Don’t Go Breaking My Heart:
Cardiovascular Effects of SGLT-2 Inhibitors & GLP-1 Receptor Agonists

A Presentation for HealthTrust Members
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Conflicts of Interest Disclosure

There are no relevant financial interest to disclose for myself or my spouse/partner within the last 12 months.

The preceptor has a financial interest/arrangement, affiliation or relationship with AstraZeneca that could be perceived as a real or apparent conflict of interest in the context of the subject of this activity.

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Learning Objectives

1. Recall current guideline-directed medical therapy, common cardiovascular risk factors, and challenges faced in the treatment of patients with diabetes
2. Identify cardiac effect and clinical outcomes of agents within the SGLT-2 inhibitor and GLP-1 receptor agonist drug classes when used in the treatment of diabetes
3. Define the role of the pharmacist in promoting positive cardiovascular outcome in patients with diabetes

Abbreviations

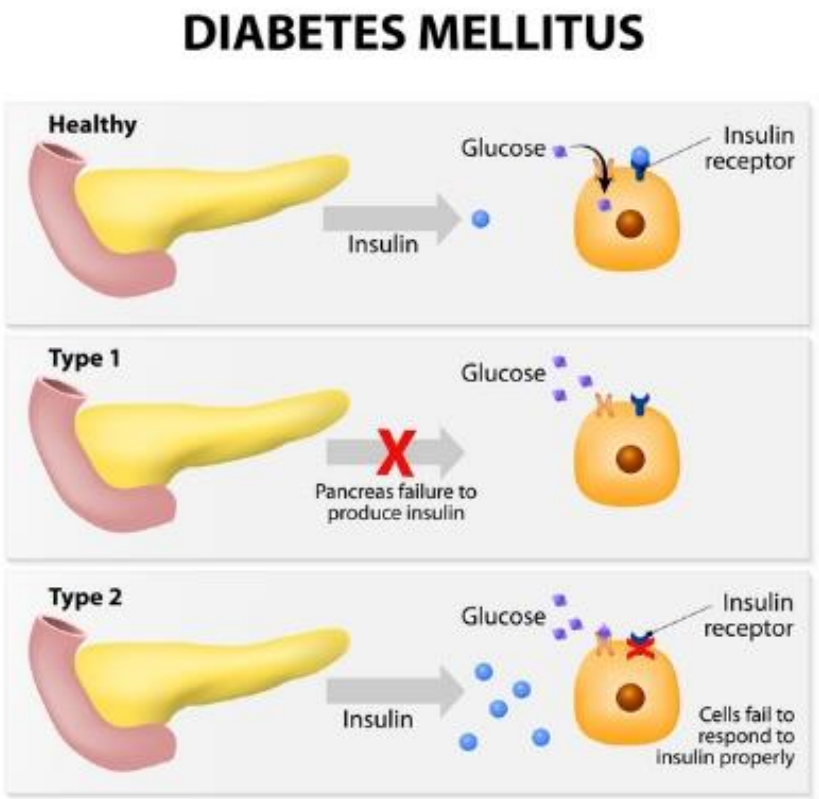
- SGLT-2: sodium-glucose cotransporter-2
- GLP-1: glucagon-like peptide 1
- ASCVD: atherosclerotic cardiovascular disease
- CV: cardiovascular
- CKD: chronic kidney disease
- eGFR: estimated glomerular filtration rate
- SQ: subcutaneous
- PO: by mouth
- HF: heart failure
- GI: gastrointestinal
- ADA: American Diabetes Association
- T2DM: type 2 diabetes mellitus
- MI: myocardial infarction
- HbA1C: glycated hemoglobin
- CrCl: creatinine clearance
- MACE: major adverse cardiovascular events
- HR: Hazard Ratio
- CI: Confidence Interval
- EPO: Erythropoietin
- BMI: body mass index

What is Diabetes?

Group of metabolic disorders causing elevated blood glucose levels and abnormal fat and protein metabolism

Type 1
- Immune-mediated
- β-cell destruction leads to insulin deficiency

Type 2
- Non-insulin dependent
- Loss of β-cell insulin secretory function coupled with insulin resistance

