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

Clinical Comparisons of GLP-1 RAs

	Generic name	Primary glucose profile target	Within class comparability of A1C lowering efficacy	Within class comparability of effect on weight	Within-class comparability of GI adverse effects	Dose	Route	Administration frequency
Short acting	Exenatide	PPG	Low	Low	High	5-10 mcg	SC	Twice daily (30-60 minutes before breakfast and dinner)
	Lixisenatide	PPG	Low	Low	High	10-20 mcg	SC	Twice daily (30-60 minutes before breakfast and dinner)
Long acting	Dulaglutide	FPG and PPG	High	Intermediate	Intermediate	0.75-1.5 mg	SC	Once weekly
	Exenatide XR	FPG and PPG	Intermediate	Intermediate	Low	2 mg	SC	Once weekly
	Liraglutide	FPG and PPG	High	High	Intermediate	0.6-1.8 mg	SC	Once daily
	Semaglutide	FPG and PPG	Highest	Highest	High	0.25-1 mg	SC	Once weekly
	Semaglutide (oral)	FPG and PPG	High	High	Intermediate	3-14 mg	PO	Once daily

FPG, fasting plasma glucose; GI, gastrointestinal; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; PO, by mouth; PPG, postprandial glucose; SC, subcutaneous.

Availability, Dosing, and Administration Requirements of GLP-1 RAs

Drug	Availability, storage, and preparation	Dosing	Missed dose recommendations	Use in renal impairment
Exenatide	• Multi-dose pens (5 mcg/dose and 10 mcg/dose; 60 doses per pen) • Pen needles not supplied with pen • Keep refrigerated • After first use, store at room temperature; discard 30 days after first use • No reconstitution required	• Start with 5 mcg twice daily • Increase to 10 mcg twice daily after 1 month, if needed for additional A1C lowering • Inject within 60 minutes prior to morning and evening meals (or before the 2 main meals of the day; administer ≥ 6 hours apart)	• Skip the dose and resume next dose at the prescribed time.	• Not recommended with severe renal impairment (eGFR or CrCl < 30 mL/min)
Lixisenatide	• Multi-dose pen (10 mcg/dose and 20 mcg/dose; 14 doses per pen) • Pen needles not supplied with pen • Keep refrigerated • After first use, store at room temperature; discard 14 days after first use • No reconstitution required	• Start with 10 mcg once daily for 14 days • Increase to 20 mcg once daily • Inject within 1 hour prior to first meal of the day	• Skip the dose and resume next dose at the prescribed time.	• No dose adjustment recommended; limited experience in severe renal impairment; avoid if eGFR < 15 mL/min
Liraglutide	• Multi-dose pen (6 mg/mL, 3-mL pen; each pen delivers doses of 0.6, 1.2, or 1.8 mg) • Pen needles not supplied with pen • Keep refrigerated • After first use, store at room temperature; discard 30 days after first use • No reconstitution required	• Start with 0.6 mg once daily for 1 week • Increase to 1.2 mg once daily • Increase to 1.8 mg once daily, if needed for additional A1C lowering • Inject at any time of day, with or without meals	• Skip the dose and resume next dose at the prescribed time.	• No dose adjustment recommended; limited experience in severe renal impairment
Exenatide XR	• Single-dose pen (2 mg): 2 pen options available with different preparation requirements (Bydureon or Bydureon BCise) • Pen needle supplied with pen • Keep refrigerated • Store flat in original packaging, protected from light • May store at room temperature for 4 weeks • Remove from refrigerator 15 minutes prior to mixing • Requires reconstitution • Dose should be administered immediately once reconstituted	• 2 mg once weekly • Inject at any time of day, with or without meals	• If within 3 days of missed dose, give right away. Resume dosing on usual day of administration. • If 3 days have passed, skip dose and resume on usual day of administration.	• Not recommended with severe renal impairment (eGFR or CrCl < 30 mL/min)

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Availability, Dosing, and Administration Requirements of GLP-1 RAs

