Updates in Diabetes Management: A Focus on SGLT-2 Inhibitors and GLP-1 Agonists

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8/2/22

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Disclosure

I have nothing to disclose

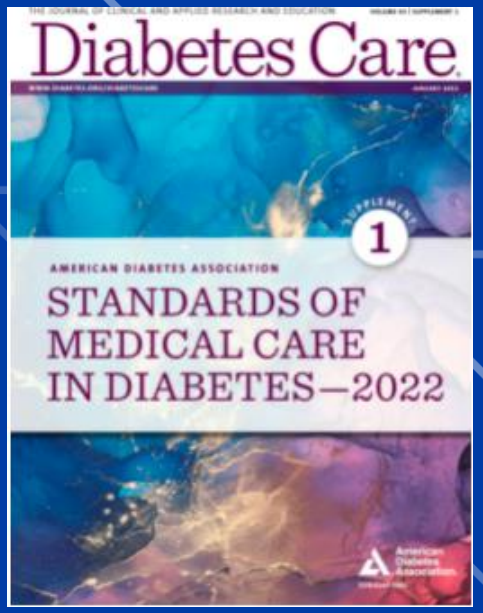
Abbreviations

- T2DM: type 2 diabetes
- SGLT-2: sodium glucose cotransporter-2
- GLP-1: glucagon-like peptide
- MI: myocardial infarction
- CV: cardiovascular
- AACE: American Association of Clinical Endocrinology
- RCT: randomized controlled trial
- MACE: major adverse cardiovascular event
- SU: sulfonylurea
- RAAS: renin-angiotensin-aldosterone system
- NSAID: non-steroidal anti-inflammatory drug
- UACR: urine albumin: creatinine ratio
- UTI: urinary tract infection
- CVD: cardiovascular disease
- BG: blood glucose
- eGFR: estimated glomerular filtration rate
- HF: heart failure
- HFrEF: heart failure with reduced ejection fraction
- HFpEF: heart failure with preserved ejection fraction
- HR: hazard ratio
- CrCl: creatinine clearance
- BMI: body mass index

Learning Objectives

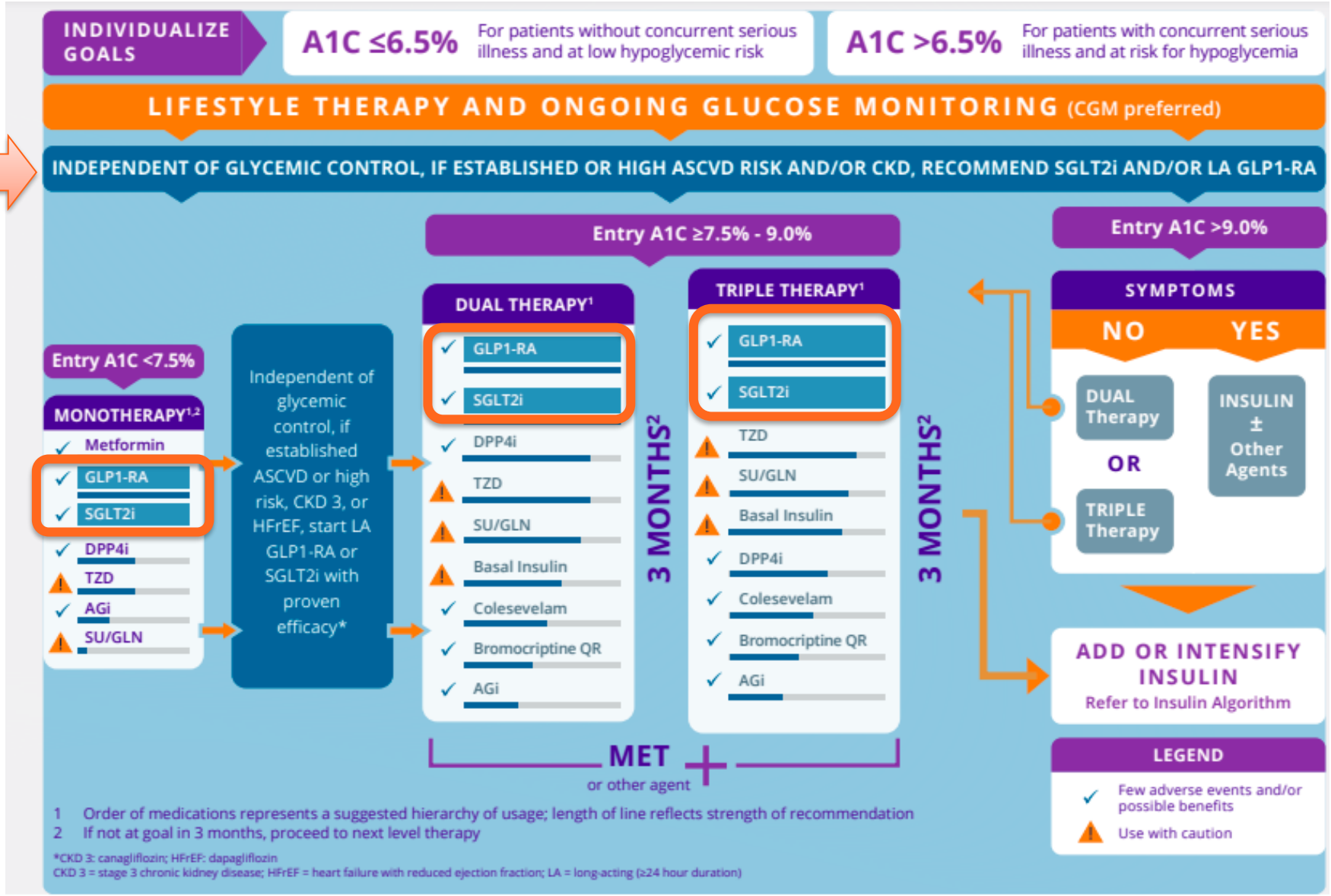
1. Explain the role of SGLT-2 inhibitors and GLP-1 agonists in relation to diabetes management
2. Describe expanded indications beyond diabetes and updates for SGLT-2 inhibitors and GLP-1 agonists
3. Apply appropriate medication management to patient cases with comorbid diabetes

American Diabetes Association – Standards of Medical Care in Diabetes 2022



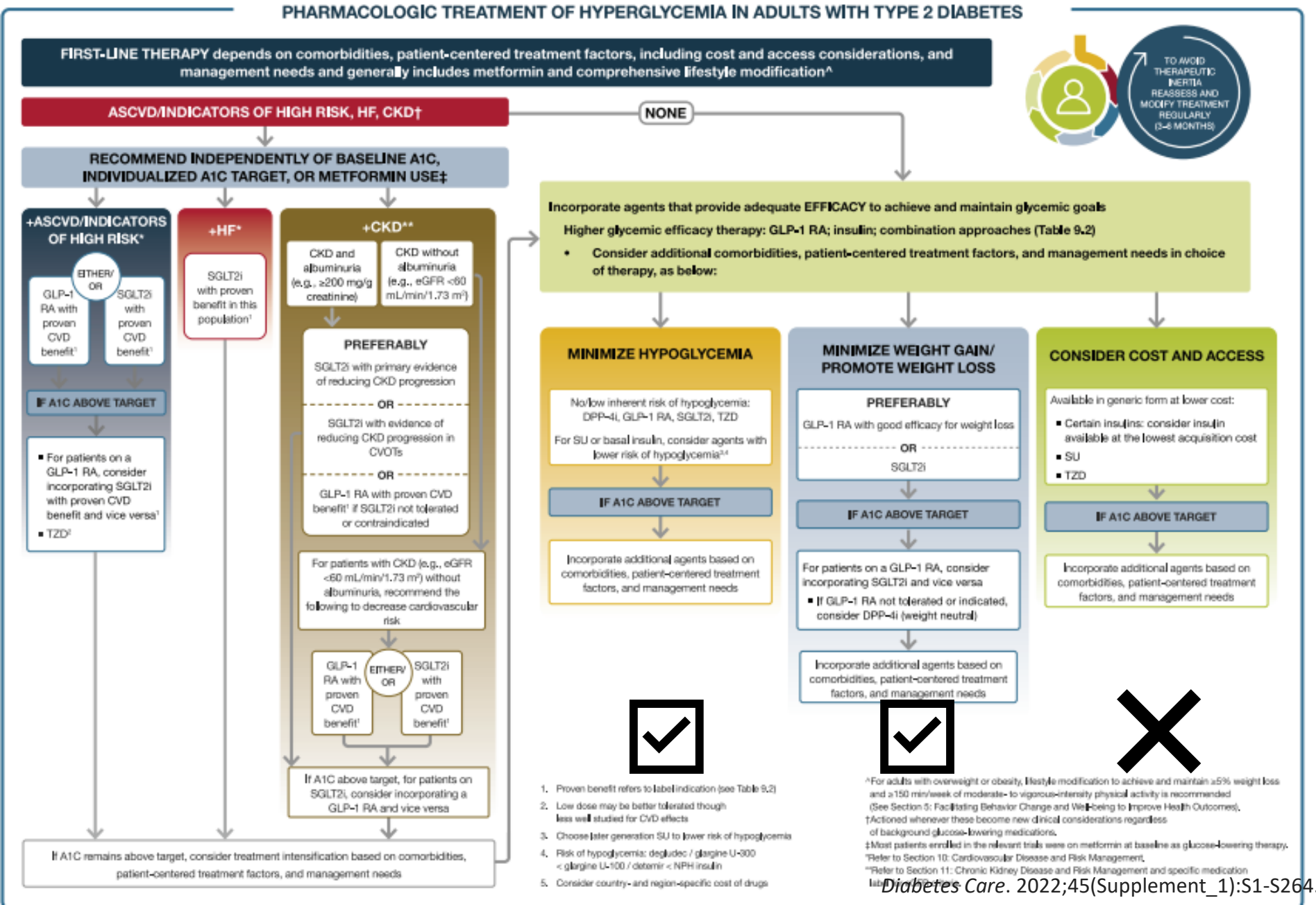
AACE Comprehensive T2DM Management Algorithm

AACE 2020



Garber AJ, et al. *Endocrine Practice*. 2020;26(1):107-139.

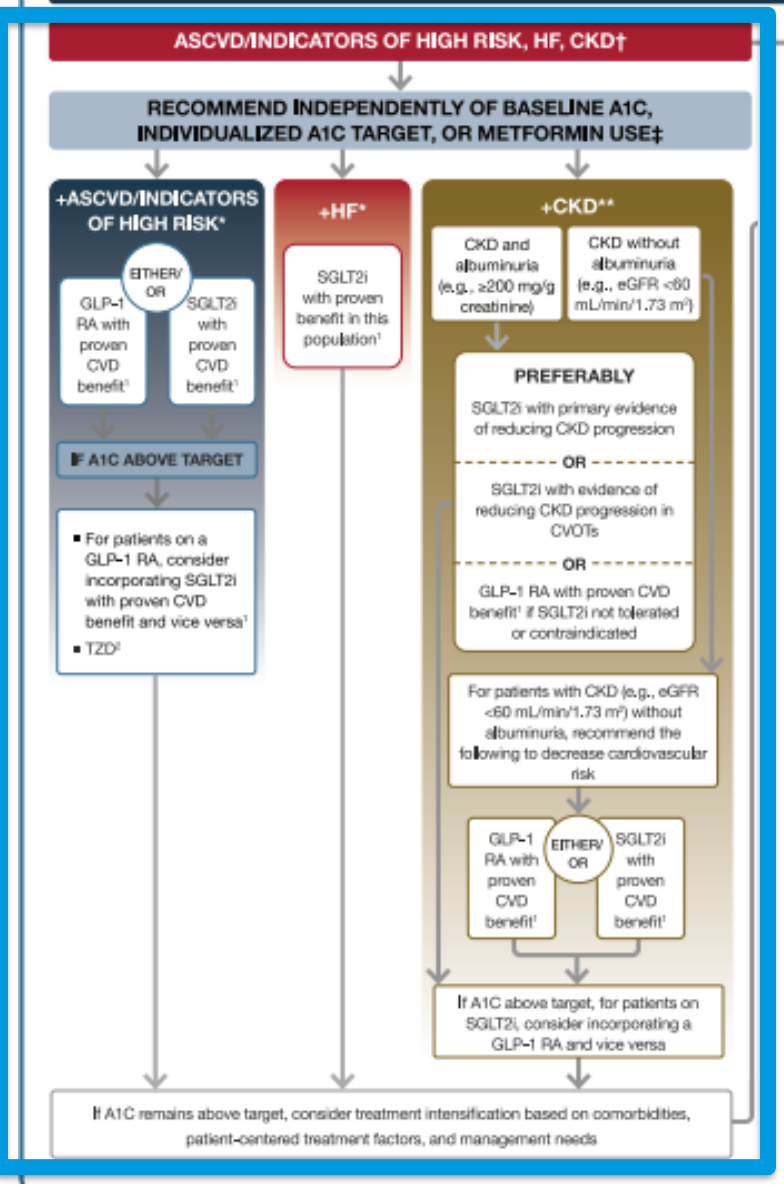
ADA 2022



Diabetes Care. 2022;45(Supplement_1):S1-S264.

PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA IN ADULTS WITH TYPE 2 DIABETES

FIRST-LINE THERAPY depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and management needs and generally includes metformin and comprehensive lifestyle modification^



- While ADA & AACE recommend SGLT2i's and GLP-1 agonists <u>independent</u> of metformin use, most insurance companies require a trial of **<u>metformin first</u>**
- Of note, **<u>~75-80%</u>** of patients in SGLT2i/GLP-1 trials were on **<u>metformin</u>**

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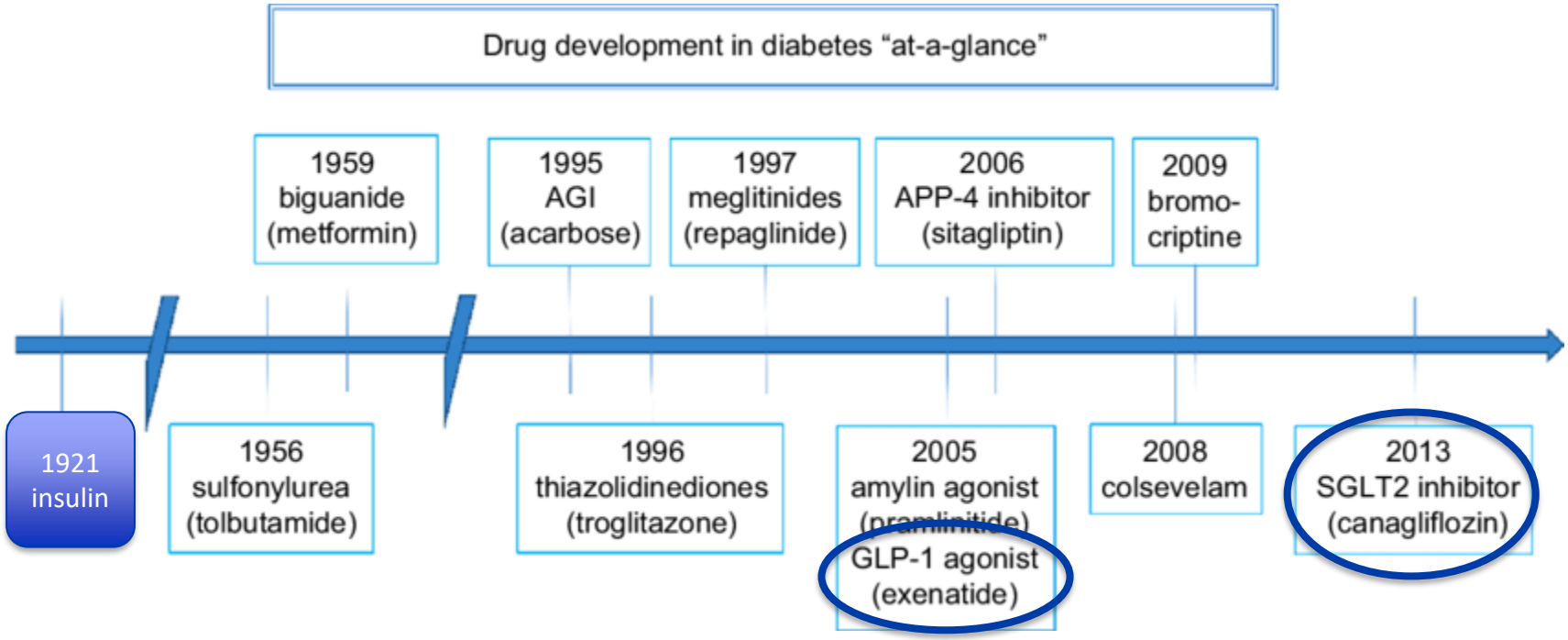
Diabetes Medication Development Timeline

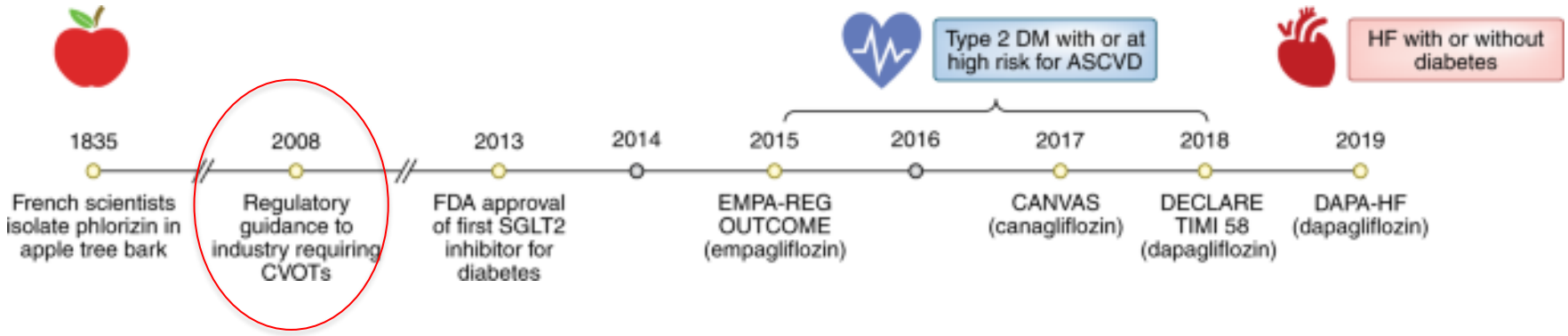


Messana JA, et al. *VHRM*. 2017;13:43-54.

Cardiovascular Outcomes Trials (CVOT)

- In 2007, rosiglitazone was associated with a significantly increased risk of MI
- 2008 FDA guidance mandates assessment of CV safety of all antihyperglycemic agents in RCTs
- Designed as non-inferiority studies to demonstrate study drug was not associated with more MACE than placebo

- If non-inferiority criteria was met, some study designs tested for superiority ***(do the study drugs lower the risk of MACE?)***
- Primary endpoint (3P MACE): composite of cardiovascular death, nonfatal MI, and nonfatal stroke



CV: cardiovascular
RCT: randomized controlled trial
MACE: major adverse cardiac event
3P: 3 point
MI: myocardial infarction

Vaduganathan M. *Nat Med*. 2019;25(11):1653-1654.
Regier EE, et al. *Clin Diabetes*. 2016;34(4):173-180

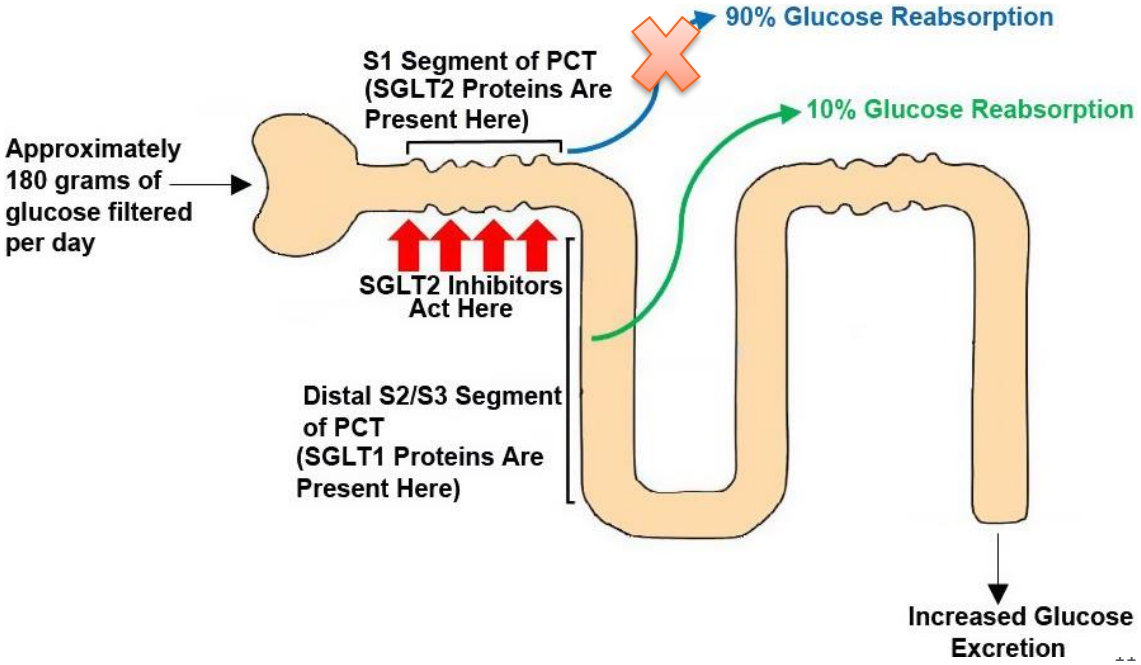
Sodium-Glucose Co-Transporter 2 (SGLT-2) Inhibitors

Canagliflozin (Invokana®)

Dapagliflozin (Farxiga®)

Empagliflozin (Jardiance®)

Ertugliflozin (Steglatro®)



Madaan, et al. *Clin Exp Pharmacol Physiol*. 2018;45(9):897-907.

SGLT-2 Inhibitor Overview

MOA	Advantages	Adverse effects	Special considerations

• Inhibits sodium-glucose co-transporter 2 (SGLT2) in the proximal tubules
• ↑ urinary excretion of glucose
	✓ Efficacy:
	○ A1C ↓ 0.5-1%
	✓ Weight loss (2.2-3.3 kg)
	✓ Low risk of hypoglycemia
	✓ Long-term CVD & CKD benefits (dependent on individual drug)
	✓ All reduce HF hospitalizations in pts w/HFrEF
		• Fungal/ bacterial infection of the genitourinary tract
		• Renal insufficiency
		• Hypotension/volume depletion
		• Increased risk of euglycemic ketoacidosis (euDKA)
		• Necrotizing fasciitis of the perineum
		• Canagliflozin
		  • **Lower limb amputation**
		  • Bone fractures
		• Dapagliflozin
		  • Newly diagnosed bladder cancer
			• Renal dose adjustments dependent on indication – most **not effective for BG** control at lower eGFRs
			• High cost (without insurance)

Diabetes Care. 2022;45(Supplement_1):S1-S264
Canagliflozin. Lexicomp. 2020

Genitourinary Infections

Prevalence	~8% (genital mycotic infections); most commonly, vulvovaginal candidiasis, Candida balanitis
Risk factors	female, history of genital infection, uncircumcised male, poor hygiene
Mechanism	altered immune function, glucosuria, altered microflora of genital region

- Mixed evidence regarding risk of UTI or severe UTIs
- Rarely, Fornier's gangrene

McGovern AP, et al. *BMJ Open Diabetes Research and Care*. 2020;8(1):e001238.
Unnikrishnan A, et al. *Indian J Endocr Metab*. 2018;22(6):837.
Sarafidis PA, et al. *Clinical Kidney Journal*. 2020;13(1):24-26.
Liu J, et al. *Sci Rep*. 2017;7:2824.
Yang H, et al. *Pharmacology Res & Perspec*. 2022;10(1).

Concomitant Diuretics and Hypotension

- SGLT2i's can lower systolic BP ~3-5 mmHg

Hypotensive/Hypovolemic	Normotensive/Euvolemic/ Age >65 yrs	Hypertensive/ Hypervolemic/Age <65yrs
• Do **not** initiate SGLT2i • Assess underlying cause • Adjust/stop diuretics or blood pressure (BP) medications as necessary	• Start SGLT2i • Consider reducing diuretic dose by 50% • If BP drops significantly or patient becomes hypovolemic, lower dose or stop diuretics (or other antihypertensives) as needed	• Start SGLT2 • Adjust BP regimen as needed

Blood pressure cuff [photo]. Shutterstock.
Gomez-Peralta F, et al. *Diabetes Ther*. 2017;8(5):953-962.
Heidenreich PA, et al. *Circulation*. 2022;145(18).

Concomitant Insulin Secretagogues

HbA1c < 8.5%

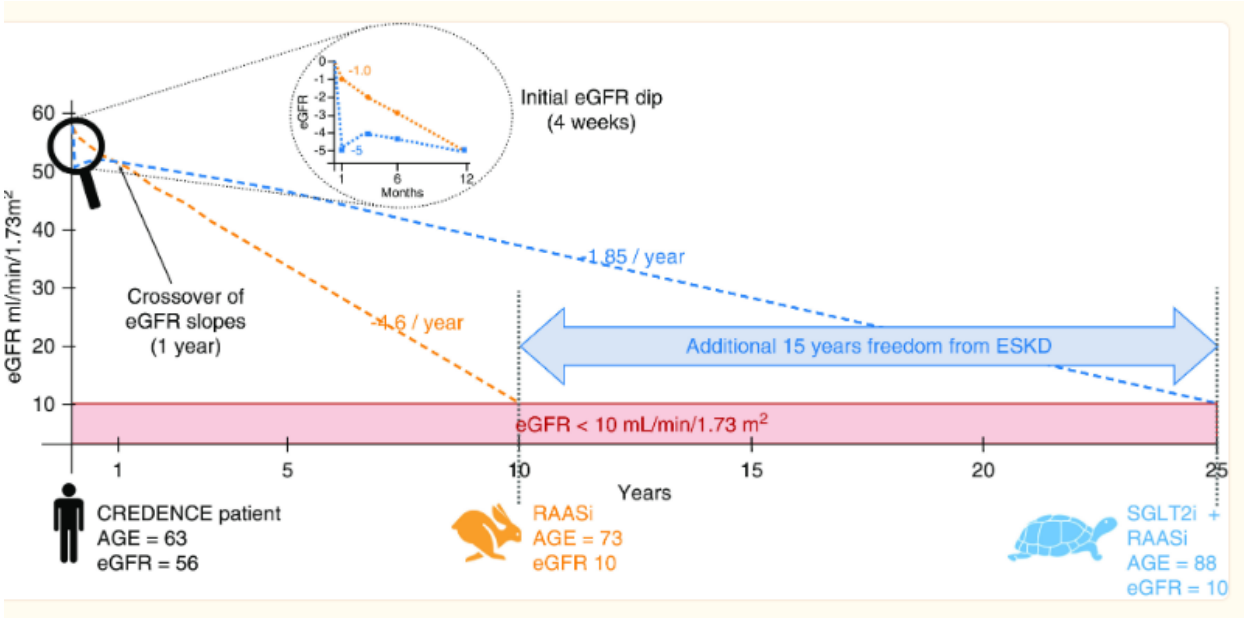
- Decrease SU or meglitinide by ~50% or stop
- Decrease rapid-acting insulin ~10-20%
- If patient is on basal insulin only, decrease ~10-20%
- Do not stop insulin abruptly (risk of euDKA)

HbA1c ≥ 8.5%

- Maintain concomitant medications
- Adjust as needed if hypoglycemia occurs

Gomez-Peralta F, et al. *Diabetes Ther*. 2017;8(5):953-962.
Tan K, et al. *Hong Kong Med J*. 2019;25(4):312-319.

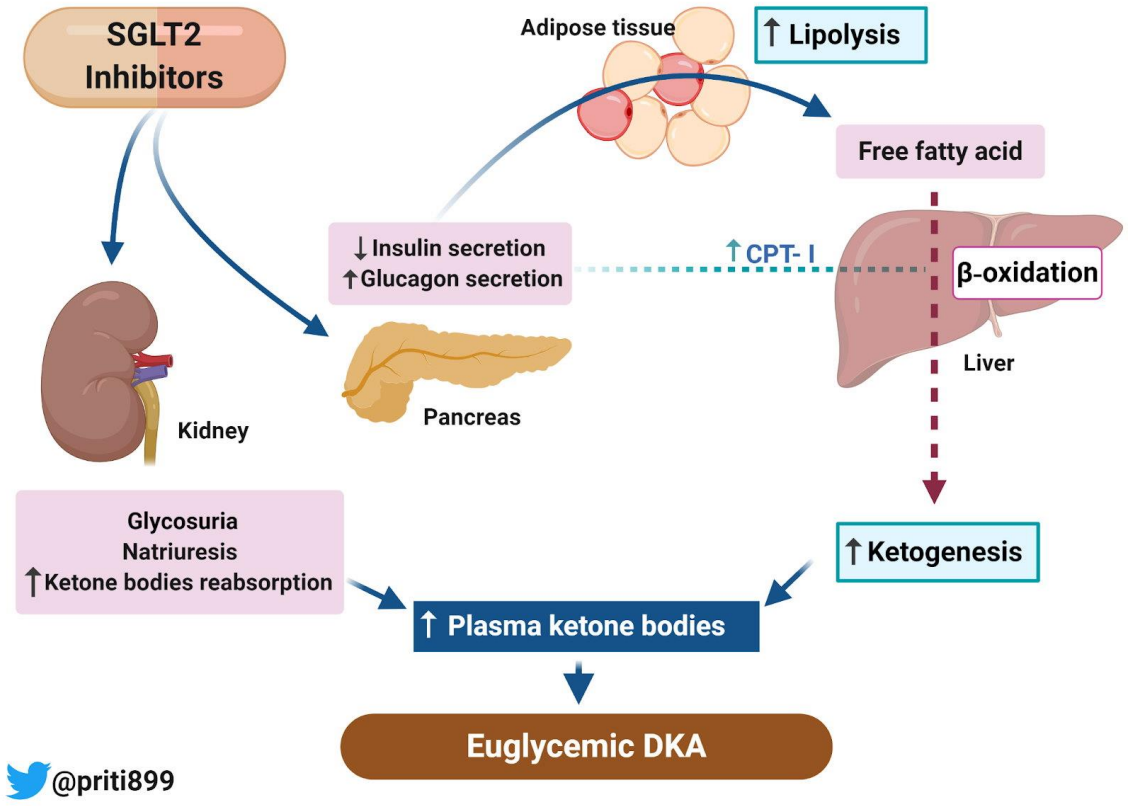
Initial eGFR decline



- Early drop in eGFR ~3-6 mL/min/1.73m^2 around weeks 2-4 with recovery around week 12
- Risk factors: hypovolemia, diuretics, RAAS, NSAIDs, heart failure
- Attenuation of eGFR slope at week 52

Meraz-Muñoz AY, et al. *Kidney360*. 2021;2(6):1042-1047.