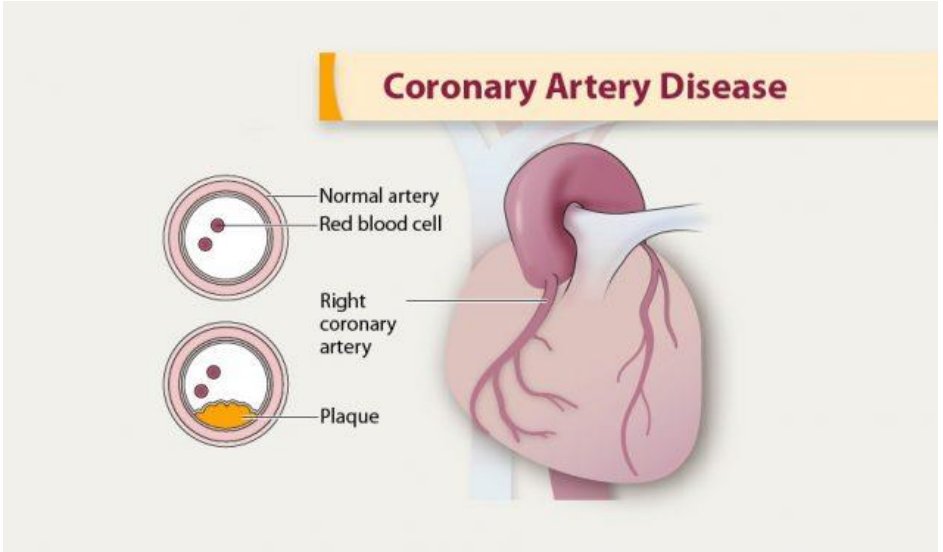


Source: https://medlineplus.gov/genetics/condition/type-2-diabetes/

Source: Trujillo J, et al. Diabetes Mellitus. In: DiPiro JT, et al. Pharmacotherapy: A Pathophysiologic Approach, 11e. McGraw-Hill.

What is ASCVD?

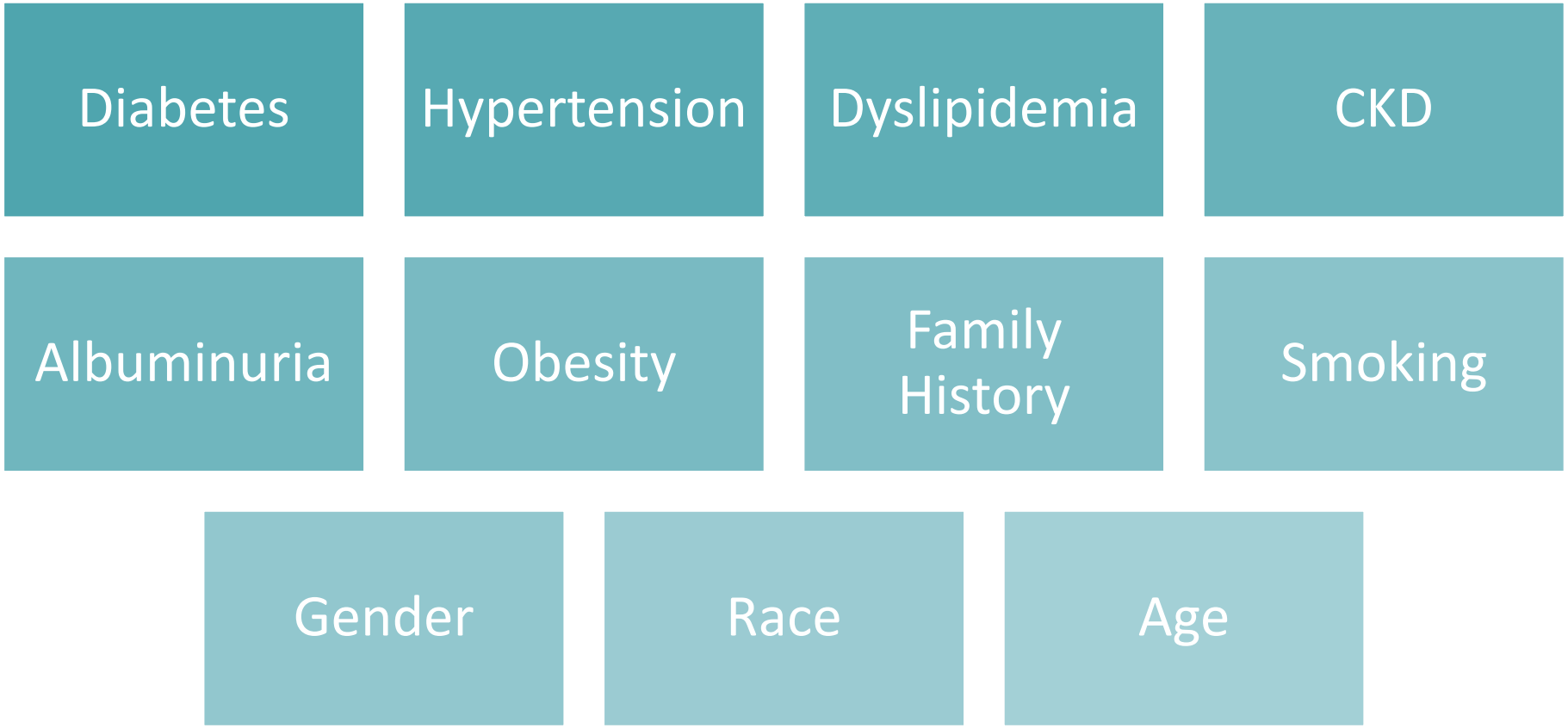
Coronary heart disease	• Myocardial infarction • Angina • Coronary artery stenosis > 50%
Cerebrovascular disease	• Transient ischemic attack • Ischemic stroke • Carotid artery stenosis > 50%
Peripheral artery disease	• Claudication



Source: https://www.cdc.gov/heartdisease/coronary_ad.htm

Source: Atherosclerotic Cardiovascular Disease (ASCVD) Primary Prevention Guideline, Kaiser Permanente.
Available from: https://wa.kaiserpermanente.org/static/pdf/public/guidelines/ascvd-primary.pdf. Updated October 2020. Accessed November 29, 2021.