Drug	Availability, storage, and preparation	Dosing	Missed dose recommendations	Use in renal impairment
Dulaglutide	• Single-dose pens (0.75 mg and 1.5 mg) • Pen needle attached • Keep refrigerated • May store at room temperature for 14 days • No reconstitution required	• Start with 0.75 mg once weekly • Increase to 1.5 mg once weekly, if needed for additional A1C lowering • Inject at any time of day, with or without meals	• If within 3 days of missed dose, give right away; resume dosing on usual day of administration • If 3 days have passed, skip dose and resume on usual day of administration	• No dose adjustment recommended; limited experience in severe renal impairment
Semaglutide	• Multi-dose pen (1.34 mg/mL; 1.5-mL pen; lower- dose pen delivers 0.25-mg or 0.5-mg doses; high-dose pen delivers 1-mg dose) • Pen needles supplied with pen • Keep refrigerated • After first use, store at room temperature; discard 56 days after first use • No reconstitution required	• Start with 0.25 mg once weekly • Increase to 0.5 mg once weekly after 4 weeks • May increase to 1 mg once weekly after 4 weeks, if needed for additional A1C lowering • Inject at any time of day, with or without meals	• If within 5 days of missed dose, give right away; resume dosing on usual day of administration • If 5 days have passed, skip dose and resume on usual day of administration	• No dose adjustment recommended
Semaglutide (oral)	• Oral tablets (3 mg, 7 mg, 14 mg)	• Start with 3 mg once daily for 30 days • Increase to 7 mg once daily • May increase to 14 mg once daily after 30 days, if needed for additional A1C lowering • Take at least 30 minutes before the first food, beverage, or other oral medication of the day with no more than 4 ounces of plain water only • Swallow tablets whole; do not crush or chew	• Skip the missed dose and resume regular schedule	• No dose adjustment recommended

CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; GLP-1 RAs, glucagon-like peptide-1 receptor agonists.

