Is this too good SGLT2 be true?

Sodium-Glucose Cotransporter 2 inhibitors in heart failure

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Speaker Disclosure

I have no financial relationships or affiliations to disclose.

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Objectives

- Describe the pathophysiology of heart failure
- Discuss the use of SGLT2 inhibitors for the management of heart failure
- Initiate an appropriate medication regimen including dosing schedule, patient counseling, and safety monitoring

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Epidemiology

- 6 million Americans have heart failure
- 800,000 annual hospital discharges
- Yearly costs related to heart failure exceeds $30 billion
- Significant ethnic disparities
    - Highest risk = Black population

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Epidemiology

- Overall 5-year survival rate = 42%
- “Sudden” death in 40% of patients
  - Serious ventricular arrhythmias
- Factors affecting prognosis:
  - Age
  - Gender
  - LVEF
  - Renal function
  - Natriuretic peptide concentrations
  - Diabetes
  - Metabolic syndrome
  - Underlying CAD
  - Blood pressure
  - Etiology
  - Drug and/or device therapy

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What is Heart Failure?

- Clinical syndrome caused by abnormal cardiac structure and/or function
- Can be caused by numerous cardiac disorders
- Principle clinical manifestations:
  - Fatigue
  - Dyspnea
  - Volume overload

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Key Terms

- Cardiac Output (CO): volume of blood ejected per unit of time
  - CO = Stroke Volume x HR
  - Normal CO at rest = 5 L/min
- Ejection Fraction (EF): measure of amount of blood pumped out of ventricle with each contraction
  - $EF = \frac{\text{Stroke Volume}}{\text{End-Diastolic Volume}}$
  - Normal EF = 50-70%

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Key Terms

- Preload: force that stretches the cardiac muscle prior to contraction

- Afterload: amount of pressure required to eject blood from the heart during ventricular contraction

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What is Heart Failure?

- Systolic dysfunction and/or diastolic dysfunction
- Classification:
  - HF with Reduced Ejection Fraction (**HFrEF**)
  - HF with Mildly Reduced Ejection Fraction (**HFmrEF**)
  - HF with Preserved Ejection Fraction (**HFpEF**)
  - HF with Improved Ejection Fraction (**HFimpEF**)

