Latest Treatment Strategies for Type 2 Diabetes and Chronic Kidney Disease

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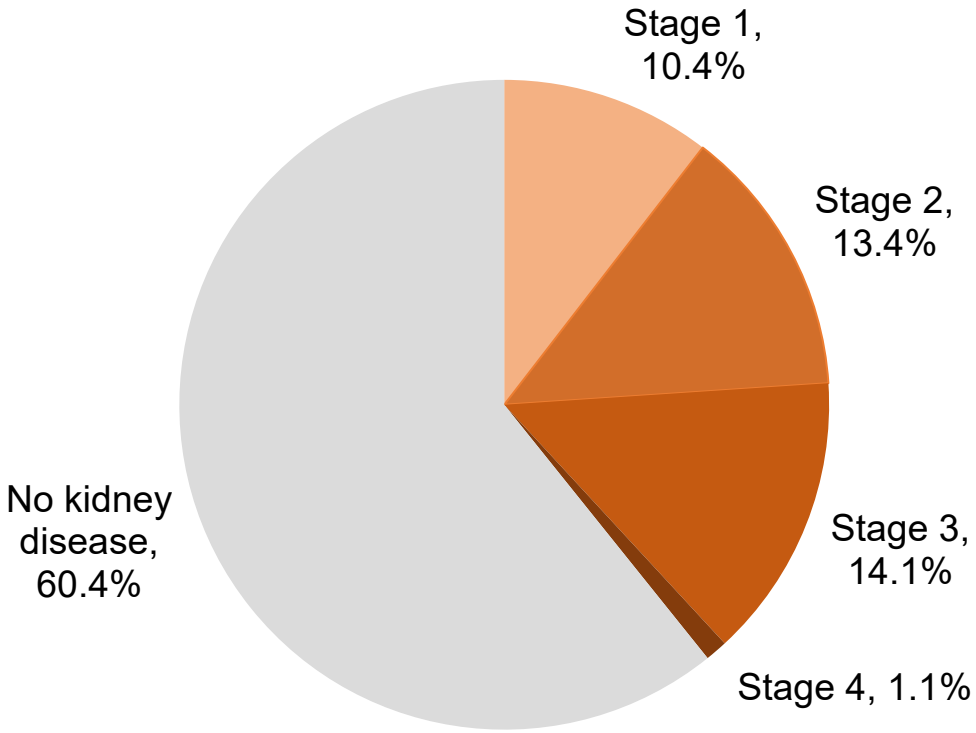
Introduction

- Diabetic Kidney Disease (DKD) is the leading cause of end stage renal disease (ESRD) in the U.S.
- DKD occurs in approximately 40% of patients with T2D
- Most excess risk of all cause and CV mortality for T2D patients is related to DKD
- Natural history of DKD
  - Glomerular hyperfiltration
  - Progressive albuminuria
  - Declining GFR
  - ESRD/dialysis

Prevalence of Chronic Kidney Disease in Diagnosed Diabetes

Diabetic Kidney Disease Is the Leading Cause of Kidney Failure in the United States



NKF Stage	Description	GFR
1	Kidney damage* with normal or ↑ GFR	≥90
2	Kidney damage* with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure or ESRD	<15 or dialysis

*Pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

ESRD, end-stage renal disease;
GFR, glomerular filtration rate (mL/min/1.73 m^2);

Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. Clin J Am Soc Nephrol. 2010 Apr;5(4):673-82. .

Diagnosis of Diabetic Kidney Disease

The clinical diagnosis of Diabetic Kidney Disease (DKD)in a patient with diabetes is based on[1,2]

Presence of albuminuria
(UACR ≥ 300 mg/g, OR
UACR 30-299 mg/g with:
- Diabetic retinopathy, and/or
- T1D ≥ 10 years' duration)

OR

Reduced kidney function
(eGFR < 60 mL/min/1.73 m^2)

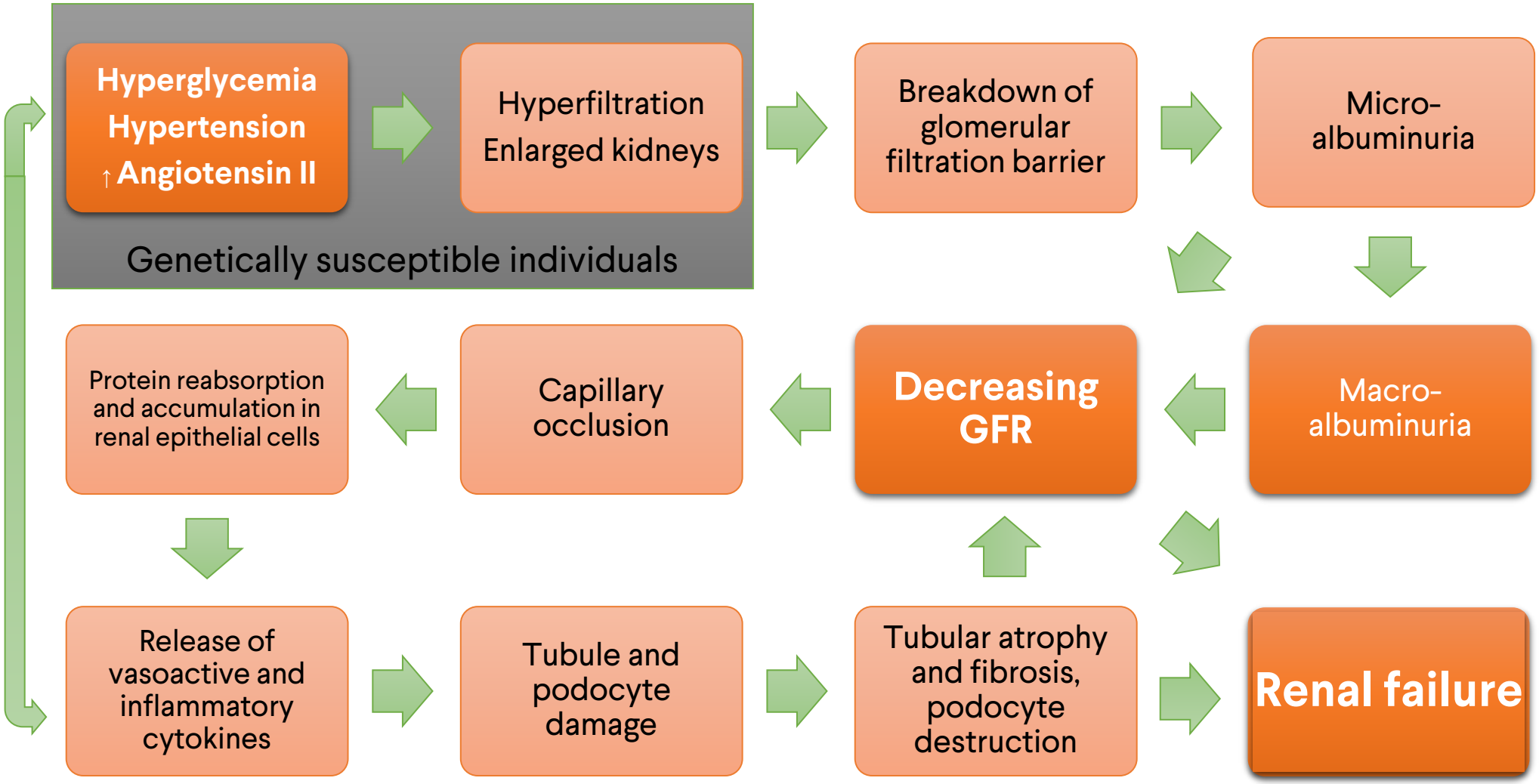
In the absence of signs or symptoms of other primary causes of kidney damage