Combination GLP-1 RA and Basal Insulin Products

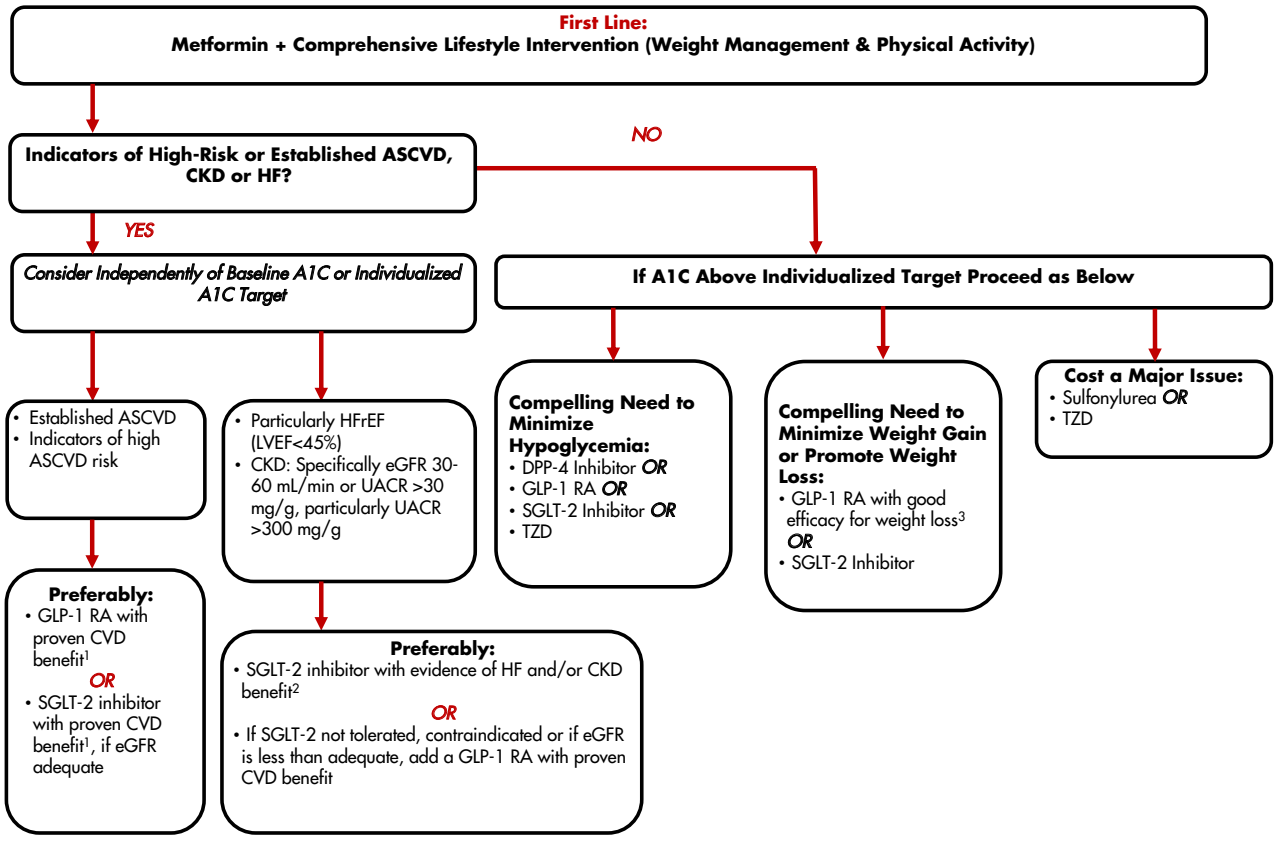
Drug	Availability, storage, preparation	Dosing
iDegLira 100/3.6 (insulin degludec and liraglutide)	• Multi-dose pen (insulin degludec 100 units/mL and liraglutide 3.6 mg/mL; 3-mL pen) • Each pen delivers doses based on insulin units; doses range from 10-50 units • Pen needles not supplied with pen • Keep refrigerated • After first use, store at room temperature; discard 21 days after first use	• If patient is insulin and GLP-1 RA naïve: start with 10 units insulin degludec/0.36 mg liraglutide once daily • If patient is currently on insulin or GLP-1 RA: discontinue current basal insulin or GLP-1 RA prior to initiation; start with 16 units insulin degludec/0.58 mg liraglutide once daily • Increase dose by 2 units every 3 to 4 days until FPG goal is reached; maximum dose is 50 units insulin degludec/1.8 mg liraglutide • Inject at any time of day, with or without meals
iGlarLixi 100/33 (insulin glargine and lixisenatide)	• Multi-dose pen (insulin glargine 100 units/mL and lixisenatide 33 mcg/mL; 3-mL pens) • Each pen delivers doses based on insulin units; doses range from 15-60 units • Pen needles not supplied with pen • Keep refrigerated • After first use, store at room temperature; discard 14 days after first use	• If patient is insulin and GLP-1 RA naïve or on < 30 units of basal insulin or on a GLP-1 RA: discontinue current basal insulin or GLP-1 RA prior to initiation; start with 15 units insulin glargine/5 mcg lixisenatide once daily • If uncontrolled on 30-60 units of basal insulin: discontinue current basal insulin or GLP-1 RA prior to initiation; start with 30 units insulin glargine/10 mcg lixisenatide once daily • Increase dose by 2-4 units every week until FPG goal is reached; maximum dose is 60 units insulin glargine/20 mcg lixisenatide • Inject within 1 hour before first meal of the day

Cardiovascular Outcome Trials Primary and Secondary Outcomes for GLP-1 RA

CV Endpoint	ELIXA lixisenatide	LEADER liraglutide	SUSTAIN semaglutide (SC)	EXSCEL Exenatide ER	PIONEER semaglutide (oral)	REWIND dulaglutide
Established ASCVD, n (%)	6068 (100)	6775 (72.5)	2735 (83.0)	2695 (84.7)	10,782 (73.1)	3114 (31.5)
Primary Endpoint reduction: 3-point MACE: composite first occurrence of CV death, nonfatal MI, nonfatal stroke	NI†	S	SS	NI	NI	S
CV Death reduction	NS	SS	NS	NS	SS*	NS
Non-fatal MI reduction	NS	NS	NS	NS	NS*	NS
Non-fatal stroke reduction	NS	NS	SS	NS	NS*	NS^
Hospitalized for heart failure reduction	NS	NS	NS	NS	NS*	NS
All cause death reduction	NS	SS	NS	NS+	SS*	NS

CV= cardiovascular
S = Superior; SS = statistically significant; NI = noninferior; NS = not statistically significant
† Primary endpoint = 3-point MACE + hospitalization for unstable angina
+Not considered statistically significant due to hierarchal testing
*Not controlled for multiple comparisons; interpreted as exploratory
^Not statistically significant due to study design requiring need to meet p-value of 0.007 for this endpoint
MACE = major adverse cardiovascular events

American Diabetes Association 2020 Standards of Medical Care in Diabetes: General Approach for Intensification to Dual Therapy in Type 2 Diabetes