Euglycemic DKA



- Mechanism: increased ketone body production & reabsorption
- May be precipitated by surgery, extensive exercise, myocardial infarction, stroke, severe infection, prolonged fasting, pancreatic insulin deficiency, dose decreases in insulin, alcohol abuse
- **<u>SGLT2i should be discontinued if this occurs</u>**

Diaz G. Euglycemic DKA [image]
Dutta S,, et al. J Family Med Prim Care. 2022;11(3):927

Summary of Advantages

Medications	T2DM	ASCVD	Diabetic kidney disease (DKD)	HFrEF	HFpEF
Canagliflozin (Invokana®)	eGFR ≥30	✓*	✓*	✓	n/a
Dapagliflozin (Farxiga®)	eGFR ≥45	^	✓* (± DM)	✓* (± DM)	n/a
Empagliflozin (Jardiance®)	eGFR ≥30	✓*	✓	✓* (± DM)	✓* (± DM)
Ertugliflozin (Steglatro®)	eGFR ≥45	X		?	n/a

*FDA label

^To reduce the risk of hospitalization for HF in adults with T2DM and established CVD or multiple risk factors

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Renal Dose Adjustments

	T2DM	ASCVD	Diabetic kidney disease (DKD)	HFrEF
Canagliflozin (Invokana®)	eGFR≥60: 100, 300 mg eGFR ≥30: 100 mg	eGFR ≥30: 100 mg	eGFR < 30: may continue 100 mg (don't start)	(*off-label*) eGFR ≥30: 100 mg

^To reduce the risk of hospitalization for HF in adults with T2DM and established CVD or multiple risk factors

Dapagliflozin. Lexi-Drugs. Lexicomp.
Empagliflozin. Lexi-Drugs. Lexicomp.
Canagliflozin. Lexi-Drugs. Lexicomp.
Ertugliflozin. Lexi-Drugs. Lexicomp.

3P MACE: composite of CV death, nonfatal MI, or nonfatal stroke

ASCVD Studies in SGLT-2i's

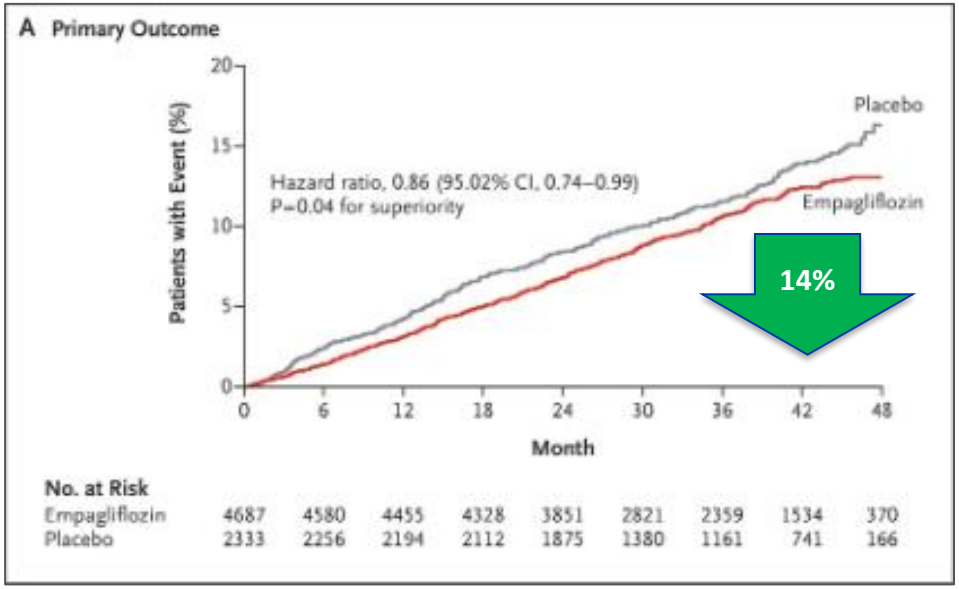
% are relative risk reductions

	EMPA-REG (2015) Jardiance® (empagliflozin)	CANVAS (2017) Invokana® (canagliflozin)
Inclusion	DM2 with established CVD	DM2 + hx of prior CV event OR age ≥50 years with ≥2 CV risk factors
Sample Size	N = 7,020 10 or 25 mG (3.1 yrs)	N=10,142 100 or 300 mG (3.6 yrs)
Primary endpoint	3P MACE: ↓**14%**	3P MACE: ↓**14%**
Notable Secondary endpoints	38% ↓in CV death 35% ↓HF hospitalization	↓33% HF hospitalization (exploratory:↓40 % in composite renal outcomes)

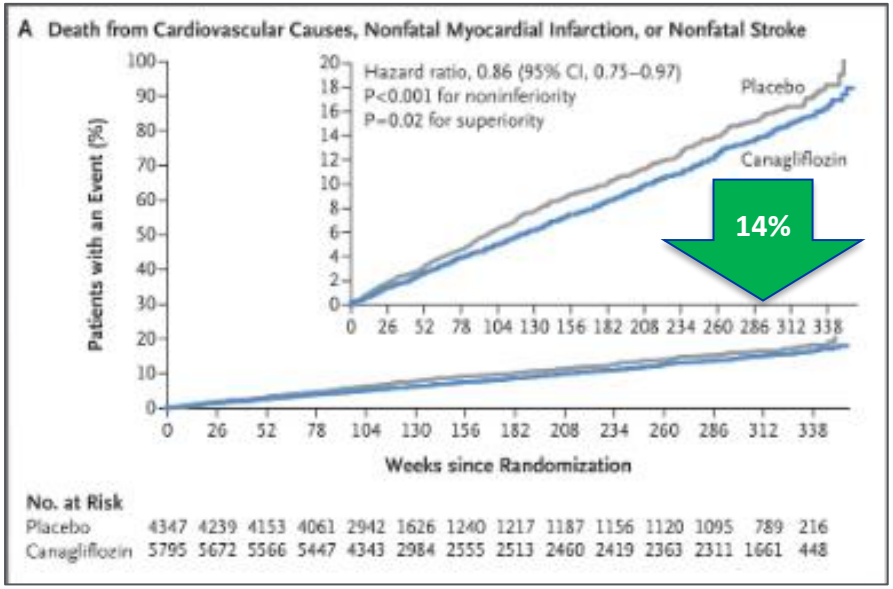
ASCVD Outcomes

3P MACE: CV death, nonfatal MI, or nonfatal stroke

EMPA-REG (2015): Empagliflozin



CANVAS (2017): Canagliflozin



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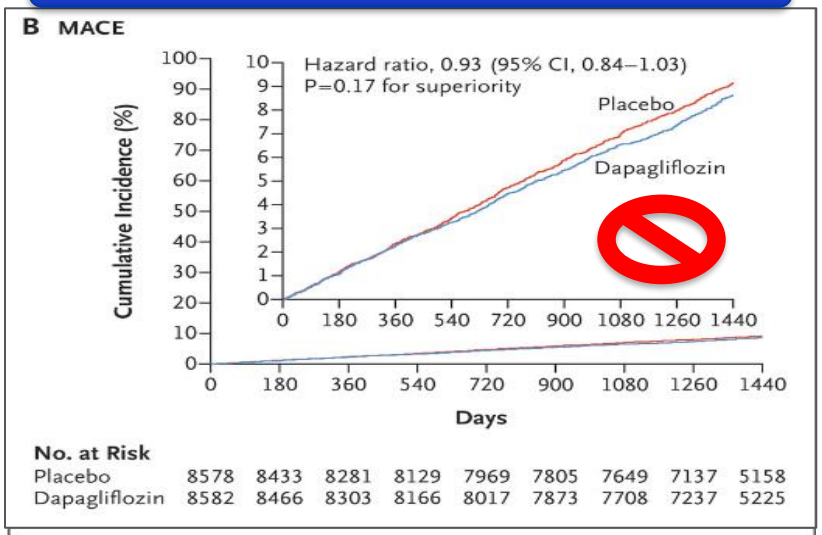
Neal B, et al. New England Journal of Medicine 2017;377(7): 644-657.
Packer M, et al. N Engl J Med. 2020;383(15):1413-1424.

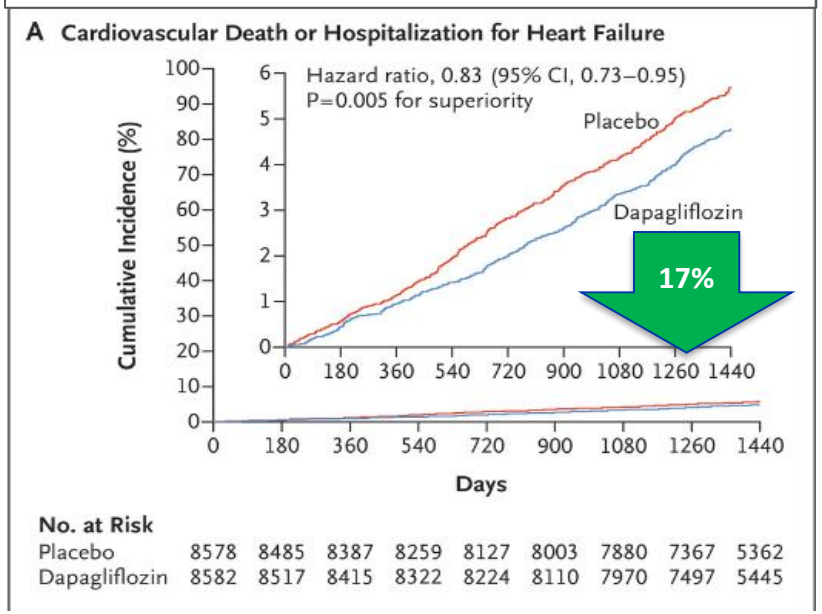
ASCVD Outcomes

Cannon CP. *N Engl J Med*. 2020;383(15):1425-1435.
Wiviott S, et al. NEJM. 2019; 380(4): 347-357.

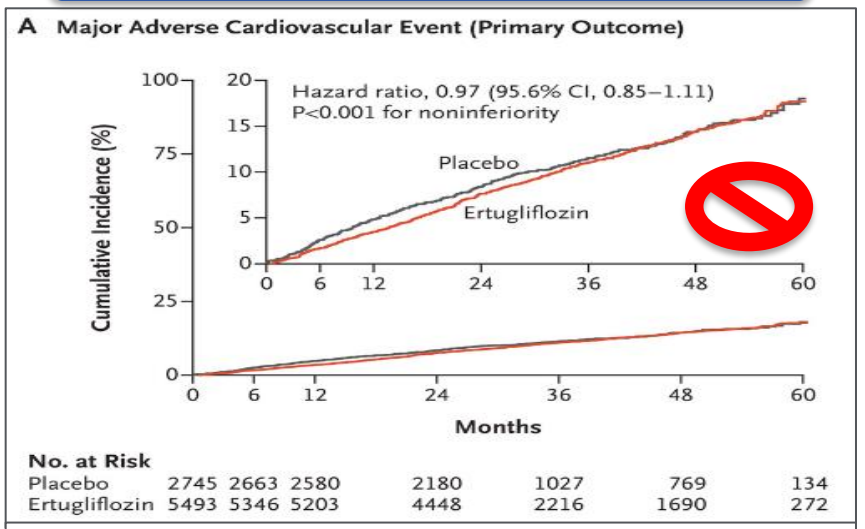
3P MACE: CV death, nonfatal MI, or nonfatal stroke

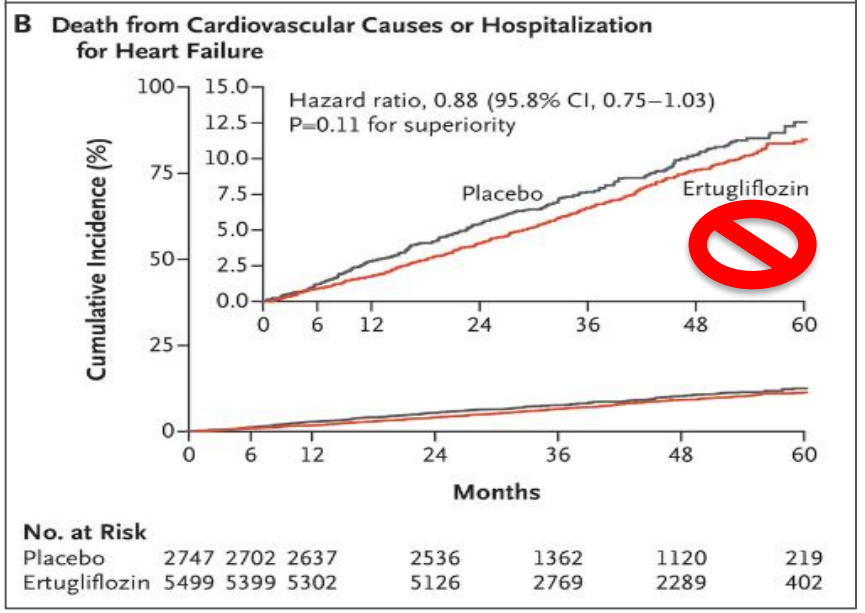
DECLARE TIMI (2019): Dapagliflozin





VERTIS CV (2020): Ertugliflozin





HF Studies in SGLT-2i's

% are relative risk reductions

	DAPA-HF (2019) Farxiga® (Dapagliflozin)	EMPEROR-Reduced (2020) Jardiance® (empagliflozin)
Inclusion	Age ≥ 18 yo NYHA class II-IV HFrEF of 40% or less with or without DM2	Age ≥ 18 yo NYHA class II-IV HFrEF of 40% or less with or without DM2
Sample Size	N =4744 (18.2 mo) 10 mG ~42% had DM2	N = 3730 (16 mo) 10 mG ~50% had DM2
Primary endpoint	Composite of worsening HF (hospitalization or an urgent visit resulting in IV therapy) or CV death: **↓26%**	Composite of CV death or hospitalization for worsening HF: **↓25%**
Notable Secondary endpoints		**Slower rate of eGFR decline** (-0.55 ± 0.23 vs. -2.28 ± 0.23, p<0.001)

