Review of Diabetes Medications: Pharmacy Perspective

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UCLA Health

Disclosures

None

Gratitude

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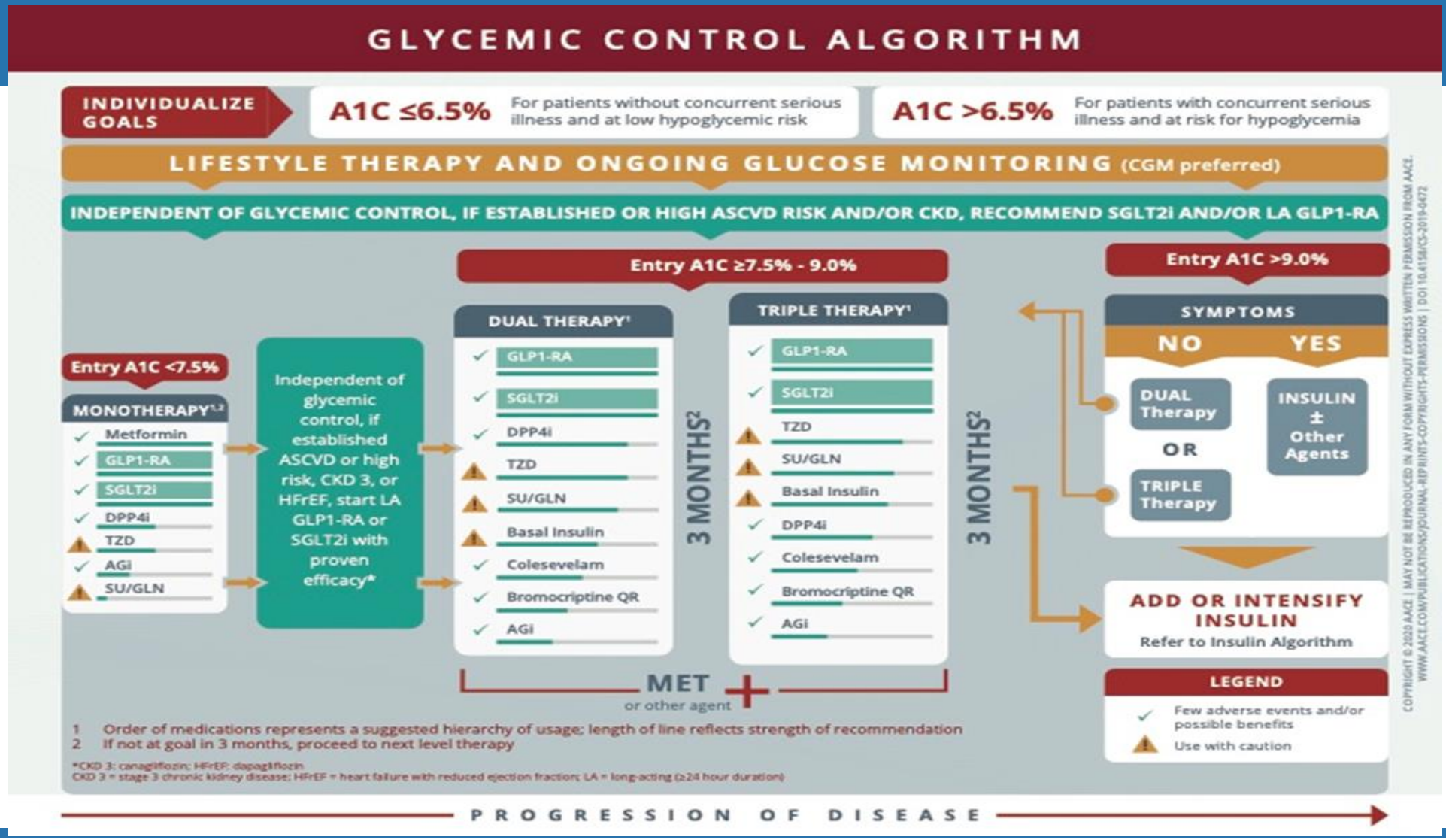
Agenda

- Review of Guidelines
- Medication Comparison
- Special Population
- Medication Access