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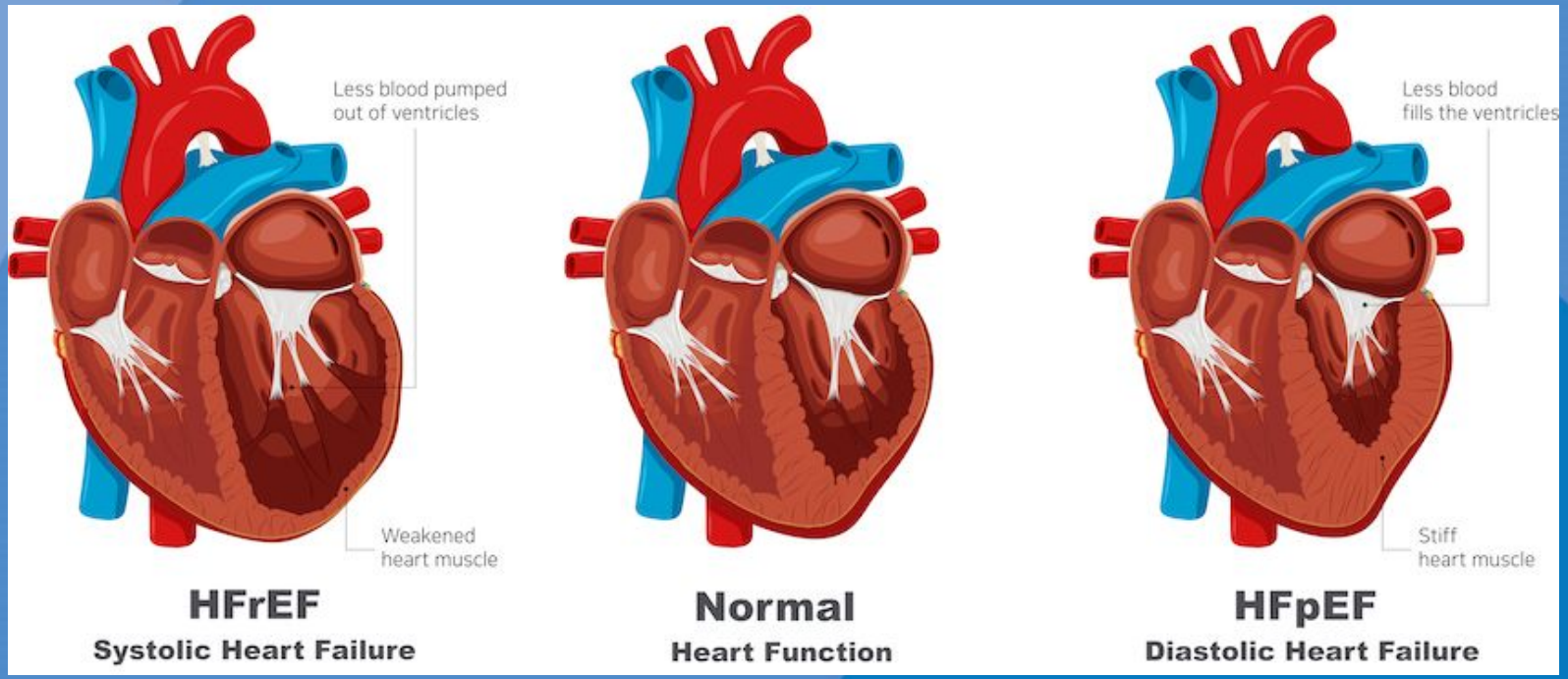
HFrEF vs. HFpEF



https://www.lexpharma.com/pipeline/sotagliflozin/about-heart-failure

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What is Heart Failure?

HFrEF	LVEF ≤ 40%
HFmrEF	LVEF 41-49%
HFpEF	LVEF ≥ 50%
HFimpEF	Baseline LVEF ≤ 40%, a ≥ 10 point increase from baseline LVEF, and a second measurement of LVEF ≥ 40%

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Common Causes - HFrEF

- Coronary artery disease
  - Myocardial infarction
  - Ischemia
- Dilated cardiomyopathies
  - Drug-induced
  - Viral infections
  - Postpartum
- Pressure overload
  - Hypertension
  - Aortic/pulmonic valvular stenosis
- Volume overload
  - Valvular regurgitation
  - Shunts
  - High-output states

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Common Causes - HFpEF

- Increased ventricular stiffness
- Ventricular hypertrophy
  - Hypertrophic cardiomyopathy
  - Hypertension
- Infiltrative myocardial diseases
  - Amyloidosis
  - Sarcoidosis
  - Endomyocardial fibrosis
- Myocardial Infarction/Ischemia
- Mitral/tricuspid valve stenosis
- Pericardial disease
  - Pericarditis
  - Pericardial tamponade

