Beyond Diabetes: Examining Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors in Heart Failure

A Presentation for HealthTrust Members
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Disclosures

The presenter and her preceptors have no financial relationships with any commercial interests pertinent to this presentation.

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Learning Objectives for Pharmacists & Nurses

Describe the proposed mechanism of action of sodium-glucose cotransporter 2 (SGLT-2) inhibitors in heart failure.

Discuss the cardiovascular outcomes described in recent literature supporting the use of SGLT-2 inhibitors in heart failure.

Describe adverse events and safety considerations of SGLT-2 inhibitors.

Learning Objectives for Pharmacy Technicians

Identify common dosing schemes of SGLT-2 inhibitors.

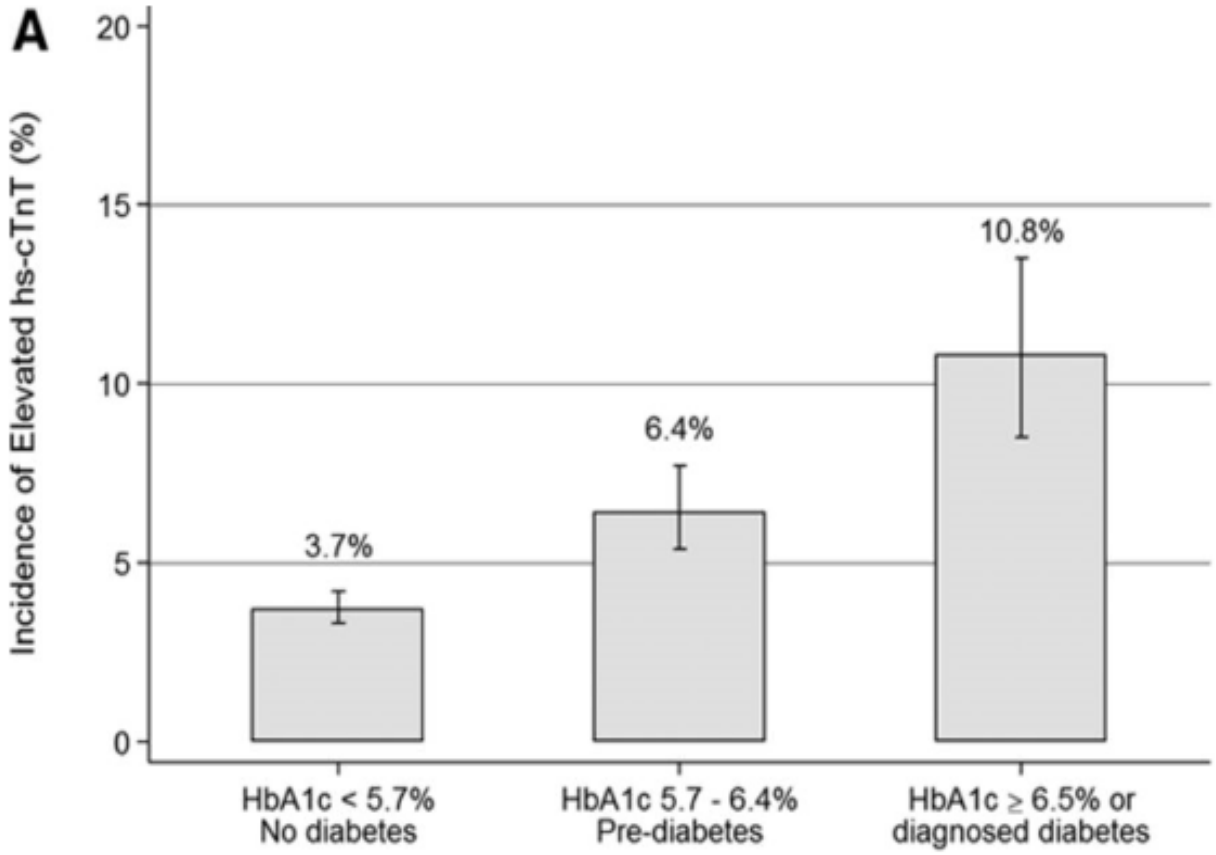
List expanded FDA indications of SGLT-2 inhibitors.

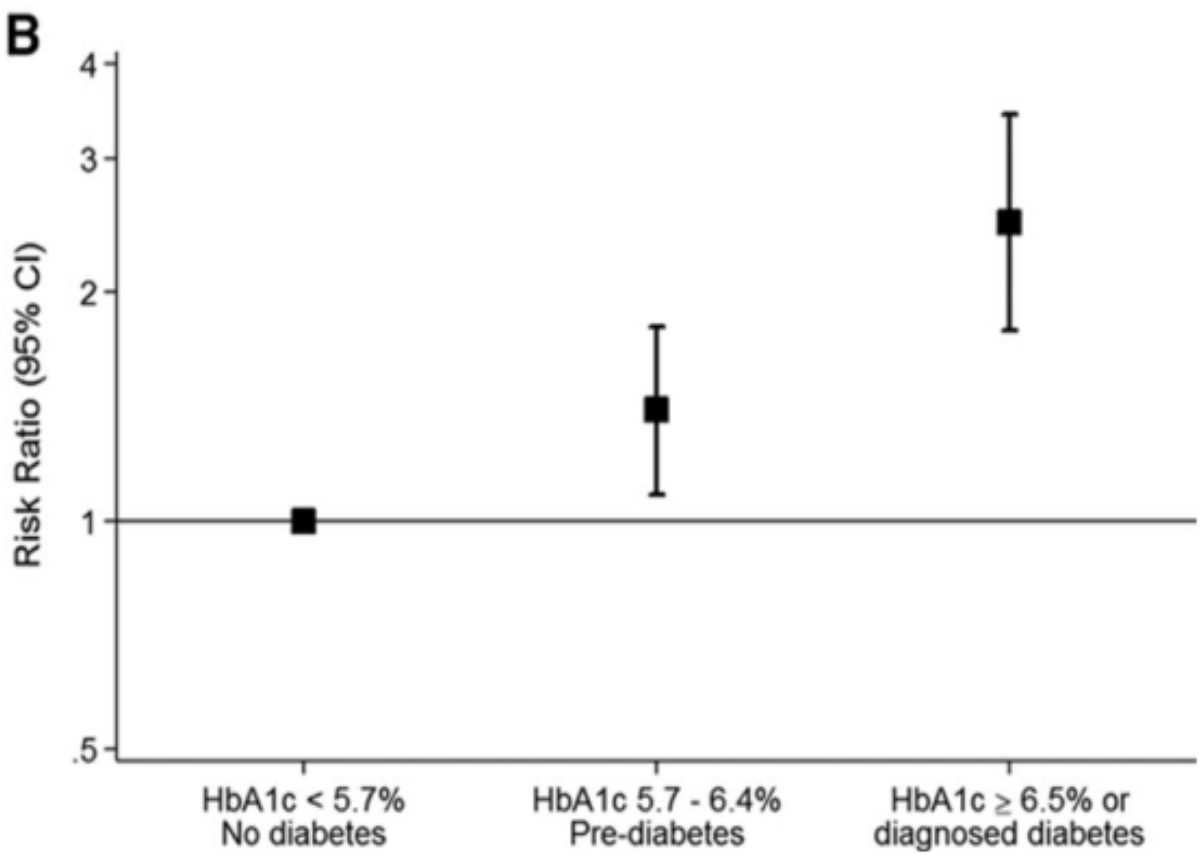
Describe adverse events and safety considerations of SGLT-2 inhibitors.

Epidemiology

- Patients with diabetes mellitus (DM) are at greater than twice the risk for developing heart failure (HF)
- DM increases the risk of HF up to 2-fold in men and 5-fold in women
- 44% of those hospitalized with HF have type 2 diabetes (T2DM)
- DM is associated with an increased risk of death and rehospitalization vs. nondiabetics with HF
- Higher hemoglobin A1c (HbA_{1c}) levels are associated with an increased incidence of HF

Source: Kenny HC, et al. *Circ Res*. 2019;124(1):121-141.





