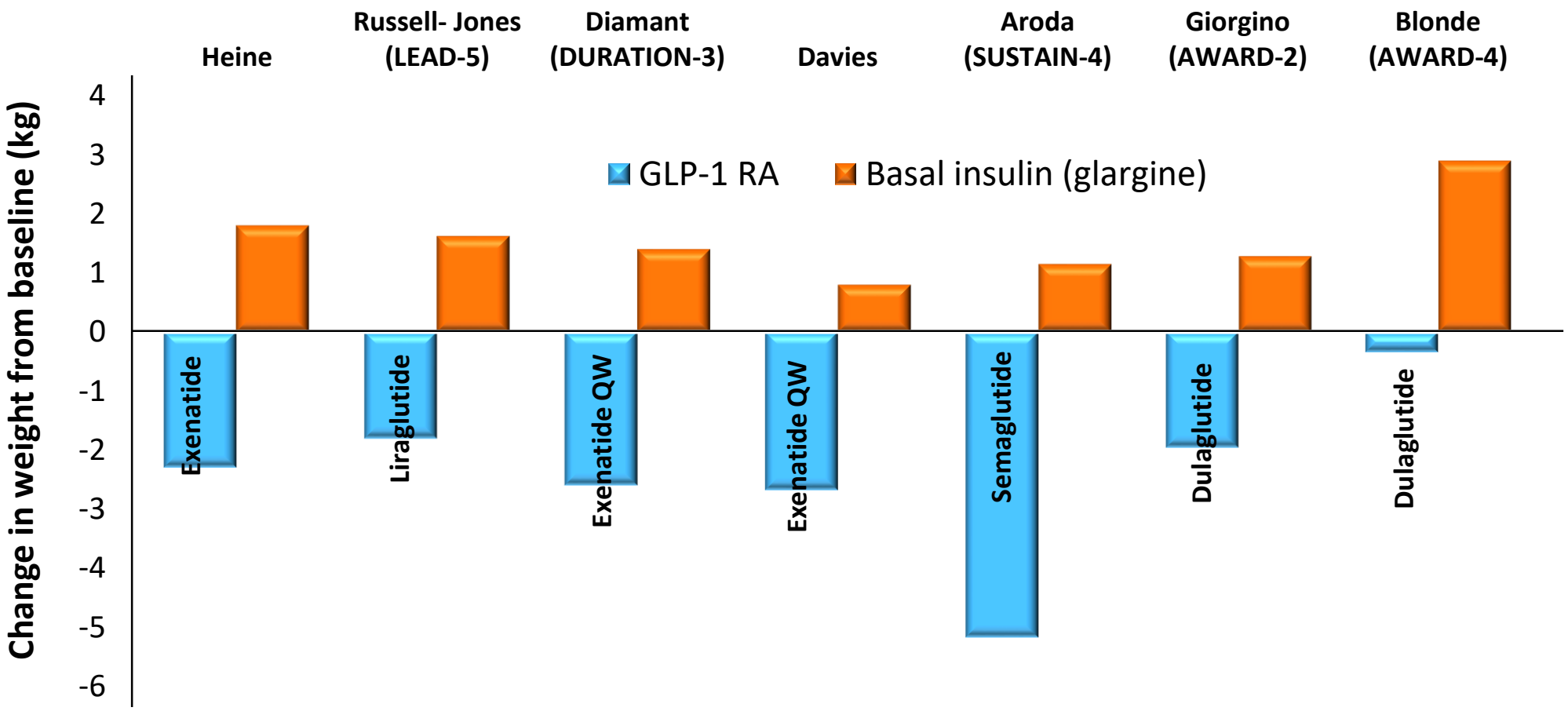
Ahrén B, et al. *Lancet Diab Endocrinol.* 2017;5(5):341-54.; Bergenstal RM, et al. *Lancet.* 2010;376(9739):431-9.; Charbonnel B, et al. *Diabetologia.* 2013;56(7):1503-11.; Nauck M, et al. *Diabetes Care.* 2014;37(8):2149-58.;Pratley RE, et al. *Lancet.* 2010;375(9724):1447-56.; Rosenstock J, et al. *JAMA*. 2019;321(15):1466-80.; Russell-Jones D, et al. *Diabetes Care.* 2012;35(2):252-8.

A1C: GLP-1 RAs vs. Basal Insulin



Heine RJ, et al. *Ann Intern Med*. 2005; Russell-Jones D, et al. *Diabetologia*. 2009; Diamant M, et al. *Lancet*. 2010; Davies M, et al. *Diabetes Care*. 2013; Aroda VR, et al. *Lancet Diabetes Endocrinol*. 2017; Giorgino F, et al. *Diabetes Care*. 2015; Blonde L, et al. *Lancet*. 2015.

Weight: GLP-1 RAs vs. Basal Insulin



Heine RJ, et al. *Ann Intern Med*. 2005; Russell-Jones D, et al. *Diabetologia*. 2009; Diamant M, et al. *Lancet*. 2010; Davies M, et al. *Diabetes Care*. 2013; Aroda VR, et al. *Lancet Diabetes Endocrinol*. 2017; Giorgino F, et al. *Diabetes Care*. 2015; Blonde L, et al. *Lancet*. 2015.

Safety Concerns

ARS Question 3

Which of the following statements is TRUE about the safety profile of GLP-1 RAs?

A. The most common adverse effect is nausea, which is typically mild and transient
B. The most common adverse effect is hypoglycemia, which is more common with the long-acting agents
C. The most common adverse effect is diarrhea, which can be mitigated by starting at a low dose and titrating slowly
D. The most common adverse effect is pancreatitis; these agents should not be used in patients with a history of pancreatitis

Documented Safety Issues

- Gastrointestinal
  - **Nausea**, vomiting, diarrhea
  - Usually mild and transient
  - Possibility that drug needs to be discontinued in a minority of patients
- Injection-site reactions
  - Pruritus
  - Nodules (exenatide XR)
- Low risk of hypoglycemia
  - Increased glucose-***dependent*** insulin secretion
  - Risk increases when used in combination with insulin or SU

Documented Safety Issues

Drug	Phase 3 clinical program	Nausea (%)^	Vomiting (%)^	Diarrhea (%)^	Injection-site reactions (%)
Exenatide	AMIGO	8-44*	4-18*	6-18*	5.1
Lixisenatide	GetGoal	25	10	8	3.9
Liraglutide	LEAD	18-20	6-9	10-12	2.0
Exenatide XR	DURATION	8.2	3.4	4	23.9
Dulaglutide	AWARD	12.4-21.1	6-12.7	8.9-12.6	0.5
Semaglutide	SUSTAIN	15.8-20.3	5-9.2	8.8-8.9	0.2
Oral semaglutide	PIONEER	11-20	6-8	9-10	N/A

^averages from phase 3 trials taken from prescribing information; ranges based on different doses, except for exenatide
*ranges based on reported data from separate studies based on background therapy

Trujillo JM. “Glucagon-Like Peptide-1 Receptor Agonists.” In: White JR, Ed. *2019 Guide to Medications for the Treatment of Diabetes Mellitus*. American Diabetes Association;2019:190-210.

Mitigation of Common Adverse Effects

- Nausea
  - Educate the patient that it is usually mild and usually transient
  - Resolves in ~90% of cases
  - Educate patients to decrease portions and eat slowly
  - Start at low dose
- Hypoglycemia
  - Consider the potential risk
  - Educate the patient
  - May need to decrease the dose of insulin or insulin secretagogue depending on baseline glucose and A1C levels

Cefalu WT, et al. *Diabetes Care.* 2014;37(9):2647-59.;
Nauck M. *Diabetes Care.* 2013;36(7):2126-32.;
Shomali M. *Clin Diabetes.* 2014;32(1):32-43.

Potential Safety Issues

- Acute pancreatitis
  - Post-marketing case reports and observational studies
  - Causal relationship has not been established
  - No established link to pancreatic cancer
  - 2 recent meta-analyses and reviews of RCTs concluded that treatment with GLP-1 RA was not associated with an increased risk of acute pancreatitis or pancreatic cancer
  - Use cautiously in patients with a history of pancreatitis
  - Monitor for signs/symptoms of pancreatitis
  - Discontinue GLP-1 RA if pancreatitis develops

RCTs, randomized controlled trials.

Monami M, et al. *Diabetes Obes Metab*. 2017;19(9):1233-41.;
Storgaard H, et al. *Diabetes Obes Metab.* 2017;19(6):906-8.