ASCVD Risk Factors

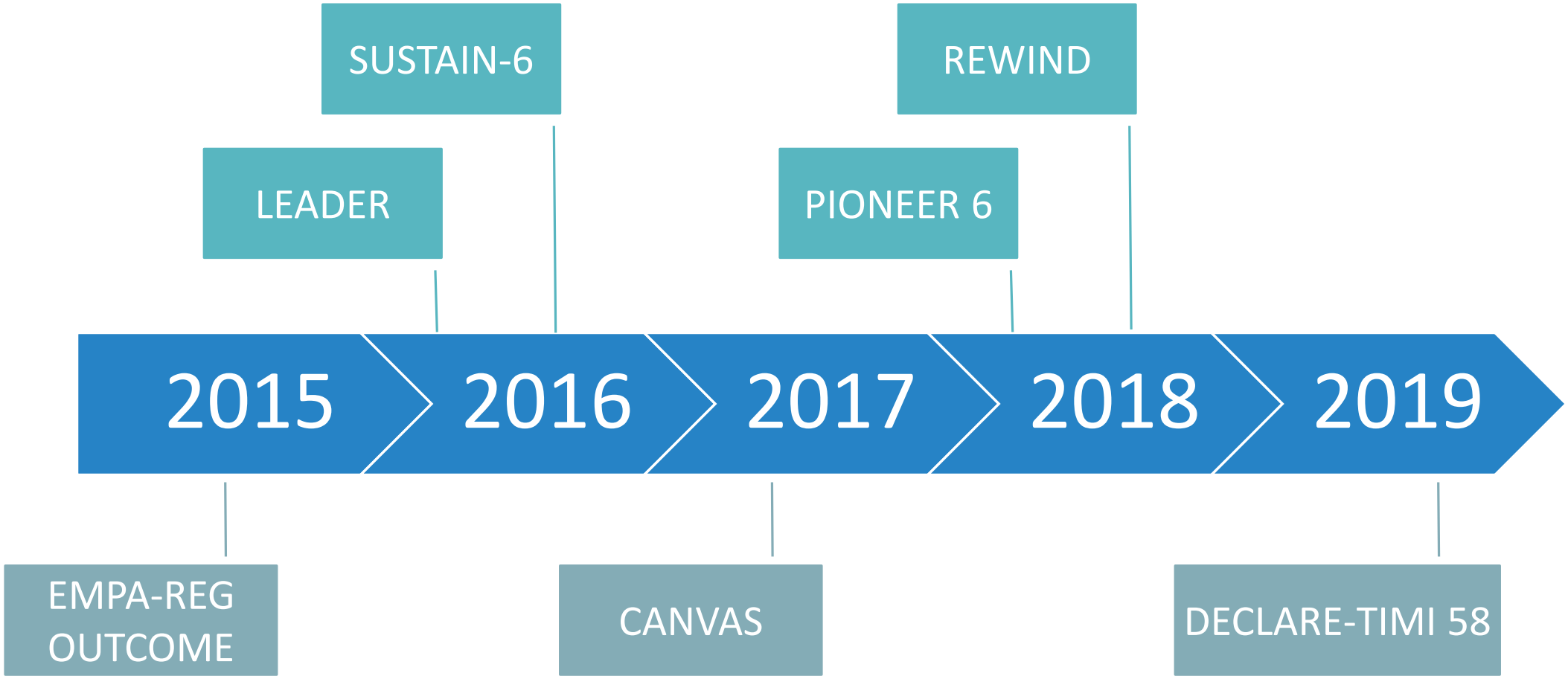


Sources:
American Diabetes Association. *Diabetes Care*. 2021 Jan;44 Suppl 1(Suppl 1).
Project risk reduction by therapy. ASCVD Risk Estimator +. https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/. Accessed November 29, 2021.