hs-CTnT: High-sensitivity assay for cardiac troponin T

Myocardial Damage and Diabetes

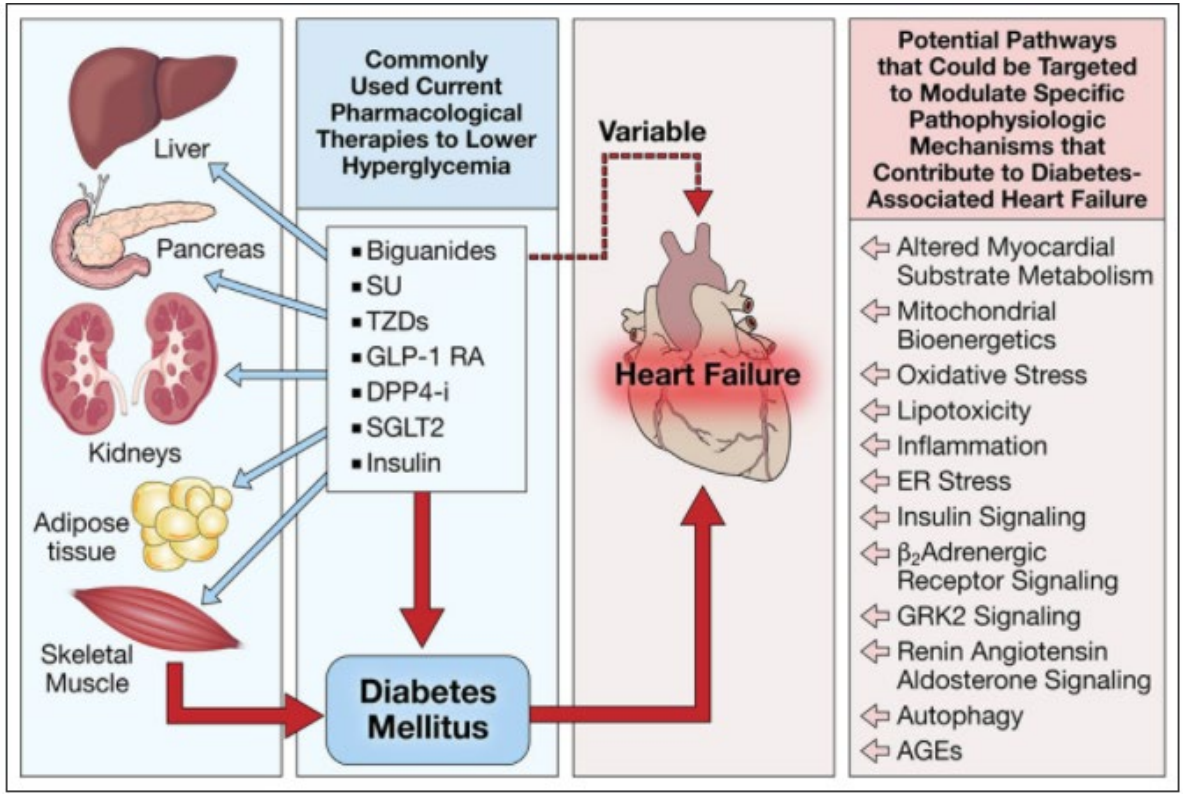
Subclinical myocardial damage increased linearly across the glycemic spectrum

- Correlates with increased risk for cardiovascular (CV) events, HF, or death

Source: Selvin E, et al. *Circulation*. 2014;130(16):1374-1382.

Diabetes & Heart Failure

- Diabetic cardiomyopathy causes increased structural/functional changes
- Tissue hypoxia ⟶ microvascular dysfunction and impaired myocardial perfusion reserve ⟶ accelerated left ventricular (LV) remodeling
- Antihyperglycemics target multiple mechanisms of cardiac injury to decrease the risk of HF



Source: Kenny HC, et al. *Circ Res*. 2019;124(1):121-141.

SGLT-2 Inhibitors

Food & Drug Administration (FDA) Approved SGLT-2 Inhibitors

Generic Name	Brand Name	FDA Approval Date	Available Doses
Canagliflozin	Invokana®	March 29, 2013	100 mg, 300 mg
Dapagliflozin	Farxiga®	January 18, 2014	5 mg, 10 mg
Empagliflozin	Jardiance®	August 01, 2014	10 mg, 25 mg
Ertugliflozin	Steglatro™	December 20, 2017	5 mg, 15 mg

Source: Hsia DS, et al. *Curr Opin Endocrinol Diabetes Obes*. 2017;24(1):73-79.

Dosing

Canagliflozin (Invokana®)	Dapagliflozin (Farxiga®)	Empagliflozin (Jardiance®)	Ertugliflozin (Steglatro™)
• 100-300 mg once daily • eGFR 30-60: 100 mg once daily • eGFR <30: Initiation not recommended • ESRD, HD: Contraindicated	• 5-10mg once daily • eGFR 30-45: Initiation not recommended • eGFR <30: Contraindicated • ESRD, HD: Contraindicated	• 10-25 mg once daily • eGFR 30-45: Initiation not recommended • eGFR <30: Contraindicated • ESRD, HD: Contraindicated	• 5-15 mg once daily • eGFR 30-60: Initiation not recommended • eGFR <30: Contraindicated • ESRD, HD: Contraindicated

eGFR: Estimated glomerular filtration rate; ESRD: End stage renal disease; HD: Hemodialysis
eGFR expressed in mL/minute/1.73 m^2

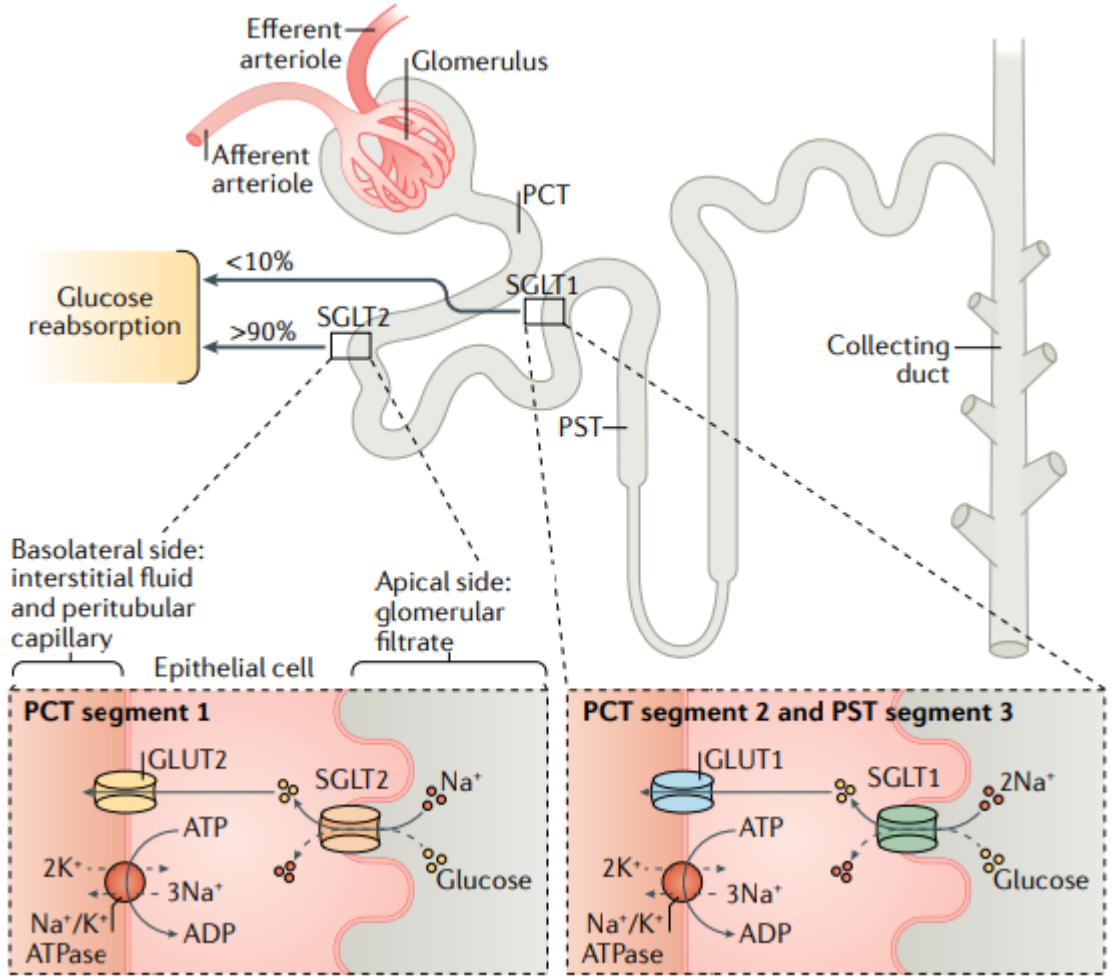
Sources: Invokana (canagliflozin) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals; July 2013
Farxiga (dapagliflozin) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; August 2014
Jardiance (empagliflozin) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; December 2016
Steglatro (ertugliflozin) [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; December 2017

SGLT Proteins

- Six isoforms in humans
- Mediate sodium (Na^+) and glucose transport across cell membranes
  - Cotransport driven by Na^+/K^+-ATPase to facilitate glucose uptake against intracellular gradient
  - Glucose exits into interstitial fluid and peritubular capillary through facilitative glucose transporter 1 (GLUT1 and glucose transporter 2 (GLUT2))

