Beyond Glycemic Control
Use of Diabetes Medications for Cardiovascular and Renal Indications

Gail Nunlee-Bland, M.D.
Howard University

Disclosures

- None

Learning Objectives

- Understand the importance of assessing cardiovascular and renal risk factors in patients with diabetes
- Review the cardiovascular outcome trials (CVOT) and renal outcome trials for select glucagon like peptide 1 receptor agonist (GLP-1) and sodium-glucose cotransporter-2 (SGLT2) inhibitors
- Select the appropriate antihyperglycemic agents for cardiovascular and renal risk factors
- Know the classes of antihyperglycemic agents, mechanism of action, benefits and side effects of these agents

Cardiovascular Risk Factors

- Atherosclerotic cardiovascular disease (ASCVD) defined as coronary heart disease (CHD), cerebrovascular disease, or peripheral arterial disease is the leading cause of morbidity and mortality for individuals with diabetes
- Heart failure with preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF) is twofold higher in patients with diabetes.

Risk of CKD progression, frequency of visits, and referral to nephrology according to glomerular filtration rate (GFR) and albuminuria.

CKD is classified based on: • Cause (C) • GFR (G) • Albuminuria (A)				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly Increased	Moderately Increased	Severely Increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (mL/min/1.73m^2) Description and range	G1	Normal to high	≥90	1 If CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 If CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

American Diabetes Association Clin Diabetes 2021;39:14-43

American Diabetes Association.

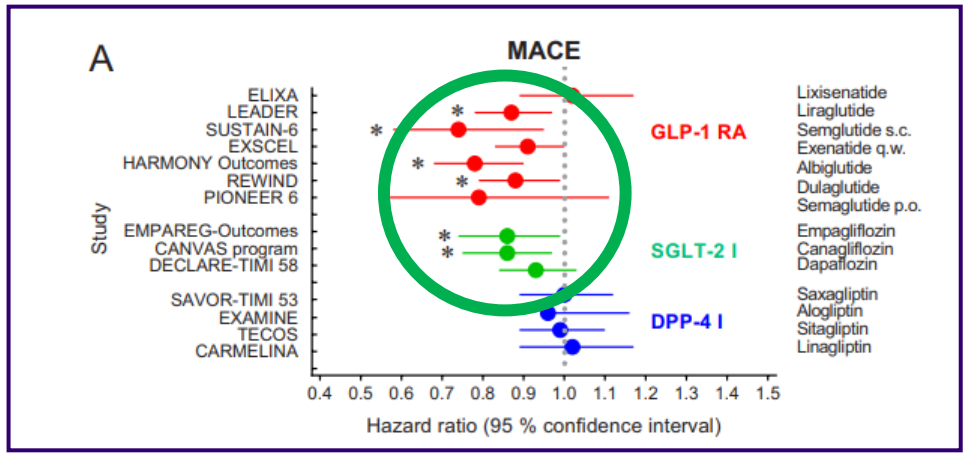
Cardiovascular Outcomes Trials: A Brief History

- 2008 FDA guidance mandating assessment of CV safety of all antihyperglycemic agents in RCTs
  - Designed as noninferiority studies to demonstrate study drug was not associated with more MACE than placebo
    - Some study designs tested for superiority if noninferiority criteria were met
  - Primary endpoint: composite of cardiovascular death, nonfatal MI, and nonfatal stroke
    - Some primary endpoints included additional components

MACE = major adverse cardiovascular events; RCTs, randomized controlled trials.

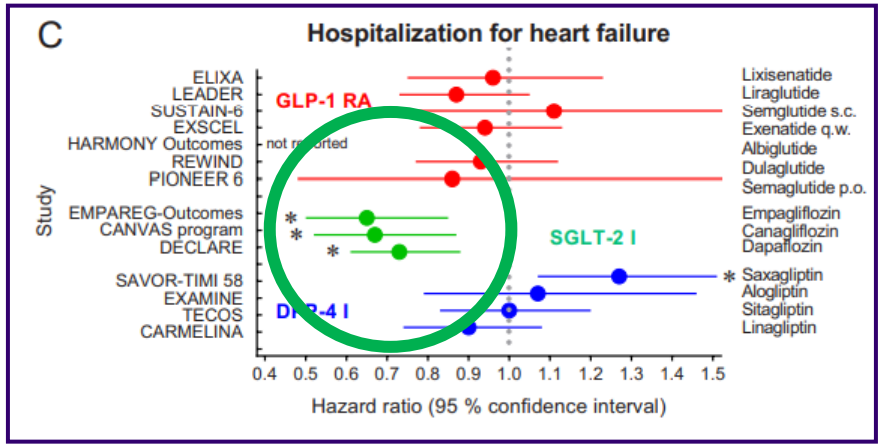
FDA. Guidance for industry: evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf.

CV Outcomes Comparison



CV Benefits and All Cause Mortality Benefit for GLP-1 RA & SGLT-2 I

**Heart Failure Benefit only in SGLT-2I



Nauck MA et al. Eur J Endocrinol. 2019 Dec;181(6):R211-R234

GLP-1 RAs and CV Risk Baseline Characteristics

	ELIXA	LEADER	SUSTAIN 6	REWIND
Drug tested	Lisixenatide	Liraglutide	Semaglutide	Dulaglutide
Dose	20 µg/d	1.8 mg/d	0.5 or 1 mg/wk	1.5 mg/wk
N	6068	9340	3297	9901
Mean age, years	60	64	65	66
Percent women	31	36	39	46
Percent prior CVD	100	81	59	31
Mean BMI, kg/m^2	30	33	31	32
Mean HbA1c, %	7.7	8.7	8.7	7.3
Primary outcome	MACE[a] or unstable angina	MACE[a]	MACE[a]	MACE[a]