Potential Safety Issues

- Medullary Thyroid Carcinoma: **Black Box Warning**
  - Increased C-cell hyperplasia and MTCs in rodents
  - Contraindicated in patients with personal or family history of MTC

WARNING: RISK OF THYROID C–CELL TUMORS

See full prescribing information for complete boxed warning.

- **Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether VICTOZA® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **VICTOZA® is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors (4, 5.1).**

MTC, medullary thyroid carcinoma.

Victoza (liraglutide) injection [product information], 2019.

Potential Safety Issues

- Diabetic retinopathy complications
  - Seen in patients receiving **semaglutide** in SUSTAIN-6 (3% vs. 1.8%; p=0.02)
    - Included vitreous hemorrhage, blindness, or need for treatment with photocoagulation or an intravitreal agent
  - Most patients had a history of retinopathy at baseline
  - May just be due to rapid glucose lowering
  - Exercise caution when using semaglutide in patients with a history of diabetic retinopathy
    - Monitor patient closely for progression of retinopathy

Marso SP, et al. *New Engl J Med.* 2016;375(19):1834-44.;
Ozempic (semaglutide) injection [product information]. 2019.

Potential Safety Issues

- Immunogenicity
  - Concern with all therapeutic proteins
  - More common with exendin-4 agents
  - Patients with antibody formation may have decreased glycemic response

- Acute cholelithiasis
  - Small but significant increased risk
  - Mechanism not understood
  - Evaluation of over 90 trials involving 17,232 patients taking a GLP-1 RA versus 14,872 taking a comparator: 141 vs. 99 cases; HR 1.3 (95% CI 1.01-1.68, p=0.041)

Monami M, et al. *Diabetes Obes Metab*. 2017;19(9):1233-41.

Within-Class Comparisons

ARS Question 4

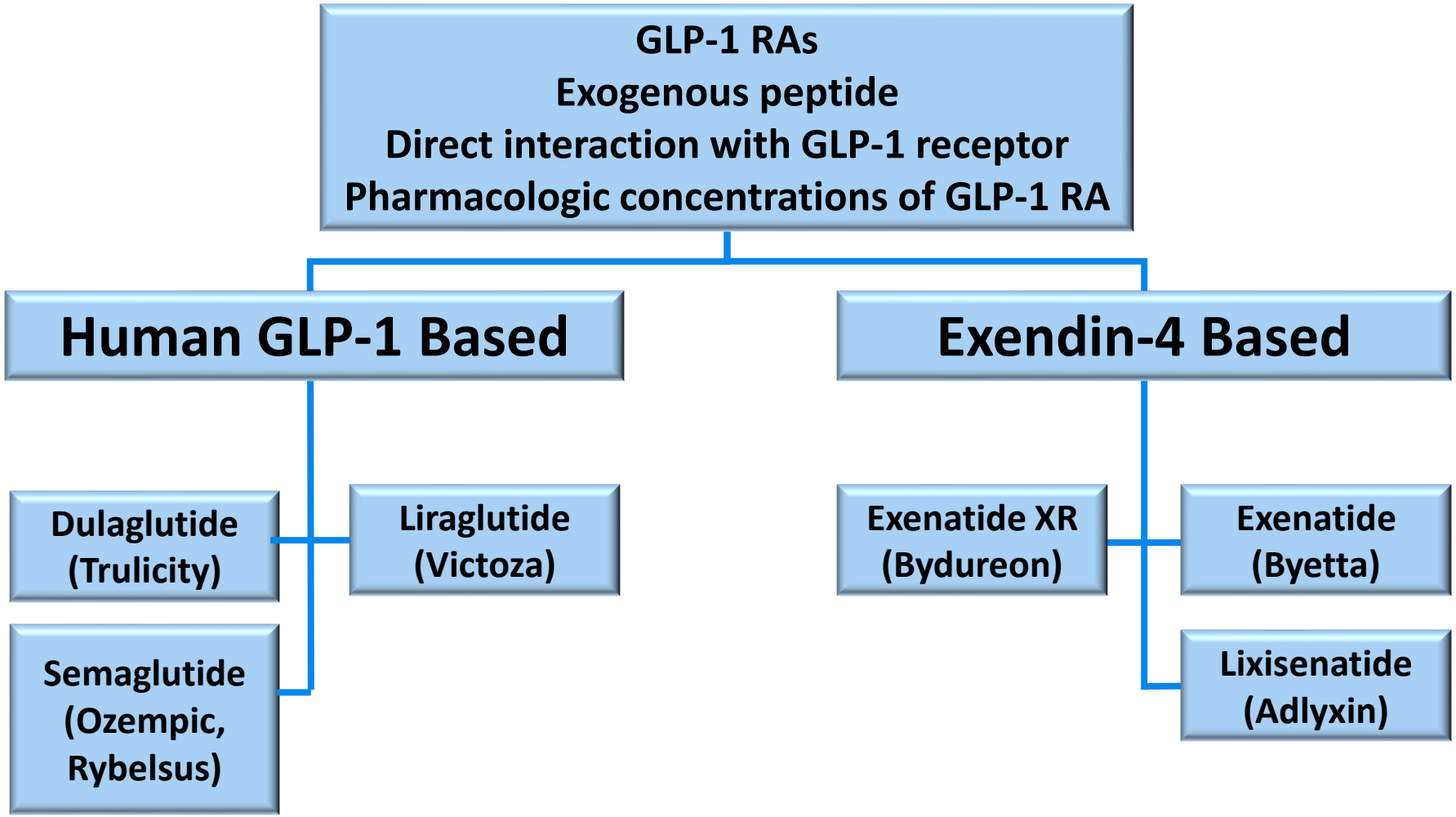
Which of the following statements is TRUE regarding the GLP-1 RA class?

A. All GLP-1 RAs lower A1C by the same amount
B. All GLP-1 RAs have the same rate of nausea
C. All GLP-1 RAs have demonstrated similar results in CVOTs
D. There are differences in efficacy and safety among GLP-1 RAs

Potential Within-Class Differences

- A1C-lowering efficacy
- Weight-lowering efficacy
- Effect on glucose profile (FPG vs. PPG)
- CV or renal protection evidence
- Rates of GI adverse effects
- Homology to native GLP; rates of immunogenicity
- Dosing, administration, ease of use, cost