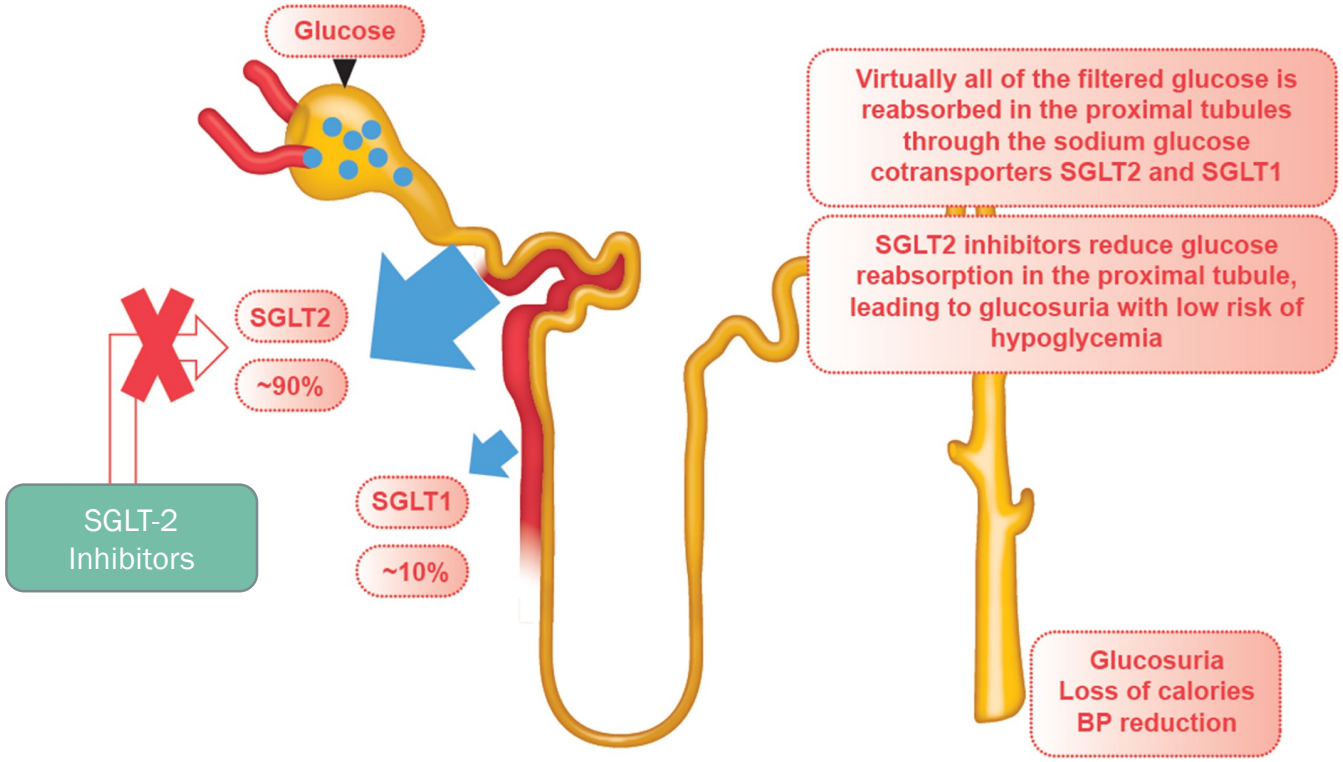
SGLT-1
- Small intestines and proximal tubules of kidneys
- Responsible for <10% of filtered glucose reabsorption

SGLT-2
- Proximal convoluted tubule (segment 1) of the kidneys
- Responsible for 90% of filtered glucose reabsorption



Sources: Hsia DS, et al. *Curr Opin Endocrinol Diabetes Obes*. 2017;24(1):73-79.
Poulsen SB, et al. *Curr Opin Nephrol Hypertens*. 2015;24(5):463-469.

Mechanism of SGLT-2 Inhibitors



- Normal renal threshold for reabsorption of glucose (RT_G) is equivalent to a glucose concentration of 180 mg/dL
  - RT_G is increased in T2DM → SGLT-2 expression is upregulated → maladaptive response
- **SGLT-2 Inhibitors**
  - Promote renal excretion of glucose
  - Reduce RT_G to as low as 40-120 mg/dL

Sources: Hsia DS, et al. *Curr Opin Endocrinol Diabetes Obes*. 2017;24(1):73-79.
Butler J,et al. *Eur J Heart Fail*. 2017;19(11):1390-1400.

Administration & Storage

Medication	Oral Administration	Storage/Stability
Canagliflozin (Invokana®)	Before the first meal of the day with or without food	25°C (77°F) Excursions permitted between 15-30°C (59-86°F)
Dapagliflozin (Farxiga®)	In the morning with or without food	20-25°C (68-77°F) Excursions permitted between 15-30°C (59-86°F)
Empagliflozin (Jardiance®)	In the morning with or without food	25°C (77°F) Excursions permitted between 15-30°C (59-86°F)
Ertugliflozin (Steglatro™)	In the morning without regards to meals	20-25°C (68-77°F) Excursions permitted between 15-30°C (59-86°F). Protect from moisture.

Sources: Invokana (canagliflozin) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals; July 2013
Farxiga (dapagliflozin) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; August 2014
Jardiance (empagliflozin) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; December 2016
Steglatro (ertugliflozin) [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; December 2017

Pharmacokinetics

	Canagliflozin (Invokana®)	Dapagliflozin (Farxiga®)	Empagliflozin (Jardiance®)	Ertugliflozin (Steglatro™)
Absorption	Not affected by food	Not affected by food	Not affected by food	Not affected by food
V_d	83.5 L	118 L	73.8 L	85.5 L
Protein binding	99%	91%	86.2%	93.6%
Metabolism	*O*-glucuronidation by UGT1A9 and UGT2B4 to two inactive metabolites	Mediated by UGT1A9 to an inactive metabolite (dapagliflozin 3-O-glucuronide)	Glucuronidation by UGT2B7, UGT1A3, UGT1A8, and UGT1A9 to minor metabolites	UGT1A9 and UGT2B7-mediated O-glucuronidation to inactive metabolites
Half-life elimination	100mg: 10.6 hours 300mg: 13.1 hours	~12.9 hours	12.4 hours	16.6 hours
Time to peak	1-2 hours	2 hours	1.5 hours	1-2 hours
Excretion	Urine: ~33% Feces: 41.5%	Urine: 75% Feces: 21%	Urine: 54.4% Feces: 41.2%	Urine: 50.2% Feces: 40.9%

V_d:Volume of distribution; UGT: UDP-Glucuronosyltransferase

Sources: Invokana (canagliflozin) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals; July 2013
Farxiga (dapagliflozin) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; August 2014
Jardiance (empagliflozin) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; December 2016
Steglatro (ertugliflozin) [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; December 2017

Assessment Question #1

A patient with heart failure with a reduced ejection fraction and type 2 diabetes is being prescribed dapagliflozin (Farxiga®). What would be the most appropriate dose and frequency?

a. 10mg by mouth once daily
b. 100mg by mouth once daily
c. 25mg by mouth once daily
d. 300mg by mouth once daily

Assessment Question #1 Answer

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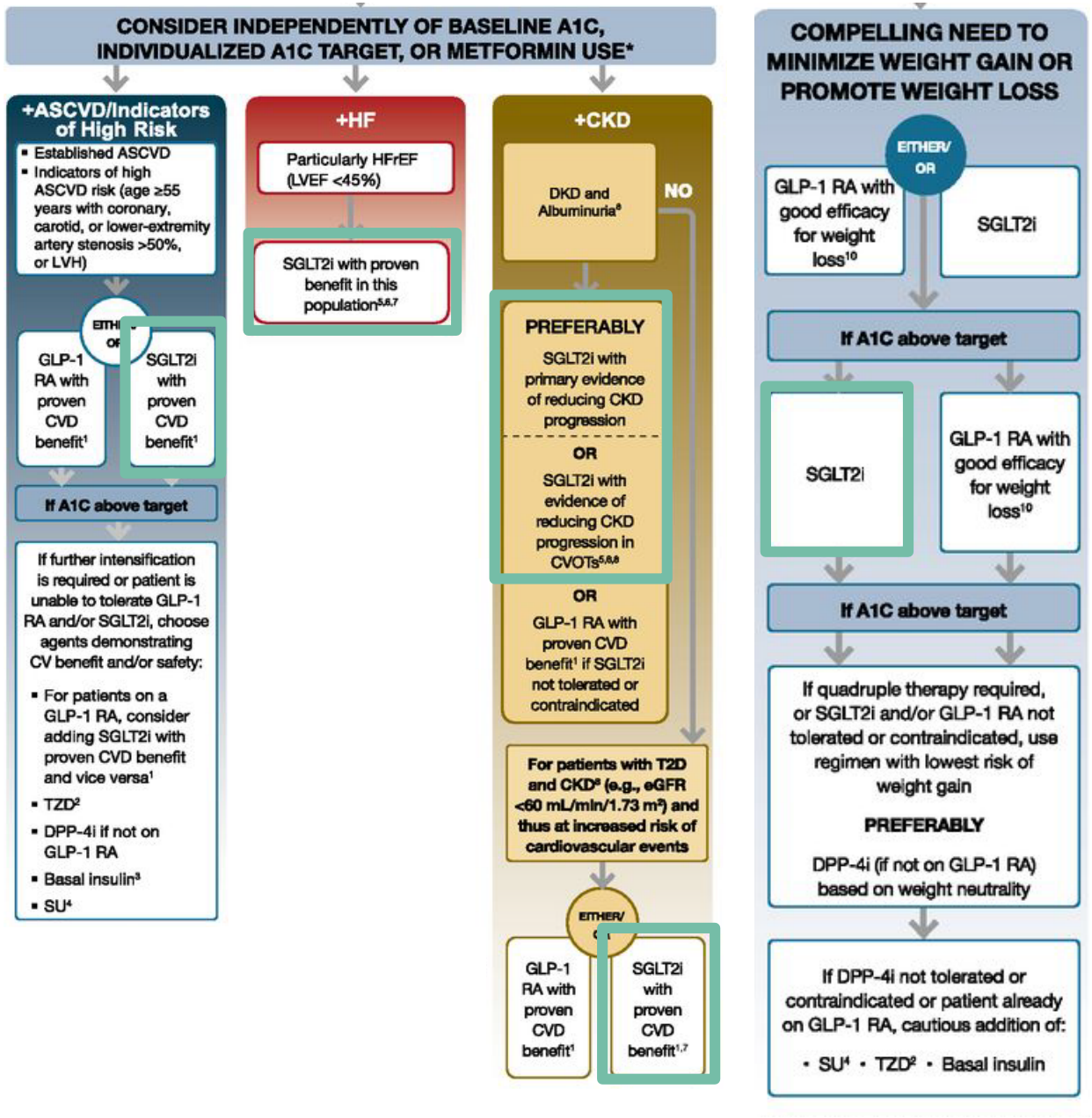
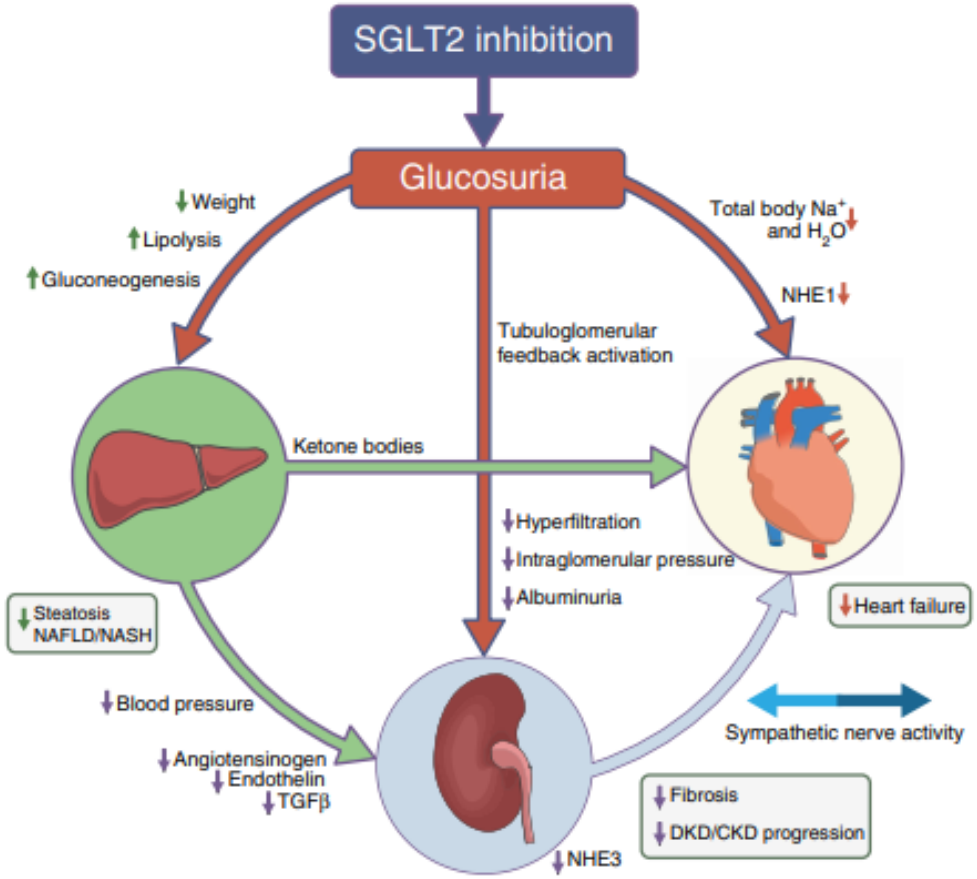