While the natural history of DKD varies, most patients eventually progress to end-stage kidney disease[2]

UACR: urine albumin:creatinine ratio

National Kidney Foundation. KDOQI Guidelines Executive Summary. 2007
Alicic et al. *Clin J Am Soc Nephrol.* 2017; 12:2032-2045.

Development of Diabetic Nephropathy



Rationale and strategies for early detection and management of diabetic kidney disease. Mayo Clin Proc. 2008 Dec;83(12):1373-81.
Pathophysiology of progressive nephropathies. N Engl J Med. 1998 Nov 12;339(20):1448-56.

Staging and Monitoring of Renal Function and Albuminuria in Diabetes

Guide to frequency of monitoring (number of times per year) by GFR and albuminuria category			Persistent albuminuria categories Description and range		
			A1	A2	A3
			Normal to mildly increased	Moderately increased	Severely increased
			‹30 mg/g ‹3 mg/mmol	30-300 mg/g 3-30 mg/mmol	›300 mg/g ›30 mg/mmol
G1	Normal or high	≥90	**1 if CKD**	**1**	**2**
G2	Mildly decreased	60-89	**1 if CKD**	**1**	**2**
G3a	Mild to moderately decreased	45-59	**1**	**2**	**3**
G3b	Moderately to severely decreased	30-44	**2**	**3**	**3**
G4	Severely decreased	15-29	**3**	**3**	**4+**
G5	Kidney failure	‹15	**4+**	**4+**	**4+**

Numbers = recommended monitoring frequency (times/year)

Increasing color intensity = higher risk of progression of DKD

CKD = chronic kidney disease; GFR = glomerular filtration rate

American Association of Clinical Endocrinologists and American College of Endocrinology - Clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015 Apr; 21 Suppl 1(Suppl 1):1-87.

Pharmacologic Treatment Options for T2D with Renoprotection

Two classes of newer agents for T2D have added renal benefits beyond glycemic control.

- **Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors**
- **Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists**

- Each will be reviewed for:
  - Mechanism
  - Summary of CV outcome trials (CVOT)
  - Benefits
  - Adverse effects

Currently Available Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- Ertugliflozin (Steglatro)

SGLT2 inhibitors: Physiologic Actions

- Selectively blocks the transporter responsible for › 90% of glucose reabsorption in the nephron (SGLT2).
- This results in reduced absorption of glucose and sodium, leading to glycosuria and natriuresis.
- Greatest rate of glycosuria occurs during periods of hyperglycemia.
- Low risk of hypoglycemia.