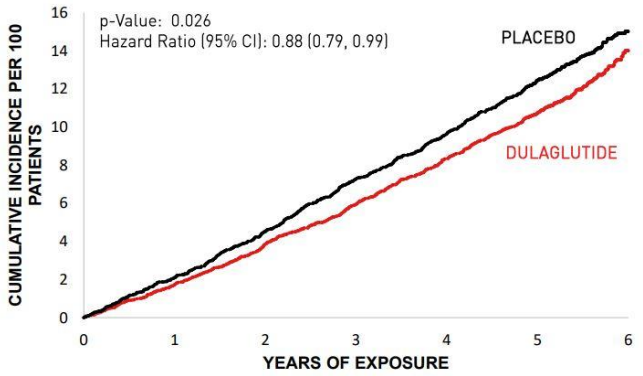
Gerstein et al. Diabetes Obes Metab. 2018 Jan;20(1):42-49

REWIND Study/ Dulaglutide

TRULICITY CV OUTCOME TRIAL

PRIMARY MACE 3 RESULT

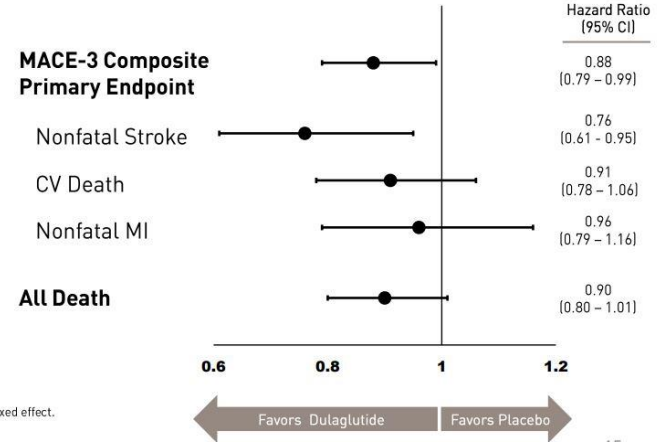
Dulaglutide significantly reduced the risk of Major Adverse Cardiovascular Events (MACE 3: CV death, non-fatal MI or non-fatal stroke) **by 12% vs. placebo**



Note: Hazard Ratio and its CI and p-value obtained from Cox Proportional Hazards Regression Model with treatment as a fixed effect.
Gerstein et al. Lancet 2019.

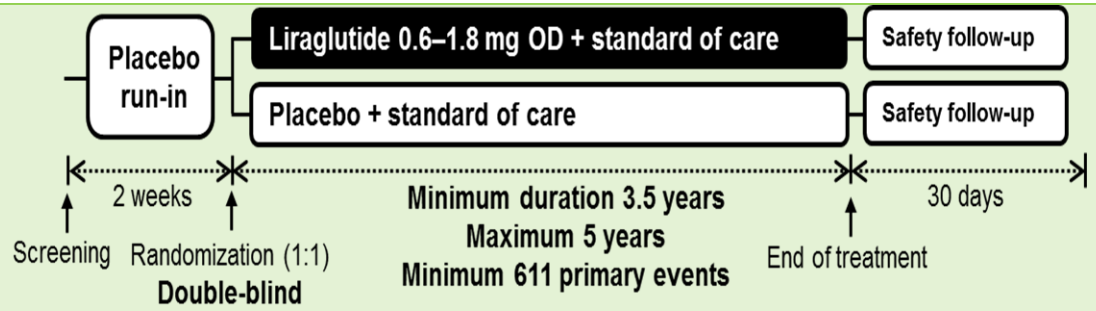
CV OUTCOMES

Consistent effect across three components of MACE, greatest difference observed in Nonfatal Stroke



SOURCE

LEADER: Study design



Key inclusion criteria

- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure

  or
- Age ≥60 years and risk factors for CV disease

Key exclusion criteria

- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

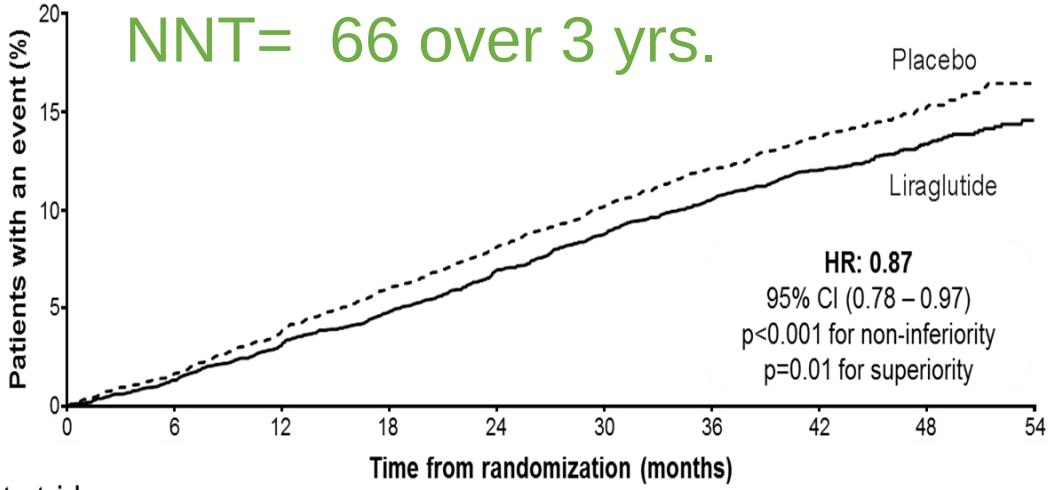
N Engl J Med 2016; 375:311-322

LEADER (Liraglutide CVOT):

- Primary outcome CV death, non-fatal myocardial infarction, or non-fatal stroke

13% RRR in CVOT (*P*=0.01)

NNT= 66 over 3 yrs.