Review of Guidelines

AACE Guidelines 2020



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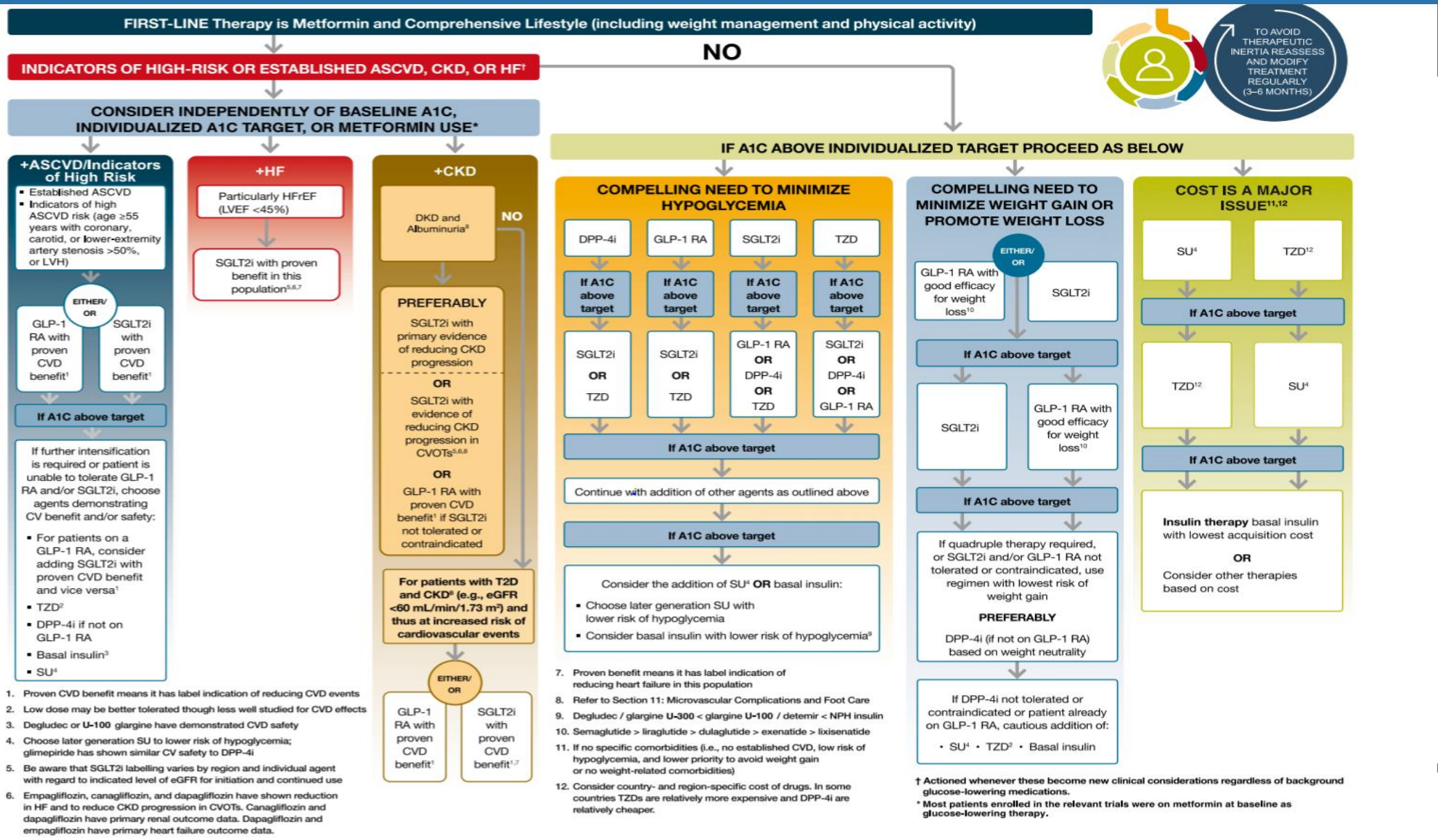
American Diabetes Association Guidelines 2021