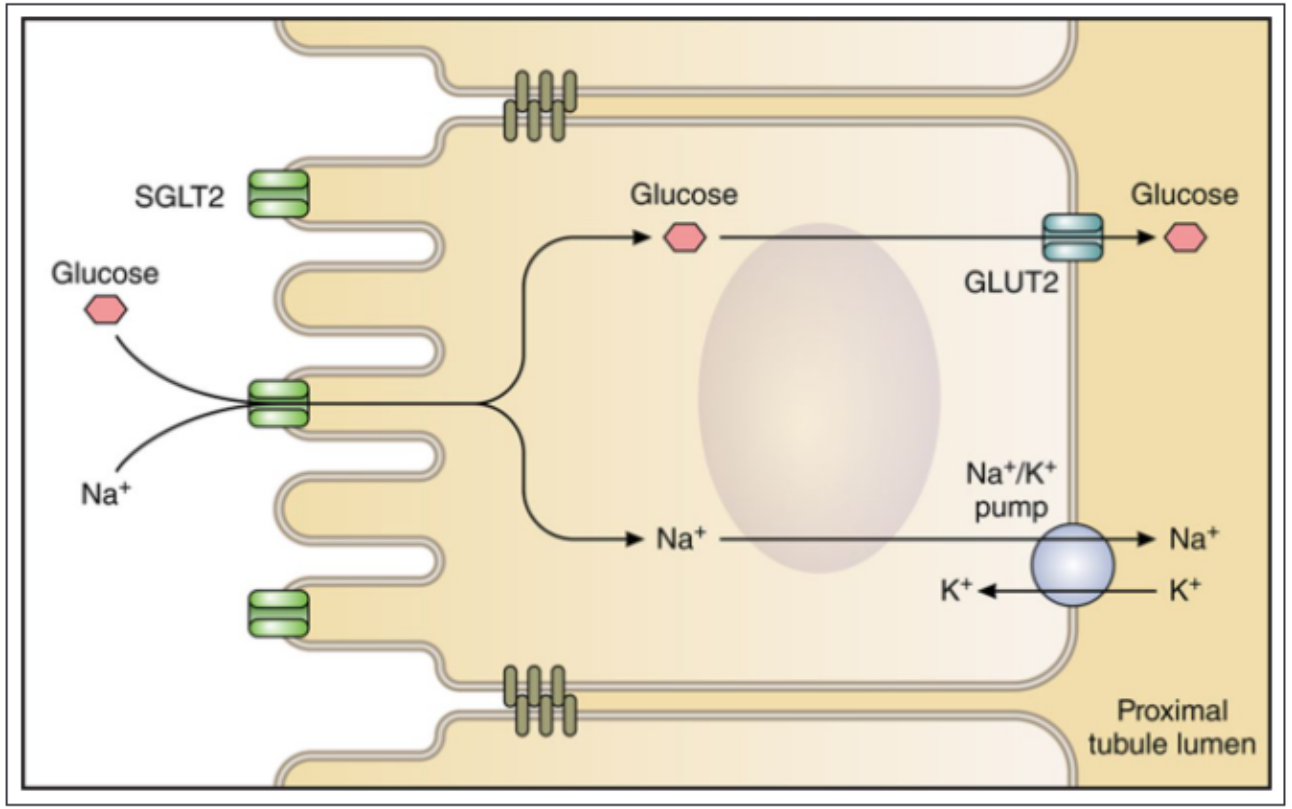
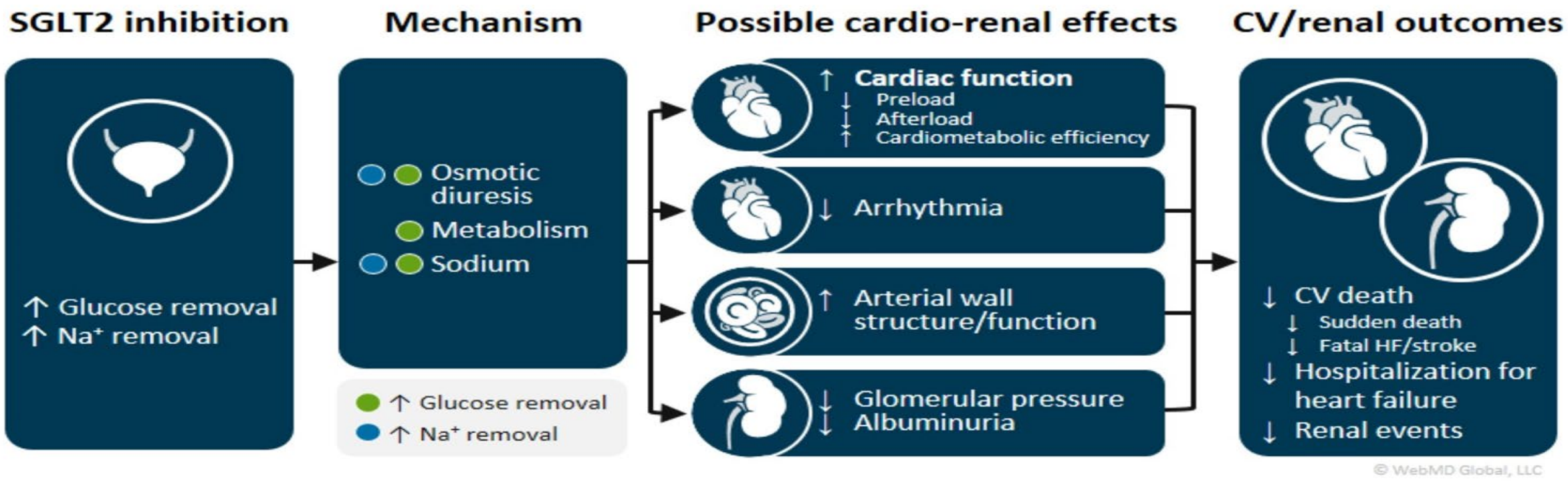


Figure 1. The sodium-glucose cotransporter-2 (SGLT2) mechanism in the proximal tubule. Modified from Bakris et al[4] with permission of the publisher. Copyright © 2009, Elsevier.

SGLT2 inhibitors: Mechanism of Action



SGLT2 inhibitors: Mechanisms of Renoprotection

- Glycosuria
- Natriuresis
- Reduced albuminuria
- Decreased glomerular pressure through restoration of tubuloglumerular feedback
- Decreased glomerular perfusion and hyperfiltration
- Decreased tubular workload and hypoxia

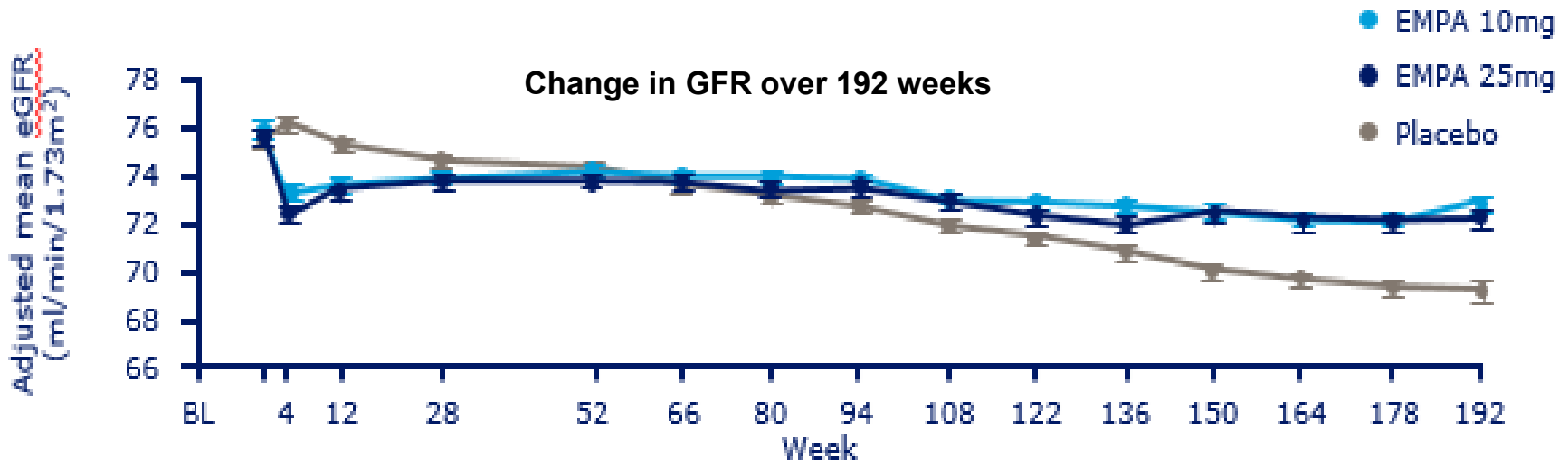
Improved Renal Outcomes in GLP-1 RA and SGLT2i Trials