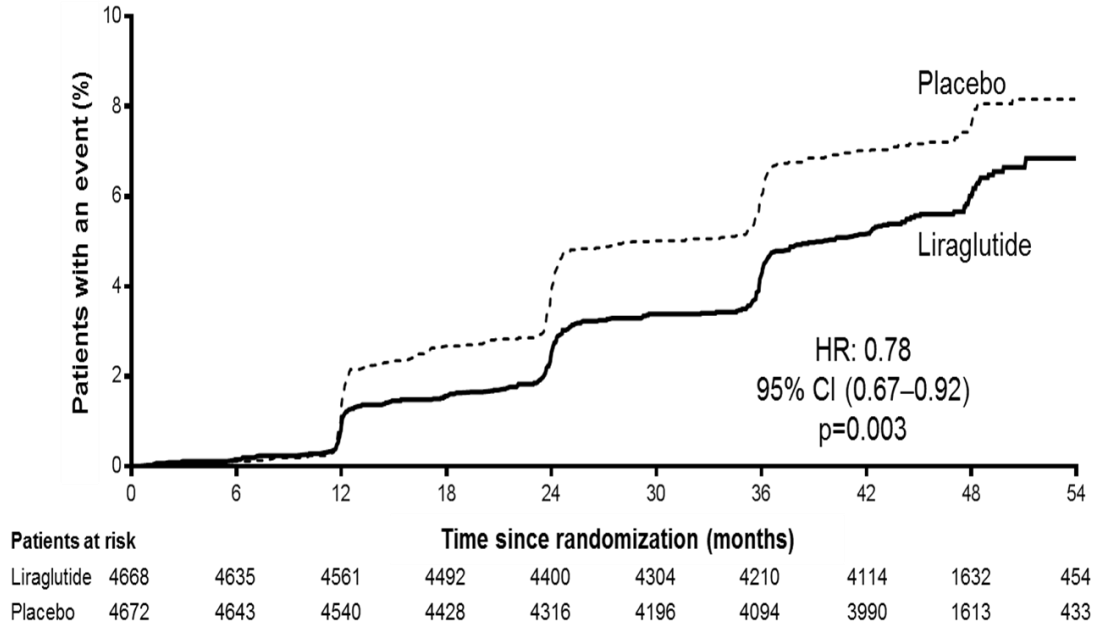
Patients at risk										
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

N Engl J Med 2016; 375:311-322

UW Medicine

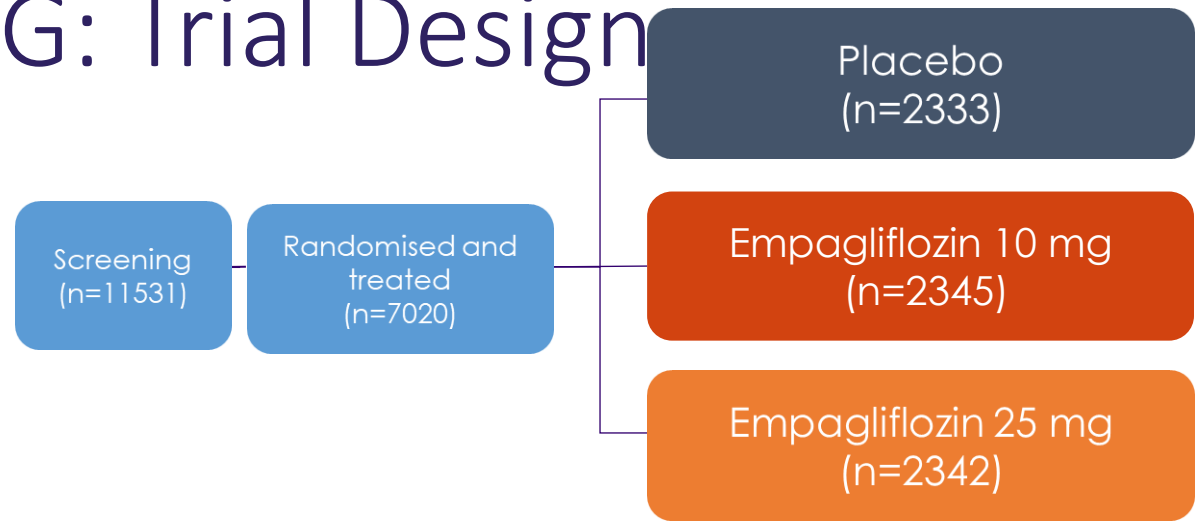
LEADER: Time to first renal event

- Macroalbuminuria, doubling of serum creatinine, ESRD, renal death



N Engl J Med 2016; 375:311-322

EMPA-REG: Trial Design

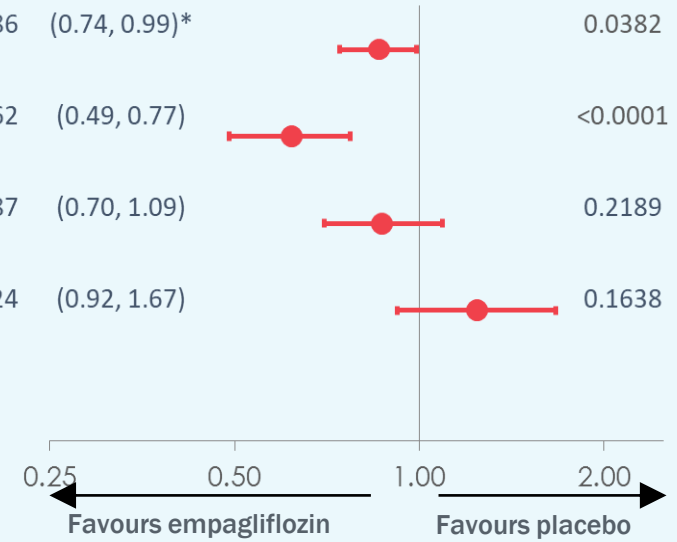


- All patients had known cardiovascular disease
- Study medication was given in addition to standard of care
- Treatment assignment double masked.
- The trial was to continue until at least 691 patients *experienced an adjudicated primary outcome event*