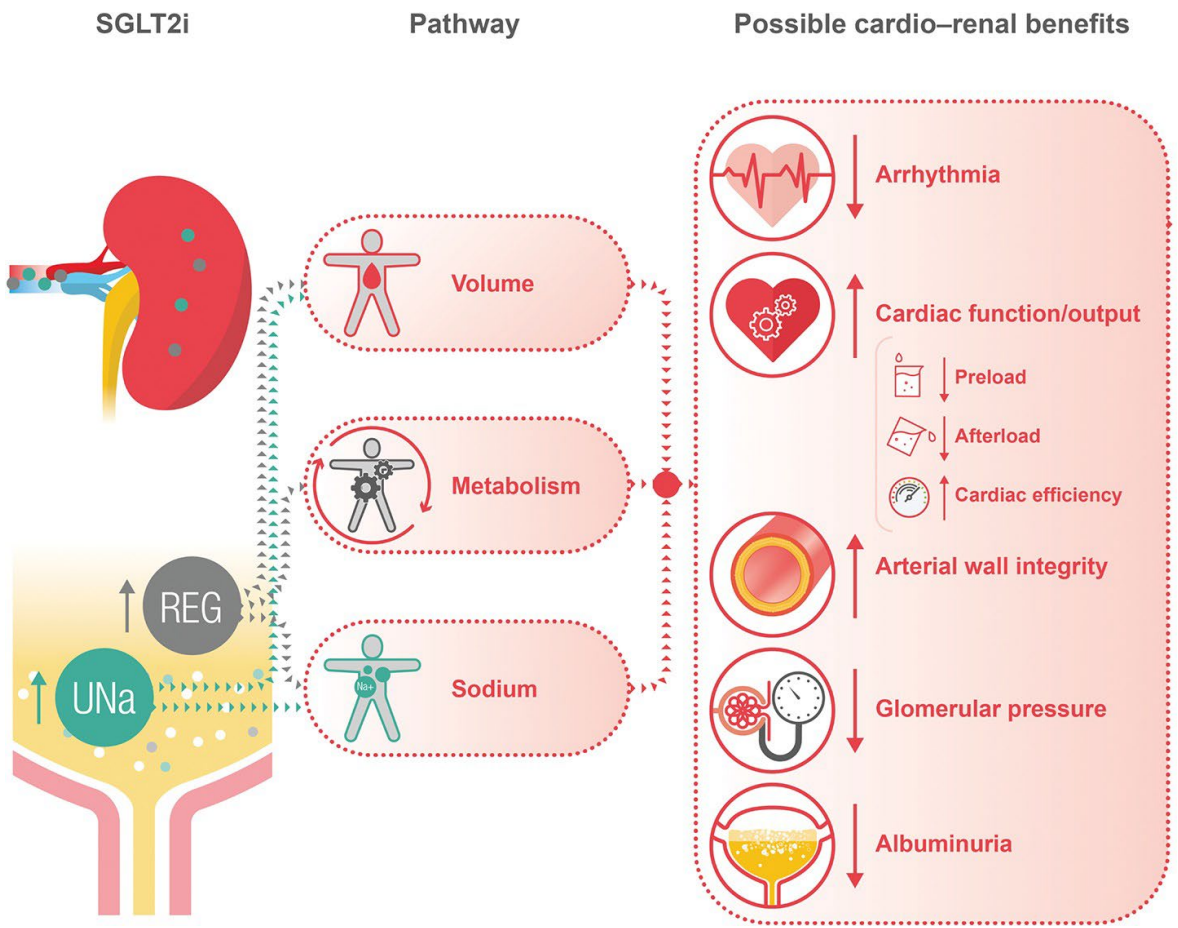
Source: American Diabetes Association. *Diabetes Care*. 2021;44(Suppl 1):S111-S124.

American Diabetes Association (ADA) 2021 Guidelines: Place in Therapy

- Recommended in T2DM with
  - Established atherosclerotic cardiovascular disease (ASCVD)
  - Diabetic kidney disease
  - Multiple ASCVD risk factors
    - Reduce the risk of major adverse cardiovascular events (MACE) and HF hospitalizations
- Dedicated decision pathway for HF

Proposed Mechanisms in Heart Failure





SGLT-2 inhibitors target multiple mechanisms on different organ systems

Sources: Wanner, C., et al. *Diabetologia* 61, 2134–2139 (2018).
Butler J, et al. *Eur J Heart Fail*. 2017;19(11):1390-1400.

Diuresis & Natriuresis

HF is associated with fluid accumulation leading to peripheral/pulmonary edema

T2DM patients have elevated skin Na^+ levels

- Predictor of LV hypertrophy in patients with chronic kidney disease (CKD)

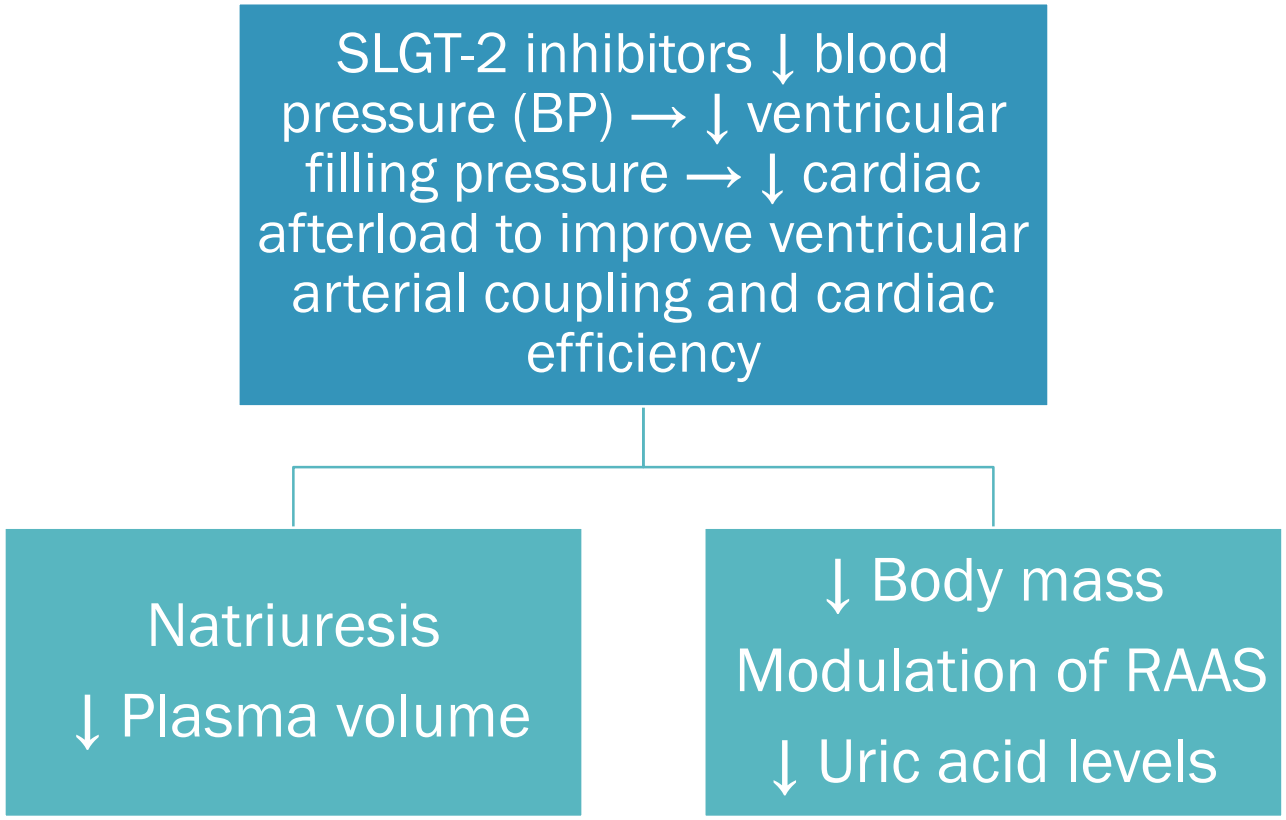
SGLT-2 inhibitors: coupled decrease of Na^+ and glucose reabsorption → sustained osmotic diuresis → glycosuria and natriuresis