FDA-Approved GLP-1 RAs



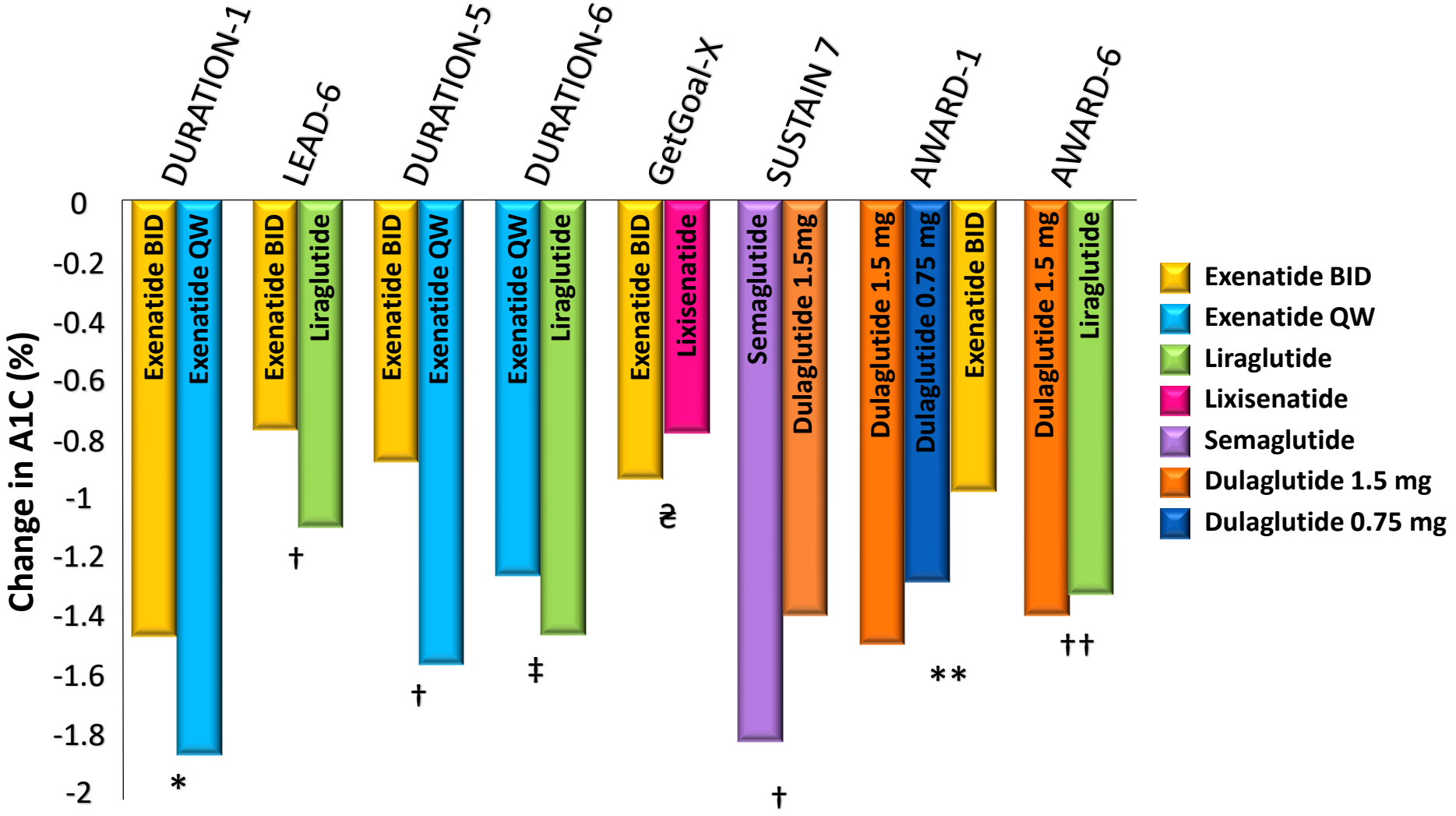
Comparison of Injectable GLP-1 RAs

	Short-acting		Long-acting			
	Exenatide (Byetta)	Lixisenatide (Adlyxin)	Liraglutide (Victoza)	Exenatide XR (Bydureon)	Dulaglutide (Trulicity)	Semaglutide (Ozempic)
Homology to native GLP-1	53%	50%	97%	53%	90%	94%
Glucose profile target	PPG	PPG	FPG/PPG	FPG > PPG	FPG > PPG	FPG > PPG
Administration	Twice daily	Once daily	Once daily	Once weekly	Once weekly	Once weekly
Delivery	Multi-use pen	Multi-use pen	Multi-use pen	Single-use pen*	Single-use pen	Multi-use pen
Renal dosing	CrCl < 30 mL/min, not recommended; CrCl 30-50 mL/min, use caution	None	None	CrCl < 30 mL/min, not recommended; CrCl 30-50 mL/min, use caution	None	None
Antidrug antibodies	44%	70%	8.6%	42.2%	1.6%	1.0%

CrCl, creatinine clearance.

*Requires reconstitution

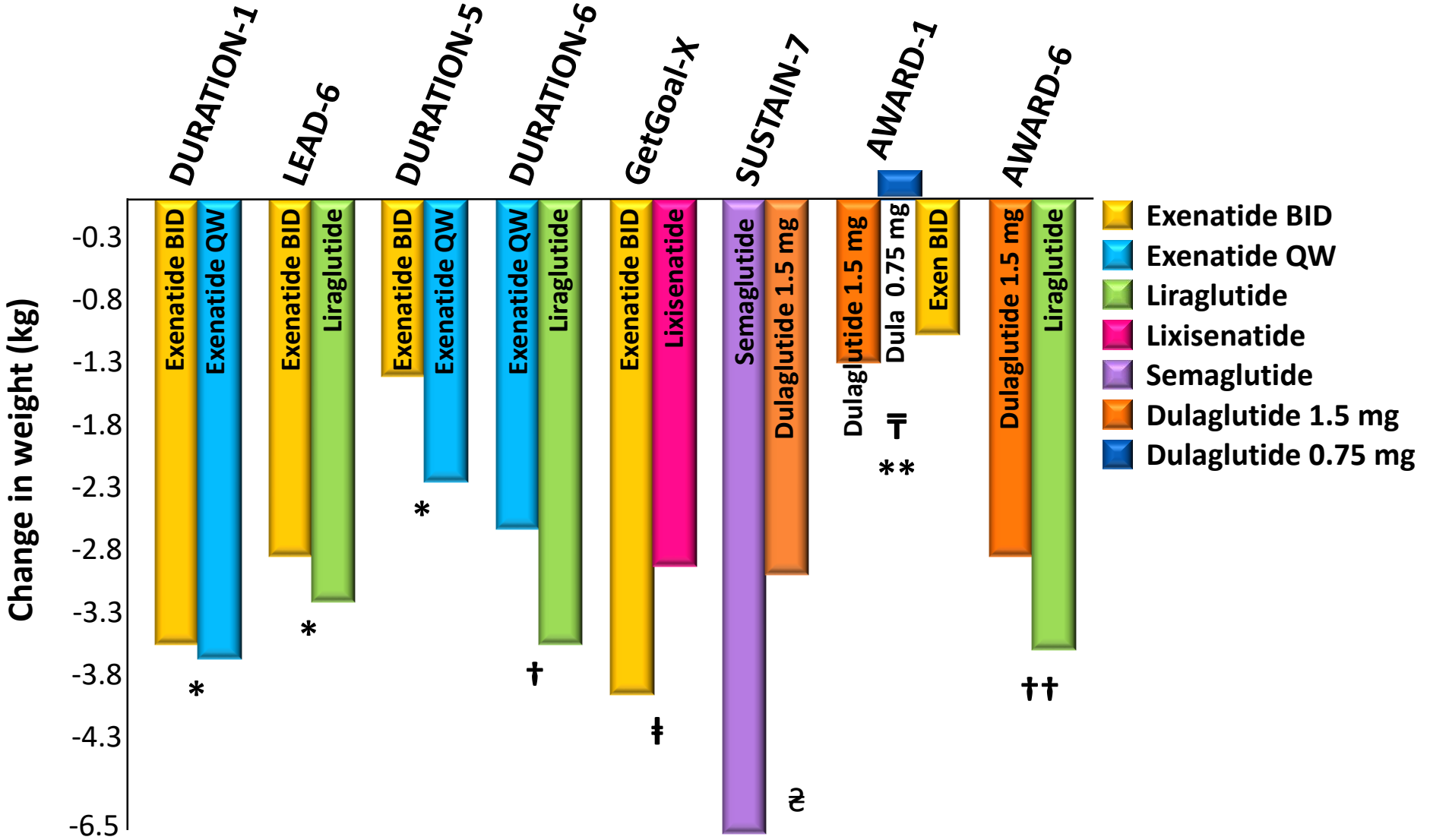
A1C: Head-to-Head Injectable GLP-1 RA Trials



*P<.0025; †P<.0001; ‡P=.02; ₴ P=NS; **P<.001; †† P=NS (non-inferiority P-value <.0001, meeting predefined non-inferiority margin)

Trujillo JM, et al. *Ther Adv Endocrinol Metab*. 2015;6(1):19-28.
Pratley RE, et al. Lancet Diab Endocrinol 2018:6(4):275-286.