N Engl J Med 2015; 373:2117-2128

EMPA-REG: CV Death, MI, and Stroke

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638

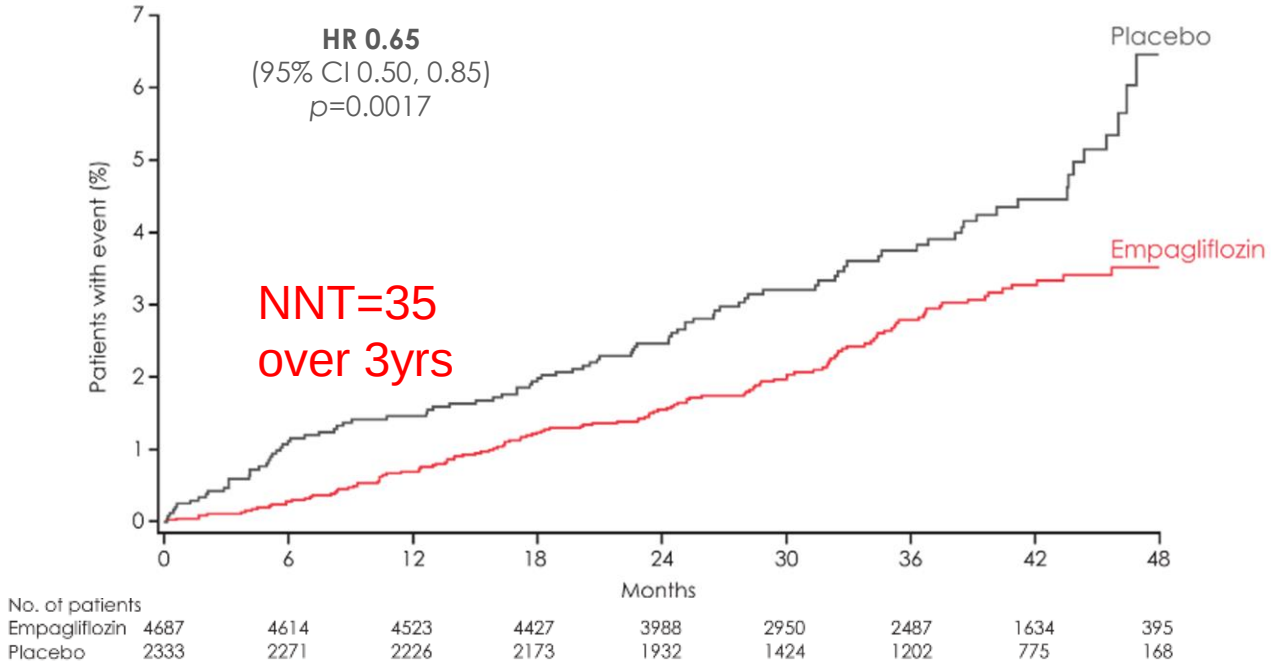


38% RRR
Cardiovascular Mortality:
NNT = 45

Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
*95.02% CI

Zinman et al. Engl J Med 2015; 373:2117-2128

Hospitalization for Heart Failure



Zinman et al. N Engl J Med 2015; 373:2117-2128

UW Medicine

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (CREDENCE)

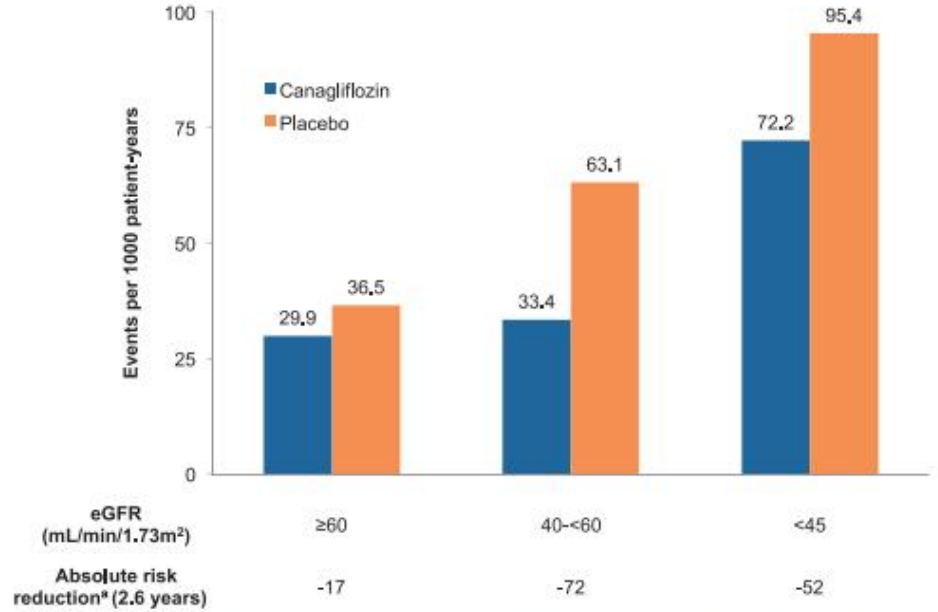


FIGURE 1: Estimated number of primary events (doubling of serum creatinine, ESKD or cardiovascular or kidney-related death) prevented per 1000 patients treated over 2.6 years in the CREDENCE trial by baseline eGFR. *Absolute risk reductions estimated as the number of events prevented per 1000 patients treated over 2.6 years.