↓ preload
↓ extracellular volume
↓ congestion without affecting blood volume

↓ vascular wall stress
↓ plasma volume → ↓ myocardial stretch
↓ Na^+ content

Sources: Cowie MR, et al. *Nat Rev Cardiol*. 2020;17(12):761-772.
Verma S, et al. *Am J Cardiol*. 2019;124 Suppl 1:S36-S44.

Reduction in Blood Pressure



RAAS: Renin-angiotensin-aldosterone system

Reduction of 4 mmHg in systolic blood pressure (SBP) and 2 mmHg in diastolic blood pressure (DBP)

Without concomitant tachycardia or symptoms of syncope in most cases

Sources: Cowie MR, et al. *Nat Rev Cardiol*. 2020;17(12):761-772.
Baker WL, et al. *J Am Soc Hypertens* 2014;**8**:262–275.e9.
Verma S, et al. *Am J Cardiol*. 2019;124 Suppl 1:S36-S44.

Decreased Arterial Stiffness

Arterial stiffness is associated with hypertension (HTN), obesity, and worsening HF

- Parameters of arterial stiffness (e.g. central pulse pressure) are associated with an increased risk of cardiovascular disease (CVD)

SGLT-2 inhibitors exert beneficial effects on central SBP and central pulse pressure

↓ afterload and ↑ arterial compliance and smooth muscle relaxation

- Due to negative Na^+ balance caused by osmotic diuresis

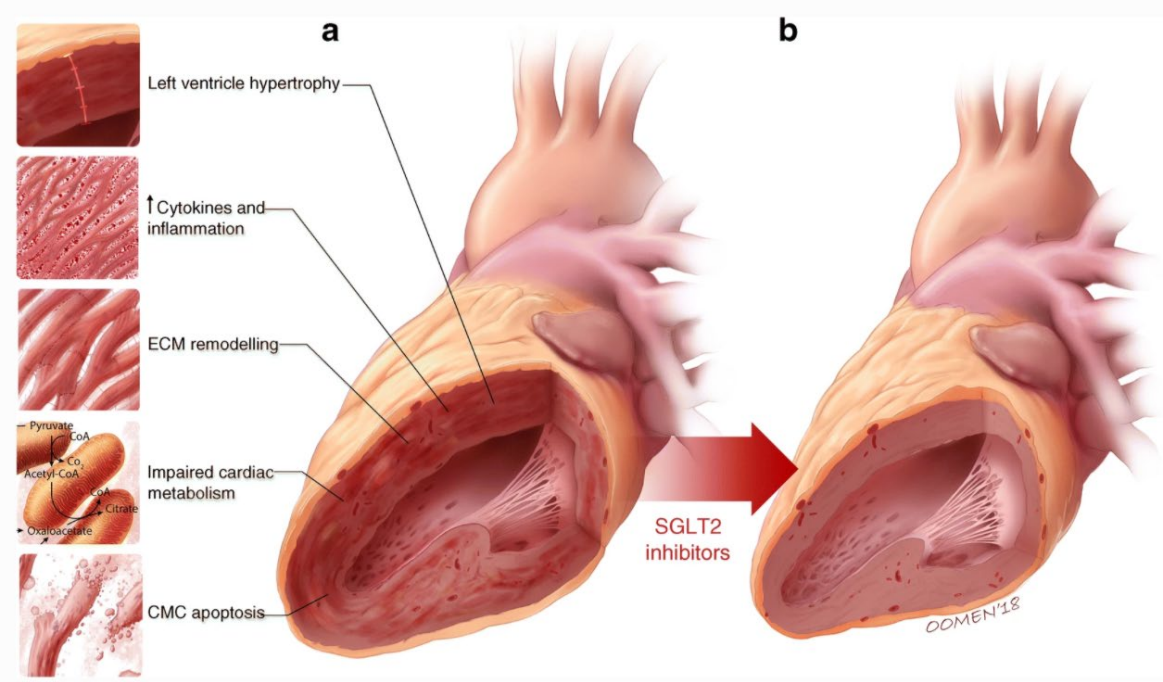
Source: Lopaschuk GD, et al. *JACC Basic Transl Sci*. 2020;5(6):632-644.

Prevention of Cardiac Remodeling

Hypertrophy, inflammation, extracellular matrix production, and cardiomyocyte death contribute to HF

SGLT-2 inhibitors

- Attenuate extracellular matrix remodeling
- Suppress expression of profibrotic markers*
- ↓ LV mass index and improve diastolic function
- ↓ Cardiac fibrosis
- ↓ LV wall stress



*Protype I collagen, alpha-smooth muscle actin, matrix metalloproteinase, and growth factor

Sources: Verma S, et al. *Am J Cardiol*. 2019;124 Suppl 1:S36-S44.
Verma S, et al. *Diabetologia*. 2018;61(10):2108-2117.

Improve Cardiac Efficiency

T2DM with a compromised heart: impaired fatty acid and glucose oxidation and impaired glucose uptake

Cardiac myocytes ↑ glucose uptake beyond oxidative capacity → impairment in cardiac function

Rely on ketone bodies and branched-chain amino acids as energy sources

SGLT-2 inhibitors ↑ production of ketone bodies → improve adenosine triphosphate (ATP) production from ketone body oxidation

Changes fuel supply from fatty acids and glucose to ketones

- Improve renal and myocardial metabolic efficiency
- Additional energy source in order to sustain contractile function

Sources: Butler J, et al. *Eur J Heart Fail*. 2017;19(11):1390-1400.
Lopaschuk GD, et al. *JACC Basic Transl Sci*. 2020;5(6):632-644.
Verma S, et al. *Am J Cardiol*. 2019;124 Suppl 1:S36-S44.

Maintenance of Kidney Function

T2DM

↑ glucose/Na^+ reabsorption → ↓ Na^+ delivery to distal tubule → afferent arteriole vasodilation → ↑GFR

Chronic hyperfiltration → nephron loss

Heart Failure

Associated with a decline in renal function

Albuminuria serves as marker of progression of kidney disease and vascular resistance

SGLT-2 inhibitors

↑ Na^+ delivery to macula densa → restore adenosine-mediated vasoconstriction of afferent arterioles → ↓ intraglomerular pressure

↓ urinary albumin excretion

Source: Wanner, C., et al. *Diabetologia* 61, 2134–2139 (2018).
Butler J,et al. *Eur J Heart Fail*. 2017;19(11):1390-1400.

Sodium-Hydrogen Exchange Inhibition

Upregulated sodium-hydrogen exchanger (NHE) activity in HF

- Associated with ↑ cytosolic Na^+ and calcium (Ca^{2+}) in cardiomyocytes ⟶ myocyte injury

SLGT-2 inhibitors inhibit NHE1 in the myocardium and NHE3 in the kidney

- ↓ Cardiomyocyte injury, fibrosis, remodeling, and hypertrophy
- ↓ Intracellular Ca^{2+}, ↑mitochondrial Ca^{2+} concentration in myocytes
- Downregulation of NHE3 in kidney ⟶ restoration of Na^+ homeostasis

Sources: Cowie MR, et al. *Nat Rev Cardiol*. 2020;17(12):761-772
Butler J, et al. *Eur J Heart Fail*. 2017;19(11):1390-1400.