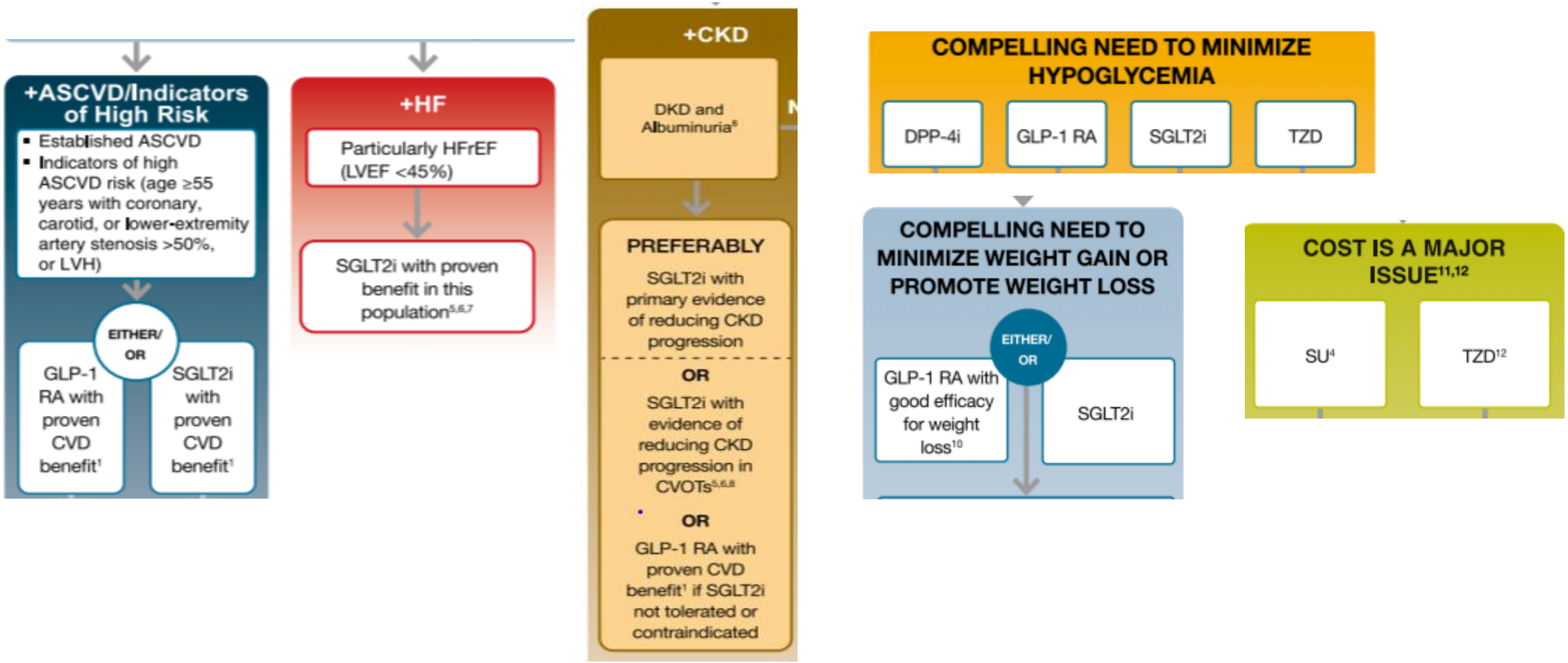


1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar 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.

After metformin: what comes next?



Medication Comparison

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Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA)

MOA: long-acting analog of human GLP-1 (incretin)

Physiological Effects:

- Increase glucose-dependent insulin secretion
- Decrease inappropriate glucagon secretion
- Increase B-cell growth / replication
- Slows gastric emptying
- Decrease food intake

Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA)

Contraindications:

- Family or personal h/o MEN-2 or MTC

Precautions:

- Pancreatitis
- Personal h/o DKA
- Gastroparesis
- H/o bariatric surgery

Side Effects:

- Nausea
- Vomiting
- Diarrhea
- Constipation

Note:

Not indicated to be used in conjunction with DPP-4i

Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA) - Clinical Trials

Abbreviation	Clinical Trial
ELIXA	Evaluation of Lixisenatide in Acute Coronary Syndrome
EXSCEL	Cardiovascular outcomes trial for exenatide weekly
HARMONY	Series of clinical trials with albiglutide
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
PIONEER	Series of Peptide Innovation for Early Diabetes Treatment with oral semaglutide
REWIND	Researching Cardiovacular Events with Weekly Incretin in Diabetes (Dulaglutide)
SUSTAIN-6	trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes

Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA) - Clinical Trials

Methodology

	LEADER	SUSTAIN-6	PIONEER-6	REWIND	ELIXA	EXSCEL
Intervention	Liraglutide 1.8mg QD (n=4668)	SC semaglutide 0.5-1mg QW (n=1648)	PO semaglutide 14mg daily (n=1591)	Dulaglutide 1.5mg QW (n=4949)	Lixisenatide 20mcg QD (n=3034)	Exenatide ER 2mg QW (n=7356)
Comparator	Placebo (n=4672)	Placebo (n=1649)	Placebo (n=1592)	Placebo (n=4952)	Placebo (n=3034)	Placebo (n=7396)
Inclusion criteria	CVD, CKD, HF or at risk of CVD	CVD (59%), CKD ≥ stage 3 (11%), HF or at risk of CVD	CVD, CKD, HF or at risk of CVD	Vascular disease/CVD (32%) or at risk of CVD (68%)	ACS	Established ASCVD (73%) or high CV risk (27%)
Median Trial Duration	3.8 years	2.1 years	1.3 years	5.4 years	2.1 years	3.2 years
Primary Outcome	3-point MACE	3-point MACE	3-point MACE	3-point MACE	4-point MACE	3-point MACE

Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA) - Clinical Trials

Baseline Characteristics

	LEADER	SUSTAIN-6	PIONEER-6	REWIND	ELIXA	EXSCEL
Intervention	Liraglutide 1.8mg QD	SC Semaglutide 0.5-1mg QW	PO Semaglutide 14mg daily	Dulaglutide 1.5mg QW	Lixisenatide 20mcg QD	Exenatide ER 2mg QW
Age	64.3 years	64.5 years	66 years	66 years	60.3 years	62 years
Duration of DM	12.8 years	13.9 years	14.9 years	9.5 years	9.4 years	12 years
HbA1C	8.0%	8.7%	8.2%	7.3%	7.6%	8.0%
HF	17.9%	22%	12.2%	8.6%	22.4%	16.2%

Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA) - Clinical Trials

Results

	LEADER	SUSTAIN-6	PIONEER-6	REWIND	ELIXA	EXSCEL
Intervention	Liraglutide 1.8mg QD	SC Semaglutide 0.5-1mg QW	PO Semaglutide 14mg daily	Dulaglutide 1.5mg QW	Lixisenatide 20mcg QD	Exenatide ER 2mg QW
Primary Outcome	**0.87 (0.78-0.97)**	**0.75 (0.58-0.95)**	0.79 (0.57-1.11)	**0.88 (0.79-0.99)**	1.02 (0.89-1.17)	0.91 (0.83-1.00)
Secondary Outcome	**0.88 (0.81-0.96)**	**0.74 (0.62-0.89)**			1.00 (0.90-1.11)	
CV Death	**0.78 (0.66-0.93)**	0.98 (0.65-1.48)	**0.49 (0.27-0.92)**	0.91 (0.78-1.06)	0.98 (0.78-1.22)	0.88 (0.76-1.02)
All-cause Mortality	**0.85 (0.74-0.97)**	1.05 (0.74-1.50)	**0.51 (0.31-0.84)**	0.90 (0.80-1.01)	0.94 (0.78-1.13)	0.86 (0.77-0.97)
HHF	0.87 (0.75-1.05)	1.11 (0.77-1.61)	0.86 (0.48-1.55)	0.93 (0.77-1.12)	0.96 (0.75-1.23)	0.94 (0.78-1.13)

Glucagon-Like Peptide-1 Receptor Agonist (GLP-1RA)

Medication	Initial Dose	Max Dose	Comments
Dulaglutide (Trulicity)	0.75 mg SQ weekly	4.5 mg SQ weekly	- Single-use prefilled pen
Liraglutide (Victoza)	0.6 mg SQ daily	1.8 mg SQ daily	- May be available as Saxenda (weight loss only) - Need to order insulin pen needles
Semaglutide injection (Ozempic)	0.25 mg SQ weekly	1 mg SQ weekly	- Multi-use prefilled pen - May be available as WeGoVy (weight loss only)
Semaglutide oral (Rybelsus)	3 mg PO daily	14 mg PO daily	- pending ASCVD outcomes

Semaglutide (Oral) - Rybelsus

- Only oral agent within the class
- Available only in special foil blister packaging
- Requires special administration techniques to improve absorption
  - Empty stomach (no food, water, or medications)
  - No more than 4 oz of water
  - Wait at least 30 minutes before eating, drinking, or other medications (the longer patient waits, the better the absorption)