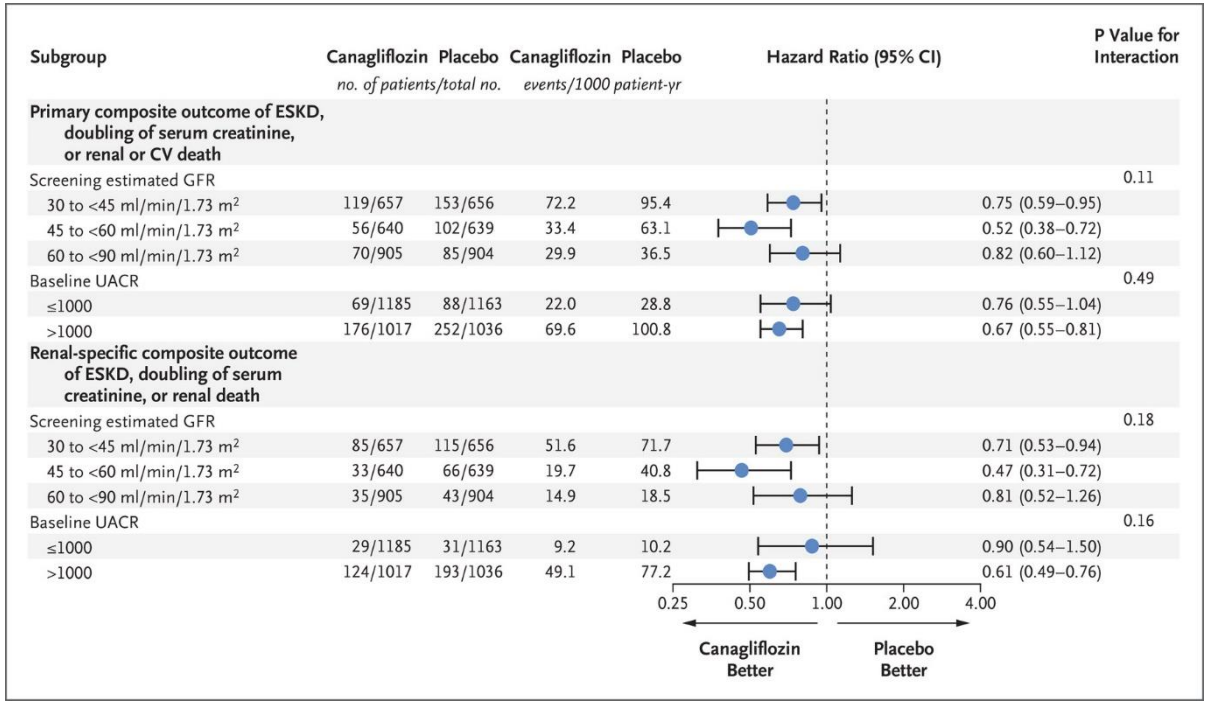
ADA guidelines: SGLT2 inhibitors for the prevention of kidney failure, cardiovascular events or both in patients with an eGFR >30 mL/min/1.73 m2

**Especially with severely increased albuminuria

Neuen BL et al. *Nephrol Dial Transplant*. 2020;35(Suppl 1) i48–i55.