Increase Hematocrit & Erythropoietin

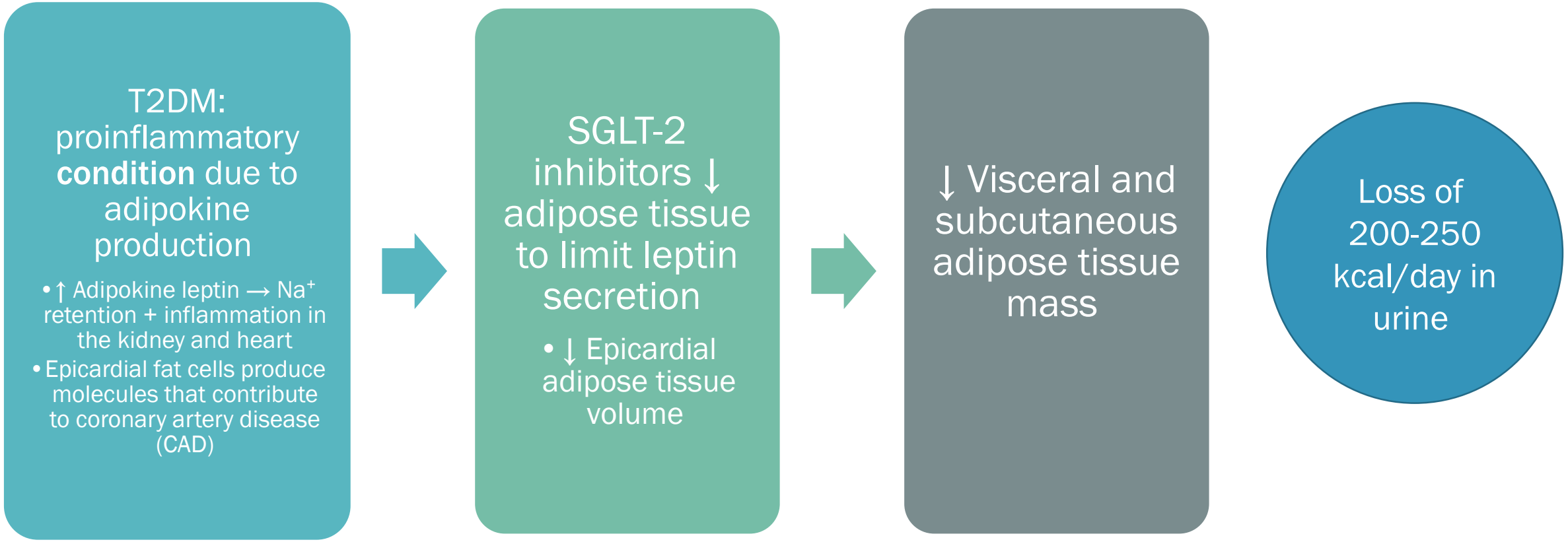
An increase in hematocrit (Hct), hemoglobin (Hgb), or albumin levels is associated with a reduced risk of CV death

SLGT-2 inhibitors ↓ plasma volume ⟶ hemoconcentration

↓ metabolic stress in proximal tubule ⟶ ↓ tubulointerstitial hypoxia ⟶ may account for stimulation of erythropoiesis	↑ erythropoietin (EPO) ⟶ improves cardiomyocyte mitochondrial function and enhances oxygen delivery to myocardial tissue

Sources: Lopaschuk GD, et al. *JACC Basic Transl Sci*. 2020;5(6):632-644.
Butler J, et al. *Eur J Heart Fail*. 2017;19(11):1390-1400.
Verma S, et al. *Am J Cardiol*. 2019;124 Suppl 1:S36-S44.

Reduction in Body Mass



Sources: Verma S, et al. *Am J Cardiol*. 2019;124 Suppl 1:S36-S44.
Butler J, et al. *Eur J Heart Fail*. 2017;19(11):1390-1400.

Other Proposed Mechanisms

- Autophagy and lysosomal degradation
- Prevention of ischemia/reperfusion injury
- Reduction in uric acid
- Prevention of increase in N-terminal pro b-type natriuretic peptide (NT-pro-BNP)
- Reduction in inflammation
- Increase vascular repair

Sources: Cowie MR, et al. *Nat Rev Cardiol*. 2020;17(12):761-772.
Verma S, et al. *Am J Cardiol*. 2019;124 Suppl 1:S36-S44.
Lopaschuk GD, et al. *JACC Basic Transl Sci*. 2020;5(6):632-644.

Assessment Question #2

Which of the following is **NOT** a proposed mechanism of action employed by SGLT-2 inhibitors in order to produce cardiovascular benefit?

a. Blood pressure lowering
b. Diuresis/Natriuresis
c. Inhibition of gastric emptying
d. Reduction of body mass

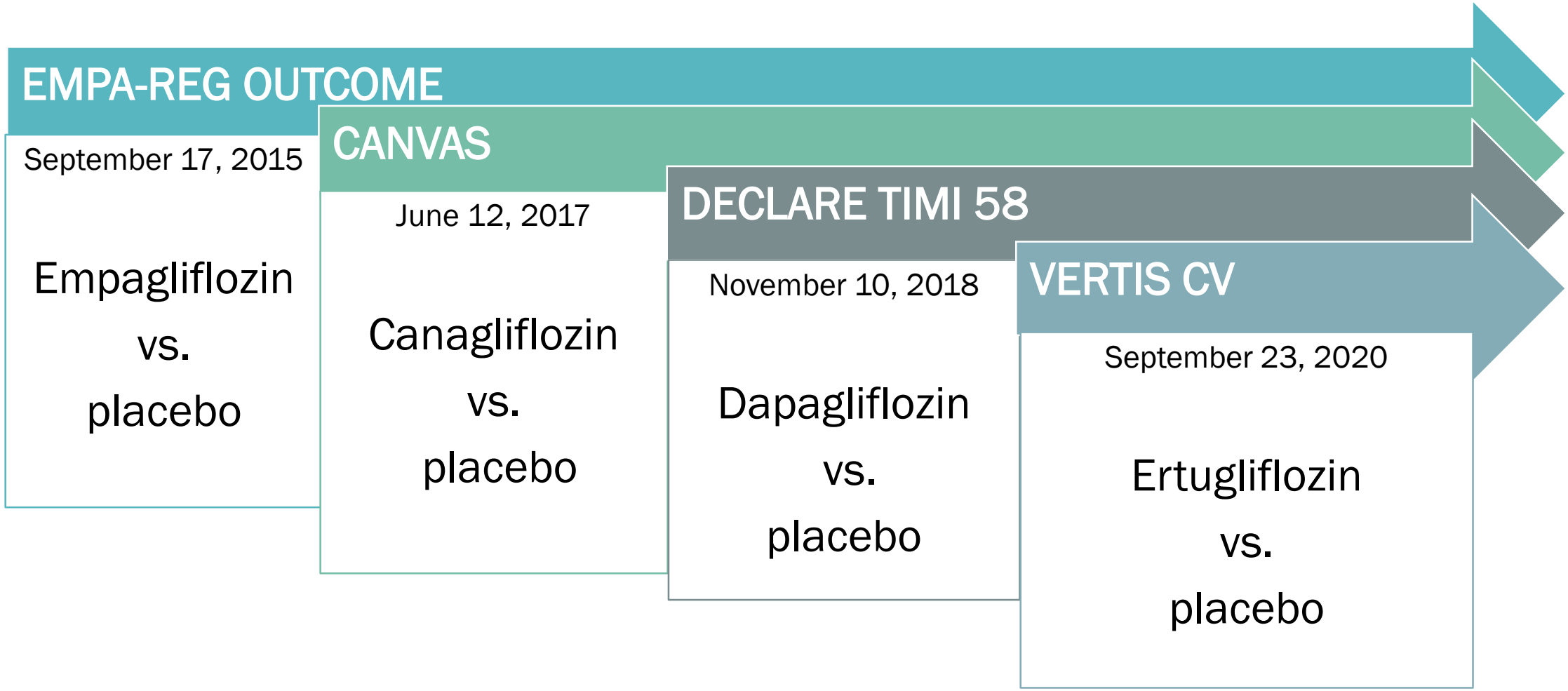
Assessment Question #2 Answer

Which of the following is **NOT** a proposed mechanism of action employed by SGLT-2 inhibitors in order to produce cardiovascular benefit?

a. Blood pressure lowering
b. Diuresis/Natriuresis
c. **Inhibition of gastric emptying**
d. Reduction of body mass

Review of the Literature

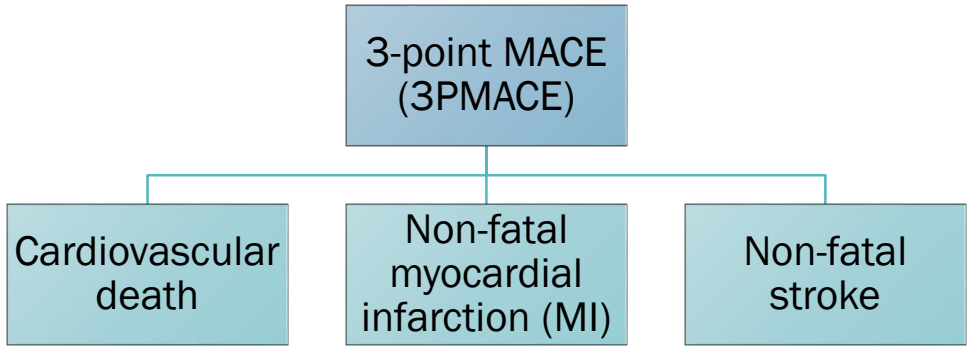
Timeline of Cardiovascular Outcomes Trials



Sources: McGuire DK, et al. *JAMA Cardiol*. 2021;6(2):148-158.
Lytvyn Y, et al. *Circulation*. 2017;136(17):1643-1658.

Trials on Cardiovascular Efficacy

- Phase 3, double-blind, placebo-controlled randomized control trials (RCTs) to assess cardiovascular safety
- Designed to demonstrate non-inferiority for MACE vs. standard antihyperglycemic therapy



- Superiority was secondary outcome

Sources: Cowie MR, et al. *Nat Rev Cardiol*. 2020;17(12):761-772.