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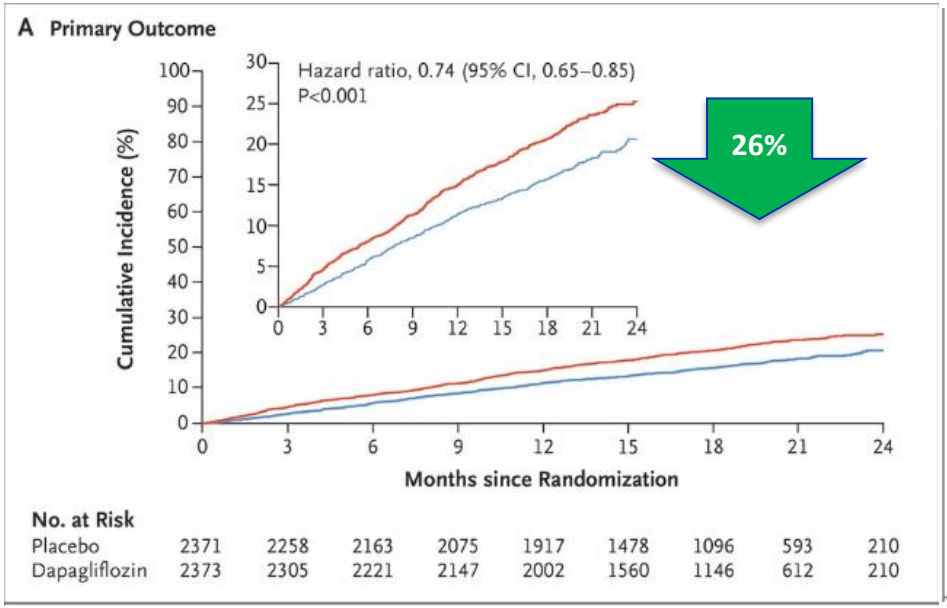
HF Outcomes

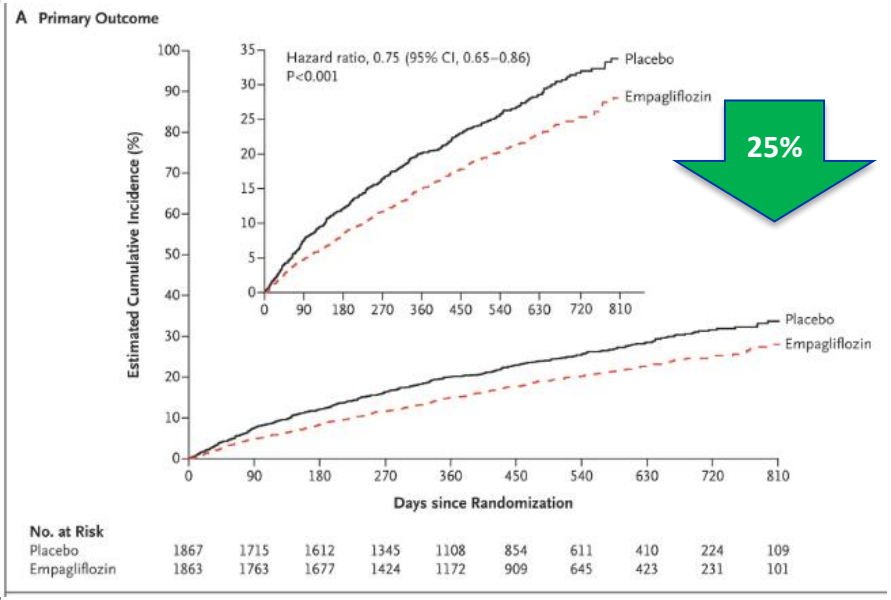
DAPA HF (2019): Dapagliflozin

Composite of death from CV causes, hospitalization for HF, or an urgent visit resulting in IV therapy for HF



EMPEROR-Reduced (2020): Empagliflozin

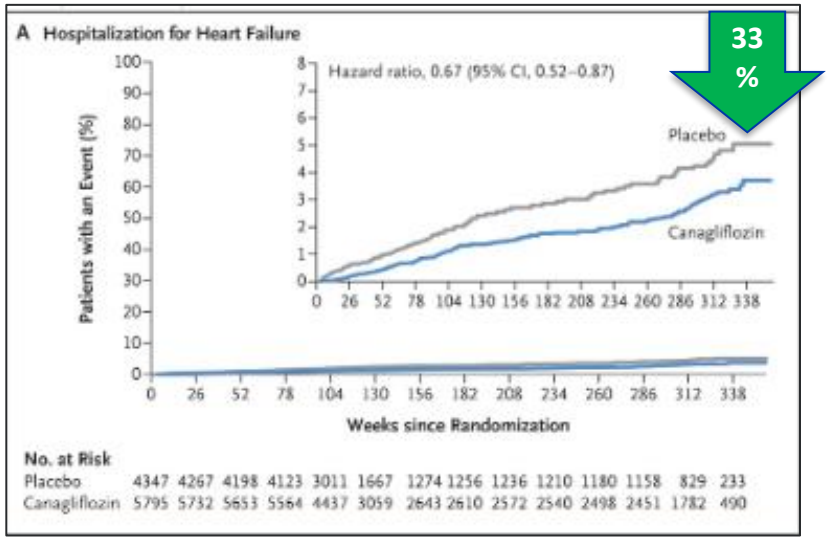
composite outcome of CV death or hospitalization for HF



McMurray JJV, et. *N Engl J Med*. 2019;381(21):1995-2008.
Packer M, et al. *N Engl J Med*. 2020;383(15):1413-1424.

HF Outcomes (Secondary)

CANVAS (2017): Canagliflozin



CREDENCE (2019): Canagliflozin

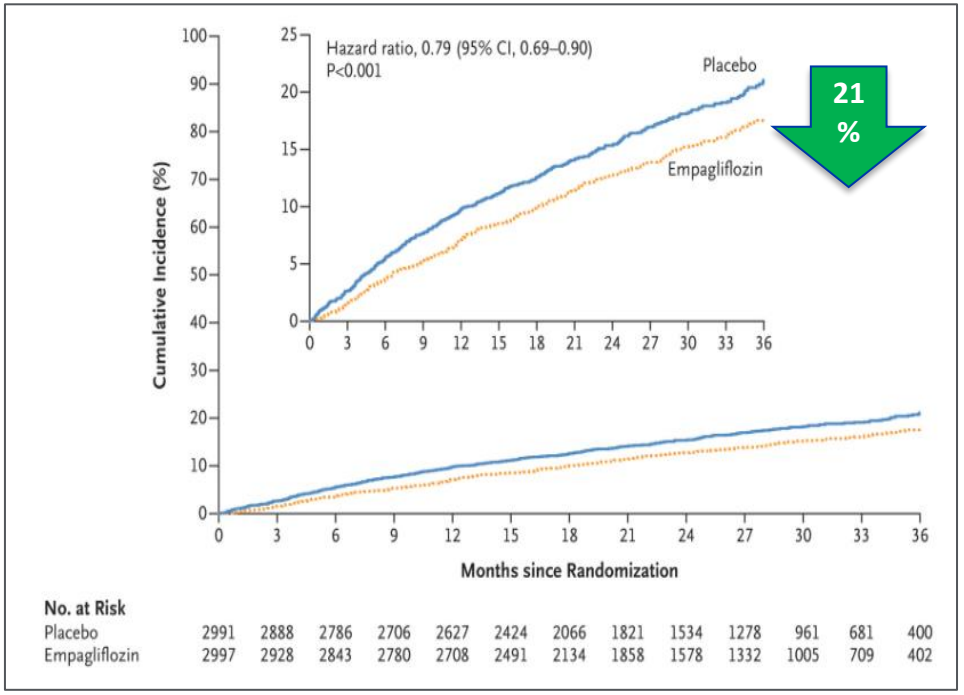
HF Hospitalization:
HR 0.61 (0.47 – 0.80), p<0.001

VERTIS CV (2020): Ertugliflozin
Hospitalization for HF
HR 0.7 (0.54 – 0.90)
Not tested for statistical significance because first key secondary outcome (death from CV causes or hHF) not significant

Neal, B, et al. New England Journal of Medicine 377(7): 644-657.
Cannon CP. *N Engl J Med*. 2020;383(15):1425-1435.

EMPEROR Preserved (2021) – Empagliflozin (Jardiance®)

Inclusion	Class II–IV heart failure and an ejection fraction > 40% with or without DM2
Sample Size	N=5988 (26.2 months), 10 mG daily
Primary endpoint	**↓21%** composite of cardiovascular death or hospitalization for heart failure **(mainly drive by ↓ HF hospitalization)**
Notable secondary endpoints	Change in mean eGFR slope/year: -1.25 vs. -2.62 (p < 0.001) Composite renal outcome 3.6% vs. 3.7% (p > 0.05)



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Anker SD, et al. *N Engl J Med*. 2021;385(16):1451-1461.

UACR: urinary albumin-to-creatinine

% are relative risk reductions

DKD/CKD trials in SGLT-2i's

	CREDENCE (2019) Invokana® (canagliflozin)	DAPA-CKD (2019) Farxiga (Dapagliflozin)
Inclusion	DM2 +eGFR 30-90 + UACR 300 to 5000 mg/g	eGFR 25-75 + UACR 200 to 5000 mg/g with or without DM2
Sample Size	N= 4401 *(2.6yr) – stopped early for efficacy!*	N = 4304 (2.4yrs)
Primary endpoint	ESKD, Doubling of Serum Creatinine, or Renal or CV Death: **↓30%**	Composite of a sustained decline in eGFR of at least 50%, ESKD, or renal or CV death: **↓39%**
Notable Secondary endpoints	CV death or HF hospitalization: **↓31%** HF hosp: **↓39%**	

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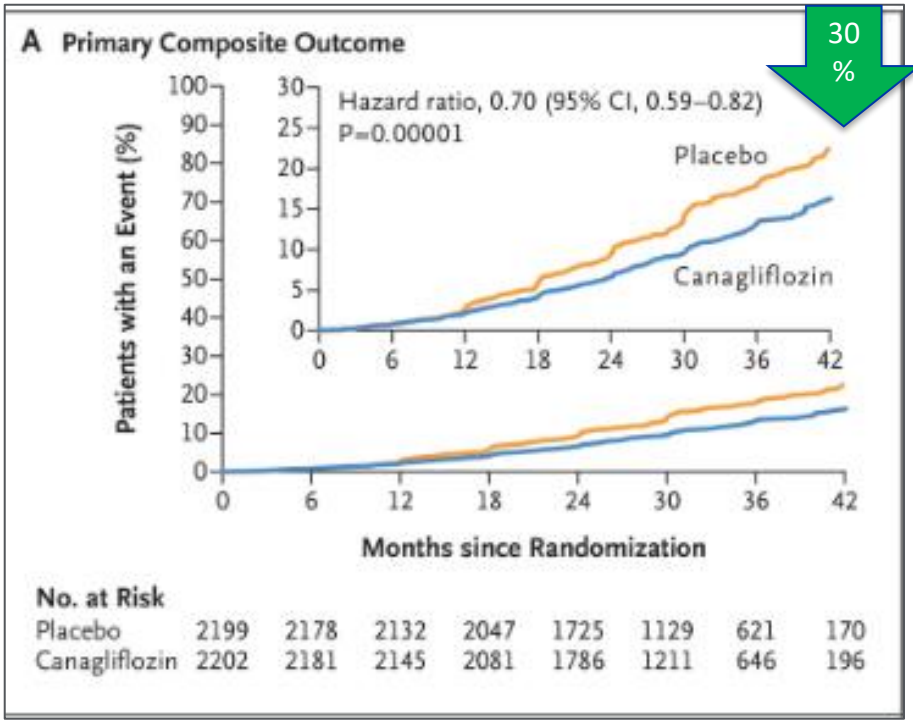
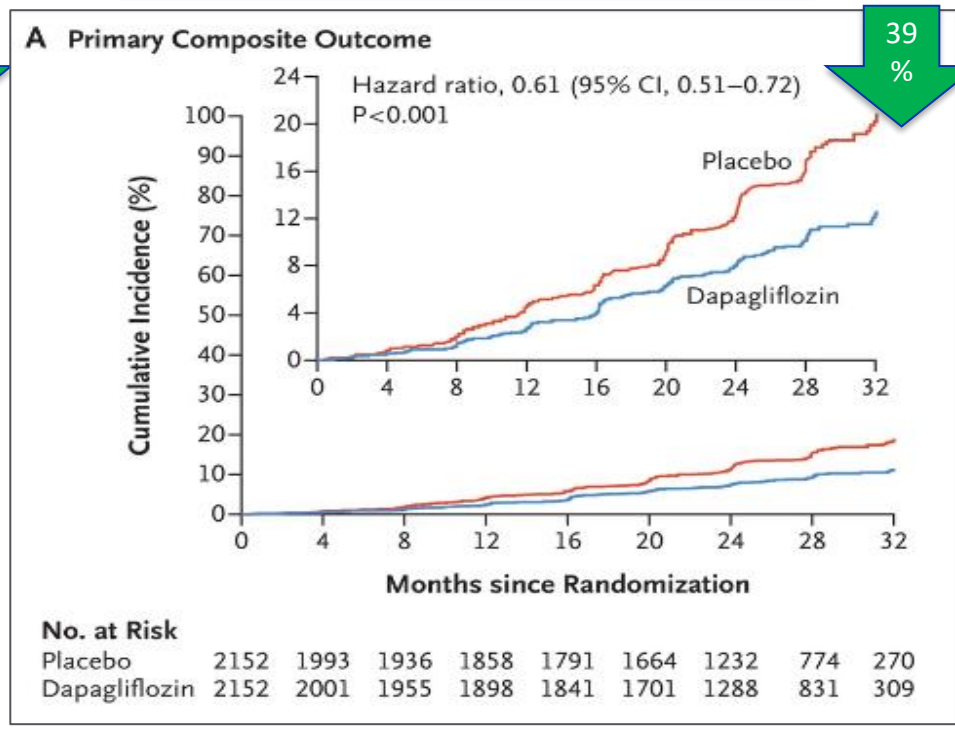
DKD/CKD Primary Outcomes

CREDENCE (2019): Canagliflozin



Composite of ESKD (dialysis, transplantation, or a sustained eGFR of <15 ml/min/1.73 m^2), a doubling of the SCr, or death from renal or CV causes