Perkovic V, et al. N Engl J Med. 2019 Jun 13;380(24):2295-2306

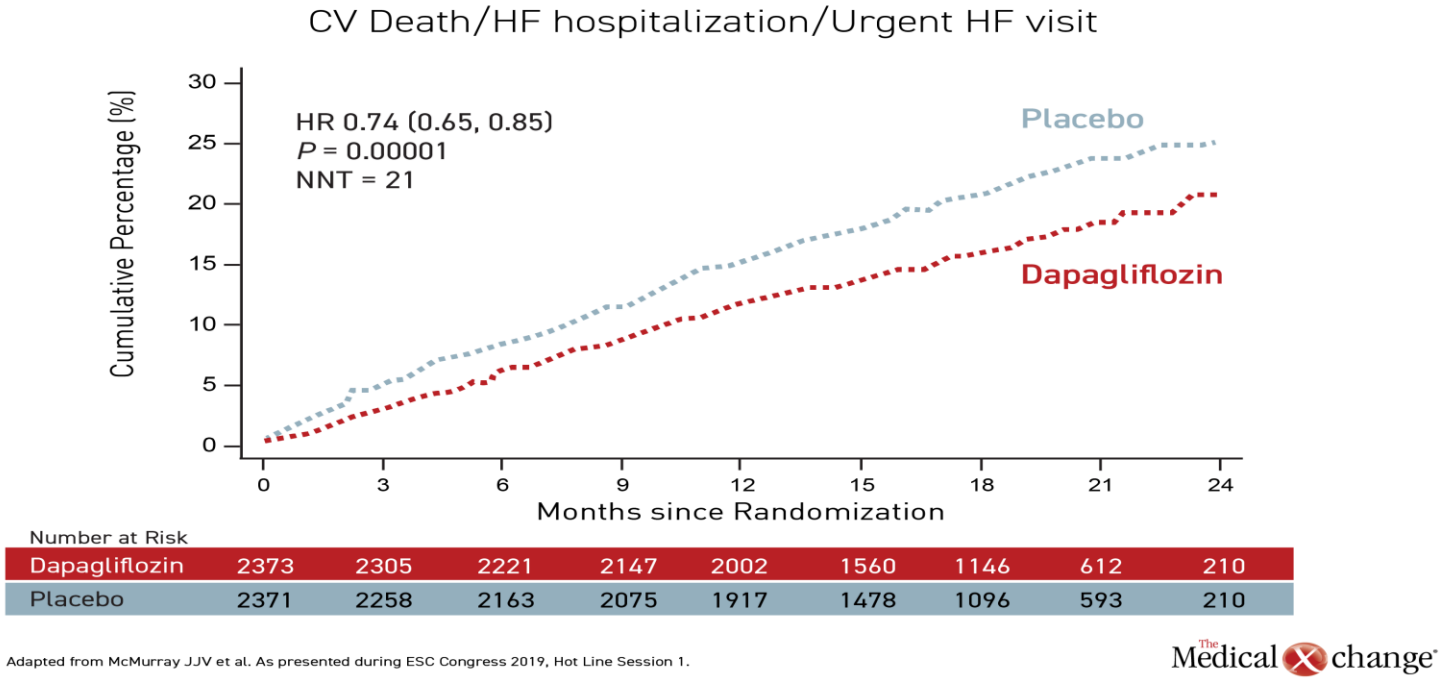
Credence study



Subgroup	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients/total no.		*events/1000 patient-yr*			
Primary composite outcome of ESKD, doubling of serum creatinine, or renal or CV death						
Screening estimated GFR						0.11
30 to <45 ml/min/1.73 m²	119/657	153/656	72.2	95.4	0.75 (0.59–0.95)	
45 to <60 ml/min/1.73 m²	56/640	102/639	33.4	63.1	0.52 (0.38–0.72)	
60 to <90 ml/min/1.73 m²	70/905	85/904	29.9	36.5	0.82 (0.60–1.12)	
Baseline UACR						0.49
≤1000	69/1185	88/1163	22.0	28.8	0.76 (0.55–1.04)	
>1000	176/1017	252/1036	69.6	100.8	0.67 (0.55–0.81)	
Renal-specific composite outcome of ESKD, doubling of serum creatinine, or renal death						
Screening estimated GFR						0.18
30 to <45 ml/min/1.73 m²	85/657	115/656	51.6	71.7	0.71 (0.53–0.94)	
45 to <60 ml/min/1.73 m²	33/640	66/639	19.7	40.8	0.47 (0.31–0.72)	
60 to <90 ml/min/1.73 m²	35/905	43/904	14.9	18.5	0.81 (0.52–1.26)	
Baseline UACR						0.16
≤1000	29/1185	31/1163	9.2	10.2	0.90 (0.54–1.50)	
>1000	124/1017	193/1036	49.1	77.2	0.61 (0.49–0.76)	

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction With and Without DM

Primary Composite Outcome

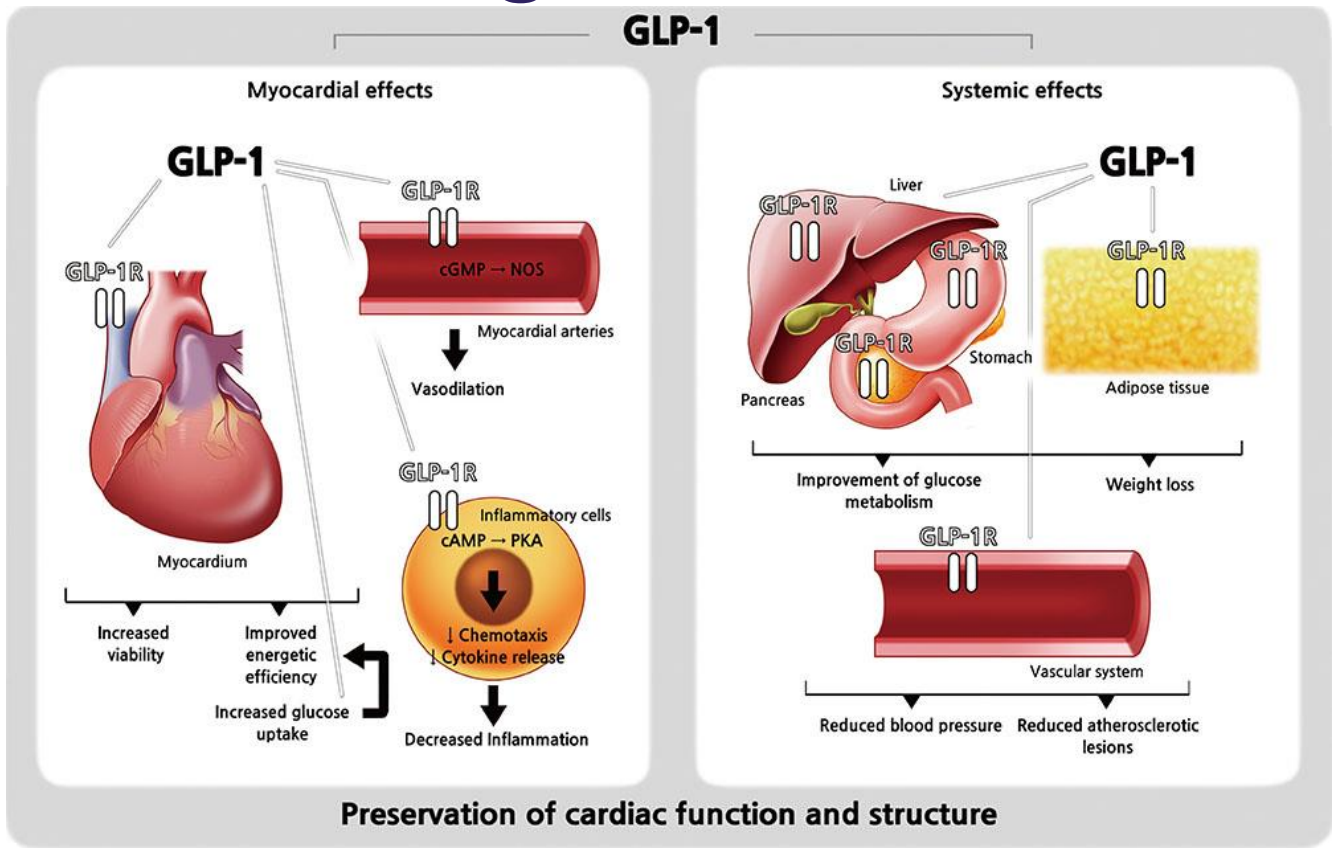


Adapted from McMurray JJV et al. As presented during ESC Congress 2019, Hot Line Session 1.

