Practical guidance: prescribing SGLT-2i or GLP-1RA

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Disclosures

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Objectives

Review the role of a cardiologist in patients with diabetes

Two parts: *SGLT-2i* then *GLP-1RA*

- Mechanism of action/benefit
- What to expect?
- What dose? Titrate or not?
- Preventing and recognizing key side effects

Case-based approaches

Role of a cardiologist in diabetes: rules of engagement

Diabetologist

- Focus on blood sugar
- Expert in wide range of hypoglycemia medications
- Expert in global care of diabetes, microvascular complications
- Defers to cardiologist on CV protection

Cardiologist

- Focus on hypertension, lipids, diet
- Expert in lipid-lowering therapies
- Management of cardiovascular disease
- Defers to diabetologist on diabetes drugs

Role of a cardiologist in diabetes: rules of engagement

MACE Outcomes in Trials of T2DM with High ASCVD Risk

	SAVOR TIMI-53	EXAMINE	TECOS	CARMELINA		
DPP-4 inhibitor	〓 NEUTRAL	〓 NEUTRAL	〓 NEUTRAL	〓 NEUTRAL		
	LEADER	**ELIXA**	**SUSTAIN-6**	**EXSCEL**	**HARMONY**	**REWIND**
GLP-1 RA	✓ BENEFICIAL	〓 NEUTRAL	✓ BENEFICIAL	〓 NEUTRAL	✓ BENEFICIAL	✓ BENEFICIAL
	EMPA-REG	**CANVAS**	**DECLARE**	**VERTIS**		
SLGT2-Inhibitor	✓ BENEFICIAL	✓ BENEFICIAL	〓 NEUTRAL	〓 NEUTRAL		

HF Outcomes in Trials of T2DM with High ASCVD Risk

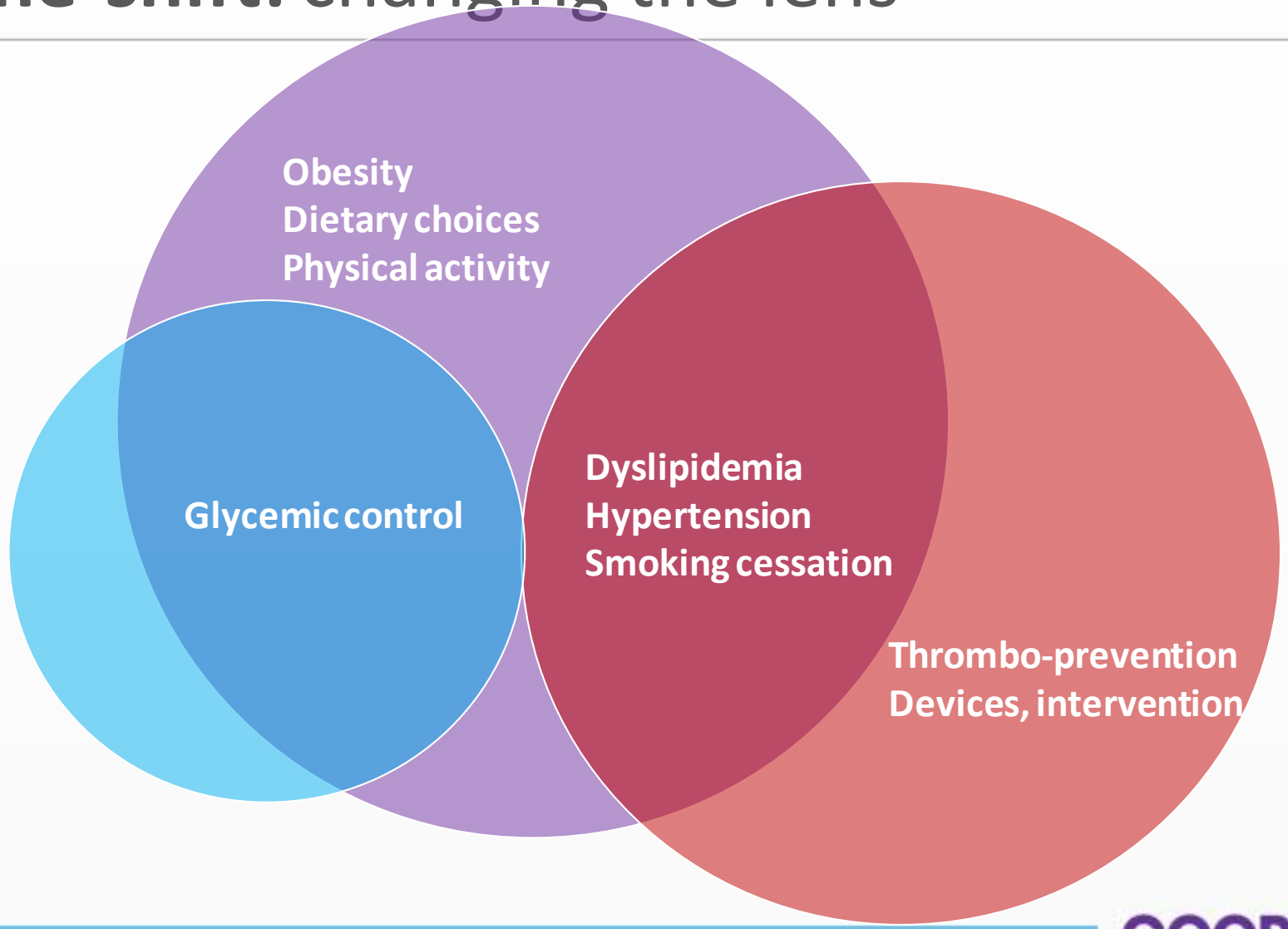
	SAVOR TIMI-53	EXAMINE	TECOS	CARMELINA		
DPP-4 inhibitor	✗ INCREASED RISK	= NEUTRAL	= NEUTRAL	= NEUTRAL		
	LEADER	**ELIXA**	**SUSTAIN-6**	**EXSCEL**	**HARMONY**	**REWIND**
GLP-1 agonist	= NEUTRAL	= NEUTRAL	= NEUTRAL	= NEUTRAL	✓ BENEFICIAL	= NEUTRAL
	EMPA-REG	**CANVAS**	**DECLARE**	**VERTIS**		
SLGT2-Inhibitor	✓ BENEFICIAL	✓ BENEFICIAL	✓ BENEFICIAL	✓ BENEFICIAL		

Comparative meta-analysis

	SGLT-2	GLP-1RA
MACE	0.87 [0.82, 0.92]	0.86 [0.80, 0.93]
HHF	0.69 [0.61, 0.79]	0.93 [0.83, 1.04]
Renal	0.55 [0.48, 0.64]	0.92 [0.80, 1.06]