ASCVD Risk in Diabetes

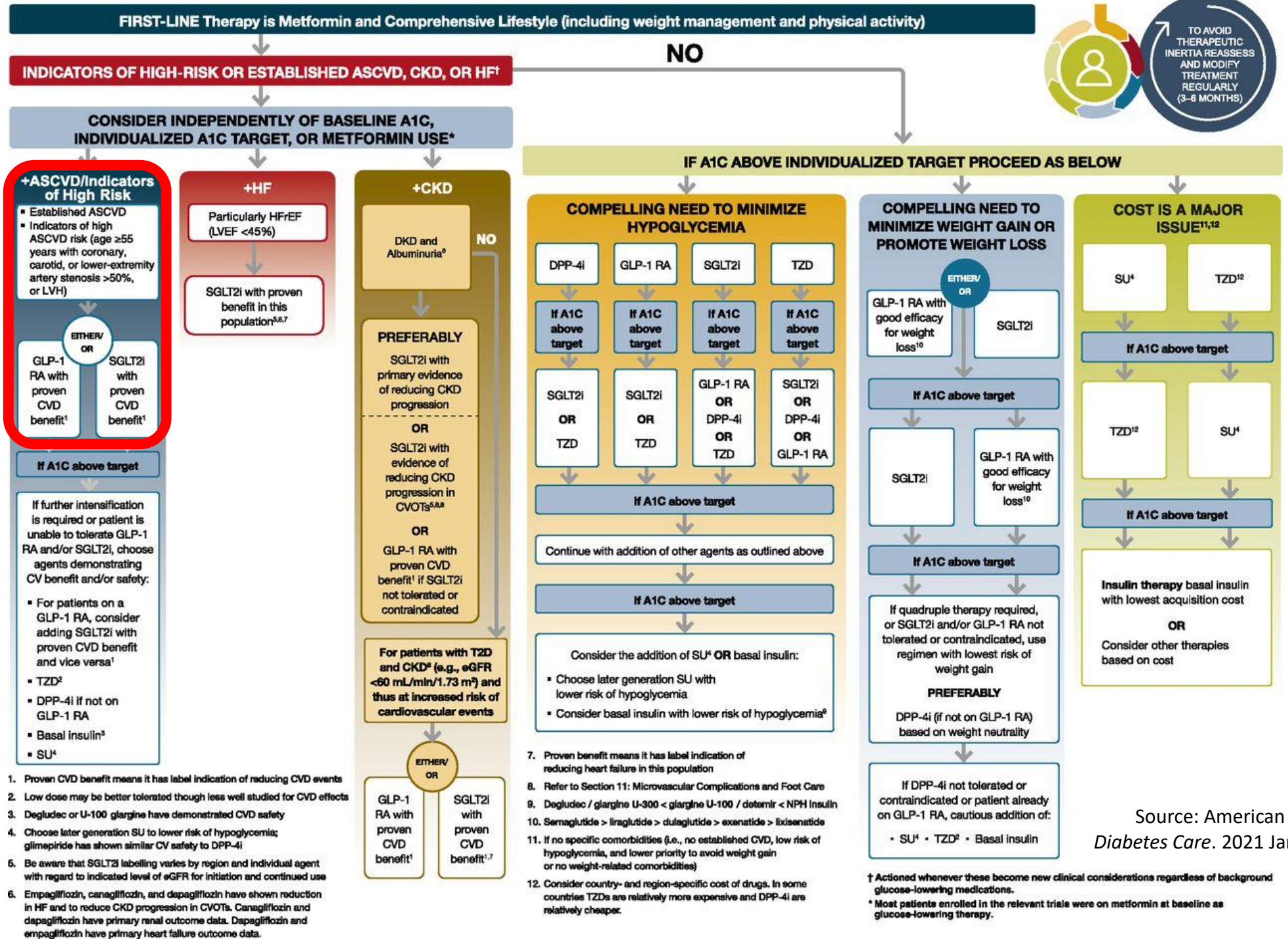
- More than 70% of patients with type 2 diabetes die of cardiovascular causes
- Manifestations of coronary heart disease are at least twofold more common in patients with type 2 diabetes than in nondiabetic individuals
- Mechanisms linking type 2 diabetes with cardiovascular disease remain poorly understood
  - Development of hyperglycemia leads to several potential mechanisms for high glucose to increase risk of atherothrombosis
  - Earliest finding in the pathogenesis of atherosclerotic lesions is impaired endothelial function, which is tightly linked to insulin resistance
- December 2008: FDA mandated long-term cardiovascular outcomes trials for safety for approval of anti-diabetes drugs for type 2 diabetes

Sources:
Laakso M. *Diabetes Care*. 2010;33(2):442-449.
Cefalu WT, et al. *Diabetes Care*. 2018;41(1):14-31.



Source: Cefalu WT, et al. *Diabetes Care*. 2018;41(1):14-31.