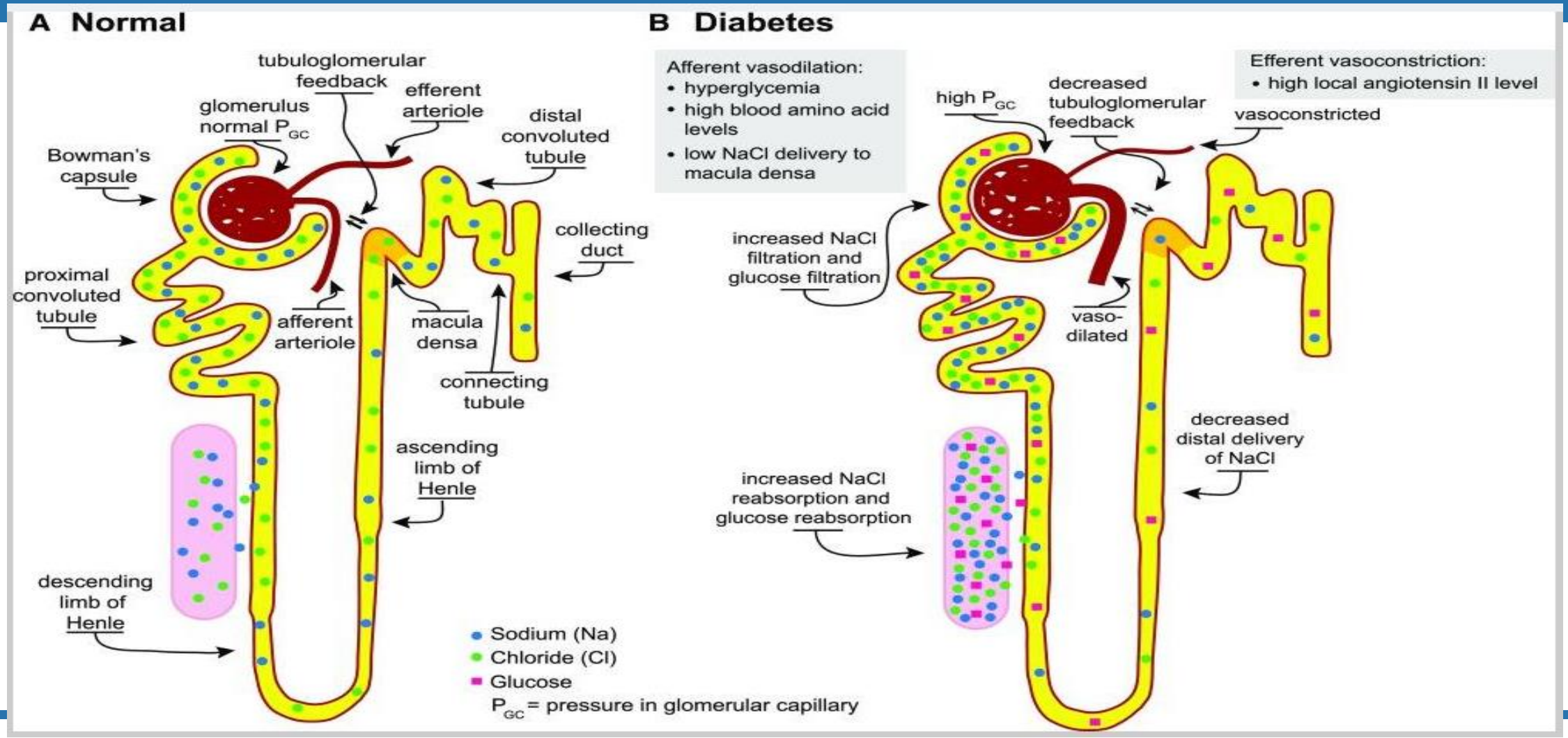
Sodium-glucose co-transporter 2 inhibitors (SGLT2i)

MOA: Inhibit SGLT-2 in the proximal renal tubules

Physiological Effects:

- Reduce reabsorption of filtered glucose from tubular lumen
- Lower renal threshold for glucose
- Promote the renal excretion of glucose

Sodium-glucose co-transporter 2 inhibitors (SGLT2i)



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Neumiller J et al JASN 2017

Sodium-glucose co-transporter 2 inhibitors (SGLT2i)

MOA: Inhibit SGLT-2 in the proximal renal tubules

Direct Effects on the Kidneys:

- SGLT2i improve TGF: ↑ Afferent arteriolar tone → ↓ intraglomerular pressure → ↓ GFR → GFR stabilization & ↓ albuminuria
- Reduced hyperfiltration
  - Reduced proximal tubular sodium reabsorption
  - Increased Na delivery to distal tubule
  - Restore TGF