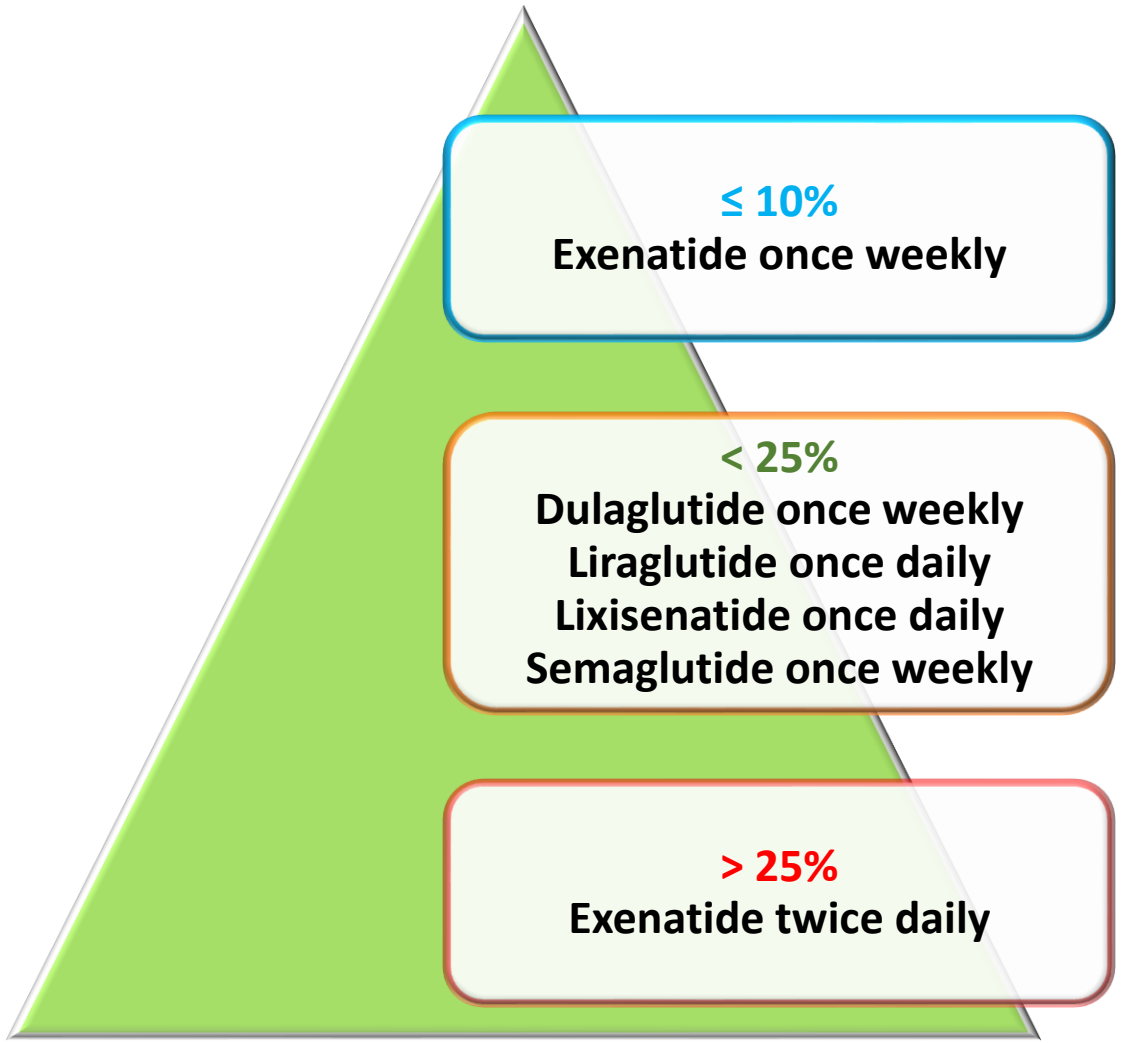
Weight: Head-to-Head Injectable GLP-1 RA Trials



*P=NS; †P=.0005; ‡P-value not reported for weight difference of 1.02 kg; ₴ P<.0001; ₸ P<.001 dulaglutide 0.75 mg vs. exenatide BID; **P=NS dulaglitide 1.5 mg vs. exenatide BID; ††P=.011

Trujillo JM, et al. *Ther Adv Endocrinol Metab*. 2015;6(1):19-28.
Pratley RE, et al. Lancet Diab Endocrinol 2018:6(4):275-286.

Prevalence of Nausea from Head-to-Head Trials



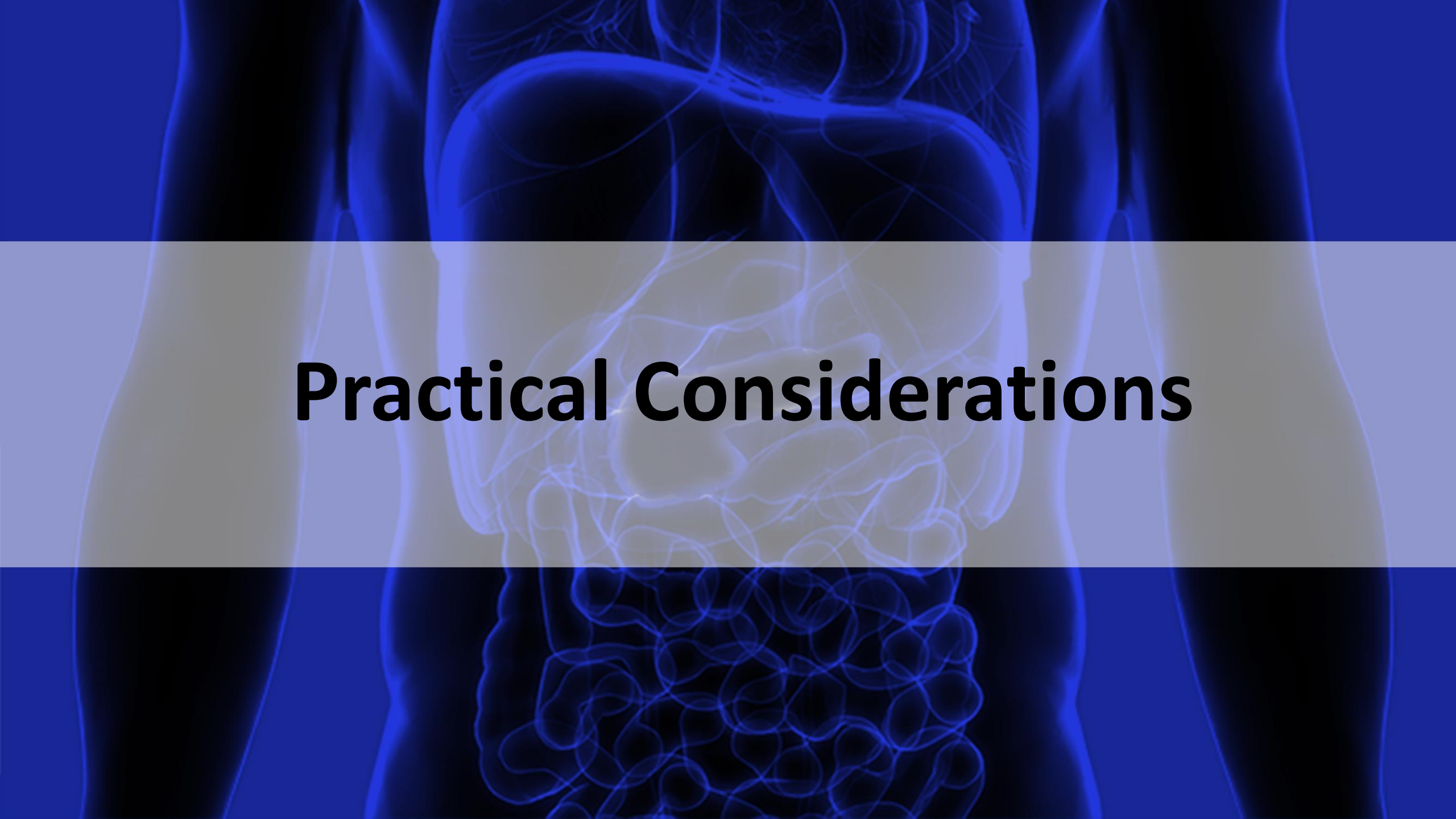
CVOTs: Injectable GLP-1 RAs

Drug	Study	Patient population	Primary Endpoint	Other endpoints
Liraglutide (Victoza)	LEADER	81% with ASCVD	↓ MACE	↓ CV mortality ↓ CKD progression
Lixisenatide (Adlyxin)	ELIXA	100% with ASCVD	Safety; no benefit	
Exenatide XR (Bydureon)	EXSCEL	73% with ASCVD	Safety; no benefit	
Semaglutide (Ozempic)	SUSTAIN	60% with ASCVD	↓ MACE	↓ Stroke ↓ CKD progression
Dulaglutide (Trulicity)	REWIND	31% with ASCVD	↓ MACE (both in 1^{o} and 2^{o} prevention)	↓ CKD progression

ASCVD, atherosclerotic cardiovascular disease;
CKD, chronic kidney disease;
MACE, major adverse cardiovascular event.