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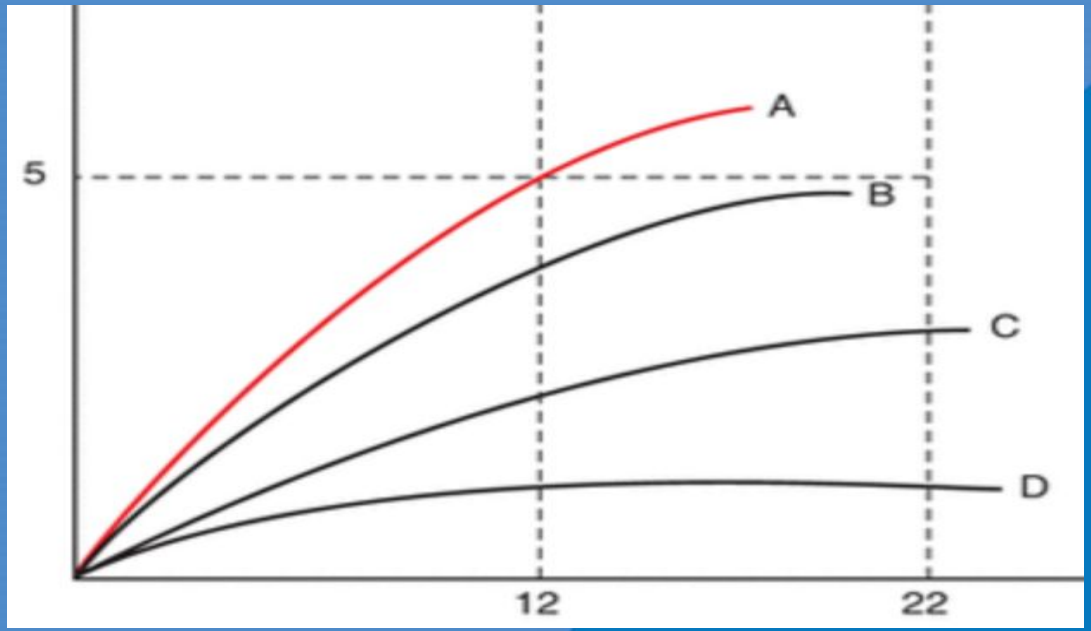
Pathophysiology

Frank-Starling Mechanism



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Pathophysiology - HF with reduced EF

- Progressive disorder
- Initiated by any event that impairs the ability of the heart to contract or relax, resulting in decreased CO
- Decreased CO results in activation of compensatory mechanisms to maintain circulation

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Pathophysiology - HF with preserved EF

- Condition in which myocardial relaxation and filling are impaired and incomplete
- Ventricle is unable to accept adequate volume, does not fill at low pressure, and/or is unable to maintain normal stroke volume

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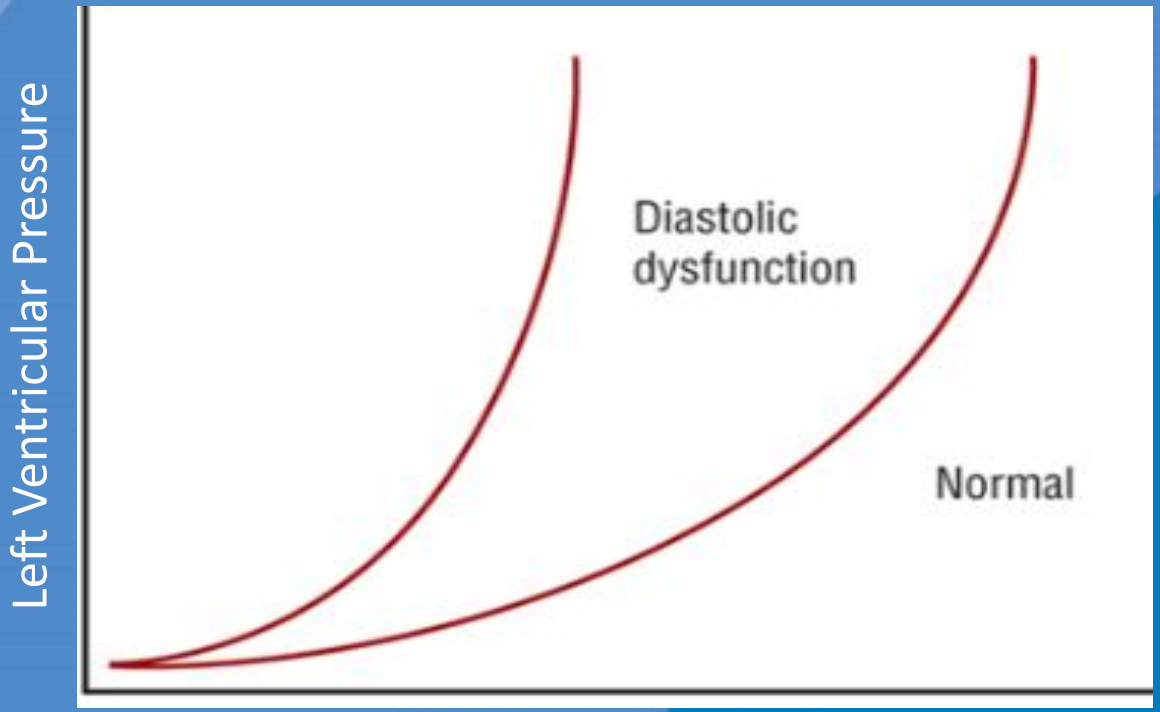
Pathophysiology - HFpEF