Perkovic et al Cur Med Res Opin 2015;31:2219-31; Neumiller J et al JASN 2017

Sodium-glucose co-transporter 2 inhibitors (SGLT2i)

MOA: Inhibit SGLT-2 in the proximal renal tubules

Indirect Effects on the Kidneys:

- Reduce hyperglycemia
- Reduce weight
- Reduce blood pressure
- Reduce hyperinsulinemia
- Decrease uric acid

Sodium-glucose co-transporter 2 inhibitors (SGLT2i)

Contraindications:

- Personal h/o DKA
- ESRD, dialysis

Precautions:

- H/o GU infections
- Dehydration
- PVD
- Bone fractures
- H/o bariatric surgery
- Pancreatitis
- Lower limb amputation

Side Effects:

- Urogenital infections/yeast infections
- Hypotension/volume depletion
- Reduced bone mass, increased risk for fractures
- Necrotizing fasciitis of the perineum (Fournier gangrene) – rare
- Euglycemic DKA

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) – Clinical Trials

Abbreviation	Clinical Trial
CANVAS	Canagliflozin Cardiovascular Assessment Study
DECLARE-TIMI 58	Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction Trial
EMPA-REG	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
VERTIS	Study of the Efficacy and Safety of Ertugliflozin
DAPA-HF	Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) – Clinical Trials

Methodology

	EMPA-REG	CANVAS	DECLARE-TIMI 58	VERTIS CV	DAPA-HF
Intervention	Emagliflozin 10-25mg (n=4687)	Canagliflozin 300mg (n=5795)	Dapagliflozin 10mg (n=8582)	Ertugliflozin 5-15mg (n=5499)	Dapagliflozin 10mg (n=2373)
Comparator	Placebo (n=2333)	Placebo (n=4347)	Placebo (n=8578)	Placebo (n=2747)	Placebo (n=2371)
Inclusion criteria	Established CVD	Established CVD (~66%) or at risk of CVD	Established ASCVD (~40%) or at risk of CVD	Established CVD	LVEF ≤ 40%, ±symptomatic
Median Trial Duration	3.1 years	2.6 years	4.2 years	3.0 years	1.5 years
Primary Outcome	3-point MACE	3-point MACE	4-point MACE	3-point MACE	HHF CV Death

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) – Clinical Trials

Baseline Characteristics

	EMPA-REG	CANVAS	DECLARE-TIMI 58	VERTIS CV	DAPA-HF
Intervention	Emagliflozin 10-25mg	Canagliflozin 300mg	Dapagliflozin 10mg	Ertugliflozin 5-15mg	Dapagliflozin 10mg
Age	63.1 years	63.3 years	63.9 years	64.4 years	66.2 years
Duration of DM	≥ 10 years	13.6 years	10.5 years	13 years	NR
HbA1C	8%	8.2%	8.3%	8.2%	NR
HF	11%	14%	10%	23.4%	100%
Hypertension	NR	90%	NR	NR	NR

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) – Clinical Trials

Results

	EMPA-REG	CANVAS	DECLARE-TIMI 58	VERTIS CV	DAPA-HF
Intervention	Emagliflozin 10-25mg	Canagliflozin 300mg	Dapagliflozin 10mg	Ertugliflozin 5-15mg	Dapagliflozin 10mg
Primary Outcome	**0.86 (0.74-0.99)**	**0.86 (0.75-0.97)**	0.93 (0.84-1.03)	0.97 (0.85-1.11)	**0.74 (0.65-0.85)**
Secondary Outcome	0.89 (0.78-1.01)	0.95 (≤1.14)	**0.83 (0.73-0.95)**	0.88 (0.75-1.03)	**0.75 (0.65-0.85)**
CV Death	**0.62 (0.49-0.77)**	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.92 (0.77-1.11)	**0.82 (0.69-0.98)**
All-cause Mortality	**0.68 (0.57-0.82)**	0.87 (0.74-1.01)	0.93 (0.82-1.04)	0.93 (0.80-1.08)	**0.83 (0.71-0.97)**
HHF	**0.65 (0.50-0.85)**	**0.67 (0.52-0.87)**	**0.73 (0.61-0.88)**	**0.70 (0.54-0.90)**	**0.70 (0.59-0.83)**

Sodium-glucose co-transporter 2 inhibitors (SGLT2i)