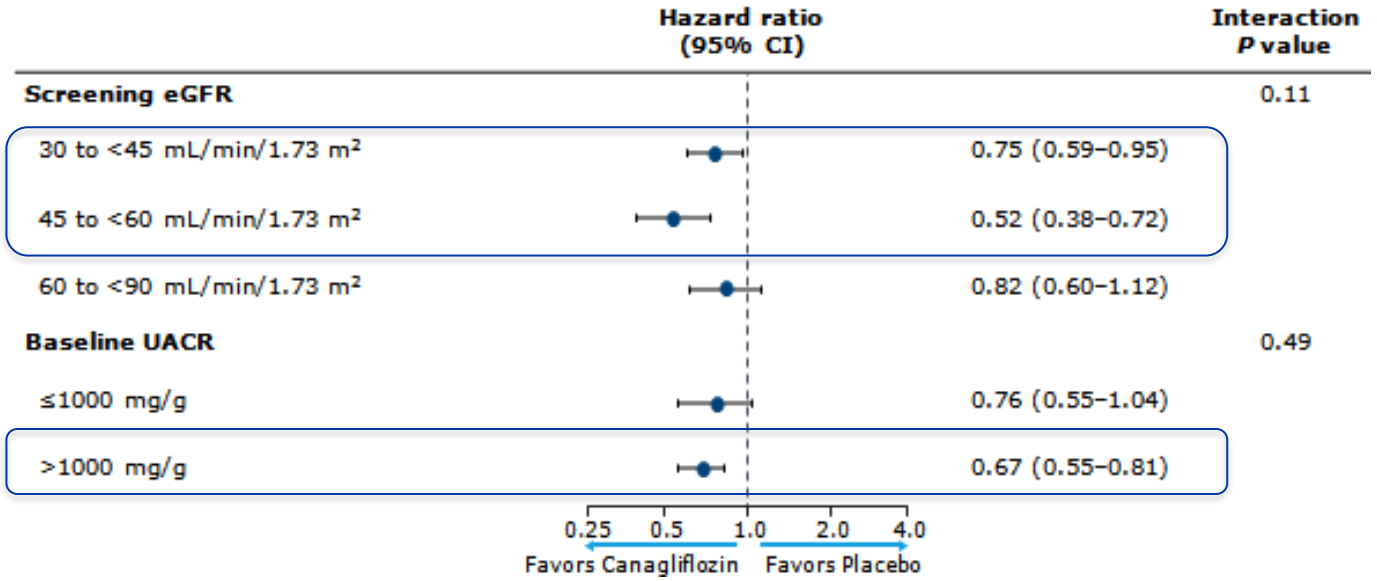
DAPA CKD (2019): Dapagliflozin

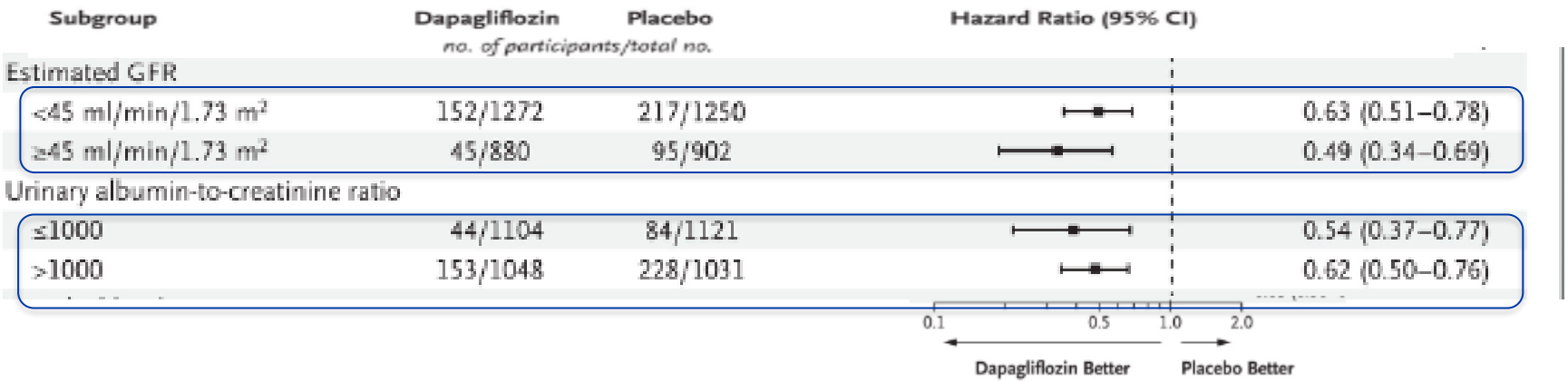


Composite of a sustained decline in the estimated glomerular filtration rate (GFR) of at least 50%, ESKD, or death from renal or CV causes

Heerspink HJL, et al. *N Engl J Med*. 2020;383(15):1436-1446.
Perkovic et al. *N Engl J Med*. 2019;380(24): 2295-2306.

Primary Outcome by Screening eGFR and Albuminuria





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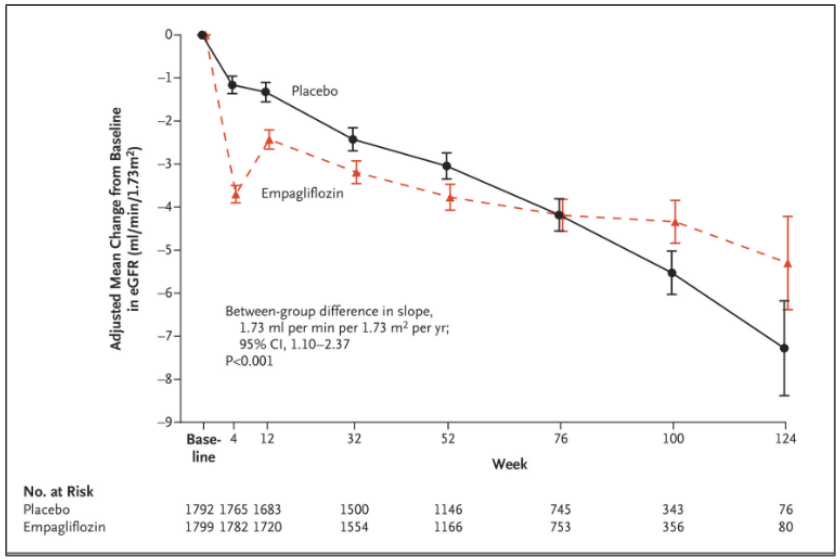
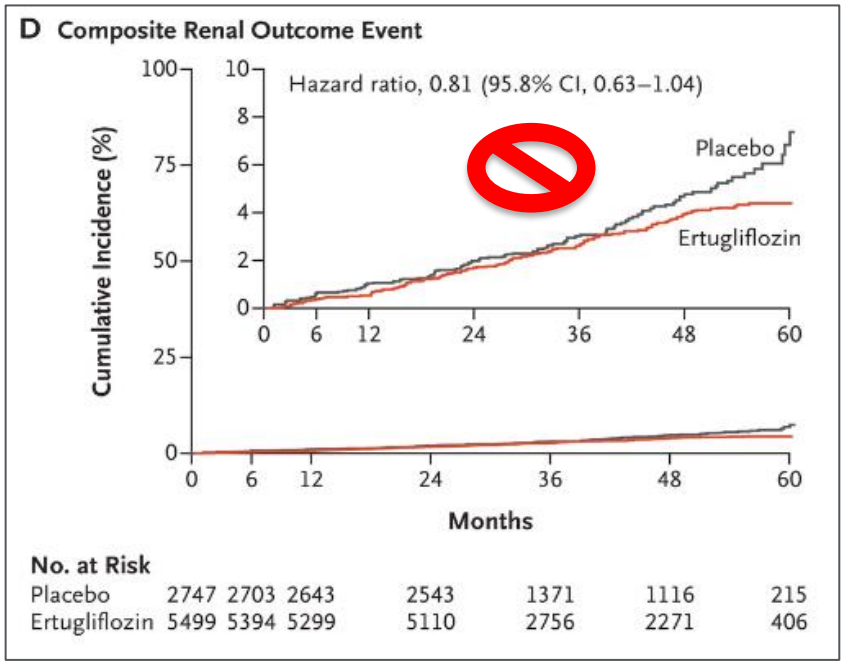
Heerspink HJL, et al. *N Engl J Med*. 2020;383(15):1436-1446.
Perkovic et al. *N Engl J Med*. 2019;380(24): 2295-2306.

DKD/CKD Secondary Outcomes

EMPEROR-Reduced (2020): Empagliflozin



VERTIS CV (2020): Ertugliflozin



Packer M, et al. *N Engl J Med*. 2020;383(15):1413-1424.
Cannon CP. *N Engl J Med*. 2020;383(15):1425-1435.

Updates to ACC/AHA/HFSA Management of Heart Failure (2022)

Stage A: Primary Prevention (Risk of HF)	Stage C (HFrEF, LVEF ≤ 40%)	HFmrEF (Symptomatic, LVEF 41 – 49%)	HFpEF (LVEF ≥ 50%)
• T2DM and either CVD or high CV risk → SGLT2i to prevent HF hospitalization (1A)	• SGLT2i first line simultaneously or in sequence (1A) • Reduce HF hospitalization and CV mortality, irrespective of T2DM	• SGLT2i (2a)	• SGLT2i can be beneficial in decreasing HF hospitalizations and CV mortality (2a B-R)

Heidenreich PA, et al. *Circulation*. 2022;145(18).

Question 1

65 yo male with PMH of CKD (eGFR 50, UACR 342 mG/G), HFrEF (EF 30%), T2DM (A1c 8.4%), and history of CAD s/p 1 stent presents to the office for wellness exam. Medications include metformin 500 mG BID, aspirin 81 mg daily, metoprolol succ 50 mg daily, atorvastatin 40 mg, furosemide 20 mG BID, and lisinopril 10 mG daily. Which additional medication would you add-on?

A. Rybelsus 3 mG daily
B. Ertugliflozin (Steglatro®) 15 mg daily
C. Dapagliflozin (Farxiga®) 10 mG daily
D. Increase metformin to 1000 mG BID

✓ HFrEF, DKD, T2DM

Consider dose adjusting furosemide to prevent over-diuresis

Question 2

True/False

Same patient 8 years later now has eGFR 40. Dapagliflozin (Farxiga®) should be stopped because it is no longer effective for preventing DKD or heart failure hospitalizations.

A. True
B. False

No longer effective for BG control! eGFR < 45
For DKD and HF, can continue until eGFR ~25

Glucagon-like Peptide (GLP-1) Agonists

GLP-1 Agonists

- Dulaglutide (Trulicity®)
- Exenatide (Byetta®)
- Exenatide ER (Bydureon®)
- Liraglutide (Victoza®)
- Lixisenatide (Adlyxin®)
- Semaglutide (Ozempic®)
- Semaglutide (Rybelsus®)
- Tirzepatide* (Mounjaro®)

*New GLP-1/GIP agonist

GLP-1 Agonist

Mechanism of Action

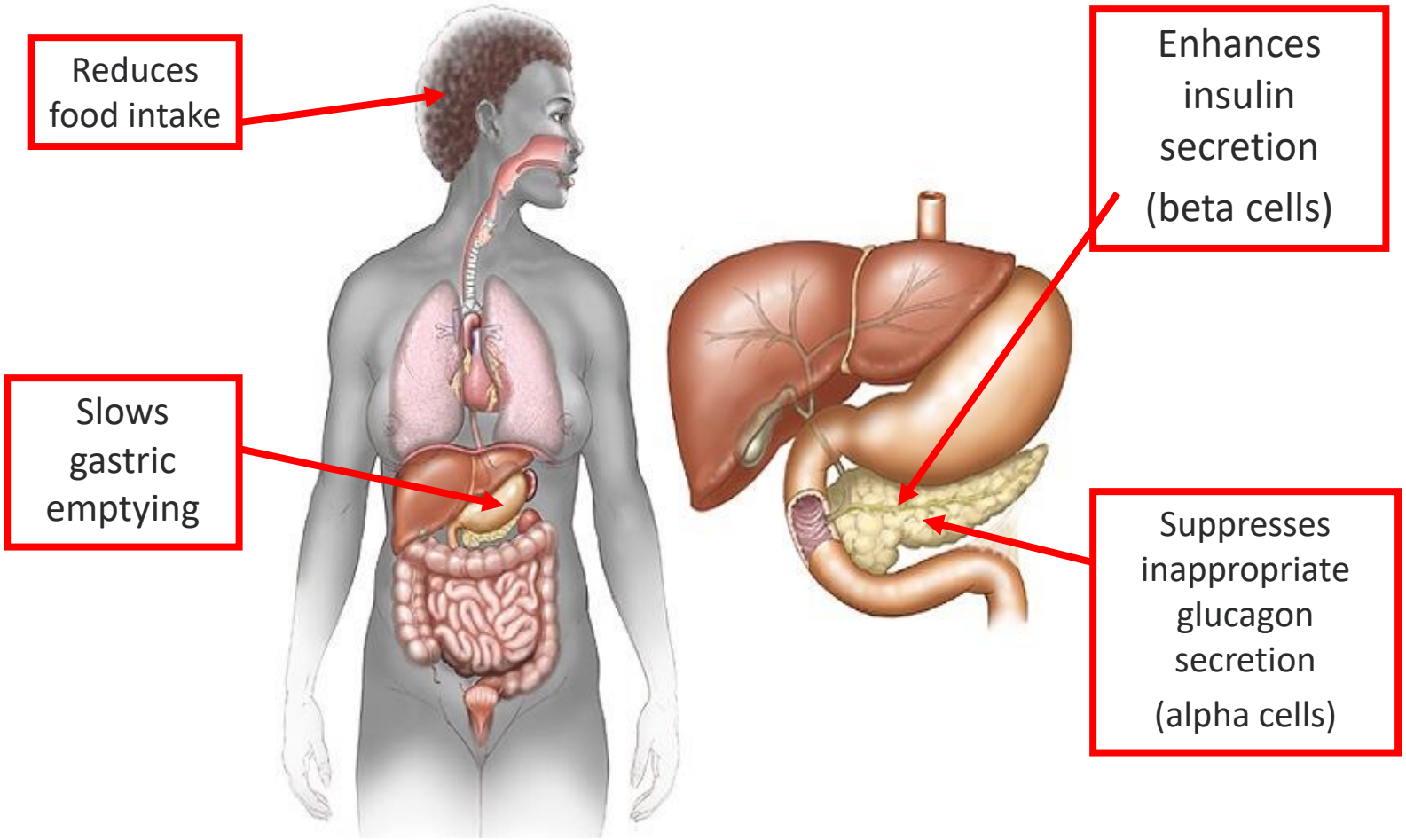


Image from Dave Carlson Jewish Medical Center [image]. Carlson Sock Art. https://www.carlsonstockart.com/gallery/human-digestive-system-gastrointestinal-tract-gi-tract-alimentary-canal/. Accessed September 30, 2019.