Zelniker et al. Circulation 2019

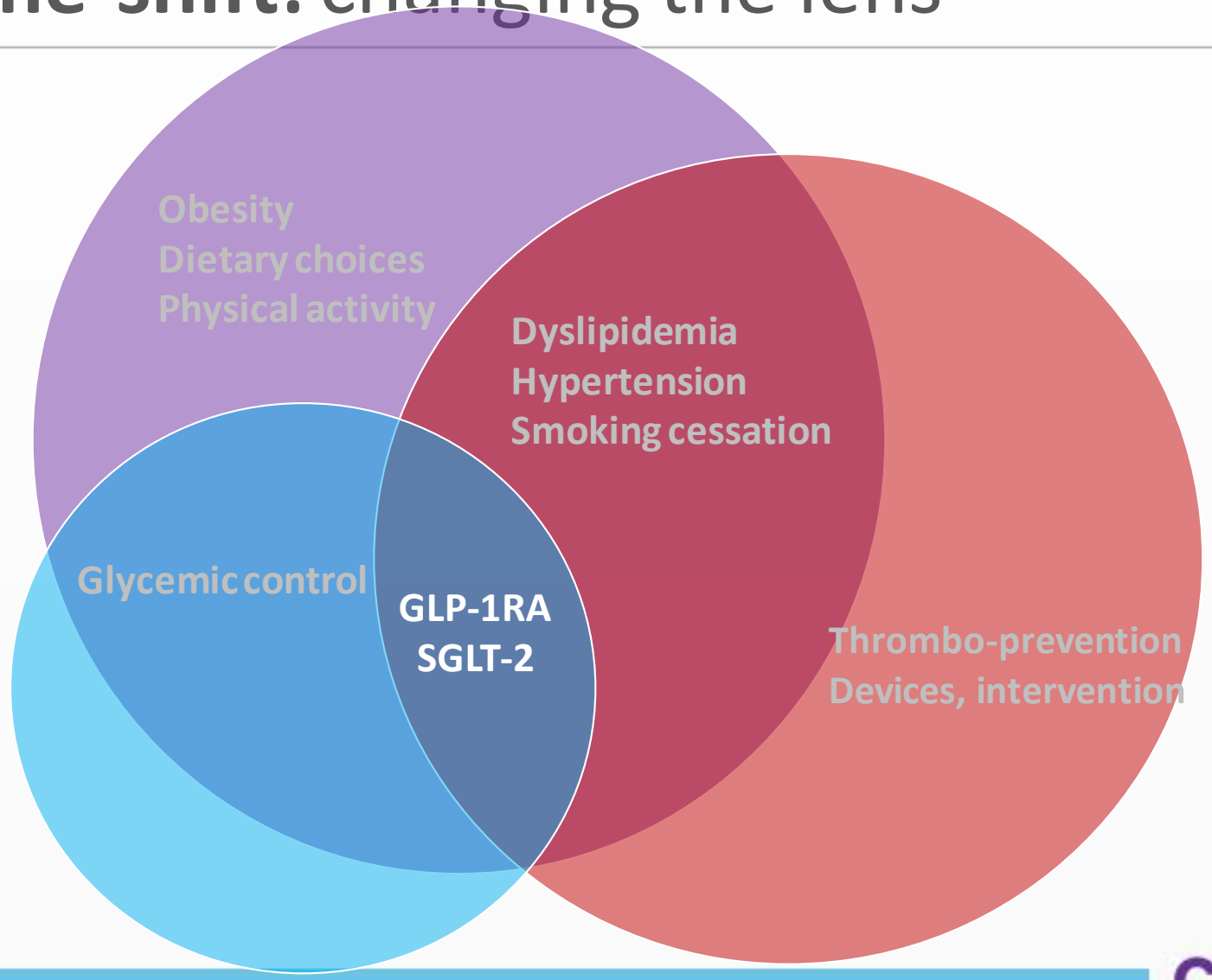
Frame-shift: changing the lens



? SGLT-2i

? GLP-1RA

Frame-shift: changing the lens



What's in a name?

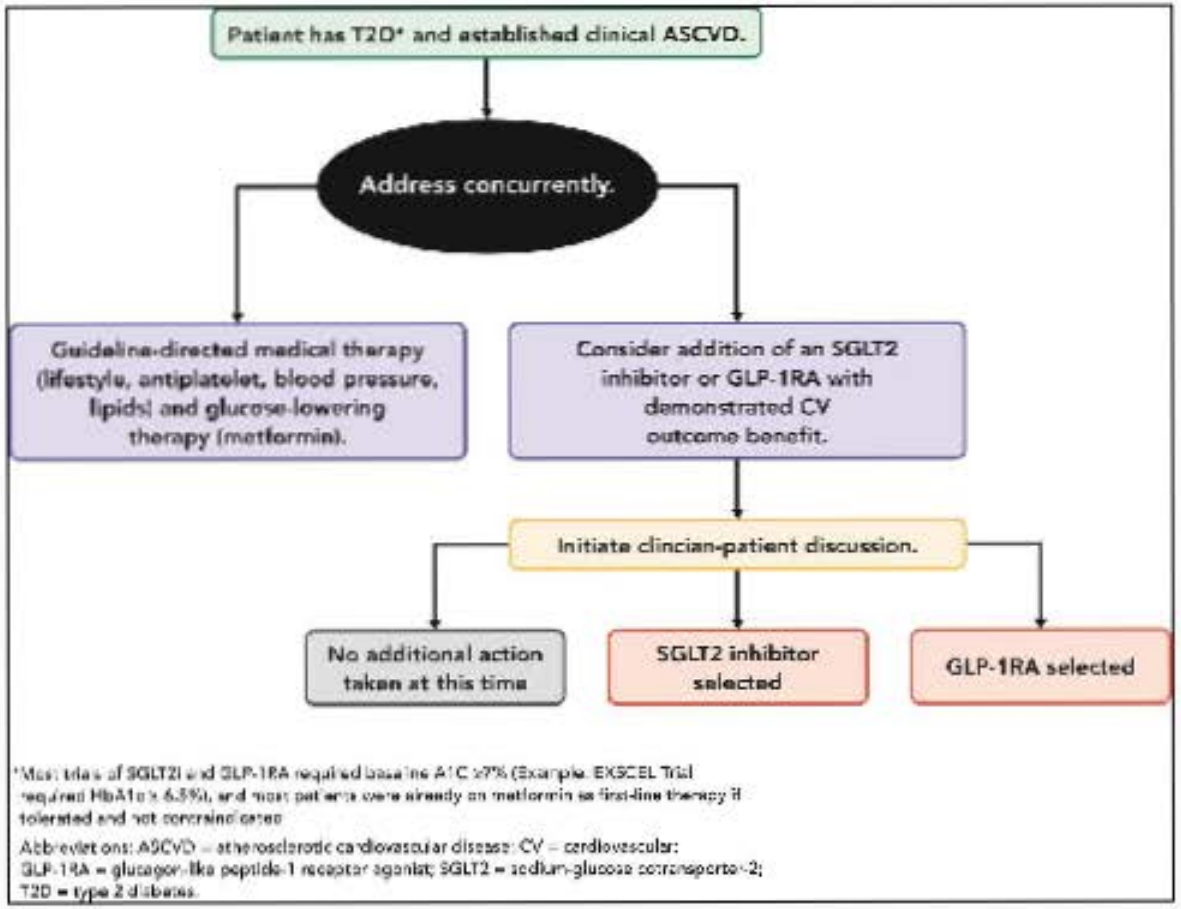
- 'Outcome drugs'
- 'pleiotropic'
- 'remodeling'