Study	Intervention	HR (95% CI)	P-value
LEADER[1,a]	Liraglutide	0.78 (0.67, 0.92)	0.003
SUSTAIN 6[2,b]	Semaglutide	0.64 (0.46, 0.88)	0.005
EMPA-REG OUTCOME[3,c]	Empagliflozin	0.61 (0.53, 0.70)	< 0.001
CANVAS[4,d]	Canagliflozin	0.60 (0.47, 0.77)	
DAPA-CKD[5,e]	Dapagliflozin	0.56 (0.45, 0.68)	< 0.001
CREDENCE[6,f]	Canagliflozin	0.70 (0.59, 0.82)	< 0.001

Composite Renal Outcomes: [a]Macroalbuminuria, doubling of serum creatinine, and eGFR ≤45 mL/min/1.73 m^2, ESRD, or renal death; [b]Macroalbuminuria, doubling of serum creatinine, and eGFR ≤45 mL/min/1.73 m^2 or need for continuous renal replacement therapy; [c]Macroalbuminuria, doubling of serum creatinine level, eGFR ≤45 mL/min/1.73 m^2, initiation of renal-replacement therapy or renal death; [d]40% reduction in eGFR, ESRD, or renal death; [e] sustained decline in eGFR ≥ 50%, ESRD, or death from renal causes; [f] doubling of serum creatinine, ESRD (GFR <15 mL/min/1.73 m^2, dialysis or transplant), renal death or CV death.

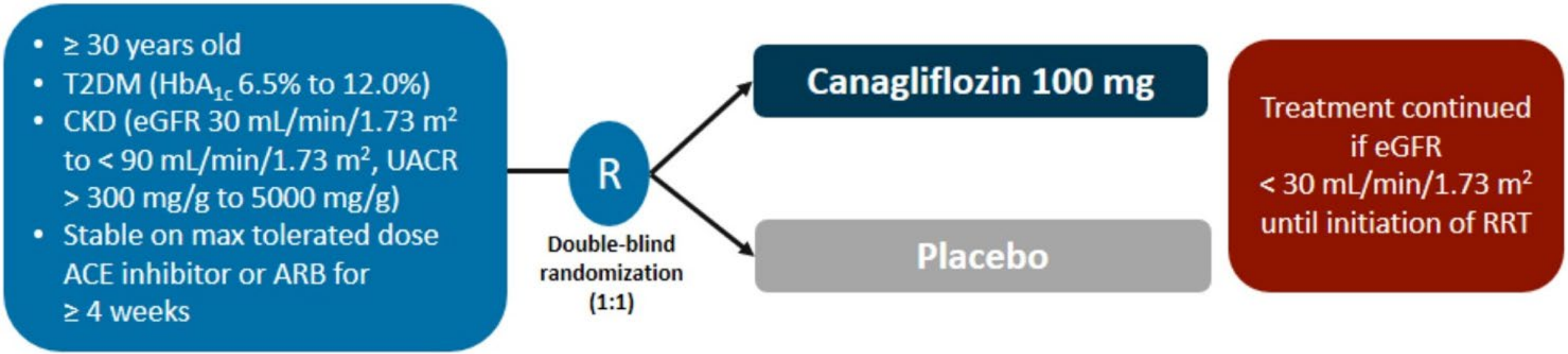
EMPA-REG Trial: Slower Progression of Renal Disease Over Time

EMPA-REG and Effect on GFR



No. at Risk:														
PBO	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
EMPA 10mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
EMPA 25mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524

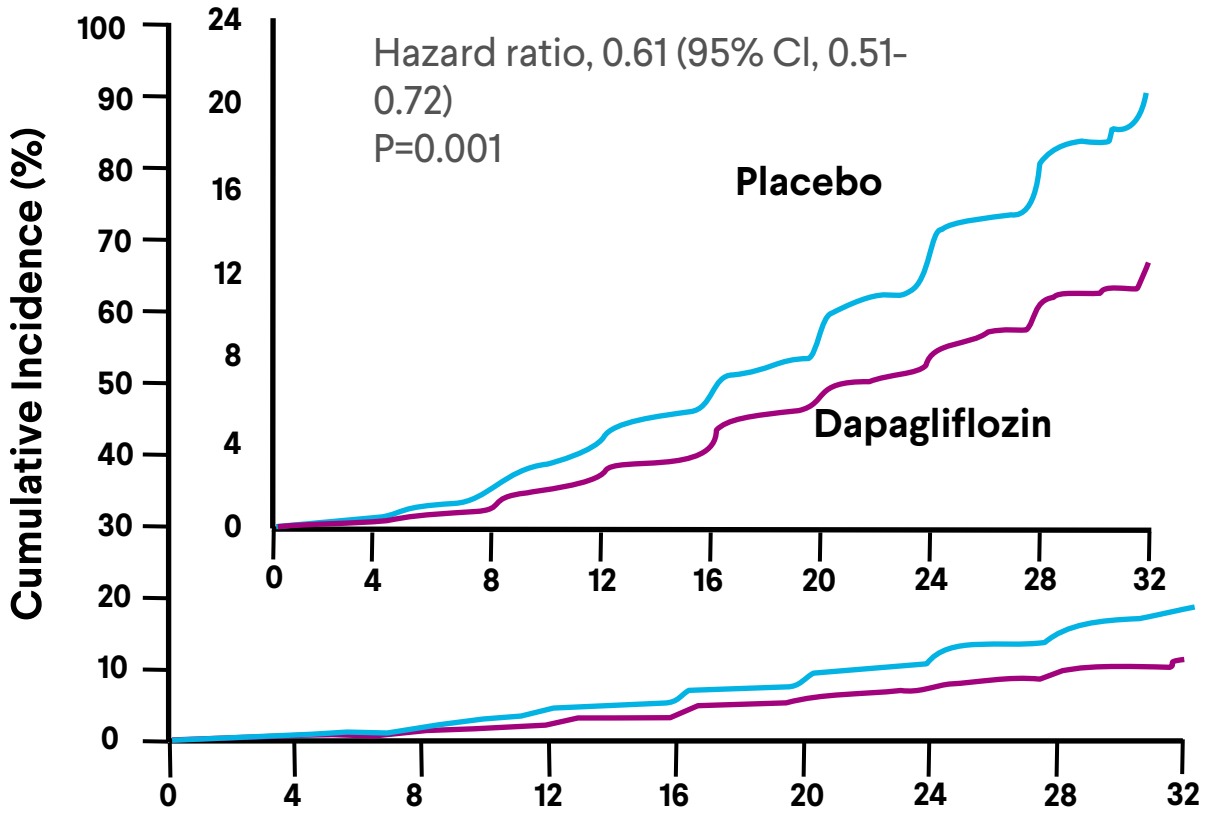
CREDENCE: Canagliflozin in T2DM and Nephropathy