EMPA-REG OUTCOME

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes	
Arms	Empagliflozin 10 mg or 25 mg daily vs. placebo
Population (n)	7,020 patients with T2DM and established CVD (99% at baseline)
Median Observation Time	3.1 years
Primary Outcome	**3PMACE (HR 0.86, 95% CI 0.74–0.99); 14% reduction** • CV death (HR 0.62, 95% CI 0.49–0.77) • Non-fatal MI (HR 0.87, 95% CI 0.70–1.09) • Non-fatal stroke (HR 1.18, 95% CI 0.89–1.56)
Secondary Outcomes	• **All cause mortality (HR 0.68, 95% CI 0.57-0.82); 32% reduction** • **Hospitalization for HF (HR 0.65, 95% CI 0.50–0.85); 35% reduction**

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

CANVAS

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes	
Arms	Canagliflozin 100 mg or 300 mg daily vs. placebo
Population (n)	10,142 patients with T2DM and established CVD (66% at baseline) or ≥2 CV risk factors
Median Observation Time	3.6 years
Primary Outcome	**3PMACE (HR 0.86, 95% CI 0.75-0.97); 14% reduction** • CV death (HR 0.87, 95% CI 0.72-1.06) • Non-fatal MI (HR 0.89, 95% CI 0.73-1.09) • Non-fatal stroke (HR 0.87, 95% CI 0.69-1.09)
Secondary Outcomes	• **Hospitalization for HF (HR 0.67, 95% CI 0.52–0.87); 33% reduction** • **CV death or hospitalization for HF (HR 0.78, 95% CI 0.67-0.91); 22% reduction** • Progression of albuminuria (HR 0.73, 95% CI 0.67-0.79); 27% reduction • **Risk of amputations with canagliflozin (HR 1.97, 95% CI 1.41-2.75)**

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

DECLARE-TIMI 58

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes	
Arms	Dapagliflozin 10 mg daily vs. placebo
Population (n)	17,160 patients with T2DM and established CVD (41% at baseline) or CV risk factors
Median Observation Time	4.2 years
Primary Outcome	3PMACE (HR 0.93, 95% CI 0.84–1.03) **CV death or hospitalization for HF (HR 0.83, 95% CI 0.73-0.95); 17% reduction** • CV death (HR 0.98, 95% CI 0.82-1.17) • Non-fatal MI (HR 0.89, 95% CI 0.77-1.01) • Non-fatal stroke (HR 1.01, 95% CI 0.84-1.21)
Secondary Outcomes	• **Hospitalization for HF (HR 0.73, 95% CI 0.61-0.88); 27% reduction** • **Renal composite outcome (sustained decrease of ≥40 in eGFR to < 60 ml/min/1.73m^2, new ESRD, or death from renal/CV cause) (HR 0.76, 95% CI 0.67-0.87); 24% reduction**

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

VERTIS CV

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes	
Arms	Ertugliflozin 5mg or 15mg once daily vs. placebo
Population (n)	8,246 patients with T2DM and established vascular complications
Median Observation Time	3.5 years
Primary Outcome	3PMACE (HR 0.97, 95% CI 0.85-1.11) • CV death (HR 0.92, 95% CI 0.77-1.11) • Non-fatal MI (HR 1.04, 95% CI 0.86-1.27) • Non-fatal stroke (HR 1.00, 95% CI 0.76-1.32)
Secondary Outcomes	• Death from CV causes or hospitalization for HF (HR 0.88, 95% CI 0.75-1.03) • Death from renal causes, renal replacement therapy, or doubling of serum creatinine (SCr) (HR 0.81, 95% CI 0.63-1.04)

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

Summary of Cardiovascular Outcome Trials

	EMPA-REG OUTCOME	CANVAS	DECLARE- TIMI 58	VERTIS CV
Agent Studied	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin
Population	T2DM + established CVD	T2DM + established CVD or ≥ 2 CV risk factors	T2DM + established CVD or CV risk factors	T2DM + atherosclerotic CVD
Mean $HgbA_{1c}$ (%)	8.1	8.2	8.3	8.2
History of HF (%)	**10.1**	**14.4**	**10.0**	**23.7**
Key findings	↓MACE by 14% ↓HF hospitalizations by 35% ↓Death from any cause by 32%	↓MACE by 14% ↓HF hospitalizations by 33% ↑ Risk of amputations	↓CV death and HF hospitalizations by 17% ↓HF hospitalizations by 27%	Noninferior with respect to MACE

Sources: Cowie MR, et al. *Nat Rev Cardiol*. 2020;17(12):761-772.
McGuire DK, et al. *JAMA Cardiol*. 2021;6(2):148-158.

SGLT-2 Inhibitors in Heart Failure

DAPA-HF

September 19, 2019

Dapagliflozin (Farxiga®) vs. placebo in patients with HFrEF

EMPEROR-Reduced

August 28, 2020

Empagliflozin (Jardiance®) vs. placebo in patients with HFrEF

DAPA-HF

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction	
Arms	Dapagliflozin 10mg once daily vs. placebo (in addition to optimal medical therapy)
Population (n)	4,744 patients with heart failure with reduced ejection fraction (HFrEF) in New York Heart Association (NYHA) class II, III or IV • 45% with T2DM, 55% without T2DM
Median Observation Time	1.5 years
Primary Outcome	**Composite of worsening heart failure (unplanned hospitalization or urgent visit with intravenous therapy for HF) or death from CV causes (HR 0.74, 95% CI 0.65-0.98); 26% reduction** • CV death (HR 0.82, 95% CI 0.69-0.98) • Hospitalization or urgent visit for HF (HR 0.70, 95% CI 0.59-0.83)
Secondary Outcomes	• **CV death or hospitalizations for HF (HHF) (HR 0.75, 95% CI 0.65–0.85); 25% reduction**

Source: McMurray JJV, et al. *N Engl J Med*. 2019;381(21):1995-2008.

Expanded FDA Indication

DAPA- HF Trial

Farxiga® (dapagliflozin)

oral tablets granted expanded FDA indication for adults with HFrEF on May 6, 2020

First drug in its class to be approved to treat adults with NYHA's functional class II-IV HFrEF

Source: *FDA approves new treatment for a type of heart failure*; 2020. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-type-heart-failure . Accessed March 13, 2021.

EMPEROR-Reduced

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure	
Arms	Empagliflozin 10mg once daily vs. placebo (in addition to optimal medical therapy
Population (n)	3,730 patients with HFrEF (EF < 40%), New York Heart Association (NYHA) class II, III or IV • 49.8% with T2DM, 50.2% without T2DM
Median Observation Time	1.3 years
Primary Outcome	**CV death or HHF (HR 0.75, 95% CI 0.65-0.86); 25% reduction** • CV death (HR 0.92, 95% CI 0.75–1.12) • Hospitalization for HF (HR 0.69, 95% CI 0.59–0.81)
Secondary Outcomes	• **Total number of HHF (HR 0.70, 95% CI 0.58 to 0.85)** • **Mean slope of change in eGFR per year (Absolute Difference 1.73, 95% CI 1.10-2.37)**

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

DAPA-HF & EMPEROR-Reduced

	DAPA-HF	EMPEROR- Reduced
Agent Studied	Dapagliflozin	Empagliflozin
Inclusion Criteria	• LVEF ≤40% + NT-proBNP ≥600 (without atrial fibrillation (AF)) or ≥900 (with AF) • LVEF ≤40% + HHF in past 12 months and NT-proBNP ≥400 (without AF) or ≥900 (with AF) • eGFR ≥30	• LVEF ≤30% and NT-proBNP ≥600 without AF and ≥1200 with AF • LVEF 31%–35% and NT-proBNP ≥1000 (without AF) and ≥2000 (with AF) • LVEF 36%–40% and NT-proBNP ≥2500 (without AF) and ≥5000 (with AF) • LVEF ≤40% and HHF in past 12 months and NT-proBNP ≥600 (without AF) and ≥1200 (with AF) • eGFR ≥20
CV death or HHF	**0.75 (0.65–0.85) P<0.001: ↓ 25%**	**0.75 (0.65–0.85) P<0.001: ↓ 25%**
HHF	**0.70 (0.59–0.83): ↓ 30%**	**0.69 (0.59–0.81): ↓ 31%**
Primary outcome	↓ Risk of worsening HF or CV death with or without DM	↓ CV death or hospitalization for HF with or without DM

NT-proBNP expressed in pg/mL
eGFR expressed in mL/minute/1.73 m^2

Sources: McMurray JJV, et al. *N Engl J Med*. 2019;381(21):1995-2008.
Packer M, et al. *N Engl J Med*. 2020;383(15):1413-1424.
Zannad F, et al. *Lancet*. 2020;396(10254):819-829.

Ongoing Trials

DELIVER (National clinical trial identifier: 03619213)		
Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure)	Population: Heart failure with preserved ejection fracture (HFpEF)	Primary outcome: Time to first occurrence of any components of composite (CV death, hospitalization for HF, urgent HF visit)
EMPEROR-Preserved (National clinical trial identifier: 03057951)		
EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction	Population: Chronic HFpEF	Primary outcome: Time to first event of CV death or hospitalization for HF

Source: Cowie MR, et al. *Nat Rev Cardiol*. 2020;17(12):761-772.