Finding the ‘comfort zone’ in diabetes care

Patient complexity

Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Single OHG	Two OHGs	Glargine + OHG	Basal/bolus + OHG	Basal/bolus
A1c 7.5%	A1c 9%	A1c 8.1%	A1c 11%	A1c 10%
GFR 91	GFR 70	GFR 55	GFR 35	On dialysis
		Neuropathic pain	Neuropathic pain	Complex neuropathy
			Recent amputation	Laser eye therapy

Finding the 'comfort zone' in diabetes care



Das SR et al. JACC 2018

Finding the 'comfort zone' in diabetes care

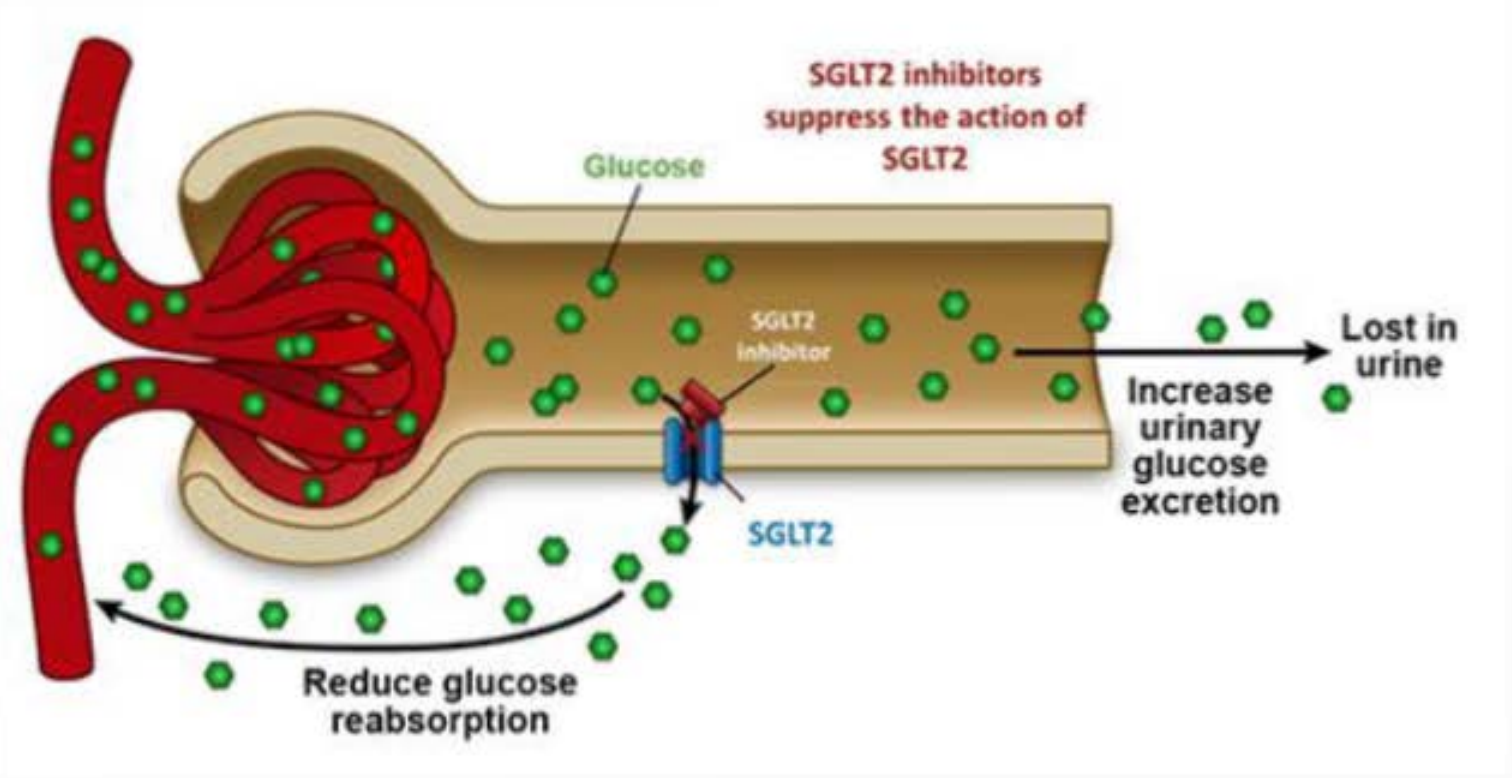
Red flags: consider engagement of diabetologist

- Complex regimens:
  - Combination insulin regimen (basal-bolus, mixed preparations)
  - ≥ 3 oral anti-hyperglycemic medications
- HbA1c >10% (*not a barrier to adding drugs with CV outcomes benefit*)
- eGFR <30ml/min/m^2
- History of severe or recurrent hypoglycemia
- Prior DKA
- Active diabetic foot wound

Das SR et al. JACC 2018

SGLT-2 Inhibitors (SGLT2i)