Trial stopped early after planned interim analysis showed RR of the primary outcome was 30% lower in the canagliflozin group than in the placebo group

Perkovic V, et al. *N Engl J Med*. 2019;380:2295-2306.

Dapagliflozin Improves Renal Outcomes: DAPA-CKD Trial (2/3 Type 2DM and 1/3 Non-DM)



No. at Risk									
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

- N = 4304 with eGFR 25-75 mL/min/1.73m^2 and ACR 200-5000 mg/g
- 1° outcome: Sustained decline in eGFR ≥ 50%, end-stage kidney disease, or death from renal or CV causes
  - 9.2% DAPA vs. 14.5% PBO
  - HR 0.61
  - NNT = 19
- Composite renal outcome:
  - HR 0.56 (95% CI, 0.45-0.68; *P* < 0.001)

Heerspink et al. N Engl J Med 2020; 383:1436-1446 DOI: 10.1056/NEJMoa2024816

SGLT2 Inhibitors: Adverse Effects

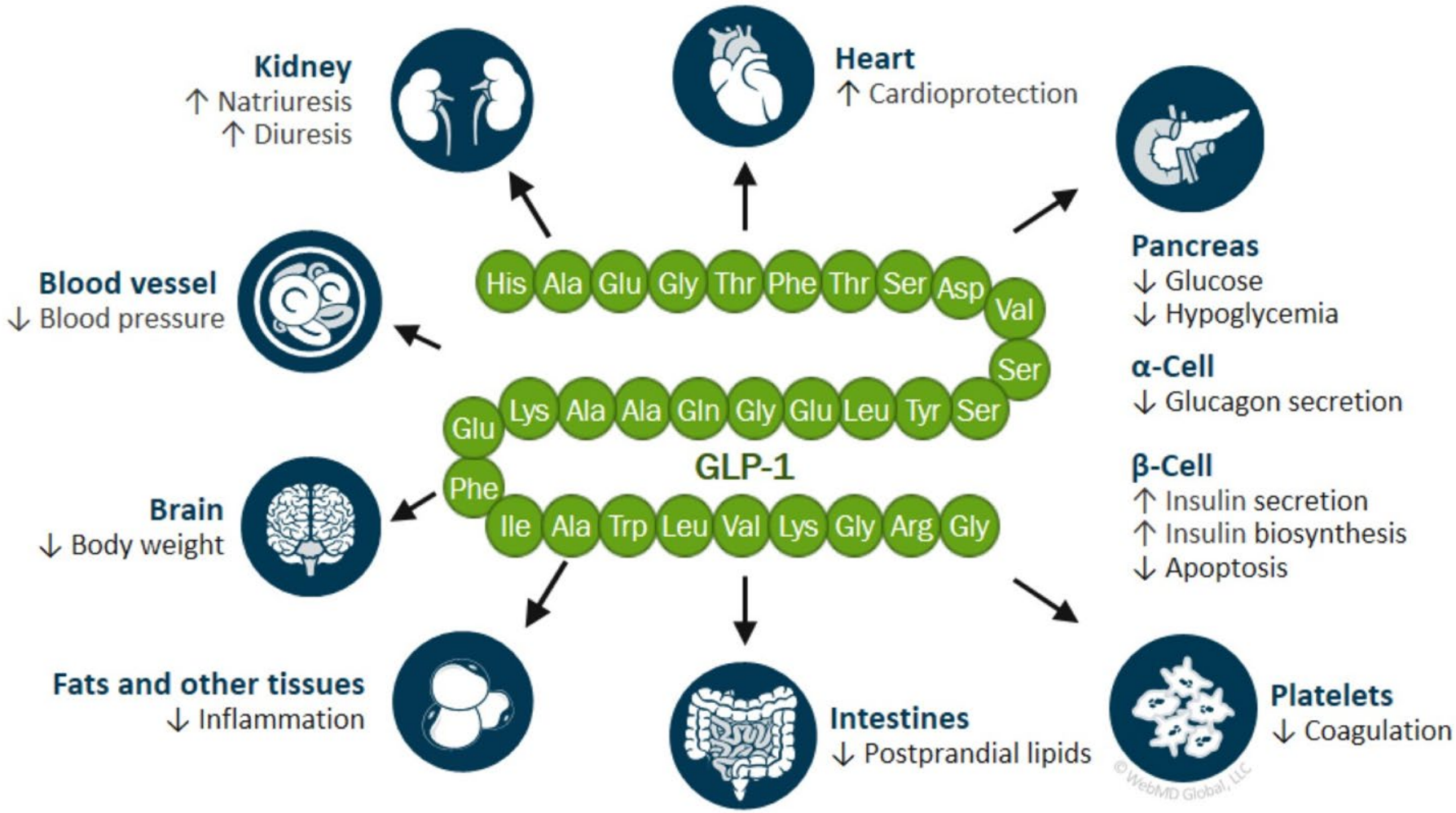
- Genital mycotic infections (women › men)
- Urinary tract infections
- Polyuria
- Volume depletion/hypotension/dizziness
- ↑ LDL-C
- ↑ Creatinine (transient)
- DKA/ euglycemic DKA
- Increased rate of lower extremity amputations (seen in CANVAS, not CREDENCE)
  - CANVAS: numerically low numbers but statistically significant; 6.3 vs. 3.4%, HR 1.97 (95%CI 1.41-2.75)
- Side effect of Fournier's gangrene
- Increased risk of bone fractures

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

Currently Available Drugs

- Exenatide (Byetta, Bydureon)
- Liraglutide (Victoza)
- Lixisenatide (Adlyxin, component of Soliqua)
- Semaglutide (Ozempic, Rybelsus)
- Dulaglutide (Trulicity)

GLP-1 RAs: Mechanism of Action



Drucker DJ. *Cell Metab.* 2016;24:15-30.