Medication Name	Initial Dose	Max Dose	Comments
Canagliflozin (Invokana)	100 mg	300 mg	- Not recommended in eGFR <30 - Approved for diabetic kidney disease with UACR >300mg/day
Dapagliflozin (Farxiga)	5 mg	10 mg	- Not recommended in eGFR <45 - Approved for HFrEF and CKD
Empagliflozin (Jardiance)	10 mg	25 mg	- Not recommended in eGFR <30 - Off label use for HFrEF
Ertagluflozin (Steglatro)	5 mg	15 mg	- Not recommended in eGFR <30

Dipeptidyl Peptidase IV Inhibitors (DPP-4i)

MOA: inhibits DPP-4 enzyme, which breaks down incretin

Physiological Effects:

- Prolong active incretin levels
- Increase glucose-dependent insulin secretion
- Decrease inappropriate glucagon secretion
- Slows gastric emptying
- Decrease food intake

Dipeptidyl Peptidase IV Inhibitors (DPP-4i)

Precautions:

- Pancreatitis
- Personal h/o DKA
- Gastroparesis
- H/o bariatric surgery

Side Effects:

- Nasopharyngitis
- Arthralgia

Note:

Not indicated to be used in conjunction with GLP-1 RA

Dipeptidyl Peptidase IV Inhibitors (DPP-4i)

Medication Name	Initial / Max Dose	Renal Adjustment	Comments
Linagliptin (Tradjenta)	5 mg	None	Do not reduce CV risk
Sitagliptin (Januvia)	100 mg	eGFR 30-45: 50 mg eGFR <30: 25 mg	Do not reduce CV risk

Thiazolidinediones (TZD)

MOA: Selective agonist for peroxisome proliferator-activated receptor-gamma (PPARgamma), which influences productions of gene products involved in glucose and lipid metabolism

Physiological Effects:

- Improve target cell response to insulin
- Does not increase pancreatic insulin production

Thiazolidinediones (TZD)

Contraindications:

- Personal h/o bladder cancer
- H/o HF (symptomatic HF or NYHA class III / IV)

Precautions:

- Edema
- Bone fractures
- H/o bariatric surgery
- T1DM or DKA
- Hepatic impairment

Side Effects:

- Weight gain
- Edema
- HF exacerbation
- Hepatic insufiicency
- Macular Edema
- Cardiac failure

Thiazolidinediones (TZD)

Medication Name	Initial Dose	Max Dose	Comments
Pioglitazone (Actos)	15 mg	45 mg	- Poor CV outcomes

Sulfonylureas (SFU) / Meglitinide

MOA: Binds to the K-ATP channel in pancreatic beta cells and leads to inhibition which alters resting potential of cell and leads to calcium influx and stimulation of insulin secretion

Physiological Effects:

- Increased responsiveness of beta cells
- Increase insulin release from pancreas

Sulfonylureas (SFU) / Meglitinide

Precautions:

- SFU only: "sulfa allergy" - only if documented with non-abx sulfa meds
- SFU only: G6PD deficiency
- H/o bariatric surgery
- Elderly
- Renal impairment

Side Effects:

- Hypoglycemia (risk increased in elderly and renal impairment)
- Weight gain

Sulfonylureas (SFU) / Meglitinide

Medication Name	Initial Dose	Max Dose	Comments
Glimepiride (Amaryl)	1-2 mg	8 mg	- Not recommended in eGFR <15 - Beers Criteria
Glyburide (Glynase)	2.5-5 mg	20 mg	- Not recommended in CKD - Beers Criteria
Glipizide (Glucotrol)	2.5 mg	20 mg	- Preferred SFU in CKD (avoid use if eGFR <10 if possible) - Food delays absorption
Repaglinide (Prandin)	0.5-1 mg TID w/ meals	4 mg / dose 16 mg / day	- Initiate at low dose if CrCl < 40
Nateglinide (Starlix)	60-120 mg TID w/ meals	120 mg TID	- Initiate cautiously at 60 mg TID if CrCl < 30

Medication Class Comparison

Class	A1c Effects	Weight	Hypoglycemia Risk	Cost
Metformin	0.6-1.5%	Slight Loss	Low	$
GLP-1 RA	0.5-1.9%	Loss	Low	$$$
SGLT-2i	0.6-0.9%	Loss	Low	$$$
DPP-4i	0.5-0.6%	Neutral	Low	$$
TZD	0.5-1.4%	Gain	Low	$
SFU / meglitinides	1-2%	Gain	High	$
Insulin(s)	unlimited	Gain	High	$$