GLP-1 Agonist Overview

MOA	Advantages	Adverse effects	Special considerations
• Increases glucose-dependent insulin secretion • Suppresses post-prandial glucagon secretion • Delays gastric emptying time • Restores beta cell function	• ↓ A1C 0.5-1.8% • ↓ weight (1-4 kg) • ↓ SBP 1 to 7 mmHg • ↓ TG 12 to 40 mg/dL • Improved markers of beta cell function • ASCVD benefit for some in class	• **Contraindicated in history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (MEN 2) (BBW)** • GI effects (↑lipase, abdominal pain, diarrhea, nausea) • Mild/Moderate hypoglycemia • ?Acute pancreatitis • Slows gastric emptying → avoid in patients with gastroparesis	• Not recommended CrCl < 30 mL/min (exenatide) or eGFR <45 (exenatide ER) • Nausea and vomiting are typically transient ○ Worse with daily injections

Diabetes Care. 2022;45(Supplement_1):S1-S264

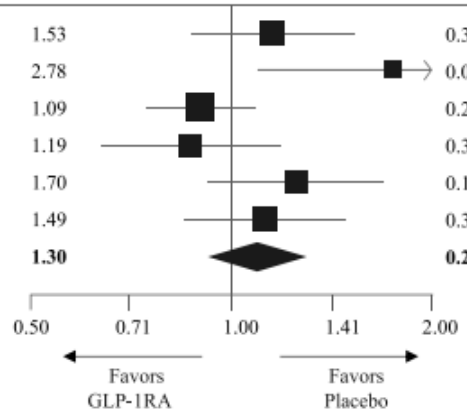
Retinopathy Risk

- For dulaglutide (Trulicity®), exenatide (Bydureon®), and semaglutide (Ozempic®), warnings were added to the package insert as rates of retinopathy were **worse** compared to placebo

- Meta-analysis (2021) showed no significant association between GLP-1 and retinopathy risk (OR 1.10; 95% CI 0.93, 1.30), however a meta-regression showed a significant association between **HbA1c reduction and retinopathy**
  - Time frame: 3 months to > 3 years to worsening after treatment intensification

Trial	GLP-1RA n/N	Placebo n/N	OR	Lower Limit	Upper Limit	p-value
LEADER (2016)	106 / 4,668	92 / 4,672	1.16	0.87	1.53	0.312
SUSTAIN-6 (2016)	50 / 1,648	29 / 1,649	1.75	1.10	2.78	0.018
EXSCEL (2017)	214 / 7,356	237 / 7,396	0.91	0.75	1.09	0.298
HARMONY (2018)	78 / 4,731	89 / 4,732	0.88	0.64	1.19	0.392
REWIND (2019)	95 / 4,949	76 / 4,952	1.26	0.93	1.70	0.142
PIONEER-6 (2019)	113 / 1,591	101 / 1,592	1.13	0.86	1.49	0.393
OVERALL	**656 / 24,943**	**624 / 24,993**	**1.10**	**0.93**	**1.30**	**0.290**

Q = 10.47 **I^2 = 52.22%**
p-value = 0.063 **T^2 = 0.023**



Dulaglutide (Trulicity). LexiComp. 2021.
Diabetic Retinopathy. CDC. https://www.cdc.gov/visionhealth/pdf/factsheet.pdf
Bethel MA, et al. *Diabetes Care*. 2021;44(1):290-296.

Pancreatitis Risk

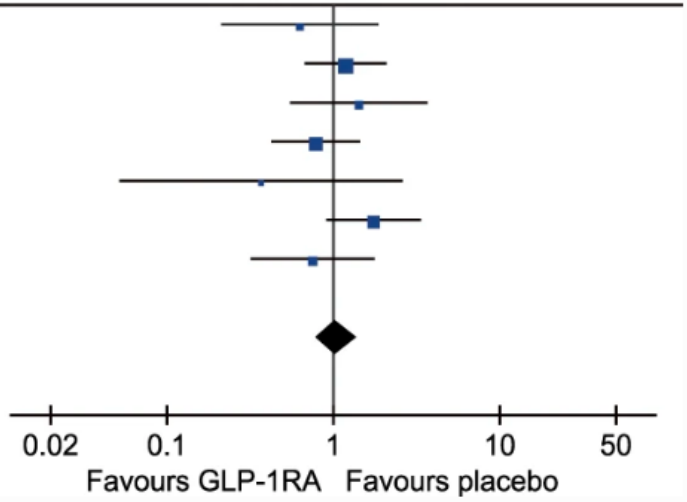
- In 2013, population-based matched case-control study found that exenatide and sitagliptin was associated with increased odds of hospitalization for acute pancreatitis
- Since then, several large meta-analyses have shown no associated risk in pancreatitis from GLP-1 agonists (but increased risk with DPP-4i's)

From: GLP-1 receptor agonists and pancreatic safety concerns in type 2 diabetic patients: data from cardiovascular outcome trials

	GLP-1RA		Placebo			Peto Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**Peto, Fixed, 95% CI**
ELIXA	5	3031	8	3032	7.2%	0.63 [0.21, 1.87]
EXSCEL	26	7344	22	7372	26.7%	1.19 [0.67, 2.09]
Harmony Outomes	10	4717	7	4715	9.5%	1.42 [0.55, 3.69]
LEADER	18	4668	23	4672	22.8%	0.78 [0.42, 1.45]
PIONEER 6	1	1591	3	1592	2.2%	0.37 [0.05, 2.61]
REWIND	23	4949	13	4952	20.0%	1.75 [0.91, 3.36]
SUSTAIN-6	9	1648	12	1649	11.6%	0.75 [0.32, 1.77]
Total (95% CI)		**27948**		**27984**	**100.0%**	**1.05 [0.78, 1.40]**
Total events	92		88			

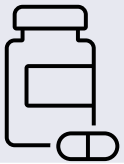
Heterogeneity: Chi² = 6.31, df = 6 (P = 0.39); I² = 5%

Test for overall effect: Z = 0.31 (P = 0.76)



Singh S, et al. *JAMA Intern Med*. 2013;173(7):534.
Zhang Z, et al. *Cardiovasc Diabetol*. 2017;16(1):31.
Cao C, et al. *Endocrine*. 2020;68(3):518-525.

Summary of Advantages

	ASCVD	Weight Loss	Lower Blood Pressure
Dulaglutide (Trulicity®)	✓	✓	✓
Exenatide (Byetta®)		✓	✓
Exenatide ER (Byudreon®)	X	✓	✓
Liraglutide (Victoza®)	✓	✓	✓
Semaglutide (Ozempic®)	✓	✓	✓
Semaglutide (Rybelsus®) Oral option 	X	✓	✓

Dulaglutide (Trulicity®)

Needle part of pen

- To reduce the risk of MACE in adults with T2DM who have established ASCVD or multiple cardiovascular risk factors **(primary and secondary prevention)**

Dosing

0.75 mG weekly	4 wks →	1.5 mG weekly	4 wks →	3 mG weekly	4 wks →	4.5 mG weekly
-1.1% A1c reduction -4.6 lb		-1.5% A1c reduction -6.6 lb		-1.6% A1c reduction -8.4 lb		-1.8% A1c reduction -10.1 lb

Prescribing

- Each strength needs a new prescription (Each box contains 2 mL or 4 pens)
- After training, patient willingness to use injectable was **94%**

Trulicity. Sanofi. 2022. https://www.trulicity.com/hcp/efficacy-weight/weight-loss-dosing

Liraglutide (Victoza®)

Needs pen needles

- To reduce the risk of MACE in adults with T2DM and established ASCVD
- T2DM age **≥10 yrs**

Dosing

0.6 mG daily → (7 days) → 1.2 mG daily → (7 days) → 1.8 mG daily

Not effective

-1.2% A1c reduction
-5.9 lbs

-1.5% A1c reduction
-7.3 lbs

Prescribing

- All strengths are on the same pen (One pen: 18 mG/3mL)
- 1.2 mG daily → order the 2 pen box (6 mL)
- 1.8 mG daily → order the 3-pen box (9 mL)
- Prescribe pen needles!

Victoza. [Novo Nordisk]. Accessed April 4, 2022. https://www.novomedlink.com/diabetes/products/treatments/victoza/about/efficacy-safety.html

Semaglutide (Ozempic®)

Pen needles included

- To reduce the risk of MACE in adults with T2DM and established ASCVD

Dosing

Available 5/2022

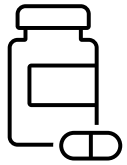
0.25 mG weekly	4 wks	0.5 mG weekly	4 wks	1 mG weekly	4 wks	2 mG weekly
Not effective		-1.4% A1c reduction -9.3 lbs		-1.6% A1c reduction -12.8 lbs		-2.1% A1c reduction -14.1 lbs

Prescribing

- 0.25 mG and 0.5 mG (2 mG/1.5 mL) is the same pen (directions should state to increase to 0.5 mG on week 5)
- Ozempic 1 mG (4 mG/3 mL) and Ozempic 2 mG (8 mG/3 mL)
- Pen needles included

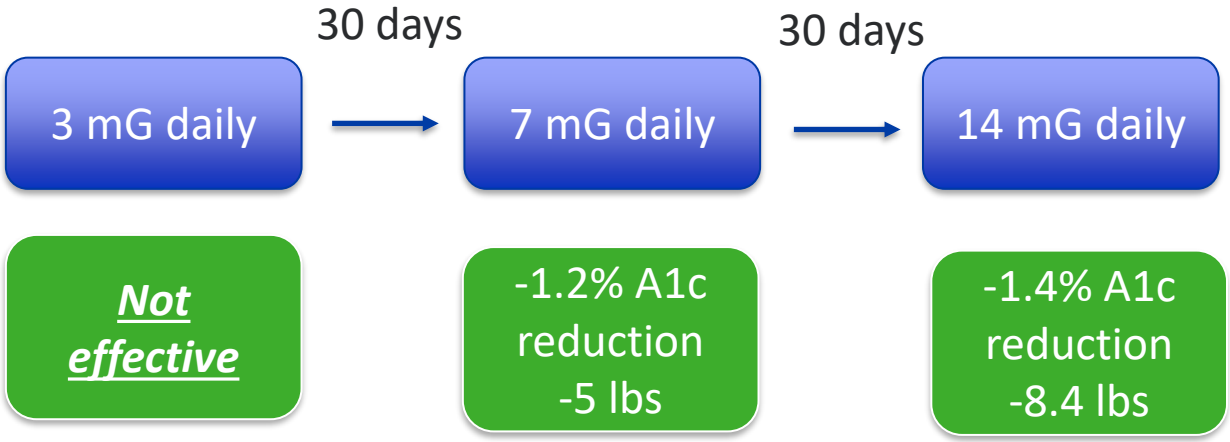
Ozempic [package insert]. Novo Nordisk. Revised September 2020.
Frias JP, et al. The Lancet Diabetes & Endocrinology. 2021;9(9):563-574.
Marso SP, et al. N Engl J Med. 2016;375(19):1834-1844.
Ozempic. [Novo Nordisk]. Accessed April 4, 2022.
https://www.novomedlink.com/diabetes/products/treatments/ozempic/efficacy-safety/ozempic-and-a1c.html

Semaglutide (Rybelsus®) *Oral*



Dosing

- Administer ≥30 minutes before the first food, beverage, or other medications (bioavailability < 1%)



- PIONEER 6 (CVOT trial): ***non-inferior*** to placebo in MACE outcomes

Rybelsus. [Novo Nordisk]. Accessed April 4, 2022. https://www.rybelsus.com/why-rybelsus/rybelsus-results.html
Husain M, et al. N Engl J Med 2019;381:841–51

ASCVD trials for GLP-1's

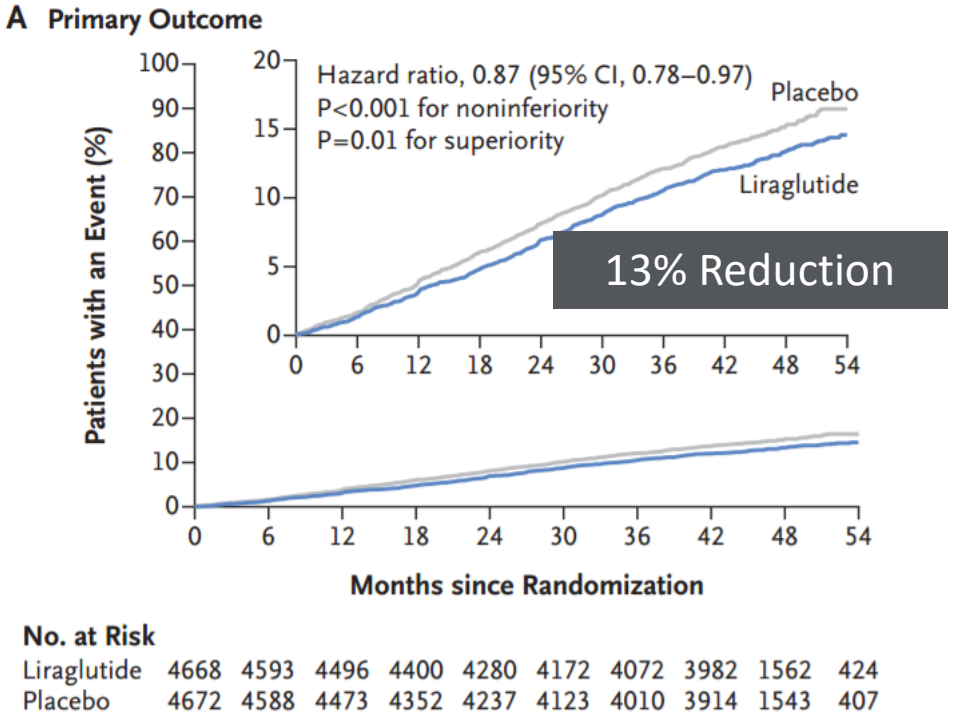
3P MACE: composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes

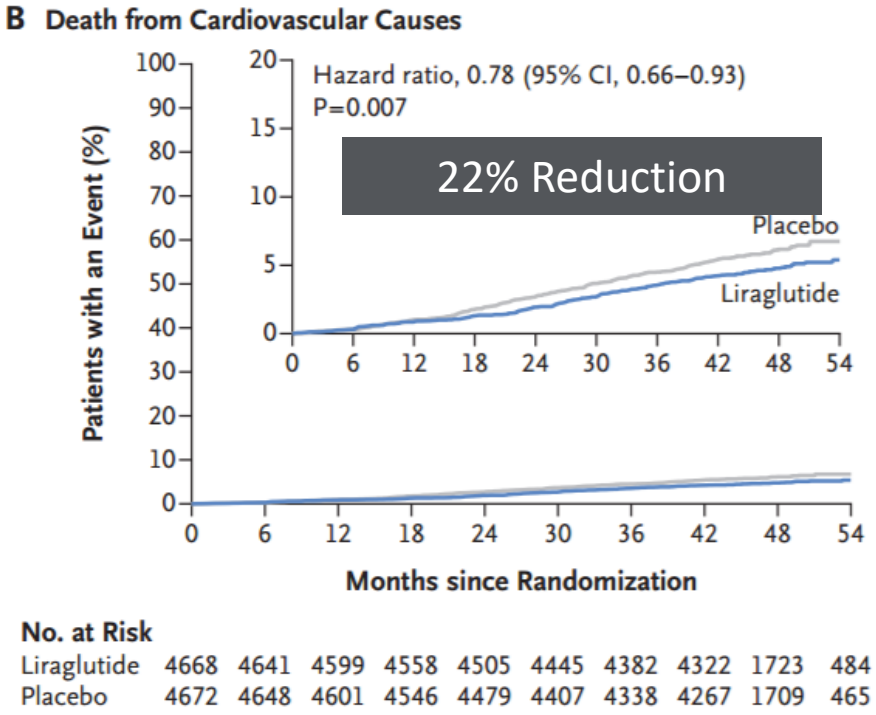
	LEADER (2016) Victoza® (liraglutide)	SUSTAIN-6 (2016) Semaglutide (Ozempic®)	REWIND (2019) Trulicity® (dulaglutide)
Inclusion	• DM2, ≥ 50 yo ASCVD, CKD 3 or greater, or CHF NYHA II-III • Or ≥ 60 years + ≥ 2 CV risk factors	• DM2, ≥50yo + ASCVD, chronic heart failure (NYHA class II-III), or CKD stage 3 or higher • Age ≥60 years with ≥ 1 risk factor	DM2, Age ≥ 50 yo w/ASCVD or ≥ 55 yo + subclinical vascular disease or ≥ 60 yo + ≥2 more CV risk factors
Sample Size	N = 9340 (3.8 yrs), 81% ASCVD Victoza 1.8 mG	N = 3297 (2.1 yrs), 83% ASCVD Ozempic 0.5 and 1 mG	N = 9901 (5.4 yrs), 31% ASCVD Trulicity 1.5 mG dose
Primary endpoint	**3P MACE: ↓13%**	**3P MACE: ↓26%**	**3P MACE: ↓12%**
Notable Secondary endpoints	There is no significant difference in HF hospitalization **↓16% composite renal (& retinal) outcomes**	There is no significant difference in HF hospitalization **↓36% new or worsening nephropathy** ↑Retinopathy complications (hazard ratio, 1.76; 95% CI, 1.11 to 2.78; P=0.02)	There is no significant difference in HF hospitalization **↓15% composite renal outcomes**