Mechanisms for Renoprotection

- Increased natriuresis
- Increased diuresis
- Blood glucose lowering
- Blood pressure lowering effects
- Decreased insulin resistance
- Weight loss

GLP1 Receptor Agonists: Renal Outcome Trials

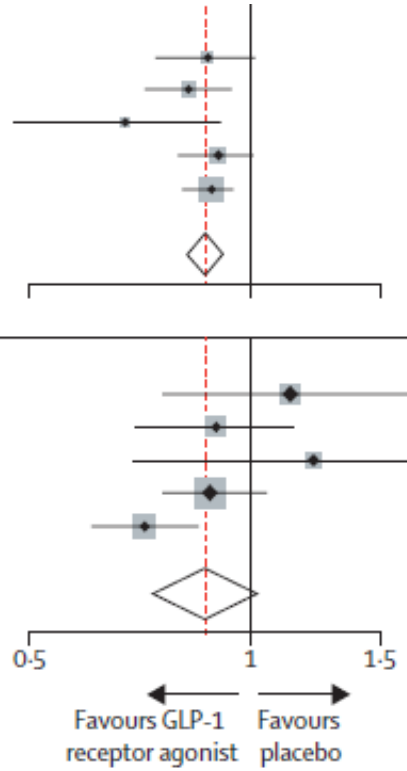
- LEADER
  - Liraglutide reduced new or worsening nephropathy by 22% (HR 0.74, 95%CI 0.60-0.91)
  - 26% reduction in macroalbuminuria
- SUSTAIN-6
  - Reduction in new or worsening nephropathy with semaglutide SC (HR 0.64, 95%CI 0.46-0.88, P=0.005)
  - 46% reduction in macroalbuminuria

GLP1 Receptor Agonists: Renal Outcome Trials

- EXSCEL
  - For a composite of 40% eGFR decline, renal replacement, renal death or new macroalbuminuria, significant reduction with Exenatide ER (HR 0.85, 95%CI 0.73-0.98), P=0.027).
- AWARD-7 / REWIND
  - Dulaglutide significantly attenuates eGFR decline compared to insulin glargine in DM2 patients with moderate to severe CKD. HR -0·05%, 95% CI, p‹0·0001)

Renal Outcomes with GLP-1 RA

	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Composite kidney outcome including macroalbuminuria					
ELIXA	172/2647 (6%)	203/2639 (8%)	0·84 (0·68–1·02)		0·083
LEADER	268/4668 (6%)	337/4672 (7%)	0·78 (0·67–0·92)		0·003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0·64 (0·46–0·88)		0·006
EXSCEL	366/6256 (6%)	407/6222 (7%)	0·88 (0·76–1·01)		0·065
REWIND	848/4949 (17%)	970/4952 (20%)	0·85 (0·77–0·93)		<0·001
Overall (I^2=0·0%, p=0·413)	**1716/20168 (9%)**	**2017/20134 (10%)**	**0·83 (0·78–0·89)**	**62 (48 to 96)**	**<0·001**
Worsening of kidney function					
ELIXA	41/3031 (1%)	35/3032 (1%)	1·16 (0·74–1·83)		0·513
LEADER	87/4668 (2%)	97/4672 (2%)	0·89 (0·67–1·19)		0·43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)	1·28 (0·64–2·58)		0·48
EXSCEL	246/6456 (4%)	273/6458 (4%)	0·88 (0·74–1·05)		0·164
REWIND	169/4949 (3%)	237/4952 (5%)	0·70 (0·57–0·85)		<0·001
Overall (I^2=42·7%, p=0·137)	**561/20752 (3%)**	**656/20763 (3%)**	**0·87 (0·73–1·03)**	**247 (119 to –1072†)**	**0·098**