Injectable GLP-1 RAs: Comparisons

	Exenatide (Byetta)	Lixisenatide (Adlyxin)	Liraglutide (Victoza)	Exenatide XR (Bydureon)	Dulaglutide (Trulicity)	Semaglutide (Ozempic)
A1C	Least	Least	Most	Middle	Middle	**Most Most**
Weight	Least	Least	Most	Middle	Middle	**Most Most**
GI adverse effects	Most	Most	Middle	**Least**	Middle	Most
Demonstrated CV effects	Not studied	Safety	**Benefit**	Safety	**Benefit**	**Benefit**



Practical Considerations

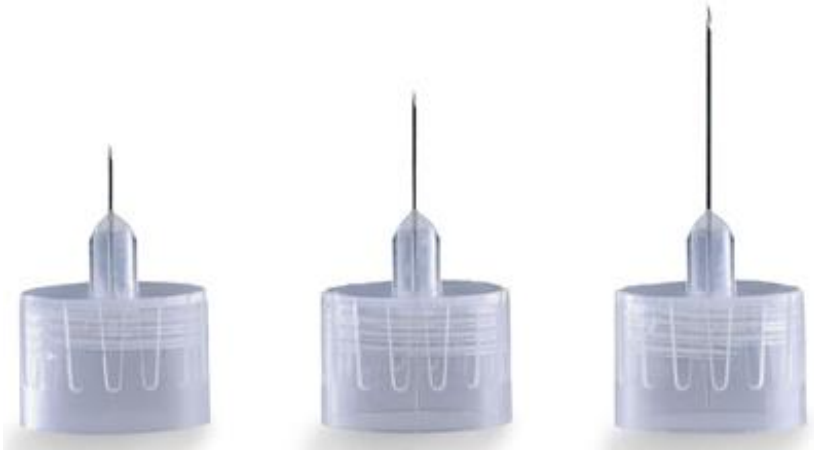
ARS Question 5

Which of the following statements is TRUE regarding the use and administration of injectable GLP-1 RAs?

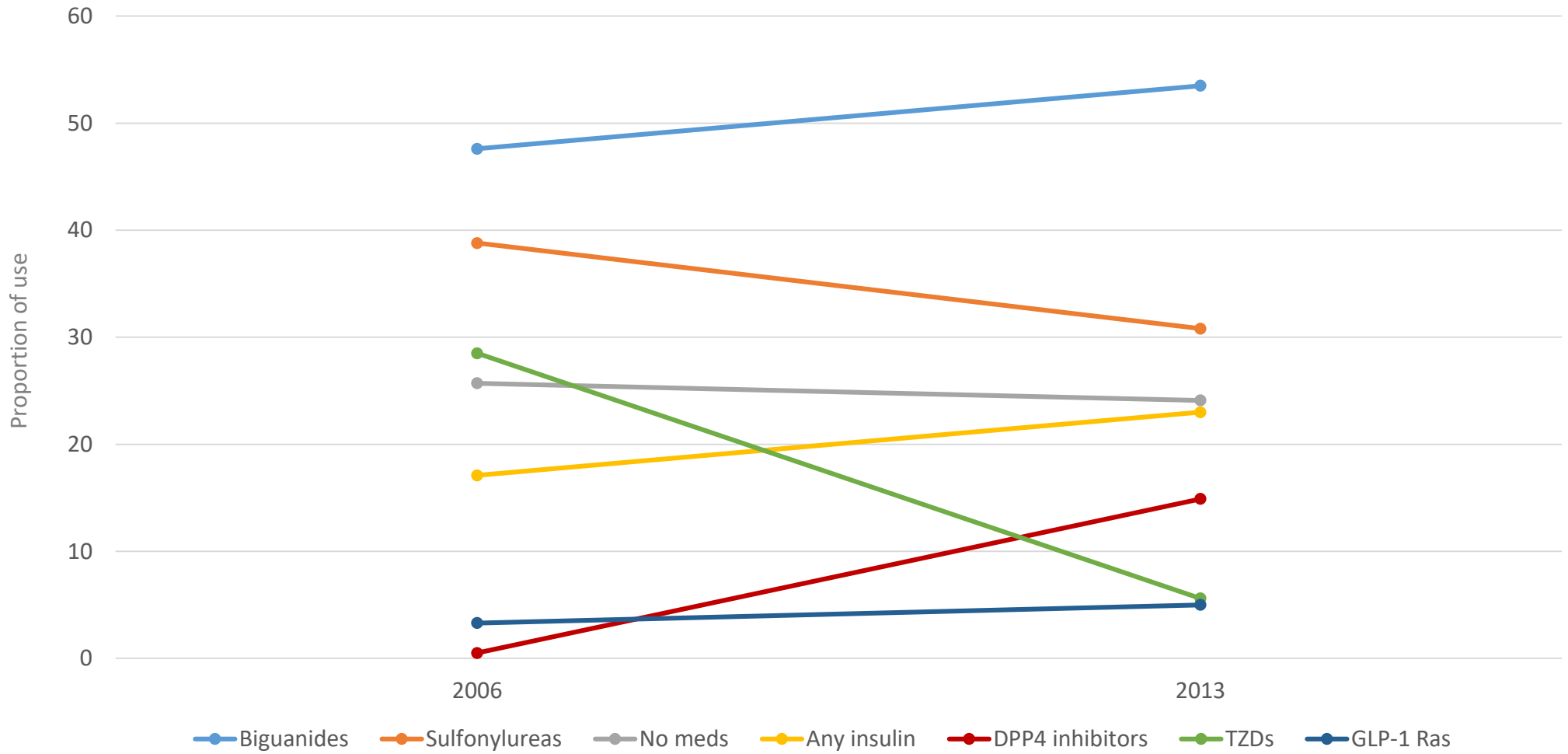
a. Liraglutide should not be used in patients with CrCl < 30 mL/min
b. Semaglutide is available in a single-dose pen device with pen needles included
c. All GLP-1 receptor agonists require dose titration to minimize GI adverse effects
d. Exenatide XR requires reconstitution immediately prior to injecting

Practical Issues with GLP-1 RAs

- Need for education and training
- Need for additional supplies or prescriptions with some products
- Low acceptance and use by primary care



Use of Medications for Type 2 Diabetes



Lipska KJ, et al. *Diabetes Care.* 2017;40(4):468-75.

Patient-Reported Outcomes

- 26-week randomized, open-label study
  - N=658
- Significantly greater improvements in treatment satisfaction and health-related quality of life with liraglutide vs. sitagliptin even with…..
  - Injectable vs. oral
  - Higher rates of side effects
- Greater perceived efficacy and weight loss

Patients are satisfied with injectable agents if they offer an advantage over oral treatments

Davies M, et al. *Diabet Med.* 2011;28(3):333-7.;
Davies M, Speight J. *Diabetes Obes Metab.* 2012;14(10):882-92.

Comparison of Injectable GLP-1 RAs

	Short-acting		Long-acting			
	Exenatide (Byetta)	Lixisenatide (Adlyxin)	Liraglutide (Victoza)	Exenatide XR (Bydureon)	Dulaglutide (Trulicity)	Semaglutide (Ozempic)
Dose	5 mcg twice daily for 1 month; increase to 10 mcg twice daily	10 mcg once daily x 14 days; increase to 20 mcg daily	0.6 mg once daily x 1 week; increase to 1.2 mg daily x 1 week; increase to 1.8 mg daily	2 mg once weekly	0.75 mg once weekly; increase to 1.5 mg once weekly	0.25 mg once weekly x 4 weeks; increase to 0.5 mg x 4 weeks; increase to 1 mg once weekly
Administration frequency	Twice daily	Once daily	Once daily	Once weekly	Once weekly	Once weekly
Specific administration requirements	Take within 60 minutes before meals	Take within 60 minutes before morning meal	Take at same time each day	Take on same day each week		
Delivery	Multi-use pen (2 strengths)	Multi-use pen (2 strengths)	Multi-use pen	Single-use pen*	Single-use pen (2 strengths)	Multi-use pen (2 pen options)
Renal dosing	CrCl < 30 mL/min, not recommended; CrCl 30-50 mL/min, use caution	None	None	CrCl < 30 mL/min, not recommended; CrCl 30-50 mL/min, use caution	None	None

*Requires reconstitution; two pen devices available (Bydureon and Bydureon BCise; both with different reconstitution and preparation requirements

GLP-1 RAs: Administration Considerations

- Storage
- Multi-use vs. single-use
- Needle attachment
- Reconstitution
- Dose titration
- Inject into subcutaneous tissue
  - abdomen, thigh, arm