ADA Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes – 2021*



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

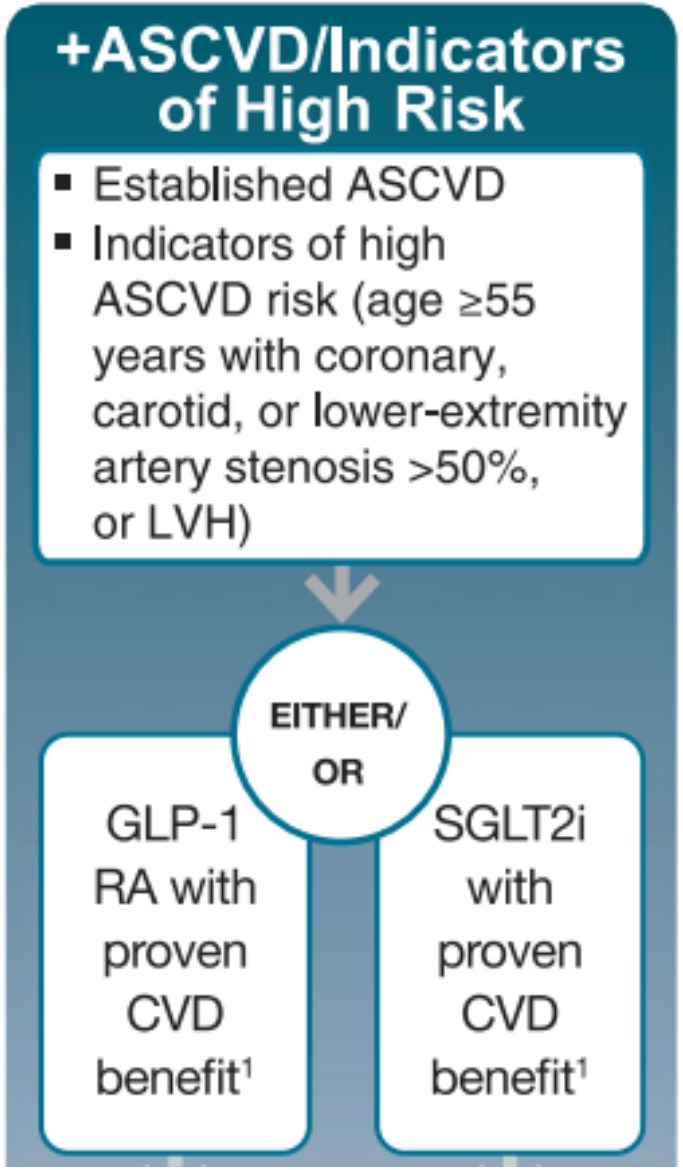
* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

Source: American Diabetes Association. *Diabetes Care*. 2021 Jan;44 Suppl 1(Suppl 1).

Liraglutide (Victoza®)

Semaglutide (Ozempic®/ Rybelsus®)

Dulaglutide (Trulicity®)



Empagliflozin (Jardiance®)

Canagliflozin (Invokana®)

Source: American Diabetes Association. *Diabetes Care*. 2021 Jan;44 Suppl 1(Suppl 1).

Question 1

Which of the following is NOT an ASCVD risk factor?

A. Smoking

B. Diabetes mellitus

C. Pregnancy

D. Age

Question 1: Response

Which of the following is NOT an ASCVD risk factor?

A. Smoking

B. Diabetes mellitus

C. Pregnancy

D. Age

GLP-1 Receptor Agonists

Generic (Brand)	Mechanism of Action	Proposed Mechanism of CV Risk Reduction

▪ **Liraglutide** (Victoza®)
▪ **Semaglutide** (Ozempic® / Rybelsus®)
▪ **Dulaglutide** (Trulicity®)
	▪ Increases glucose-dependent insulin secretion
	▪ Reduces gastric emptying
	▪ Increases satiety
		▪ Exact mechanism is unclear
		▪ Proposed theories:
		  ▪ Reduction in blood pressure
		  ▪ Weight loss
		  ▪ Anti-oxidative and anti-inflammatory effects

Sources:
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/.
Cox, Emily, et al. US Endocrinology. 16. 80. 10.17925/USE.2020.16.2.80.

LEADER

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes			
Study Population	**Interventions**	**Clinical Endpoints**	**Outcomes**

▪ T2DM with HbA1C% ≥ 7%
▪ Age ≥ 50 years with at least one CV condition
▪ Age ≥ 60 years with at least one CV risk factor
▪ N = 9340
	▪ 1.8 mg liraglutide SQ injection once daily
	▪ Placebo SQ injection once daily
		▪ Primary composite outcome
		  ▪ Death from CV causes
		  ▪ Nonfatal MI
		  ▪ Nonfatal stroke
		▪ Additional exploratory outcomes
		  ▪ Coronary revascularization
		  ▪ Hospitalization for unstable angina pectoris or HF
			▪ Primary outcome
			  ▪ Liraglutide: 13%
			  ▪ Placebo: 14.9%
			  ▪ HR 0.87; 95% CI, 0.78 to 0.97, p<0.001 for noninferiority, p=0.01 for superiority
			▪ No significant difference seen in rates of nonfatal MI, nonfatal stroke, or hospitalization for HF

Source: Marso SP, et al. *N Engl J Med*. 2016;375(4):311-322.

SUSTAIN-6

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes			
Study Population	**Interventions**	**Clinical Endpoints**	**Outcomes**

▪ T2DM with HbA1C% ≥ 7%
▪ Age ≥ 50 years with established ASCVD
▪ Age ≥ 60 years with at least one CV risk factor
▪ CKD stage 3 or higher
▪ N = 3297
	▪ 0.5 mg semaglutide SQ injection once weekly
	▪ 1 mg semaglutide SQ injection once weekly
	▪ Volume-matched placebo (n = 1649)
	▪ Fixed-dose escalation procedure:
	  ▪ 0.25 mg for 4 weeks
	  ▪ Escalated to 0.5 mg for 4 weeks until maintenance dose reached
		▪ Primary composite outcome
		  ▪ Death from CV causes
		  ▪ Nonfatal MI
		  ▪ Nonfatal stroke
			▪ Primary outcome
			  ▪ Semaglutide: 6.6%
			  ▪ Placebo: 8.9%
			  ▪ HR 0.74; 95% CI, 0.58 to 0.95; p<0.001 for noninferiority
			▪ Rates of death from CV causes were similar
			▪ Many patients discontinued treatment due to GI effects

Source: Marso SP, et al. *N Engl J Med*. 2016;375(19):1834-1844.