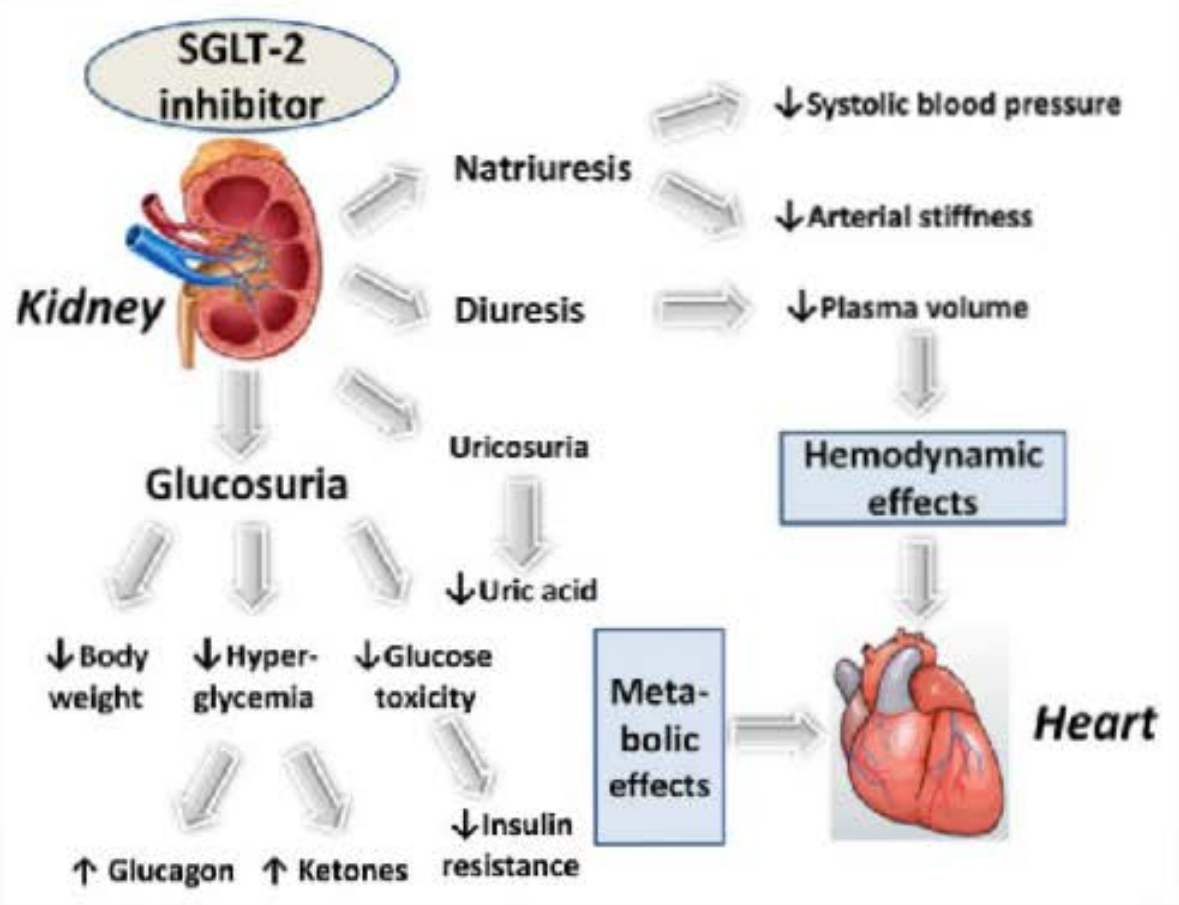
SGLT-2i: mechanism of action



Wright EM et al. Physiol Rev 2011

SGLT-2i: mechanism of benefit

↓ glomerular pressure



Scheen et al. Circ. Res. 2018

SGLT-2i: selection + dosing

CV, renal benefits appear largely consistent across class

- *Note: ertugliflozin demonstrated reduction in only HHF in VERTIS trial*

Potential differences in risks

- Increased risks amputations/fractures with canagliflozin in the CANVAS trial, but not seen in subsequent CREDENCE trial with implementation of standard foot care. No longer a black box warning.

CV benefit is **not** dose dependent, so lowest doses OK for CV risk reduction

SGLT-2i: pharmacokinetics/dynamics

Generic	Trade Name	Starting dose	Half life	Clearance	Minimum GFR (regulatory)
empagliflozin	Jardiance	10mg	12 hours	glucuronidation	20ml/min/1.73m^2
canagliflozin	Invokana	100mg	10 hours	glucuronidation	30ml/min/1.73m^2
dapagliflozin	Farxiga	5mg	13 hours	glucuronidation	25ml/min/1.73m^2
*ertugliflozin**	*Steglatro*	*5mg*	*16 hours*	*glucuronidation*	*60ml/min/1.73m^2*

*Minimum eGFR is higher for ertugliflozin, as it is indicated only for glucose lowering in T2DM

Zinman B et al. NEJM 2015; Neal B et al. NEJM 2017

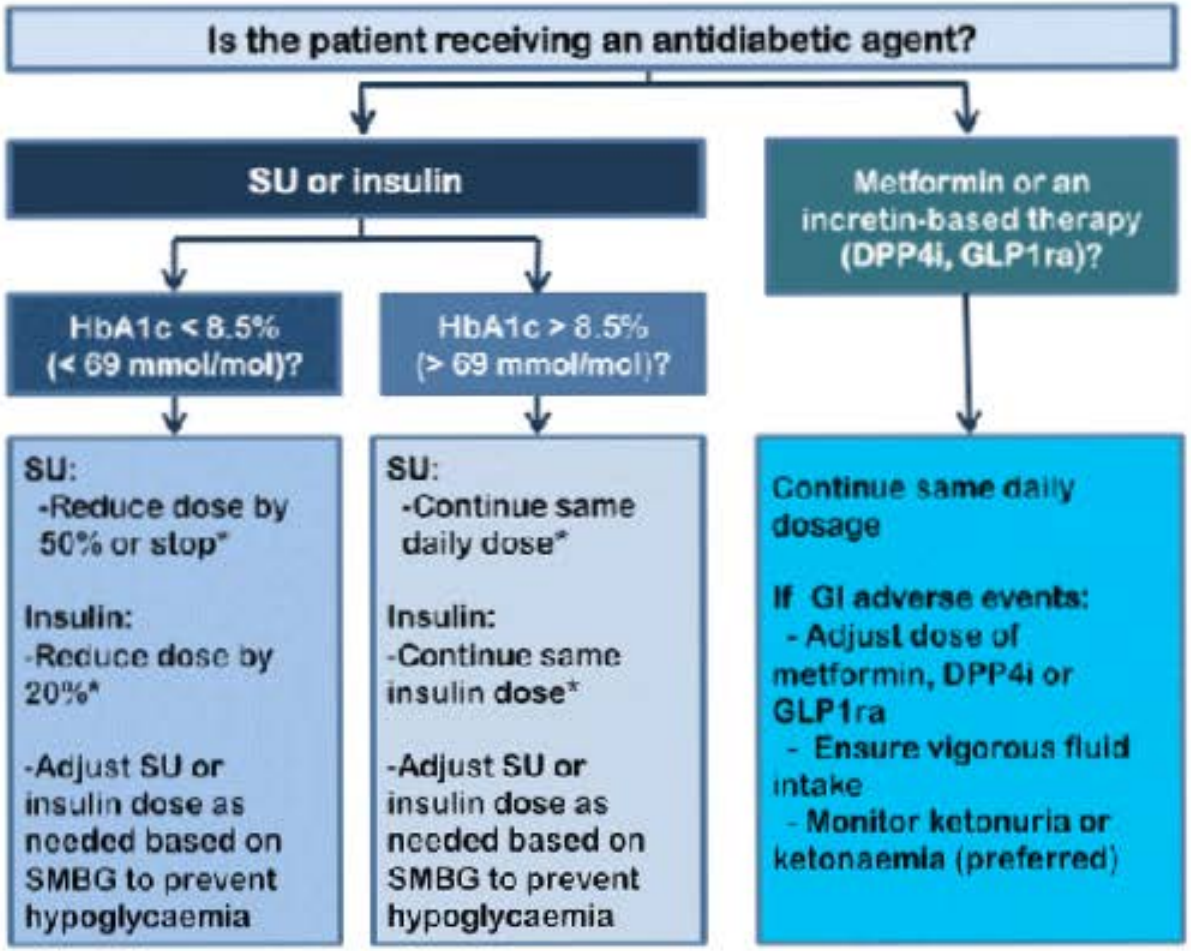
SGLT-2i: anticipatory guidance

BP	A1c (if eGFR ≥ 40-45)	LDL	HDL	Weight	Uric acid
↓3-5mmHg ***↓8% plasma volume***	**↓~0.5-0.8%**	↑6%	↑8%	**↓1-3kg**	↓10-15% (0.6mg/dL)