Cost and Formulary Considerations

Monthly costs of GLP-1 RAs*					
Exenatide (Byetta)	Lixisenatide (Adlyxin)	Liraglutide (Victoza)	Exenatide XR (Bydureon)	Dulaglutide (Trulicity)	Semaglutide (Ozempic)
$731	**$622**	**$921**	**$691**	**$657**	**$773**

- What the health plan assumes
- What the patient assumes
- Cost versus other agents: consider total cost
  - Cost of hypoglycemia
  - Cost of supplies, additional self-monitoring of blood glucose
- Use of co-pay cards

**Monthly costs taken from goodrx.com on November 11, 2019.*

New and Emerging Agents

Injectable Fixed-Ratio Combinations

- IDegLira (Xultophy 100/3.6)
  - Insulin degludec (basal insulin) + liraglutide (GLP-1 RA)
  - Fixed ratio
    - Each dose step = 1 unit insulin degludec + 0.036 mg liraglutide
- iGlarLixi (Soliqua 100/33)
  - Insulin glargine (basal insulin) + lixisenatide (GLP-1 RA)
  - Fixed ratio
    - Each dose step = 3 units insulin glargine + 1 µg lixisenatide

Aroda VR, et al. *Diabetes Care.* 2016;39(11):1972-80.;
Gough SCL, et al. *Expert Rev Endocrinol Metab.* 2016;11(1):7-19.

GLP-1 RAs + Basal Insulin

- **GLP-1 RAs**

✓Fasting and post-prandial glycemic control

✓Weight reduction

✓Low hypoglycemic risk

❖GI adverse effects

- **Basal insulin**

✓Fasting glycemic control

✓Individualized dosing

❖Hypoglycemic risk

❖Weight gain

GLP-1 RAs + Basal Insulin

- Meta-analysis: 15 studies included
- GLP-1 RA + basal insulin vs. other treatments
- Variety of background therapies and active comparators
- Results
  - Improved mean reduction in A1C: -0.44%
    (95% CI, -0.60 to -0.29)
  - No increased relative risk of hypoglycemia
    (HR 0.99; 95% CI, 0.76-1.29)
  - Mean reduction in weight: -3.22 kg (95% CI, -4.90 to -1.54)

Fixed-Ratio Combinations: Clinical Evidence

	Treatment groups	Δ A1C from baseline (%)	Δ Weight from baseline (kg)	Hypoglycemia (%)	Nausea (%)
LixiLan-O (metformin ± 2nd OAD)	iGlarLixi	-1.6	-0.3	25.6	9.6
	iGlar	-1.3	+1.1	23.6	3.6
	Lixisenatide	-0.9	-2.3	6.4	24
LixiLan-L (basal ± 2 OADs)	iGlarLixi	-1.1	-0.7	40	10.4
	iGlar	-0.6	+0.7	42.5	0.5
DUAL-1 (metformin ± pioglitazone)	iDegLira	-1.9	-0.5	32	8.8
	iDeg	-1.4	+1.6	39	3.6
	Liraglutide	-1.3	-3.0	7	19.7
DUAL-2 (basal + metformin ± SU)	iDegLira	-1.9	-2.7	24	6.5
	iDeg	-0.9	0	25	3.5

OAD, oral antidiabetic drug.

Aroda VR, et al. *Diabetes Care.* 2016;39(11):1972-80.; Buse JB, et al. *Diabetes Care.* 2014;37(11):2926-33.; Gough SCL, et al. *Expert Rev Endocrinol Metab.* 2016;11(1):7-19.; Rosenstock J, et al. *Diabetes Care.* 2016;39(11):2026-35.

Injectable Fixed-Ratio Combinations

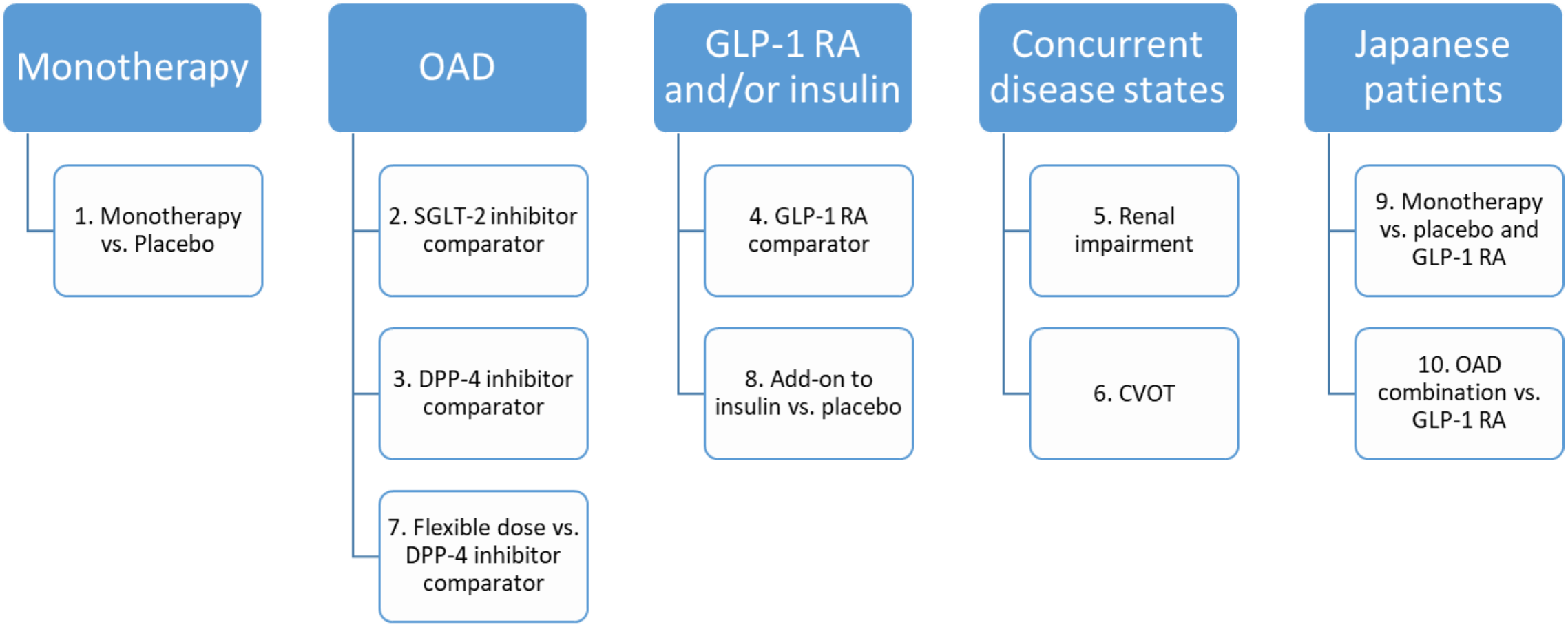
- **Indication recently expanded**: adjunct to diet and exercise
- iDegLira (Xultophy 100/3.6)
  - Starting dose
    - Insulin or GLP-1 RA naïve: 10 units (10 units iDeg and 0.36 mg Lira)
    - On basal insulin or GLP-1 RA: 16 units (16 units iDeg and 0.58 mg Lira)
  - Max dose: 50 units (50 units iDeg and 1.8 mg Lira)
- iGlarLixi (Soliqua 100/33)
  - Starting dose
    - If insulin or GLP-1 RA naïve or if on < 30 units/day of basal insulin: 15 units (15 units iGlar and 5 mcg Lixi)
    - If on 30-60 units/day of basal insulin: 30 units (30 units iGlar and 10 mcg Lixi)
  - Max dose: 60 units (60 units iGlar and 20 mcg Lixi)

Aroda VR, et al. *Diabetes Care.* 2016;39(11):1972-80.;
Gough SCL, et al. *Expert Rev Endocrinol Metab.* 2016;11(1):7-19.