PIONEER 6

Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes			
Study Population	**Interventions**	**Clinical Endpoints**	**Outcomes**

▪ Patients with T2DM
▪ Age ≥ 50 years with established ASCVD or CKD
▪ Age ≥ 60 years with CV risk factors
▪ N = 3183
	▪ Target dose 14 mg oral semaglutide once daily
	▪ Placebo
	▪ Dose-escalation schedule used to minimize GI effects
		▪ Primary outcomes
		  ▪ Time to first occurrence of MACE
		  ▪ Death from CV causes, nonfatal MI, nonfatal stroke
			▪ MACE
			  ▪ Semaglutide: 3.8%
			  ▪ Placebo: 4.8%
			  ▪ HR 0.79; 95% CI, 0.57 to 1.11; p<0.001 for noninferiority
			▪ Discontinuation of treatment due to GI effects commonly seen in semaglutide group

Source: Husain M, et al. *N Engl J Med*. 2019;381(9):841-851.

REWIND

Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial			
Study Population	**Interventions**	**Clinical Endpoints**	**Outcomes**

▪ Patients ≥ 50 years with T2DM with HbA1C% ≤ 9.5%, established ASCVD or CV risk factors
▪ N = 9901
	▪ 1.5 mg dulaglutide SQ injection once weekly
	▪ Placebo SQ injection once weekly
		▪ Primary endpoint
		  ▪ Death from CV or unknown causes
		  ▪ Nonfatal MI
		  ▪ Nonfatal stroke
			▪ Primary composite outcome
			  ▪ Dulaglutide: 12%
			  ▪ Placebo: 13.4%
			  ▪ HR 0.88, 95% CI, 0.79 to 0.99; p=0.026
			▪ All-cause mortality did not differ between groups

Source: Gerstein HC, et al. *Lancet*. 2019;394(10193):121-130.

Treatment with GLP-1 Receptor Agonists

Drug	Usual Adult Dose	Renal Dose Adjustment?	Adverse Effects	Monitoring
Liraglutide (Victoza®)	0.6 mg once daily, then increase to 1.2 mg daily, then may increase up to 1.8 mg daily	No	▪ **Black Box Warning:** thyroid C-cell tumors ▪ GI symptoms ▪ Pancreatitis ▪ Injection-site nodule	▪ Blood glucose ▪ Renal function ▪ Triglycerides
Semaglutide (Ozempic®)	0.25 mg once weekly for 4 weeks, then increase to 0.5 mg weekly, then may increase up to 1 mg weekly	No		
Semaglutide (Rybelsus®)	3 mg once daily for 30 days, then increase to 7 mg daily, then may increase up to 14 mg daily	No		
Dulaglutide (Trulicity®)	0.75 mg once weekly, may increase to 1.5 mg weekly after 4-8 weeks, may increase to 3 mg weekly, then max of 4.5 mg weekly	No		

Sources:
Cox, Emily, et al. US Endocrinology. 16. 80. 10.17925/USE.2020.16.2.80.
Vuylsteke VA, et al. Diabetes Mellitus. ACCP/ASHP 2020 Ambulatory Care Pharmacy Preparatory Review and Recertification Course. Updated 2020. Accessed November 29, 2021.

GLP-1 Receptor Agonist Summary

Drug	**Liraglutide** (Victoza®)	**Semaglutide** (Ozempic®)	**Semaglutide** (Rybelsus®)	**Dulaglutide** (Trulicity®)
Patients with T2DM				
FDA Approval for CV Risk Reduction?	Yes	Yes	No	Yes
Indication	↓ risk of MACE in patients with established ASCVD	↓ risk of MACE in patients with established ASCVD	Noninferior to placebo for MACE	↓ risk of MACE in patients with established ASCVD or multiple risk factors
Supporting Evidence	LEADER	SUSTAIN-6	PIONEER 6	REWIND

Source: Cox, Emily, et al. US Endocrinology. 16. 80. 10.17925/USE.2020.16.2.80.

SGLT-2 Inhibitors

Generic (Brand)	Mechanism of Action	Proposed Mechanism of CV Risk Reduction

▪ **Empagliflozin** (Jardiance®)
▪ **Dapagliflozin** (Farxiga®)
▪ **Canagliflozin** (Invokana®)
▪ **Ertugliflozin** (Steglatro®)
	▪ Inhibits SGLT-2 in proximal renal tubules
	▪ Decreases glucose reabsorption
		▪ Exact mechanism is unclear
		▪ Proposed theories:
		  ▪ Increased diuresis
		  ▪ Weight loss
		  ▪ Enhanced EPO secretion
		  ▪ Improved vascular function

Sources:
Lexi-Drugs. Hudson, OH: Lexicomp, 2021. http://online.lexi.com/.
Lopaschuk GD, et al. *JACC Basic Transl Sci*. 2020;5(6):632-644.