Hypoglycemia	UTIs	eGFR	Genital mycotic infections	Orthostatic symptoms	Ketoacidosis
No increase unless added to insulin, SU	No convincing signal	**↓3-5 mL/min/1.73m2** NOT an indication of kidney injury	**RR 3-4 x (~5% vs. 1%)**	**OR 2.68 (95%CI 1.14-6.29)**	**0.5/1000 patient years**

Scheen AJ Current Diabetes Reports 2016

SGLT-2i: starting with other antiglycemic medications



Gomez-Peralta F et al. Diabetes Ther 2017

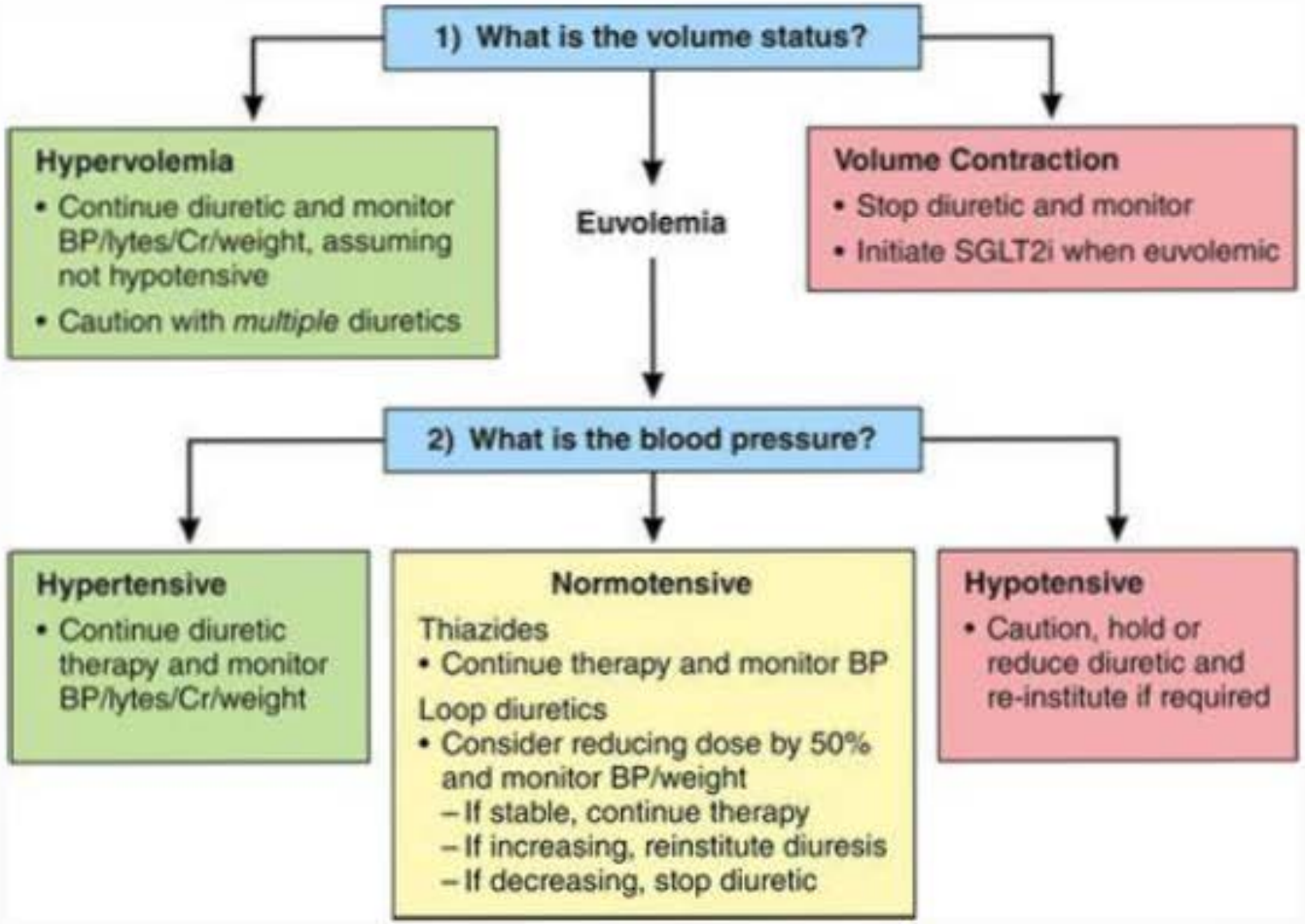
SGLT-2i: patient counselling

Orthostatic hypotension

- Driven by reduction in plasma volume
- Risk factors: age >75, diuretics, anti-HTN agents, baseline volume depletion
- If high risk, consider monitoring for first week of therapy:
    - daily weights – phone PCP if ↓5lbs/week and symptomatic
    - blood pressure

https://www.thediabetescouncil.com/yeast-infection-an-important-sign-of-diabetes/

SGLT-2i: If patient on diuretic therapy



Cherney DZI et al. Circulation 2016

SGLT-2i: patient counselling

Genital mycotic infections (vaginitis/balanitis)

- Higher risk (in general) for DM (functional immunosuppression)
- SGLT-2i risk from induced glycosuria
- Small number of reported cases of Fournier's gangrene

Male conditions	**Symptoms**
Balanitis	Soreness, redness at glans
Balanoposthitis	Thick discharge under foreskin
Urethritis	Itching, burning sensation
Epididymo-orchitis	Pain in scrotal area

Female conditions	**Symptoms**
Vulval infection	Itching, burning, red skin
Vaginal infection	Thick, malodorous discharge
PID	Pelvic pain

Scheen AJ Current Diabetes Reports 2016

SGLT-2i: patient counselling

Genital mycotic infections (vaginitis/balanitis)

- **Prevention**
  - Maintain hydration
  - Choose cotton/breathable underwear fabrics
  - Avoid scented soaps/tampons/pads/douching
  - Dry well after bathing – particularly around skin folds/genitals
  - Pat dry after urination – including uncircumcised men
- **Consider alternative therapy (e.g. GLP-1RA) in patients with chronic incontinence**

https://www.thediabetescouncil.com/yeast-infection-an-important-sign-of-diabetes/

SGLT-2i: patient counselling

Genital mycotic infections (vaginitis/balanitis)

- Management:
  - If febrile, severe pain -> urgent care
  - If afebrile -> PCP
    - Generally treatable with topical or oral antifungal
      - *No indication that cases are less responsive to usual Rx*
    - Most cases occur early in course of therapy, and do not recur

Nyirjesy P et al. Curr Med Res Opin. 2014;30(6):1109-19; Kim G et al. American Diabetes Association 73rd Scientific Sessions. 21st-25th June 2013. Chicago, IL.