Kristensen et al. Lancet Diabetes Endocrinol **2019; 7: 776–85**

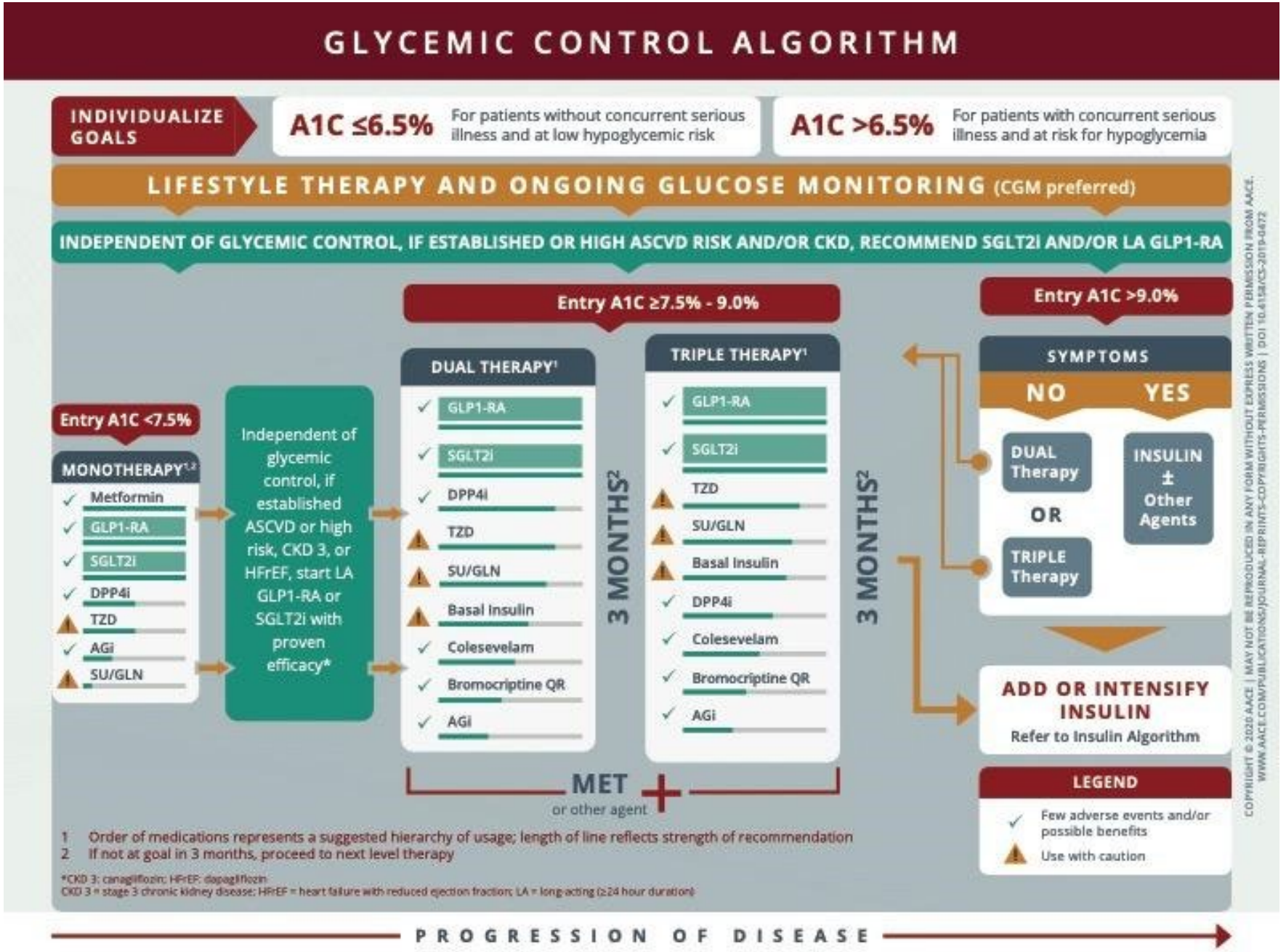
Kristensen, S., Rasmus, R. et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. The Lancet Diabetes and Endo Vol 7, Issue 10 P776-785, October 1, 2019

GLP1 Receptor Agonists: Benefits

- ↓ Postprandial glucose excursions
- Weight loss: Average weight loss of 2-4 kg
- Increased satiety
- ↓ LDL-C and ↓ triglycerides
- Low rate of hypoglycemia
- Cardiac and renal protection

GLP1 Receptor Agonists: Adverse Effects

- Gastrointestinal side effects
  - Nausea, vomiting most common
  - Diarrhea
  - Association with acute gallstone disease
- ↑ Heart rate
- Acute pancreatitis
  - Risk not confirmed in CVOT



AACE/ACE Comprehensive Type 2 Diabetes Algorithm App. American Association of Clinical Endocrinologists (AACE) 25th Annual Scientific & Clinical Congress, May 25-29, 2016. Orlando, FL.

AACE/ACE Comprehensive Type 2 Diabetes Management Algorithm

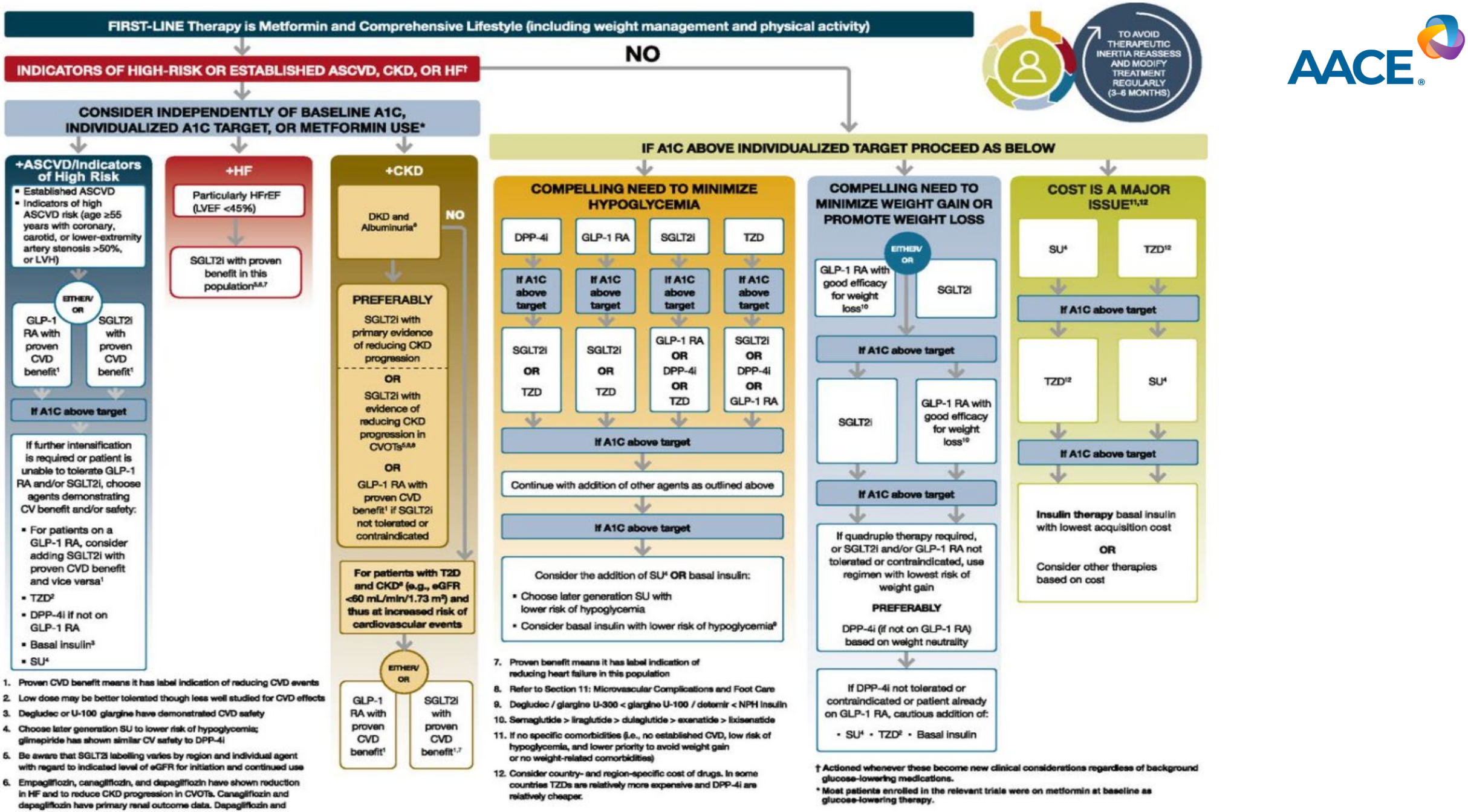
PROFILES OF ANTIHYPERGLYCEMIC MEDICATIONS