Oral Semaglutide

- Co-formulated with an absorption enhancer: sodium-N-[8 (2-hydroxylbenzoyl) amino] caprylate (SNAC)
- Absorbed in the stomach where SNAC causes a localized increase in pH
  - Leads to higher solubility and protection against proteolytic degradation
- Long half-life, low molecular weight, high potency, molecular stability
- Approved by the FDA on September 20, 2019 (Rybelsus)

PIONEER Phase 3 Clinical Trial Program



Oral Semaglutide Phase 3 Program

Study	Design	Main results
PIONEER 1	Monotherapy vs. placebo	Superior reduction in A1C and weight
PIONEER 2	Semaglutide vs. empagliflozin	Superior reduction in A1C No significant difference in weight loss
PIONEER 3	Semaglutide vs. sitagliptin	Superior reduction in A1C and weight
PIONEER 4	Semaglutide vs. liraglutide	Non-inferior reduction in A1C Superior reduction in weight
PIONEER 5	Moderate renal impairment vs. placebo	Superior reductions in A1C and weight
PIONEER 6	CVOT	Non-inferior
PIONEER 7	Flexible dosing escalation vs. sitagliptin	Superior reductions in A1C and weight
PIONEER 8	Insulin add-on vs. placebo	Superior reduction in A1C, weight, and insulin dose
PIONEER 9	Monotherapy vs. placebo and liraglutide (Japan)	Not published
PIONEER 10	Semaglutide vs. dulaglutide (Japan)	Not published

Oral Semaglutide: Administration Requirements

- Take at least 30 minutes before the first food, beverage, or other oral medication of the day
- Take with no more than 4 ounces of plain water only
- Swallow tablets whole: do not crush or chew

- Start with 3 mg once daily for 30 days
- Increase to 7 mg once daily for 30 days
- Dose may be increased to 14 mg once daily if needed

Rybelsus (semaglutide) tablets [product information]. 2019.

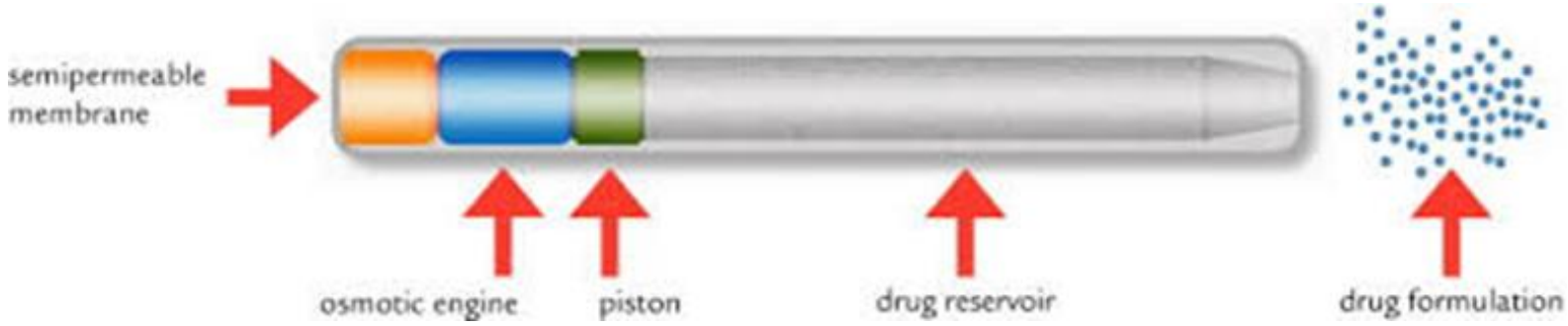
Oral Semaglutide: Place in Therapy

- Add-on to metformin
- Desire for weight loss
- Desire to avoid hypoglycemia
- Unable or unwilling to use injectable agent
- Able to adhere to oral administration instructions
- Renal function status that precludes use of metformin or SGLT2i

❖Has not demonstrated CV or renal protection

ITCA 650: Exenatide Implant

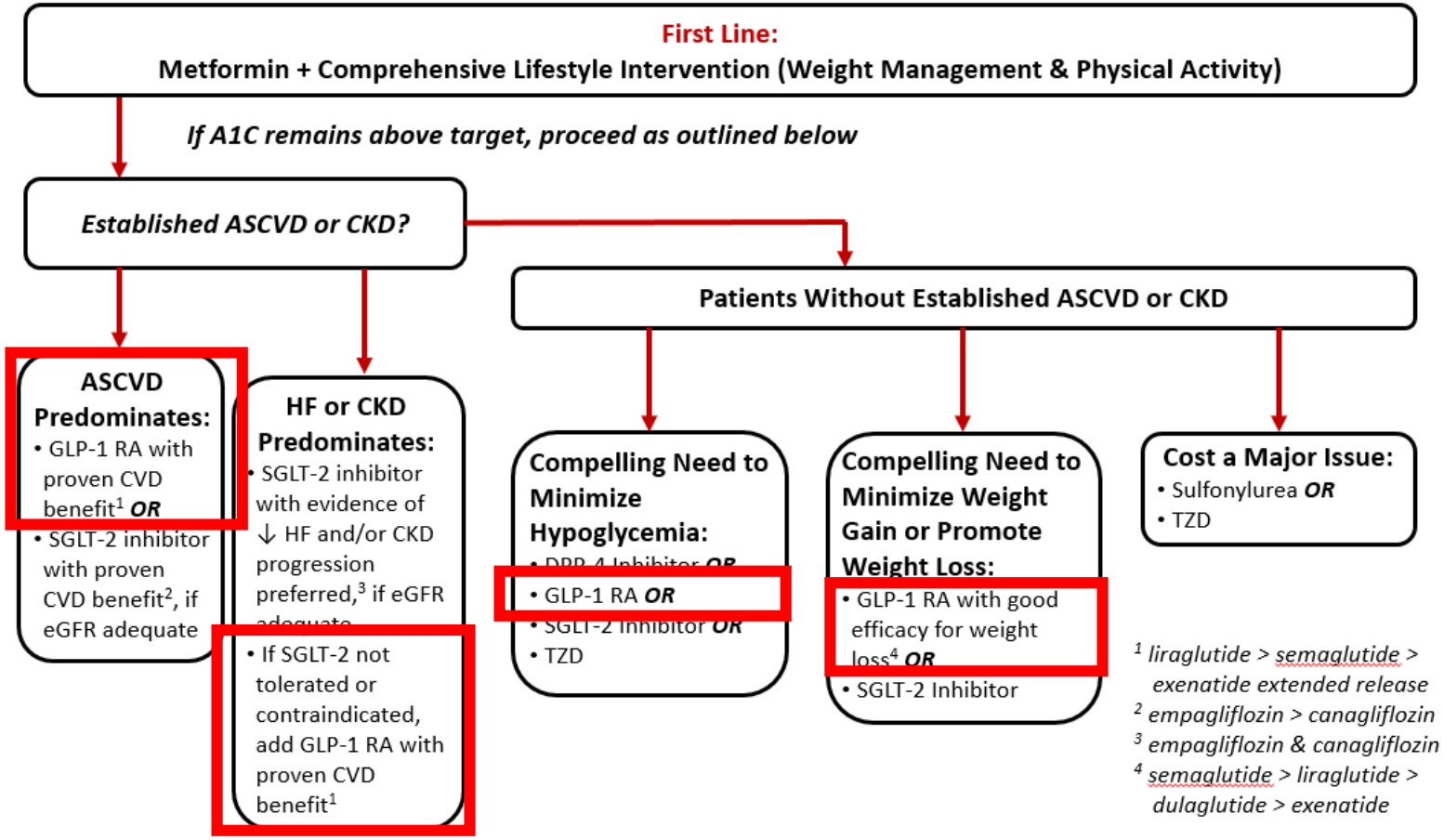
- Continuous and controlled subcutaneous delivery of exenatide
- NDA resubmitted to FDA in Sept 2019.



Bertsch T. et al. Clin Diabetes 2018;36(3):265-67.