SGLT-2i: patient counselling

Amputations

- Signal observed with canagliflozin (in CANVAS but not CREDENCE)
  - Risk highest in those with prior amputations
- Remind patient about regular DM foot exams and annual podiatry review
- In very high risk patients (e.g. those with active foot wound) consider GLP-1RA as alternative for CV risk reduction

SGLT-2i: patient counselling

Ketoacidosis

- "Euglycemic" ketoacidosis - does occur in type 2 diabetes
- 'Sick day' management includes holding medication:
    - During periods of reduced PO intake/acute illness
    - For 3 days prior to major surgery
- Discourage excessive EtOH, extremely low carb diets
- *Selective* counselling regarding DKA needing medical attention:
    - fruity odor, thirst, polyuria, nausea, vomiting, abdo pain

SGLT-2i: communication

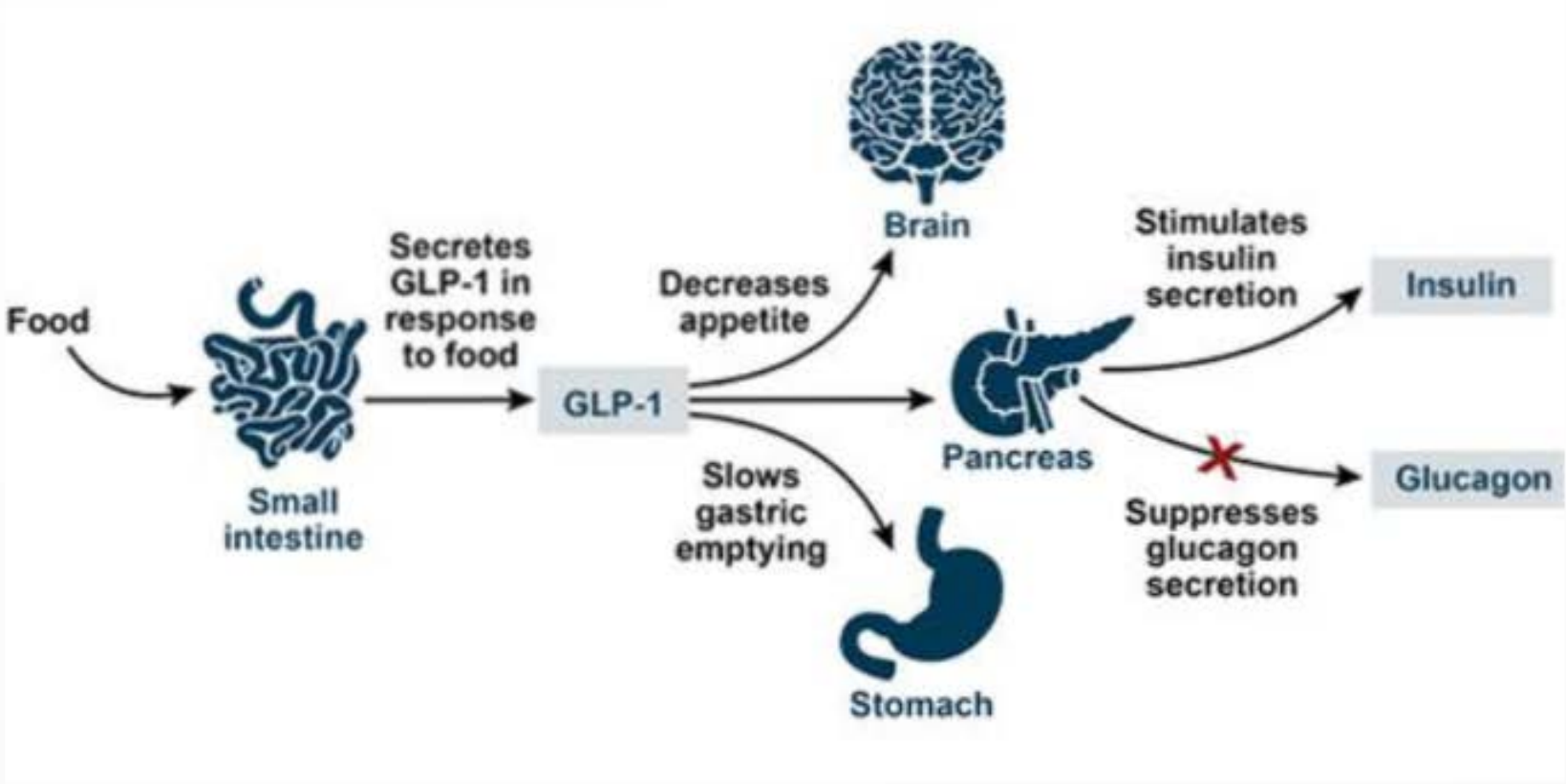
Ensure prescription of medication is communicated to diabetes care provider (PCP or endocrinologist)

- Can help with adjustment and follow up of:
  - Any change to insulin, SU dosing
  - volume status, BP
  - occurrence of genital infections

Up-titration and general control of HbA1c cannot become 'core' cardiologist role – but the cardiologist can initiate appropriate changes in care

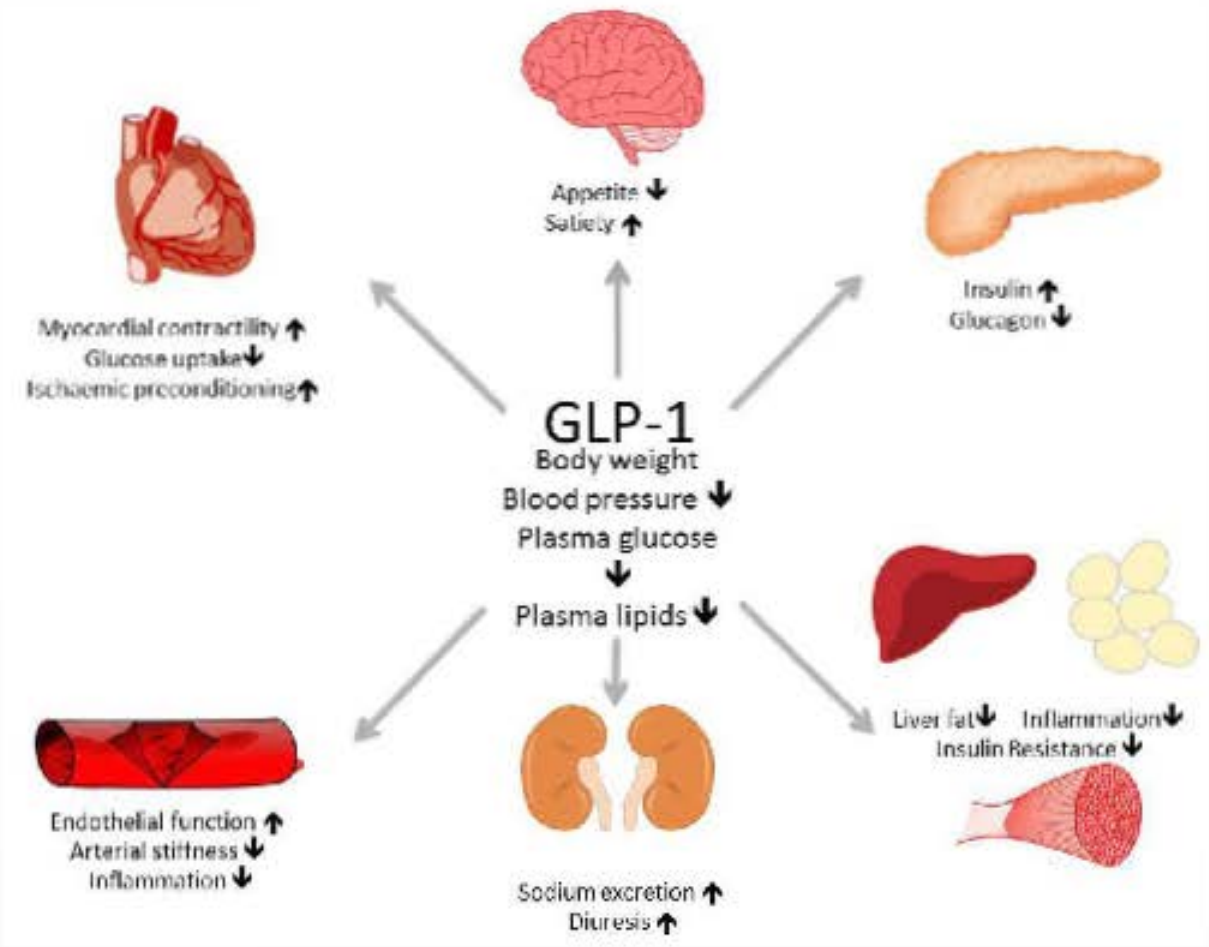
GLP-1 Receptor Agonists (GLP-1 RA)