	MET	GLP1-RA	SGLT2i	DPP4i	AGi	TZD (moderate dose)	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	SU: Moderate/Severe; GLN: Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contra-indicated if eGFR <30 mL/min/1.73 m²	Exenatide Not Indicated CrCl <30; Potential Benefit of LA GLP1-RA	Not Indicated for eGFR <45 mL/min/1.73 m²; See #1; Genital Mycotic Infections; Potential CKD Benefit; See #1	Dose Adjustment Necessary (Except Linagliptin); Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Neutral	Prevent HF Hospitalization Manage HFrEF, See #2	See #4	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
CARDIAC ASCVD		Potential Benefit of LA GLP1-RA	See #3			May Reduce Stroke Risk	Possible ASCVD Risk	Lowers LDL-C	Safe	Neutral	
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits
Use with caution
Likelihood of adverse effects

1. Canagliflozin indicated for eGFR ≥30 mL/min/1.73 m² in patients with CKD 3 + albuminuria.
2. Dapagliflozin—potential primary prevention of HF hospitalization & demonstrated efficacy in HFrEF.
3. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin—FDA approved to reduce MACE events.
4. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

DOI 10.4158/CS-2019-0472



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.

Medication Access/Medication Cost

- Despite promising data described above, many patients are unable to utilize these classes of medications due to high cost involved and economic hardship.
- Uninsured patients, and even some insured patients, with high copays or deductibles may be limited in their ability to obtain diabetes medications with the best profiles for organ protection.
- Often a particular insurance company will only cover one agent within a particular class so ability to select a specific drug may be limited.
- Be aware of limitations when prescribing and consider options for cost-reduction or alternative medications if cost remains prohibitive.

Conclusions

Diabetes is a multifactorial disease

Many people with T2DM have ASCVD, kidney disease, and/or HF

Role for PCPs, cardiologists, nephrologists, and diabetologists in risk management for T2DM and CVD, or CKD, or risk factors

We can prevent progression of diabetes complications

Latest guidelines recommend SGLT2 inhibitors and GLP-1 RAs for organ protection in individualized diabetes care

Novel glucose-lowering drugs have a role beyond T2DM: in HF, ASCVD, and kidney disease

Practice Patient Scenario 1

64-year-old male with DM2 is admitted to the hospital for dyspnea and lower extremity edema. Transthoracic echo demonstrates EF 15%. Patient is treated for congestive heart failure with diuretics, and initially required oxygen therapy which improved closer to discharge. He is found with newly diagnosed Type 2 DM, HbA1c 7.9%. His GFR is ›45.

Question: Aside from lifestyle modifications, what diabetes therapy would you recommend for this patient at hospital discharge?

Answer choices

- Metformin
- Sulfonylurea
- DPP4 inhibitor
- SGLT2-inhibitor

Practice Patient Scenario 1

Correct Answer: SGLT2-inhibitor

Rationale: SGLT2-I can be utilized as first line therapy for DM in a high-risk patient, specifically in the setting of both HF and CKD for organ protection. Although metformin has traditionally been used for first line therapy, it would not be initiated for GFR ‹ 45 and caution should be used for patients with severely reduced EF. Some DPP4 inhibitors have a neutral profile for HF but some in the class were associated with worse outcomes. Sulfonylureas would not confer any cardiac or renal benefit.

Practice Patient Scenario 2

A 59-year-old female presents for evaluation after a recent ischemic stroke. Her current diabetes therapy includes metformin 1000mg BID and Januvia 100mg daily. HBA1c 7.5%. Renal function and transthoracic echo are within normal limits.

Question: Which change in diabetes therapy would you recommend?

Answer Choices

- Stop Januvia and add a GLP1-RA
- Add a SGLT2 inhibitor
- Add basal insulin therapy
- No change is needed

Practice Patient Scenario 2

Correct Answer: Stop Januvia and add a GLP1-RA

Rationale: Given the history of stroke the patient would benefit from addition of a GLP1-RA. Since Januvia, a DPP4 agent is in a related class this drug would need to be discontinued once starting a GLP1-RA. Given the absence of HF or CKD in this patient, GLP1-RA would be preferential over SGLT2-i.

Practice Patient Scenario 3

70-year-old female with a history of DM2 but not currently on therapy, presents to the hospital with severe hyperglycemia to 600s, polyuria, polydipsia and weight loss, and is found with diabetic ketoacidosis (DKA), HbA1c 14%. She is treated with IV insulin therapy with resolution of DKA. She has a history of CKD but no prior known CAD. BMI 18.2.

Question: What diabetes therapy would you recommend for hospital discharge?

Answer Choices

- Basal and bolus insulin therapy
- SGLT2 inhibitor
- GLP1 RA
- Metformin + SGLT2 inhibitor

Practice Patient Scenario 3

Correct Answer: Basal and bolus insulin therapy

Rationale: Although the patient has a history of CKD it would not be appropriate to initiate SGLT2-i in a patient with a recent diagnosis of DKA. Given the DKA, the severity of the HbA1c and the weight loss/BMI is low – this patient appears to be in an insulin deficient state and would benefit from insulin therapy at this time. Furthermore, drugs which cause weight loss such as GLP1-RA and SGLT2-I, would not be appropriate given the patient is currently underweight. She should be ruled out for LADA/ Type 1 DM as well.

References

Slide 4: National Kidney Foundation. KDOQI Guidelines Executive Summary. 2007

Slide 4: Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clin J Am Soc Nephrol. 2017 Dec 7;12(12):2032-2045.

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