Special Populations

Population	Preferred Agents	Agents to Avoid
ASCVD	GLP-1 RA SGLT-2i	TZD DPP-4i* select agents only
CKD (stage 3 or with albuminuria)	SGLT-2i GLP-1 RA	Metformin SFU / meglitinides
Geriatrics	Metformin DPP-4i	SFU
HFrEF	SGLT-2i	TZD DPP-4i* select agents only
Hypoglycemia	Metformin GLP-1 RA SGLT-2i DPP-4i	SFU / meglitinides
Overweight/Obese	Metformin GLP-1 RA	SFU / meglitinides TZD

Practice Points

- Liragltuide, subcutaneous semaglutide, and dulaglutide significantly reduced 3-point MACE in patients with established CVD and those at high risk of CVD
- Empagliflozin and canagliflozin have also reduced MACE in patients with established CVD and those at high risk for CVD
- All SGLT2i have decreased the risk of hospitalization for heart failure
- Dapagliflozin is the only SGLT2i approved for pts w/ HF & CKD regardless of DM2 status for now
- Expect an initial decline in eGFR when initiating SGLT2i for renal benefit
- DPP-4i have relative CV safety/glycemic control, but no benefit with respect to MACE; however saxagliptin and alogliptin increase the risk of HHF especially in patients with a history of HF and CKD

Medication Access

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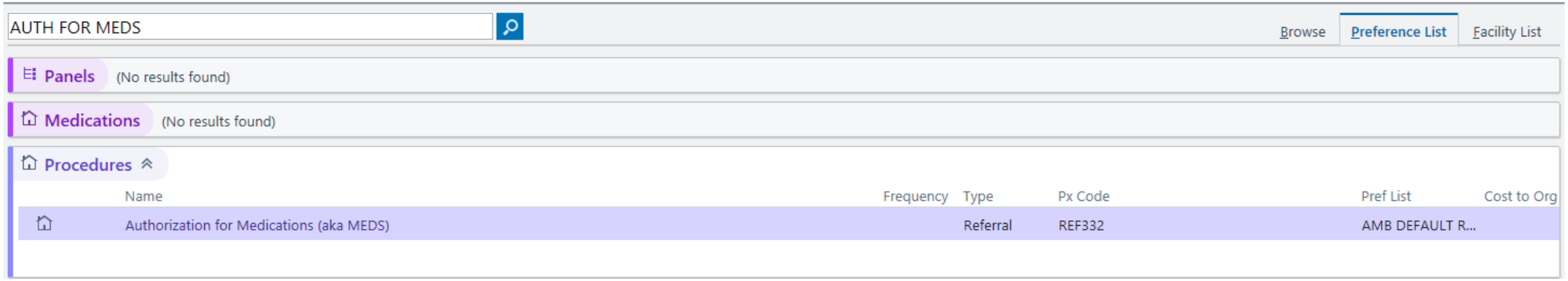
UCLA Health Net Med-Group

- Place UM Referral for Self-Injectables (including GLP-1 RA)
- Preferred Pharmacies: UCLA (internal referral)
- Cost: $25-50 per 30-day supply



Medicare Part D

- Deductible: < $445
- Initial coverage: ~$50 / month
- Coverage gap: 25% drug cost
- Affected Medication Classes: GLP-1 RA, SGLT-2i, DPP-4i, insulin*
- Manufacturer coupons not applicable for Medicare/Medicaid patients

* New guidelines may lower cost

Q & A

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Additional GLP-1 RA Agents

Medication Name	Initial Dose	Max Dose	Comments
Exenatide (Byetta)	5 mcg SQ twice daily	10 mcg twice daily	- Avoid in CrCl < 30 mL/min
Exenatide long-acting (Bydureon BCise)	2 mg SQ once weekly	2 mg SQ once weekly	- No ASCVD outcomes - Avoid in eGFR < 45 mL/min/1.73m2
Lixisenatide (Adlyxin)	10 mcg SQ daily	20 mcg SQ daily	- No ASCVD outcomes - Available as combination with insulin glargine 100 units / mL

Additional DPP-4 Inhibitors

Medication Name	Initial / Max Dose	Renal Adjustment	Comments
Aloglitpin (Nesina)	25 mg	CrCl 30-60: 12.5 mg CrCl 15-29 or ESRD: 6.25 mg	Do not use in HF
Saxagliptin (Onglyza)	5 mg	eGFR < 45 or ESRD: 2.5 mg	Do not use in HF

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