EMPA-REG OUTCOME

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes			
Study Population	**Interventions**	**Clinical Endpoints**	**Outcomes**

▪ Adults with T2DM
▪ BMI ≤ 45 kg/m^2
▪ eGFR ≥ 30 mL/min/1.73 m^2
▪ Established ASCVD
▪ N = 7020
	▪ 10 mg empagliflozin
	▪ 25 mg empagliflozin
	▪ Placebo (n = 2333)
		▪ Primary composite outcome
		  ▪ Death from CV causes
		  ▪ Nonfatal MI
		  ▪ Nonfatal stroke
		▪ Secondary composite outcome
		  ▪ Primary outcomes
		  ▪ Hospitalization for unstable angina
			▪ Primary outcome
			  ▪ Empagliflozin: 10.5%
			  ▪ Placebo: 12.1%
			  ▪ HR 0.86; 95.02% CI, 0.74 to 0.99; p=0.04
			▪ Secondary outcome
			  ▪ No significant difference (p=0.08)

Source: Zinman B, et al. *N Engl J Med*. 2015;373(22):2117-2128.

DECLARE-TIMI 58

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes			
Study Population	**Interventions**	**Clinical Endpoints**	**Outcomes**

▪ Patients ≥ 40 years with T2DM
▪ HbA1C% ≥ 6.5%, but < 12.0%
▪ CrCl ≥ 60 mL/min
▪ Multiple ASCVD risk factors
▪ N = 17,160
	▪ 10 mg dapagliflozin
	▪ Placebo
		▪ Primary safety outcome
		  ▪ MACE
		▪ Primary efficacy outcome
		  ▪ MACE
		  ▪ CV death or hospitalization for HF
		▪ Secondary efficacy outcomes
		  ▪ Renal composite outcome
		  ▪ Death from any cause
			▪ Primary safety outcome
			  ▪ Dapagliflozin was non-inferior to placebo
			  ▪ p<0.001
			▪ Primary efficacy outcomes
			  ▪ Dapagliflozin: 8.8%
			  ▪ Placebo: 9.4%
			  ▪ HR 0.93; 95% CI, 0.84 to 1.03; p=0.17

Source: Wiviott SD, et al. *N Engl J Med*. 2019;380(4):347-357.

CANVAS

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes			
Study Population	**Interventions**	**Clinical Endpoints**	**Outcomes**

▪ T2DM and either:
  ▪ ≥ 30 years with history of symptomatic ASCVD
  ▪ ≥ 50 years with 2 or more ASCVD risk factors
▪ eGFR ≥ 30 mL/min/1.73 m^2
▪ N = 10,142
	▪ 100 mg canagliflozin
	▪ 300 mg canagliflozin
	▪ Placebo
		▪ Primary composite outcome
		  ▪ Death from CV causes
		  ▪ Nonfatal MI
		  ▪ Nonfatal stroke
			▪ Primary outcome
			  ▪ Canagliflozin: 26.9 participants per 1000 patient-years
			  ▪ Placebo: 31.5 participants per 1000 patient-years
			  ▪ HR 0.86; 95% CI, 0.67 to 0.79; p<0.001

Source: Neal B, et al. *N Engl J Med*. 2017;377(7):644-657.

Treatment with SGLT-2 Inhibitors

Drug	Usual Adult Dose	Renal Dose Adjustment?	Adverse Effects	Monitoring
Empagliflozin (Jardiance®)	10 mg PO once daily, may increase up to 25 mg once daily	Yes	▪ Hyperkalemia ▪ Genital mycotic infections ▪ Increased urination	▪ Blood glucose ▪ Renal function ▪ Volume status ▪ Infections
Dapagliflozin (Farxiga®)	5 mg PO once daily, may increase up to 10 mg once daily	Yes		
Canagliflozin (Invokana®)	100 mg PO once daily before first meal of day, may increase up to 300 mg once daily	Yes		
Ertugliflozin (Steglatro®)	5 mg once daily, may increase up to 15 mg once daily	Yes		

Source: Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors Comparison Chart, The Medical Letter. Available from: https://secure.medicalletter.org/downloads/1611f_table.pdf. Updated May 2021. Accessed November 29, 2021.

SGLT-2 Inhibitors Summary

Drug	**Empagliflozin** (Jardiance®)	**Dapagliflozin** (Farxiga®)	**Canagliflozin** (Invokana®)
Patients with T2DM			
FDA Approval for CV Risk Reduction?	Yes	Yes	Yes
Indication	↓ risk of CV death in patients with established ASCVD	↓ risk of hospitalization for HF in patients with established ASCVD or multiple risk factors	↓ risk of MACE in patients with established ASCVD
Supporting Evidence	EMPA-REG OUTCOME	DECLARE-TIMI 58	CANVAS

Source: Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors Comparison Chart, The Medical Letter. Available from: https://secure.medicalletter.org/downloads/1611f_table.pdf. Updated May 2021. Accessed November 29, 2021.

Question 2

Which of the following represents a clinical endpoint for the EMPA-REG Outcome trial?

A. Change in A1C%

B. Nonfatal myocardial infarction

C. eGFR

D. Diabetic ketoacidosis

Question 2: Response

Which of the following represents a clinical endpoint for the EMPA-REG Outcome trial?