Gerstein et al, The Lancet, Volume 394, Issue 10193, 121 – 130
Marso SP et al. New England Journal of Medicine. 2016; **375**(4): 311-22
Marso SP et al., N Engl J Med 2016; 375:1834-1844

LEADER (2016): liraglutide (Victoza®)

Primary outcome: 3P MACE (First occurrence of CV mortality, nonfatal MI, or non-fatal stroke)





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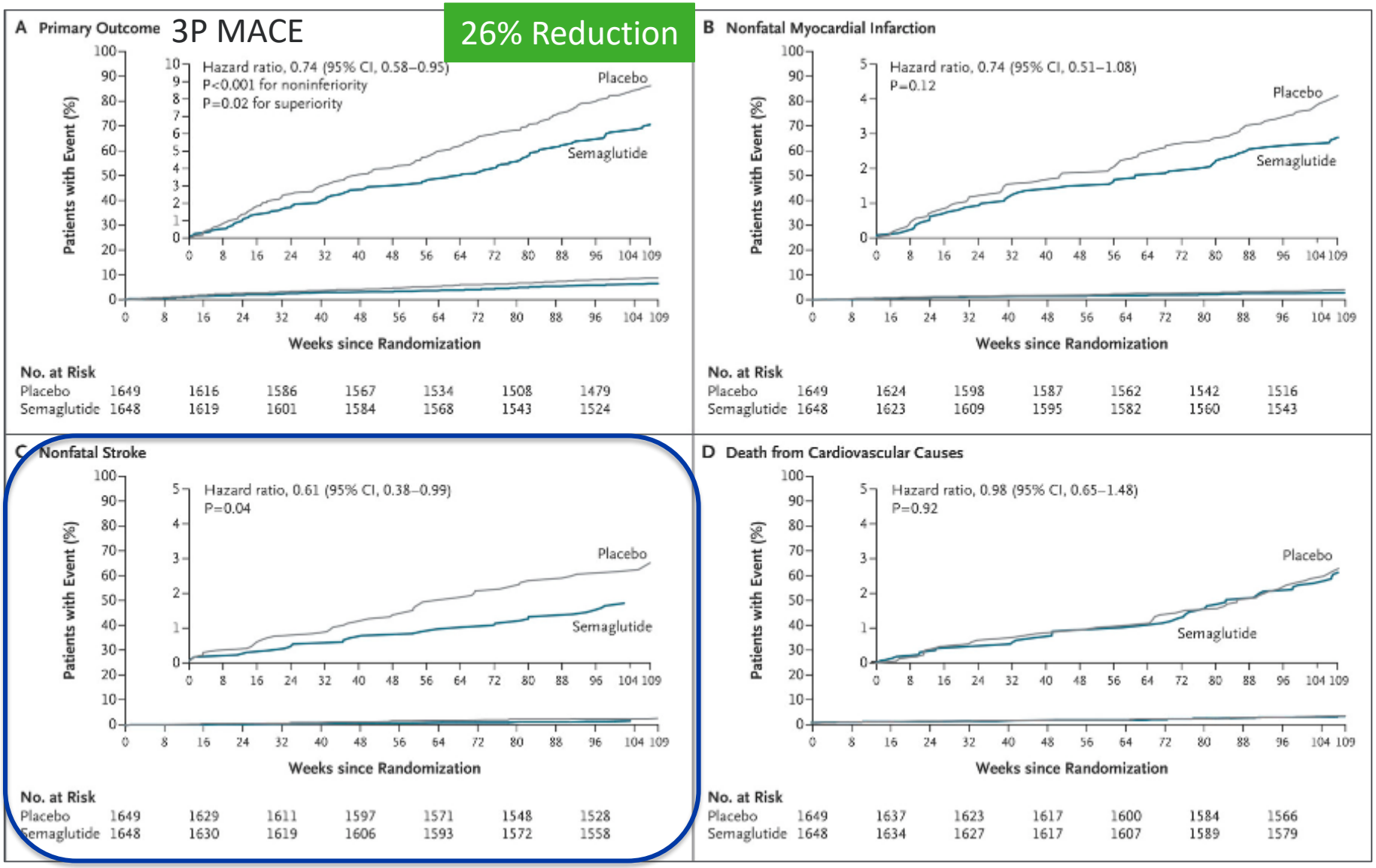
SUSTAIN 6 (2016): Semaglutide (Ozempic®)



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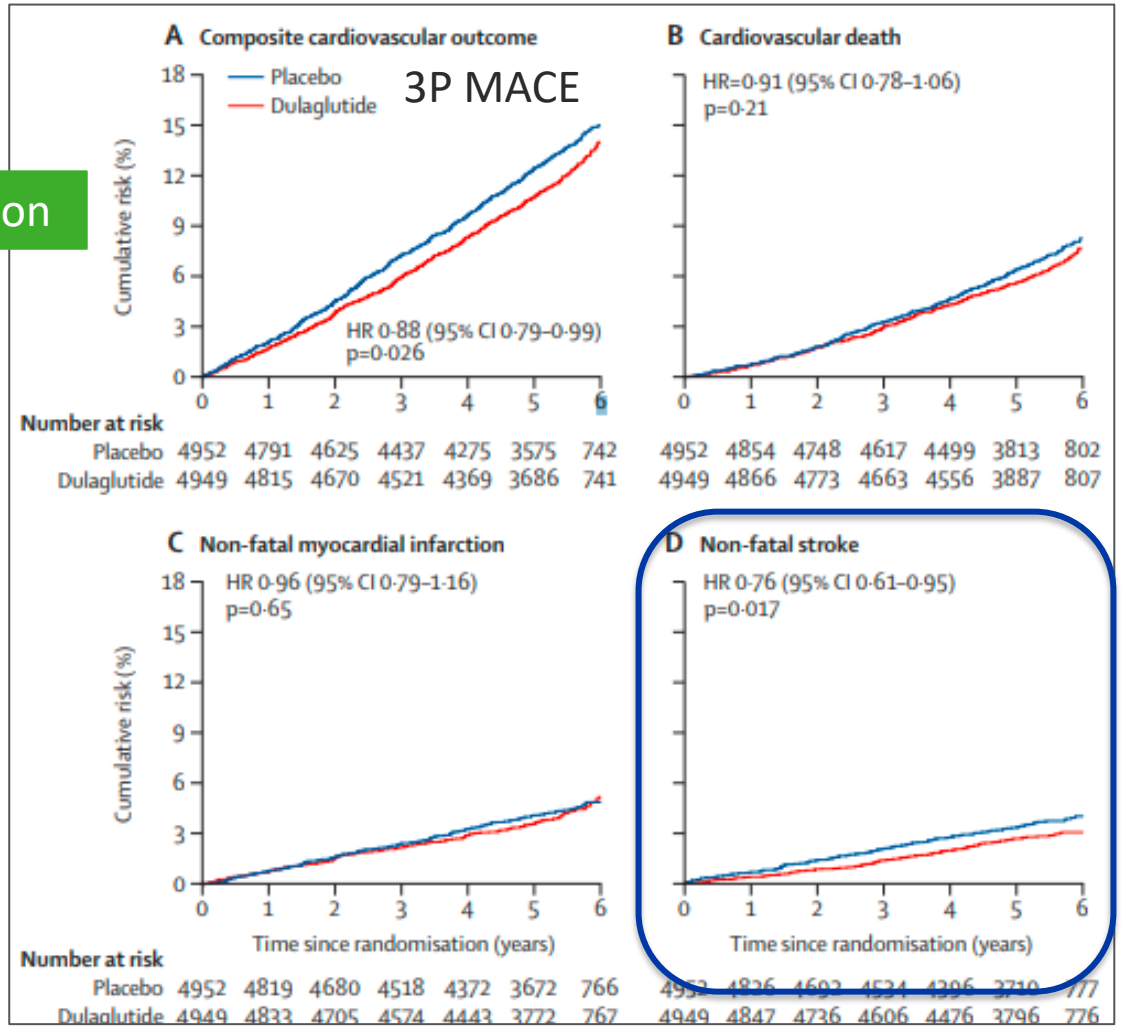
Marso SP et al., N Engl J Med 2016; 375:1834-1844

REWIND (2019): Dulaglutide (Trulicity®)

12% Reduction



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Gerstein et al, The Lancet, Volume 394, Issue 10193, 121 - 130

Secondary: Renal and Eye Outcomes

LEADER: Liraglutide (Victoza®)

Outcome	Liraglutide (N=4668)	Incidence Rate	Placebo (N=4672)	Incidence Rate	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/ 100 patient-yr*	*no. of patients (%)*	*no. of events/ 100 patient-yr*		
Microvascular event	355 (7.6)	2.0	416 (8.9)	2.3	0.84 (0.73–0.97)	0.02
Retinopathy	106 (2.3)	0.6	92 (2.0)	0.5	1.15 (0.87–1.52)	0.33
Nephropathy	268 (5.7)	1.5	337 (7.2)	1.9	0.78 (0.67–0.92)	0.003

REWIND: Dulaglutide (Trulicity®)

Composite microvascular outcome (eye or renal outcome)	910 (18·4%)	3·76	1019 (20·6%)	4·31	0·87 (0·79–0·95)	0·0020
Eye outcome‡	95 (1·9%)	0·37	76 (1·5%)	0·30	1·24 (0·92–1·68)	0·16
Renal outcome§	848 (17·1%)	3·47	970 (19·6%)	4·07	0·85 (0·77–0·93)	0·0004

SUSTAIN-6: Semaglutide (Ozempic®)

Retinopathy complications§	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46–0.88)	0.005

Combination GIP/GLP-1 Agonist

Glucose-dependent insulinotropic polypeptide (GIP): increases glucagon while fasting or hypoglycemia and promotes insulin release when hyperglycemic

Comparison of Proposed Actions of GIP And GLP-1[5]

Brain

GIP Activity
- ⬇ Reduced food intake

GLP-1 Activity
- ⬇ Reduced food intake
- ⬆ Increased satiety

Whole-Body

GIP Activity
- ⬆ Increased insulin sensitivity

Pancreas

GIP Activity
- ⬆ Increased insulin
- ⬆ Increased glucagon

GLP-1 Activity
- ⬆ Increased insulin
- ⬇ Reduced glucagon

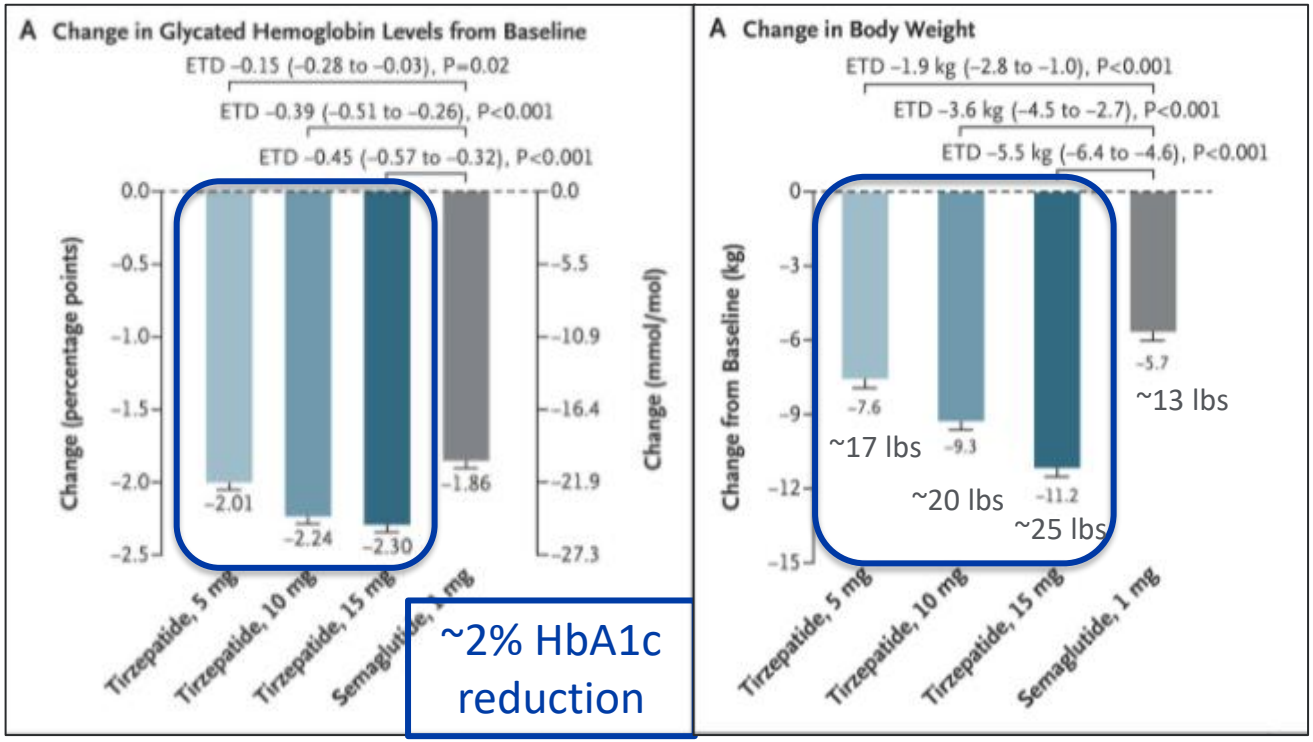
Stomach

GLP-1 Activity
- ⬇ Reduced gastric emptying

Samms RJ, Coghlan MP, Sloop KW. How may GIP enhance the therapeutic efficacy of GLP-1? *Trends Endocrinol Metab*. 2020;31(6):416.4

Mounjaro® (Tirzepatide): Combination GLP-1/GIP Agonist

- **SURPASS-2 trial (2021)**: tirzepatide had greater A1c reduction and weight loss compared to Ozempic® 1 mG weekly