GLP-1RA: mechanism of action



Meier JJ et al. Nat Rev Endocrinol. 2012

GLP-1RA: mechanism of benefit



Boyle JG et al. Clinical Science 2018

GLP-1RA: selection + dosing

CV outcomes effects appear to vary across class:

- Liraglutide, injected semaglutide and dulaglutide have demonstrated CV benefit (vs. exenatide and lixisenatide)
- CVOTs for oral semaglutide and tirzepatide (dual GLP+GIP agonist) still underway

Considerations:

- Daily vs. weekly administration
- Insurance coverage/cost
- Differences in metabolic potency and possibly side effects

GLP-1RA: pharmacokinetics/dynamics

Generic	Trade Name	Starting dose	Half life	Frequency	In relation to meals	GFR safety
lixisenatide	Adlyxin	10µg	3 hours	Daily	Within 60 mins	eGFR < 15 not recommended
liraglutide	**Victoza**	**0.6mg**	**13 hours**	**Daily**	**Anytime**	**Limited ESRD data**
Semaglutide injection	**Ozempic**	**0.25mg**	**1 week**	**Weekly**	**Anytime**	**Limited ESRD data**
Exenatide*	Bydureon	2mg	2 weeks	Weekly	Anytime	eGFR < 30 not recommended
dulaglutide	Trulicity	0.75mg	5 days	Weekly	Anytime	eGFR < 30 not recommended

**Exenatide also comes in an immediate release formulation*
Albiglutide information not shown as drug no longer produced

Zinman B et al. NEJM 2015; Neal B et al. NEJM 2017

GLP-1RA: contraindications and considerations

Contraindications

- Personal or family history of medullary thyroid cancer
- MEN2 (medullary thyroid, parathyroid, pheochromocytoma)
- These are very rare conditions which do not often pose an obstacle to treatment

Other Considerations:

- Pancreatitis history, risk
- Prior gastric surgery (e.g. bariatric surgery)
- Existing significant diabetic retinopathy (signal of worsening with semaglutide)
- Injections require some degree of dexterity

GLP-1RA: anticipatory guidance

BP	A1c	LDL	TG	Weight
↓1-3mmHg (not in normotensive)	**↓0.8-1.4%**	↓6%	↓12%	**↓1-4kg**

Degree of weight loss will vary. May be significant with higher doses of more potent agents.

Olmo Garcia MI et al. J Diabetes Res. 2018

GLP-1RA: starting with other antiglycemic medications

If A1c well-controlled at baseline or recent hypoglycemia:

- Reduce sulfonylurea by ≥ 50% or basal insulin by 20% (same as for SGLT-2i)

Stop DPP-4 inhibitor if using (no evidence for synergistic benefit)

Das et al. JACC 2018

GLP-1RA: anticipatory guidance (ADRs)

Hypoglycemia	Nausea + vomiting	Pancreatitis	Injection site	Dehydration	Retinopathy
Low/no risk in absence of SU/insulin.	**Initially up to 50% but generally improves with continued use.** **Best tolerated if started on low dose and uptitrated slowly.** **Helpful to eat smaller meals throughout day (vs. 1-2 large, high-fat meals)**	Associated with incretin-based therapy. Not seen in GLP-1RA CVOTs/meta-analysis, but limitation to use	Low risk injection site reaction	Exclusively in context of GI effects; if severe, may be associated with AKI.	Suggestion of increased signal with semaglutide (3% vs. 1.8%) – higher risk with established retinopathy (8.2 vs. 5.2%)

Scheen AJ Current Diabetes Reports 2016; Monami M Diabetes Obes Metab 2017; Romera I Diabetes Ther 2019; Macconnell L et al Diabetes Metab Obes Res 2012; Levin PA Diabetes Metab Syndr Obes 2017

GLP-1RA: patient counselling

Nausea + vomiting

- Related to GLP-1 activity by slowing gastric motility (and promoting satiety)
- On commencement, eat slowly, consume small meals, stop before 'full'
- If up-titrating, follow the recommendations for each drug
  - Often beneficial to titrate more slowly than recommended
  - Can decrease dose if uptitration not tolerated

Loose Stools/Diarrhea

- Less common than N/V, but similar management strategies apply. Consider decreasing concomitant metformin dose if persistent

Scheen AJ Current Diabetes Reports 2016

GLP-1RA: patient counselling

Administration education

- Patient information contained within packing is highly instructive
- Consider:
    - training up practice nursing staff to assist
    - Referral to local pharmacist for education
    - Referral back to diabetes care provider if not feasible

https://youtu.be/K7rdXpiKDtQ

GLP-1RA: communication

Ensure prescription of medication is communicated to diabetes care provider (PCP/endocrinologist) in order to:

- Alter other antihyperglycemic therapy
- Assess tolerability
- Further uptitrate as needed

Up-titration and general control of HbA1c cannot become 'core' cardiologist role

Cardiologist's role is to start the medication in appropriate patients

Case 1: Sally

62-year-old woman

PMHx: T2DM, hypercholesterolemia, hypertension, coronary heart disease (STEMI 2016)

Medications: metformin 1gm BID, glipizide 10mg BID, pioglitazone 15mg OD, lisinopril/HCT 20/12.5mg daily, atorvastatin 20 mg daily

Physical examination: obese (BMI 33); BP 145/92mmHg; pulse 88bpm.