A. Change in A1C%

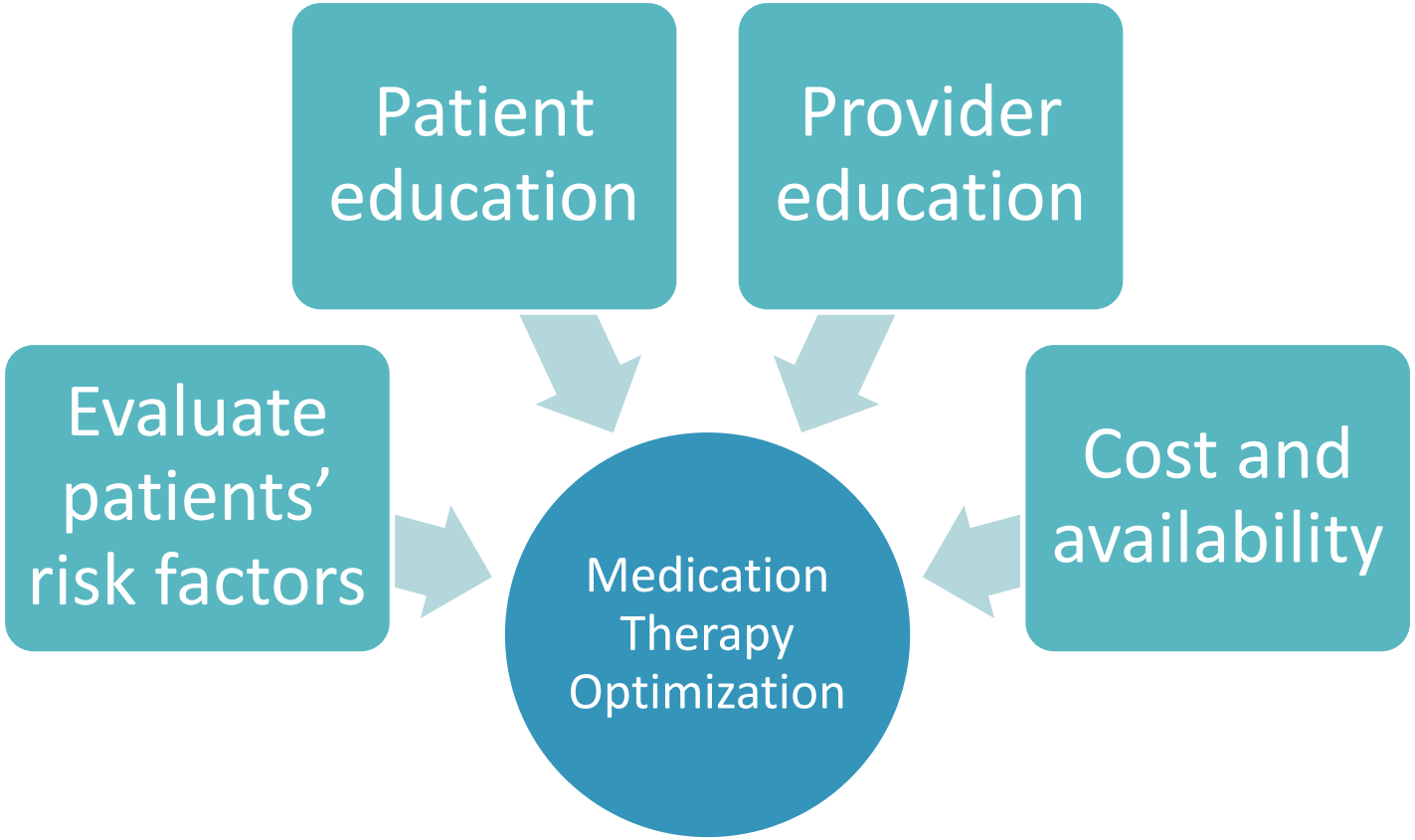
B. Nonfatal myocardial infarction

C. eGFR

D. Diabetic ketoacidosis

Pharmacist’s Role

Pharmacist's Role



Source: Cox, Emily, et al. US Endocrinology. 16. 80. 10.17925/USE.2020.16.2.80.

Resources for Additional Information

- ADA Standards of Medical Care in Diabetes-2022
- Diabetesed.net
- Medical Letter
- Diatribe.org

Question 3

Which of the following represents a role a pharmacist may play in optimizing diabetes management in patients with ASCVD risk? **Select all that apply.**

A. Monitoring for adverse effects

B. Suggesting an SGLT-2 inhibitor or GLP-1 receptor agonist with CV risk reduction

C. Allowing a patient to be lost to follow-up

D. Counseling patients on proper administration techniques

Question 3: Response

Which of the following represents a role a pharmacist may play in optimizing diabetes management in patients with ASCVD risk? **Select all that apply.**

A. Monitoring for adverse effects

B. Suggesting an SGLT-2 inhibitor or GLP-1 receptor agonist with CV risk reduction

C. Allowing a patient to be lost to follow-up

D. Counseling patients on proper administration techniques

Conclusions

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Thank You!

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