~2% HbA1c reduction

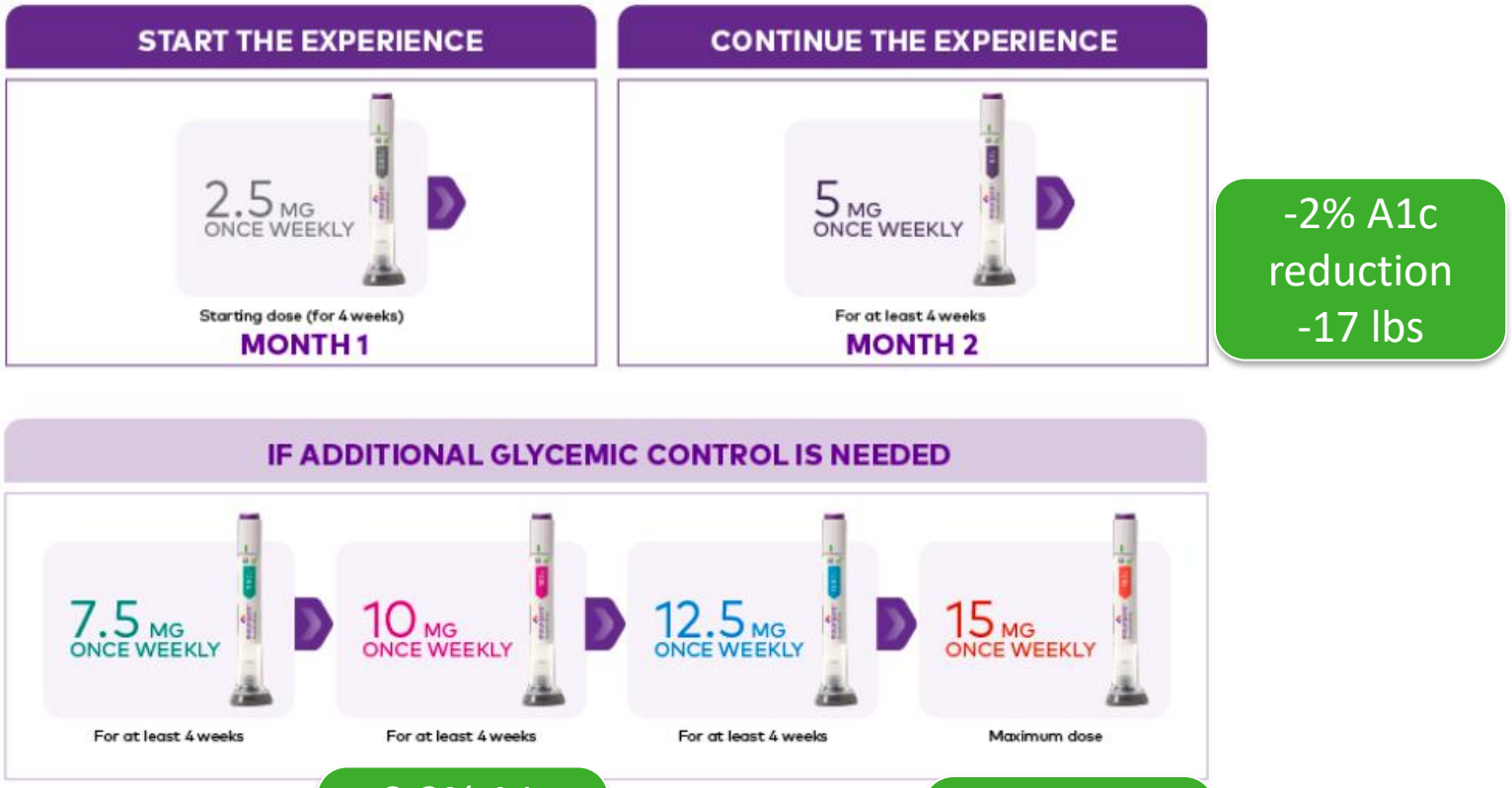
Tirzepatide ~17 – 25 lbs vs. semaglutide ~13 lbs

Also being tested for HFpEF (2023), obesity (2024), cardiovascular outcomes (2024)

Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med*. 2021;385(6):503-515.

Tirzepatide (Mounjaro®)

- Tirzepatide may decrease the serum concentration of Hormonal Contraceptives
  - Especially for 4 weeks after initiation and 4 weeks after dose increase



-2% A1c reduction
-17 lbs

-2.2% A1c reduction
-21 lbs

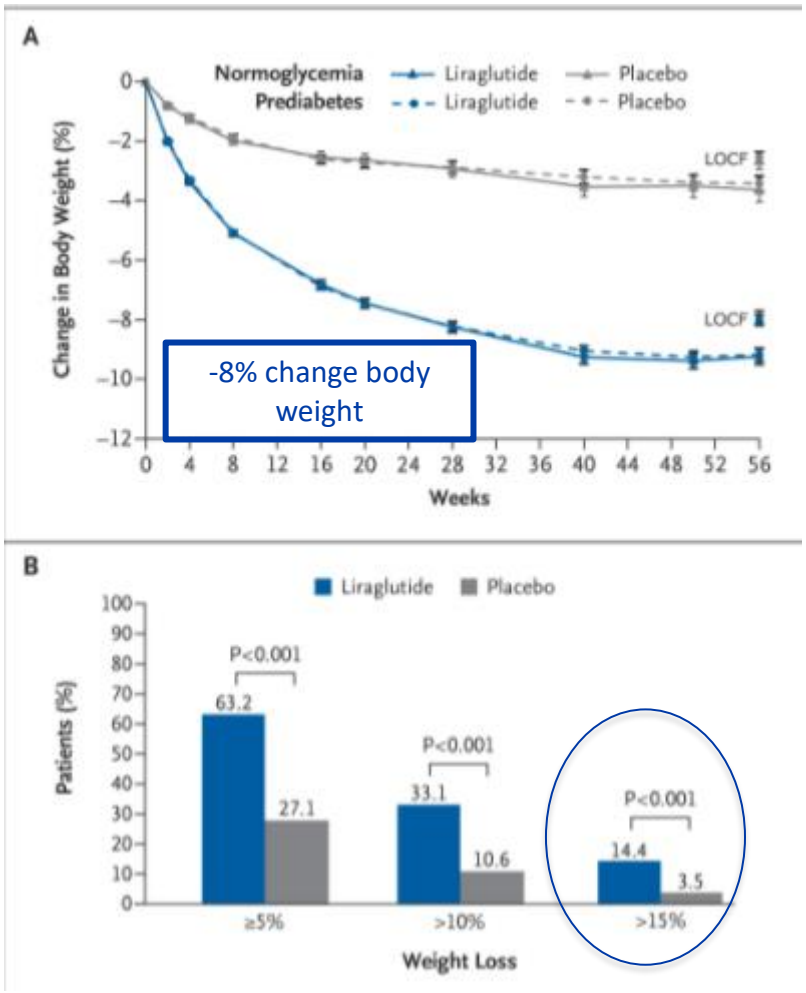
-2.3% A1c reduction
-25 lbs

GLP-1 Agonist for Weight Loss

Saxenda® (liraglutide): A Word on Weight-Loss Indication

- Adjunct to diet/exercise w/BMI ≥30 kG/m^2 or BMI ≥27 kG/m^2 and ≥1 weight-associated comorbidity (i.e., HTN, dyslipidemia)
- Age ≥ 12 yrs: weight >60 kG and BMI ≥30 kG/m^2

- 0.6 mG once daily x1 week; increase by 0.6 mG daily at weekly intervals to a target dose of 3 mg once daily



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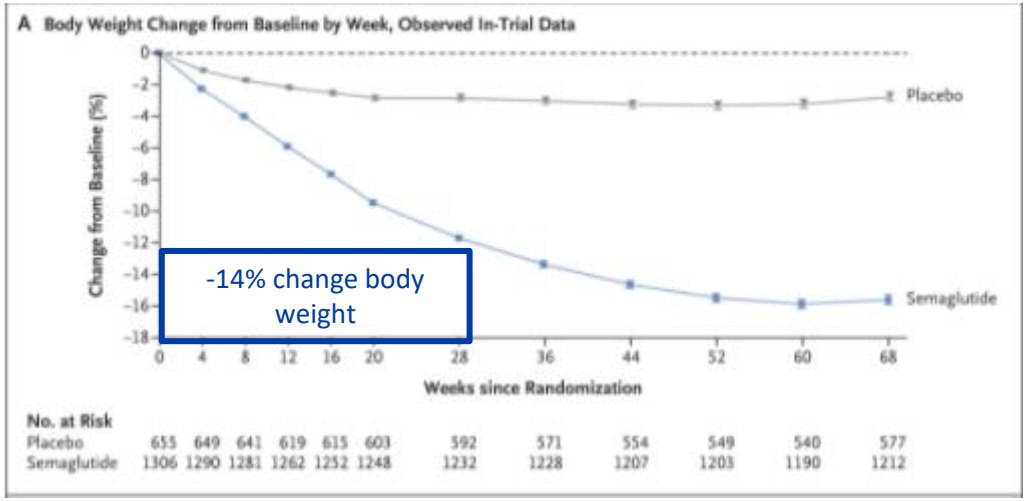
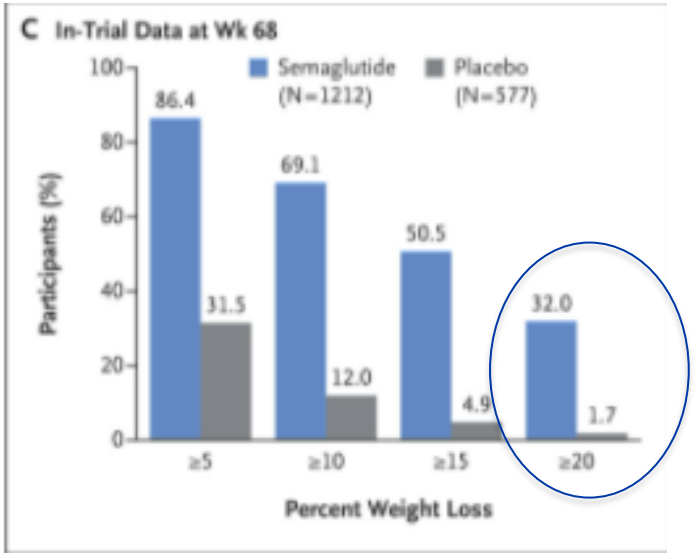
Pi-Sunyer X, et al. *N Engl J Med*. 2015;373(1):11-22.

Wegovy® (semaglutide): A Word on Weight-Loss Indication

- Adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with a BMI of ≥ 30 kG/m^2 (obesity), or ≥27 kG/m^2 (overweight) in the presence of a weight-related comorbidity
- Dosing: every 4 weeks as follows: 0.25 mG weekly → 0.5 mG → 1 mG → 1.7 mG → 2.4 mG (week 17 and onward)
- Each strength needs a **new prescription** and each pen comes with an integrated needle already
- Each Wegovy pen is one-time use only





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https://www.nejm.org/doi/full/10.1056/NEJMoa2032183

Deciding between SGLT-2i and GLP-1 agonist?

Greater Benefit	GLP-1 or SGLT-2?
Weight Loss	GLP-1 agonist > SGLT2i
A1c reduction	GLP-1 agonist > SGLT2i
Prevent hospitalization for heart failure w/reduced ejection fraction	SGLT-2i
Slow progression of Chronic Kidney Disease	SGLT-2i > GLP-1
Lower Blood Pressure	SGLT-2i > GLP-1
ASCVD	Depends on drug – Trulicity® (dulaglutide), Victoza® (liraglutide), Ozempic® (semaglutide), Jardiance® (empagliflozin), Invokana® (canagliflozin)

Deciding between SGLT-2i and GLP-1 agonist?

Past medical history	GLP-1 or SGLT-2?
Gastroparesis, pancreatitis	SGLT-2i
Uncontrolled diabetic retinopathy	SGLT-2i
Extreme Needle Phobia	SGLT-2i (or Rybelsus®)
Recurrent genital mycotic infections or UTI's	GLP-1 agonist
Low baseline blood pressure/Hypotension	GLP-1 agonist

Case 1/Question 3

48 year old female with T2DM x 10 years

- Walks a mile every day and tries to do exercise class at senior center. ***Is very interested in losing weight***
- Limited food choices as she gets her food from the shelter
- PMH: HTN (presently at goal) and hyperlipidemia (on statin)
- BMI 38
- HbA1c 9.2%
- Meds: Metformin ER 1000mg twice daily, Atorvastatin 40mg daily, Losartan 50mg daily, Aspirin 81mg

In choosing an additional diabetes medication, what additional effects would you want from the medication?

a) Secondary ASCVD prevention
b) Weight loss
c) A1c reduction
d) Both B and C

Case 1/Question 4 (continued case from previous slide)

Which diabetes medication would provide the greatest benefit for our patient?

a) Ozempic® (semaglutide) starting at 0.25 mG weekly and titrating up
b) Pioglitazone 15 mG daily
c) Glimepiride 4 mG daily
d) Invokana® (canagliflozin) 100 mG daily

	A1c	Weight
Invokana® 100 mG Invokana® 300 mG	-0.77% -1.03%	-3.5 lbs
Ozempic 0.5 mG Ozempic 1 mG	-1.4% -1.6%	-9 lbs -13 lbs

Case 2/Question 5

65 year old male with T2DM x 8 years

- Patient recently had a heart attack with 2 stents placed
- His echo showed his ejection fraction is 25% (HFrEF)
- BP is uncontrolled (160/95 mmHg)
- eGFR 45 with positive UACR (protein in the urine >300 mG/g)
- BMI is 22
- A1c is 7%

Choose all that apply. In choosing a diabetes medication, what additional effects would you want from the medication?

a) Greater A1c reduction
b) Weight Loss
c) ☑ Blood pressure control
d) ☑ Slow progression of nephropathy
e) ☑ Prevent heart failure hospitalization
f) ☑ Prevent future MACE events

Case 2/Question 6

Which diabetes medication would provide the greatest benefit for our patient?

a) Rybelsus (semaglutide) 3 mg daily
b) Jardiance (empagliflozin) 10 mG daily
c) Pioglitazone 15 mG daily
d) Lantus (insulin glargine) 15 units at bedtime

✓ ASCVD protection
✓ Prevent HFrEF hospitalization
✓ Improve BP
✓ Helps slow kidney decline – (larger study pending)

Case 3/Question 7

48 yo female with T2DM, HTN, HLD, and obesity (BMI 32) presents to the office for diabetes management. Her HbA1c is 8.9% on metformin 1G BID and Januvia 100 mG. The decision is made with the patient to start Trulicity 0.75 mg weekly. What should be verified prior to starting?

A. Januvia should be discontinued
B. Yearly ophthalmology exam
C. Insurance coverage
D. History of pancreatitis
E. All of the Above

Additionally verify that the patient doesn't have Hx or FH of medullary thyroid CA or gastroparesis

Any Questions?

References

1. American Diabetes Association Professional Practice Committee. Standards of Medical Care in Diabetes—2022. *Diabetes Care*. 2022;45(Supplement_1):S1-S264.
2. Lantus® [package insert]. Bridgewater, NJ: sanofi-aventis; 2018.
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