The Medical Xchange

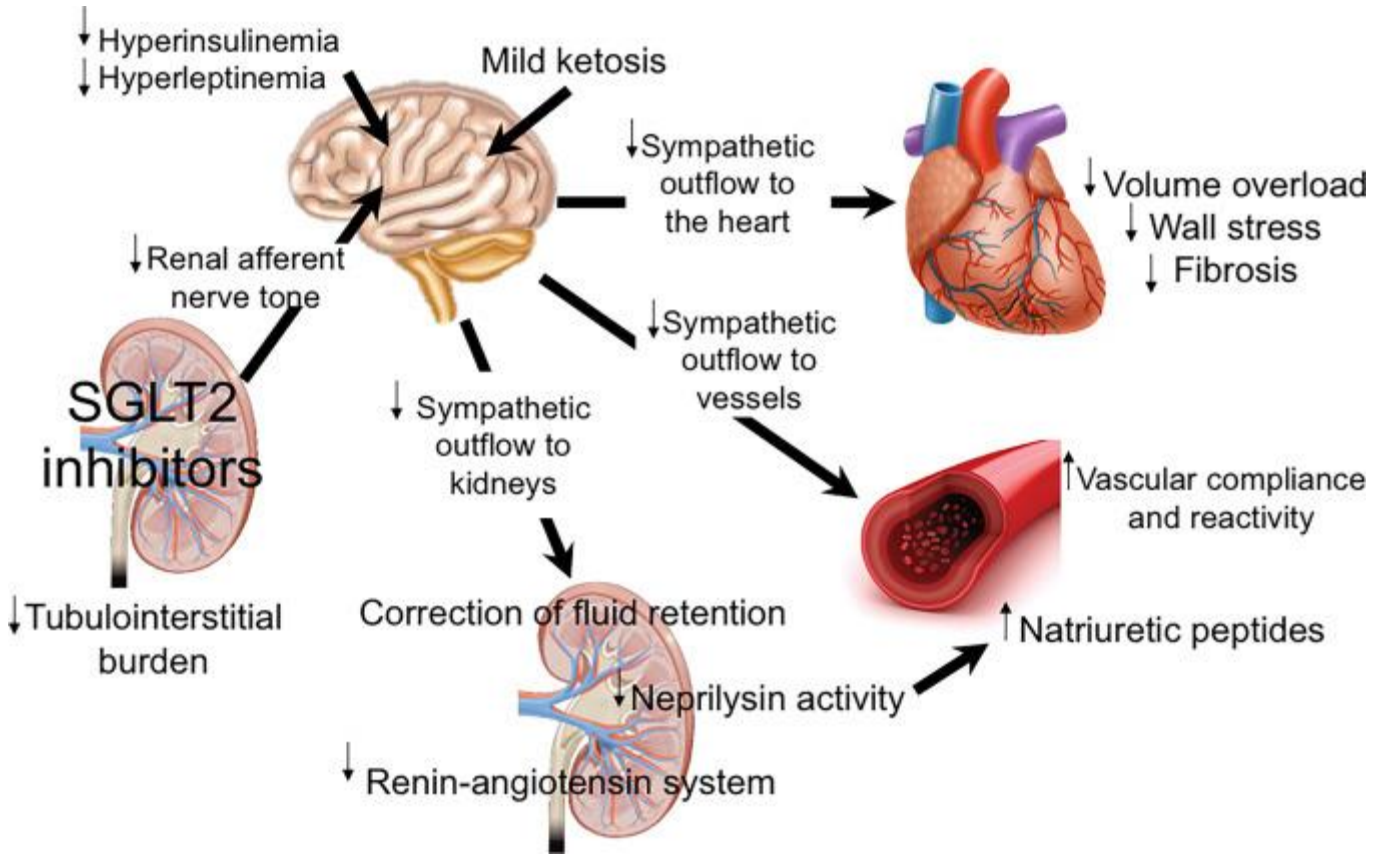
N Engl J Med 2019; 381:1995-2008

Effect of GLP-1 Agonists



Kang et Endocrinol Metab. 2016 Jun;31(2):258-274

Effect of SGLT2i



	GLP-1 receptor agonists								GLP-1 receptor agonist/ basal insulin fixed-dose combinations	
Pen devices for injection										
Drug name: Generic	Exenatide b.i.d.	Lixisenatide	Liraglutide	Exenatide once weekly		Dulaglutide	Albiglutide	Semaglutide	IdegLira	iGlarLixi
Pen for single or multiple use?	multiple	multiple	multiple	single	single	single	single	multiple	multiple	multiple
Pen for pre-determined single dose/ variable dosing	single	single	variable (0.6, 1.2, or 1.8 mg)	single	single	single	single	single	variable, for titration	variable, for titration
Pen devices available (maximum dose)	5 or 10 µg	10 or 20 µg	1.8 mg	2 mg	2 mg	0.75 or 1.5 mg	30 or 50 mg	0.25, 0.5 or 1.0 mg	Up to 1.8 mg (plus insulin *degludec* up to 50 IU)	Up to 20 µg (plus insulin *glargine* up to 60 IU)
Resuspension before injection necessary?	no	no	no	yes	No, but thorrough mixing	no	yes	no	no	no

Nauck MA et al. Eur J Endocrinol. 2019 Dec;181(6):R211-R234

Oral Semaglutide

Take on an empty stomach

Take with a a small amount of water (no more than 4 oz).

Wait 30 minutes after taking it and then eat food

Sodium-Glucose Co-Transporter Inhibitors (SGLT2I)