1 Proven CVD benefit = drug has a label indication for reducing CVD events

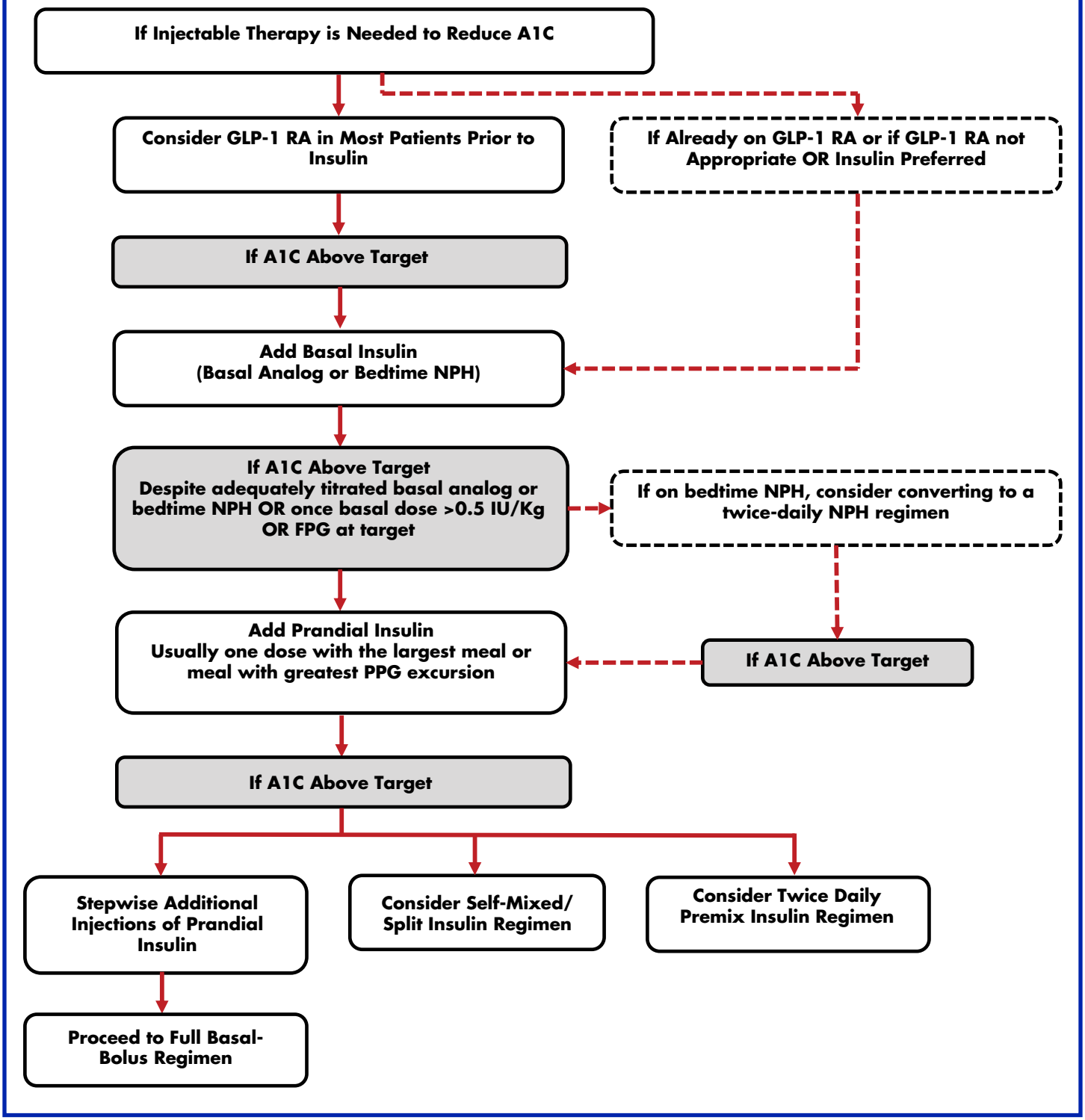
2 Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary heart failure outcome from DAPA-HF.

3 semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide

Adapted from:

Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - 2020. Diabetes Care 2020;43(Suppl. 1):S98-S11

American Diabetes Association 2020 Standards of Medical Care in Diabetes: Intensification to Injectable Therapies in Type 2 Diabetes



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