Place in Therapy

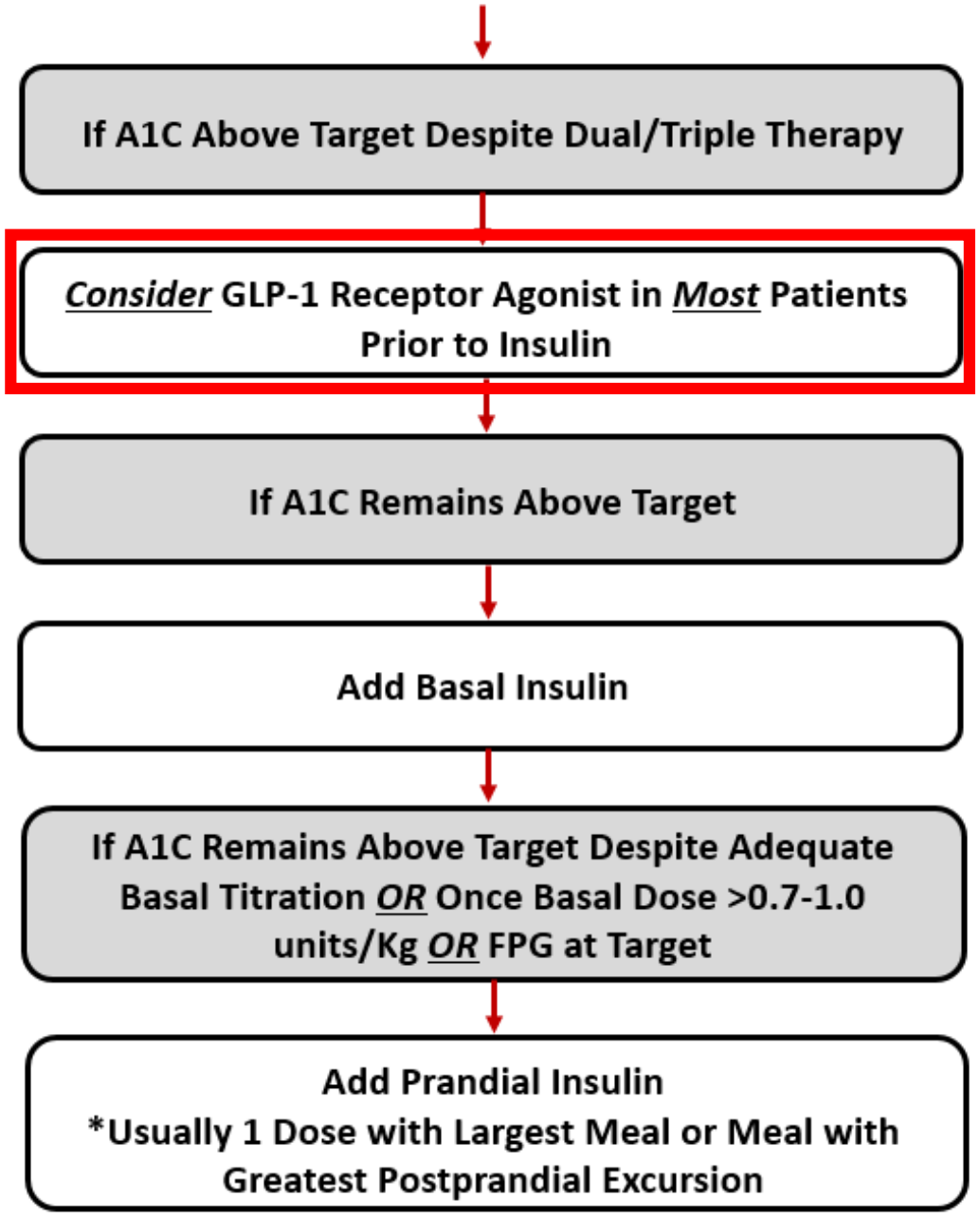
Where are the GLP-1 RAs in the guidelines?



American Diabetes Association. *Diabetes Care.* 2019;42(Suppl 1):S90-S102.

Where are the GLP-1 RAs in the guidelines?

- Consider GLP-1 RA as first injectable prior to insulin



American Diabetes Association. *Diabetes Care.* 2019;42(Suppl 1):S90-S102.

GLP-1 RAs: Pros & Cons

Pros:

- High efficacy
- Low hypoglycemia risk (monotherapy or combination with metformin)
- Cardiovascular & renal benefits
- Weight loss

Potential cons:

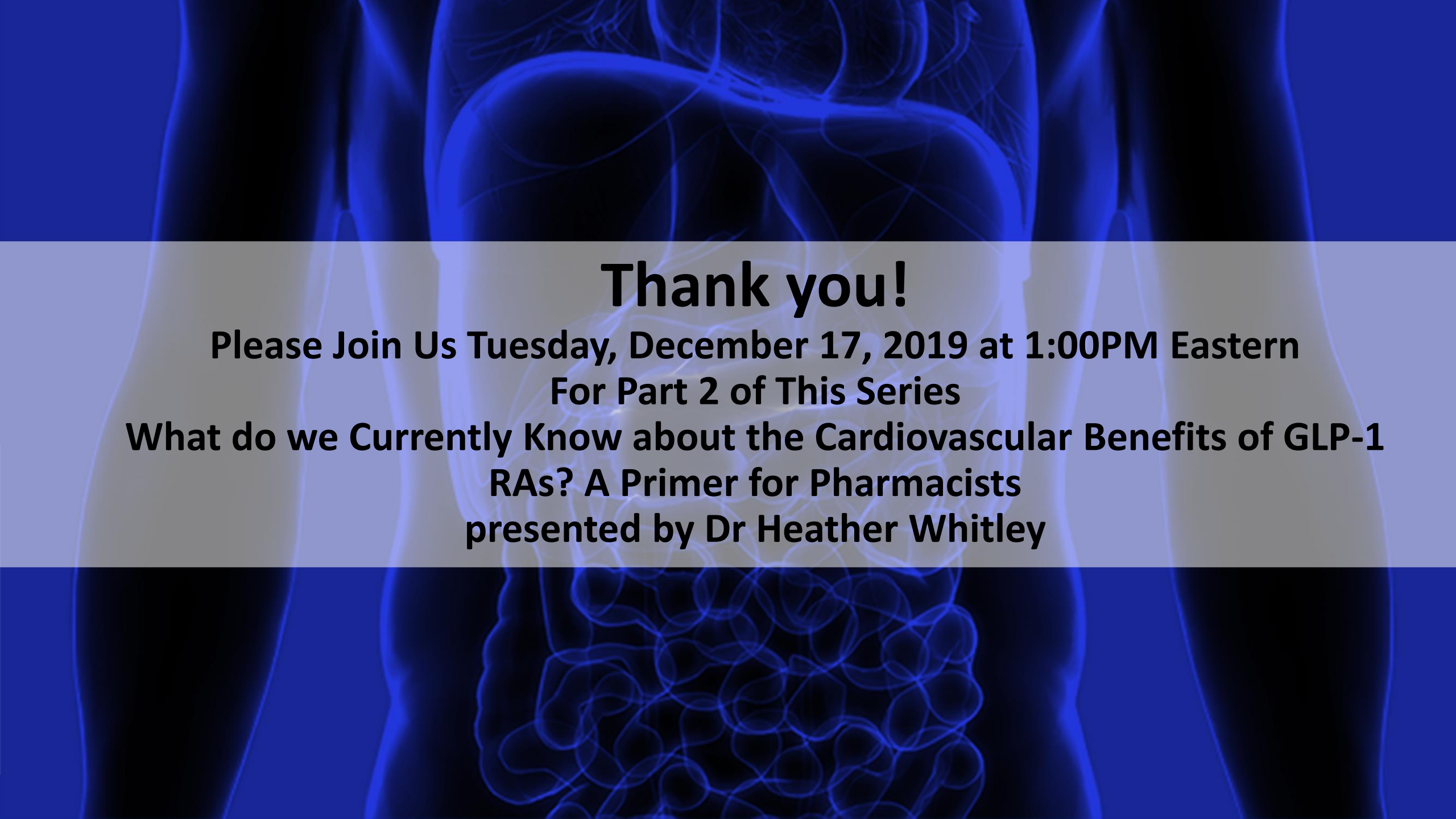
- Cost
- Need for renal dose adjustment (some)
- Injectable (most)
- GI intolerance (nausea, vomiting, diarrhea)
- **Rare/serious safety concerns**: thyroid C-cell tumors (long-acting agents), acute pancreatitis

American Diabetes Association. *Diabetes Care.* 2019;42(Suppl 1):S90-S102.


Question & Answer

Go to: https://www.powerpak.com/course/preamble/118952

- *Power-Pak* users
  - Sign-in with your ***PowerPak.com*** username and password
  - Click on the ***Take Evaluation*** button at the bottom of the page
- New *Power-Pak* users
  - Create a ***Power-Pak*** account
  - Click on the ***Take Evaluation*** button at the bottom of the page
- Your credit will be automatically uploaded to CPE Monitor
- Answers to the pre-/post-test questions will be available on the *Power-Pak* activity page



Thank you!

Please Join Us Tuesday, December 17, 2019 at 1:00PM Eastern
For Part 2 of This Series
What do we Currently Know about the Cardiovascular Benefits of GLP-1 RAs? A Primer for Pharmacists
presented by Dr Heather Whitley