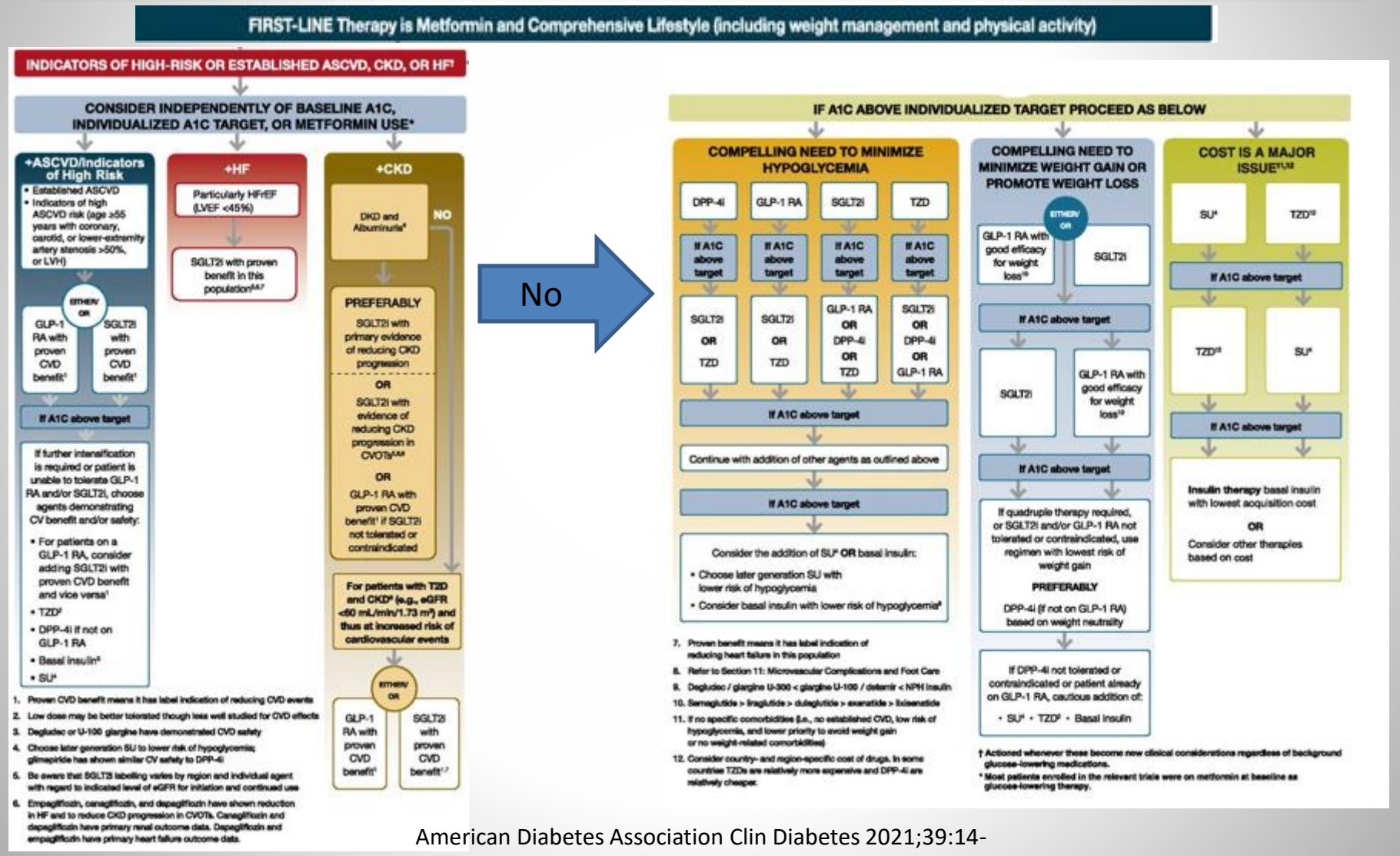
TABLE. A1C REDUCTION VERSUS PLACEBO

Medication	Mean A1C Reduction (95% CI)
Canagliflozin 300 mg	−0.86% (−0.96 to −0.76)
Canagliflozin 100 mg	−0.76% (−0.86 to −0.66)
Dapagliflozin 10 mg	−0.66% (−0.74 to −0.58)
Dapagliflozin 5 mg	−0.56% (−0.67 to −0.44)
Empagliflozin 25 mg	−0.66% (−0.76 to −0.56)
Empagliflozin 10 mg	−0.60% (−0.70 to −0.50)

A1C = glycated hemoglobin.

Zaccardi F et al. *Diabetes Obes Metab*. 2016;18(8):783-794

Hyperglycemic Agents Algorithm



American Diabetes Association Clin Diabetes 2021;39:14-43

Treatment Guidelines

First –Line Metformin and Lifestyle

High Risk/ ASCVD
- Established ASCVD
- Age>55 with coronary carotid or lower-extremity artery stenosis >50% or LVH

Either
or

GLP-1RA

SGLT2i

HF
HFrEF
LVEF <45%

SGLT2i

DKD and albuminuria

SGLT2i

Selected Glucose Lowering Agents

	Efficacy	Hypoglycemia	Weight change	CV effects		Cost	Oral/SQ	Renal effects		Additional considerations
				ASCVD	HF			Progression of DKD	Dosing/use considerations*	
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Low	Oral	Neutral	• Contraindicated with eGFR <30 mL/min/1.73 m²	• Gastrointestinal side effects common (diarrhea, nausea) • Potential for B12 deficiency
SGLT-2 inhibitors	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	High	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin	• Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	• **FDA Black Box:** Risk of amputation (**canagliflozin**) • Risk of bone fractures (canagliflozin) • DKA risk (all agents, rare in T2DM) • Genitourinary infections • Risk of volume depletion, hypotension • ↑LDL cholesterol • Risk of Fournier's gangrene
GLP-1 RAs	High	No	Loss	Neutral: lixisenatide Benefit: See label indication of reducing CVD events	Neutral	High	SQ; oral (semaglutide)	Benefit: liraglutide	• Renal dose adjustment required (exenatide, lixisenatide) • Caution when initiating or increasing dose due to potential risk of acute kidney injury	• **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**) • Gastrointestinal side effects common (nausea, vomiting, diarrhea) • Injection site reactions • ?Acute pancreatitis risk

Adapted Clinical Diabetes 2020 Jan; 38(1): 10-38.

CV Effects Indications

ASCVD

- SGLT2i
  - Empagliflozin
  - Canagliflozin
- GLP-1 RA
  - Liraglutide
  - Semaglutide
  - Dulaglutide

HF

- SGLT2i
  - Empagliflozin
  - Canagliflozin
  - Dapagliflozin

Renal Effects Indications

- Progression of DKD
  - SGLT2i
    - Empagliflozin
    - Canagliflozin
    - Dapagliflozin
  - GLP-1RA
    - Liraglutide

Side Effects GLP-1 RA

- Nausea, vomiting, diarrhea
- Injection site reactions
- Acute pancreatitis?
- Black box risk of thyroid c-cell tumors
- Renal dose adjustment for exenatide

Side Effects SGLT2i

- Risk of bone fractures – canagliflozin
- DKA risk
- Genitourinary infections
- Risk of volume depletion
- ↑ LDL
- Risk of Fournier's gangrene
- Not recommended for eGFR < 30 ml/min/1.73m^2

DC Medicaid Formularies

Medication	Amerihealth	Medstar	Carefirst	DC Medicaid
SGLT2	Ertugliflozin	Ertugliflozin	Empagliflozin (PA)	Empagliflozin
Semiglutide	+	+	-	-
Dulaglutide	+	+	PA	+
Liraglutide	+	+	-	+

thank you!