Laboratory evaluation:

HbA1c: 8.2%, LDL: 120 mg/dL, TG: 148 mg/dL, eGFR: 51, UACR: 64 mg/g

Case 1: Sally

62-year-old woman with T2DM and ASCVD

Medications: metformin 1gm BID, glipizide 10mg BID, pioglitazone 15mg OD, lisinopril/HCTZ 20/12.5mg daily, atorvastatin 20 mg daily

Physical examination: obese (BMI 33); BP 145/92mmHg; pulse 88bpm.

Laboratory evaluation: HbA1c: 8.2%, LDL: 120 mg/dL, TG: 148 mg/dL, eGFR: 51, UACR: 64 mg/g

SGLT-2: BP above goal on low dose HCTZ; would not alter if added

GLP-1RA: No obvious contraindications.

PLAN: Add either SGLT-2 or GLP-1RA; SGLT2i may be preferred given CKD. Consider halving or ceasing SU (glipizide)

Case 2: Stephan

67-year-old man

PMHx: T2DM with proliferative retinopathy, CKD, hypertension, coronary heart disease (NSTEMI 2016)

Medications: metformin 1gm QD, insulin glargine 45 units daily, aspart insulin 6-10 units three times daily with meals, perindopril 8mg daily, atorvastatin 80 mg daily

Physical examination: overweight (BMI 28); BP 160/92mmHg; pulse 88bpm.

Laboratory evaluation: HbA1c: 11.2%, LDL: 90 mg/dL, TG: 118 mg/dL, eGFR: 32, UACR: 450 mg/g; TTE LVEF 45%

Case 2: Stephan

67-year-old man with T2DM and proliferative retinopathy, CKD, hypertension, ASCVD, LVEF 45%

Medications: metformin 1gm QD, insulin glargine 45 units daily, aspart insulin 6-10 units three times daily with meals, perindopril 8mg daily, atorvastatin 80 mg daily

Physical examination: overweight (BMI 28); BP 160/92mmHg; pulse 88bpm.

Laboratory evaluation: HbA1c: 11.2%, LDL: 90 mg/dL, TG: 118 mg/dL, eGFR: 32, ACR: 450 mg/g

SGLT-2: ideal in setting of ASCVD, CKD, reduced LVEF

GLP-1RA: preferred with lower GFR; not semaglutide given retinopathy.

PLAN: Add SGLT2i now. Given high A1c may also benefit from addition GLP-1RA - engage with diabetes care provider to make this change!

Case 3: James

51-year-old man

PMHx: T2DM, hypertension, coronary heart disease (NSTEMI 2013), PVD (toe amputation)

Medications: metformin 1gm BID, sitagliptin 100mg OD, glipizide 10 mg BID

candesartan 16mg OD, atorvastatin/ezetimibe 40/10 mg daily

Physical examination: overweight (BMI 28); BP 160/92mmHg; pulse 88bpm.

Laboratory evaluation:

HbA1c: 7.2%, LDL: 140 mg/dL, TG: 130 mg/dL, eGFR: 62, ACR: 11 mg/g

Case 3: James

51-year-old man with T2DM, hypertension, coronary heart disease (NSTEMI 2013), PVD (toe amputation)

Medications: metformin 1gm BID, sitagliptin 100mg OD, glipizide 10 mg BID
candesartan 16mg OD, atorvastatin/ezetimibe 40/10 mg daily

Physical examination: overweight (BMI 28); BP 160/92mmHg; pulse 88bpm.

Laboratory evaluation: HbA1c: 7.2%, LDL: 140 mg/dL, TG: 130 mg/dL, eGFR: 62

SGLT-2: prior amputation; not a clear contraindication if no active issues

GLP-1RA: no issues; stop sitagliptin (DPP4i) if this option is chosen

PLAN: Add either class; would reduce or d/c glipizide given HbA1c of 7.2%

Case 4: Shirley

71-year-old woman

PMHx: T2DM, prior ischemic stroke, hypertension/labile BP, poor eyesight

Medications: metformin 1gm BID, glargine insulin 10 units daily,
irbesartan 300mg OD, amlodipine/HCTZ 10/12.5 mg OD,
furosemide 40mg BID, atorvastatin 40mg daily

Physical examination: Overweight (BMI 29); BP 135/90mmHg; pulse 81bpm.

Laboratory evaluation:

HbA1c: 8.2%, LDL: 110 mg/dL, TG: 114 mg/dL, eGFR: 62, ACR: 20 mg/g

Case 4: Shirley

71-year-old woman with ischemic stroke, hypertension/labile BP, poor eyesight

Medications: metformin 1gm BID, glargine insulin 10 units daily, irbesartan 300mg OD, amlodipine/HCTZ 10/12.5 mg OD, furosemide 40mg BID, atorvastatin 40mg daily

Physical examination: Overweight (BMI 29); BP 135/90mmHg; pulse 81bpm.

Laboratory evaluation: HbA1c: 8.2%, LDL: 110 mg/dL, TG: 114 mg/dL, eGFR: 62

SGLT-2: consider impact on BP; decrease furosemide if started

GLP-1RA: poor eyesight (but manages insulin)

PLAN: Either class could be added; reduce insulin by ≥ 20% (may be able to d/c)

Case 5: Jon

46-year-old man

PMHx: T2DM, coronary heart disease (NSTEMI 2017), HTN, pancreatitis, poor adherence

Medications: metformin 1gm OD,

ramipril 10mg 300mg OD, amlodipine 10mg, atorvastatin 40mg daily

Physical examination: obese (BMI 33); BP 155/92mmHg; pulse 81bpm.

Laboratory evaluation:

HbA1c: 8.6%, LDL: 122 mg/dL, TG: 124 mg/dL, eGFR: 69, ACR: 15 mg/g

Case 5: Jon

46-year-old man with T2DM, coronary heart disease, HTN, pancreatitis, poor adherence

Medications: metformin 1gm OD,

ramipril 10mg 300mg OD, amlodipine 10mg, atorvastatin 40mg daily

Physical examination: obese (BMI 33); BP 155/92mmHg; pulse 81bpm.

Laboratory evaluation: HbA1c: 8.6%, LDL: 122 mg/dL, TG: 124 mg/dL, eGFR: 69

SGLT-2: no specific concerns

GLP-1RA: prior history of pancreatitis; injections a possible barrier given adherence

PLAN: Add SGLT-2. No need to reduce BP medication doses. Attempt to re-engage.

Summary

- Use of beneficial DM medications in patients with ASCVD is the responsibility of diabetologists, cardiologists and primary care physicians
    - **View every case as an opportunity for a CVOT DM medication**

Summary

- Find your diabetes ‘comfort zone’
- Practical approach to choosing either SGLT-2i or GLP-1RA
- Educate about potential side effects, *but*
  - Most are quite manageable, or rare
  - Should not serve as a barrier to use of beneficial medications

Communicate and coordinate – don’t let your patient fall through the cracks…