Assessment Question #3

Which SGLT-2 inhibitor is FDA approved in the US for heart failure?

a. Canagliflozin
b. Empagliflozin
c. Dapagliflozin
d. Ertugliflozin

Assessment Question #3 Answer

Which SGLT-2 inhibitor is FDA approved in the US for heart failure?

a. Canagliflozin
b. Empagliflozin
c. Dapagliflozin
d. Ertugliflozin

Assessment Question #4

Which primary outcome did both EMPEROR-Reduced (empagliflozin) and DAPA-HF (dapagliflozin) share?

a. SGLT-2 inhibition reduced combined risk of cardiovascular death and hospitalization for heart failure in those with HFrEF with or without diabetes.
b. SGLT-2 inhibition was non-inferior to placebo with respect to a composite of MACE defined as death, myocardial infarction, or ischemic stroke.
c. SGLT-2 inhibition was associated with a lower risk of a composite of end-stage kidney disease (dialysis, transplantation, or sustained estimated GFR of 15 ml/min/1.73 m^2)

Assessment Question #4 Answer

Which primary outcome did both EMPEROR-Reduced (empagliflozin) and DAPA-HF (dapagliflozin) share?

a. **SGLT-2 inhibition reduced combined risk of cardiovascular death and hospitalization for heart failure in those with HFrEF with or without diabetes**
b. SGLT-2 inhibition was non-inferior to placebo with respect to a composite of MACE defined as death, myocardial infarction, or ischemic stroke
c. SGLT-2 inhibition was associated with a lower risk of a composite of end-stage kidney disease (dialysis, transplantation, or sustained estimated GFR of 15 ml/min/1.73 m^2)

Adverse Events & Safety Considerations

Genital Infections

Mechanism

- Increase glucose load in urinary tract leads to fungal growth

Prevalence

- SGLT-2 inhibitors significantly associated with:
- 5-fold increase in risk of genital mycotic infections (OR 5.06 [95% CI 3.44, 7.45])
- Small increase in urinary tract infections (UTIs) (OR 5.06 [95% CI 3.44, 7.45])

Prevention/Management

- Maintain perineal hygiene
- Treatment with antifungal therapy

Source: Hsia DS, et al. *Curr Opin Endocrinol Diabetes Obes*. 2017;24(1):73-79.
Vasilakou D, et al. *Ann Intern Med* 159:262–274

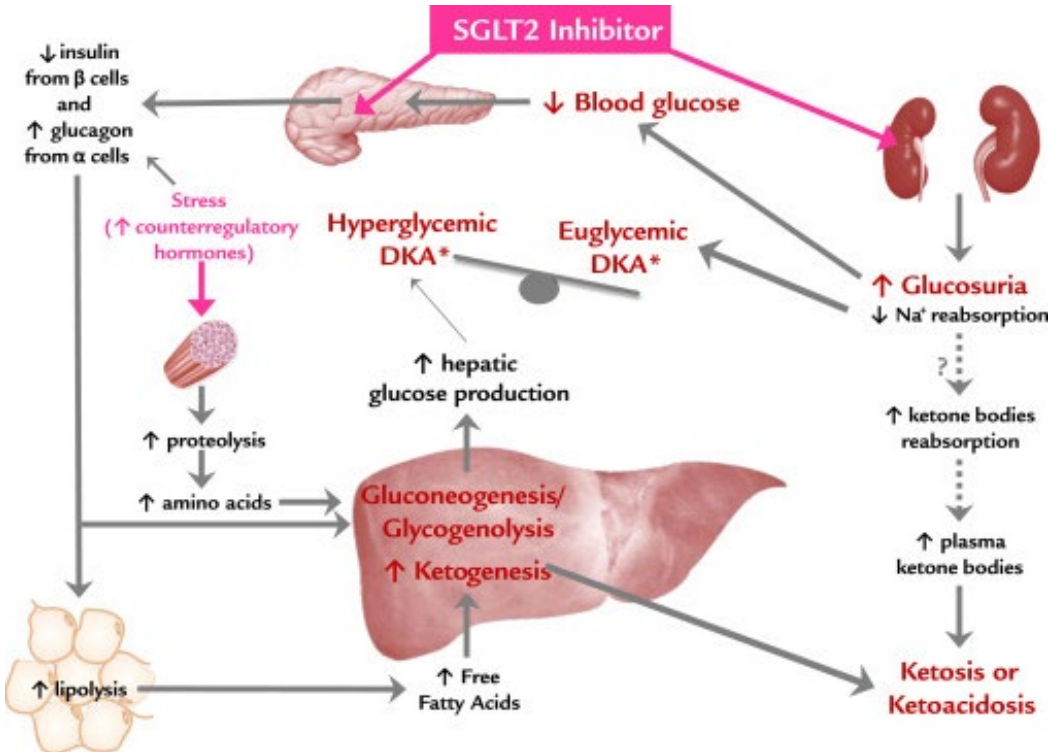
Euglycemic Ketoacidosis

Mechanism

- ↓ glucose leads to ↓ insulin → compensatory ↑ in glucagon
- Shift in hormones → released inhibition of gluconeogenesis in liver and endogenous glucose production
  - Lower insulin-to- glucagon ratio → stimulation of lipolysis → augment FFA delivery to liver → stimulation of ketogenesis

Presentation

- Nausea, vomiting, malaise
- Euglycemia (plasma glucose <250 mg/dL) due to glycosuria
- Positive serum/urine ketones
- Anion-gap metabolic acidosis



Source: Douros A, et al. *Ann Intern Med*. 2020;173(6):417-425.
Lupsa, B.C., et al. *Diabetologia* 61, 2118–2125 (2018).

Euglycemic Ketoacidosis *cont.*

Prevalence

- Population-based cohort study: SGLT-2 inhibitors were associated with almost 3-fold increased risk of DKA vs. dipeptidyl peptidase 4 (DPP-4) inhibitors (HR 2.85, 95% CI 1.99-4.08)
  - Canagliflozin associated with highest risk

Prevention

- Early recognition by both patient and clinician despite absence of hyperglycemia
- If patients have symptoms of nausea, vomiting, or malaise, serum ketones should be obtained and SGLT-2 inhibitors should be discontinued if acidosis present
- Stop SGLT-2 prior to surgery
  - Canagliflozin, dapagliflozin, and empagliflozin should be stopped ≥3 days prior to surgery; ertugliflozin should be stopped ≥4 days prior to surgery

Source: Douros A, et al. *Ann Intern Med*. 2020;173(6):417-425.
Lupsa, B.C., et al. *Diabetologia* 61, 2118–2125 (2018).

Hypotension/Volume Depletion

Mechanism

- Osmotic diuresis → volume depletion (350-450 ml/day)
- Accompanied by increased thirst, urinary frequency, and orthostatic hypotension

Risk Factors

- Age > 75 years old
- GFR < 60 mL/min/1.73m^2
- Concomitant use of other antihypertensive medications

Prevention

- Use with caution in patients taking other antihypertensive medications (loop diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers)

Source: Lupsa, B.C., et al. *Diabetologia* 61, 2118–2125 (2018).

Acute Kidney Injury

Mechanism

- Proximal tubular natriuresis on tubuloglomerular feedback → reversible intrarenal hemodynamics
- Acute decline in eGFR by 3-5 ml/min/1.73 m^2 prior to occurrence of renoprotective effects

Prevalence

- Post-marketing reports of acute kidney injury (AKI) with canagliflozin and dapagliflozin; however later findings suggest there is no evidence for increased AKI

Risk Factors

- Volume depletion
- Hypotension
- Taking other medications that affect kidneys

Prevention

- Dose adjustments and frequent monitoring in patients with impaired renal function (eGFR 45-60ml/min)

Sources: Nadkarni GN, et al. *Diabetes Care*. 2017;40(11):1479-1485.
Taylor SI, et al. *J Clin Endocrinol Metab*. 2015;100(8):2849-2852.

Limb Injury

Mechanism

- Hypothesized that ↓ plasma volume → ↓ perfusion in lower limbs

Prevalence

- Two- fold increased risk of lower limb amputations with canagliflozin vs. placebo
- Incidence of 5.9 per 1000 patient years for canagliflozin vs. 2.8 per 1000 patient years for placebo

Risk Factors

- Neuropathy
- Foot deformities or history of ulceration
- Vascular disease

Prevention

- Should be avoided in those at high risk for foot amputation
- Frequent foot exams

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

Bone Fractures

Mechanism

- Disordered calcium and phosphate homeostasis → ↑ parathyroid hormone (PTH) → ↓ 1,25-dihydroxy vitamin D levels → adversely impact bone density and metabolism
- Orthostatic hypotension leading to postural dizziness → falls

Prevalence

- Canagliflozin (OR 1.15; 95% CI 0.71-1.88), dapagliflozin (OR 0.68; 95% CI 0.37-1.25) and empagliflozin (OR 0.93; 95% CI 0.74-1.18) vs. placebo
  - Not significantly associated with an increased risk of fracture

Prevention

- Education on the prevention of falls
- Assessment of vertebral fractures and bone mineral density (BMD) measurements should be considered in patients with histories of fractures

Source: Tang HL, et al. *Diabetes Obes Metab*. 2016;18(12):1199-1206
Lupsa, B.C., et al. *Diabetologia* 61, 2118–2125 (2018).
Ye Y, et al. *Front Pharmacol*. 2019;9:1517.

Assessment Question #5

Which of the following is **NOT** an adverse event associated with SGLT-2 inhibitors?

a. Euglycemic diabetic ketoacidosis
b. Genitourinary fungal infections
c. Pancreatitis
d. Limb injury (toe, foot, lower limb amputations)

Assessment Question #5 Answer

Which of the following is **NOT** an adverse event associated with SGLT-2 inhibitors?

a. Euglycemic diabetic ketoacidosis
b. Genitourinary fungal infections
c. **Pancreatitis**
d. Limb injury (toe, foot, lower limb amputations)

Conclusion

- SGLT-2 inhibitors play a vital role in the reduction of ASCVD in patients with T2DM
- There are multiple proposed mechanisms aside from glycemic control that may be responsible for the cardiorenal benefits of SGLT-2 inhibitors
- Emerging literature shows that SGLT-2 inhibitors may have CV benefits in patients with and without T2DM
- Adverse events should be carefully monitored in patients taking SGLT-2 inhibitors

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Thank You!

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