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Pathophysiology - Compensatory Responses

- Sodium and water retention
- Vasoconstriction
- Tachycardia and increased contractility
- Ventricular hypertrophy and remodeling

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Pathophysiology - Compensatory Responses

- Sodium and water retention
  - Benefits:
    - Increases preload
    - Optimizes SV
  - Detrimental effects:
    - Pulmonary/systemic congestion and edema
    - Increased myocardial O_2 consumption

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Pathophysiology - Compensatory Responses

- Vasoconstriction
  - Benefits:
    - Maintains BP
    - Shunts blood from non-essential organs
  - Detrimental effects:
    - Increased afterload leads to decreased SV
    - Increased myocardial O_2 consumption

Pathophysiology - Compensatory Responses

- Tachycardia and increased contractility
  - Benefits:
    - Maintains CO
  - Detrimental effects:
    - Shortened diastolic filling time
    - β1 receptor down-regulation
    - Worsening of ventricular arrhythmias
    - Increased myocardial O_2 consumption

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Pathophysiology - Compensatory Responses

- Ventricular hypertrophy and remodeling
  - Benefits:
    - Maintains CO
    - Reduces myocardial wall stress
    - Decreases myocardial O_2 consumption
  - Detrimental effects:
    - Diastolic/systolic dysfunction
    - Increased risk of myocardial ischemia/cell death

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Clinical Presentation

- Most common:
  - Dyspnea
  - Orthopnea
  - Exercise intolerance
  - Fatigue
  - Swollen ankles/extremities
  - Bendopnea

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Specific Signs for HF

- Jugular venous distention
- Cardiomegaly
- Lateral displacement of apical impulse
- Hepatojugular reflux
- S3 gallop
- Cheyne-Stokes respiration (advanced HF)

Stages of Heart Failure

Stage	Definition
A (at-risk)	At-risk for HF but no signs/symptoms and no structural, biomarker, or genetic markers
B (pre-HF)	No signs/symptoms but evidence of <u>one</u> of the following: • Structural heart disease • Abnormal cardiac function • Elevated biomarkers
C (heart failure)	Signs/symptoms caused by structural and/or cardiac abnormality
D (advanced HF)	Severe signs/symptoms at rest, recurrent hospitalizations despite GDMT, refractory or intolerant to GDMT (requires advanced therapies)

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NYHA Functional Classification

Functional Class	Physical Limitations and Symptoms
Class I	No limitations of physical activity; normal physical activity does not cause undue fatigue, dyspnea, or palpitation
Class II	Slight limitations of physical activity; normal physical activity results in fatigue, palpitation, dyspnea, or angina
Class III	Significant limitation of physical activity; less than normal activity will lead to symptoms
Class IV	Unable to carry on physical activity without discomfort; symptoms present at rest

Guideline Recommended Drug Therapies

- Loop diuretics
- ACE inhibitors
- ARBs
- ACEi/ARNi
- Beta-Blockers
- Aldosterone antagonists
- **SGLT2 Inhibitors**

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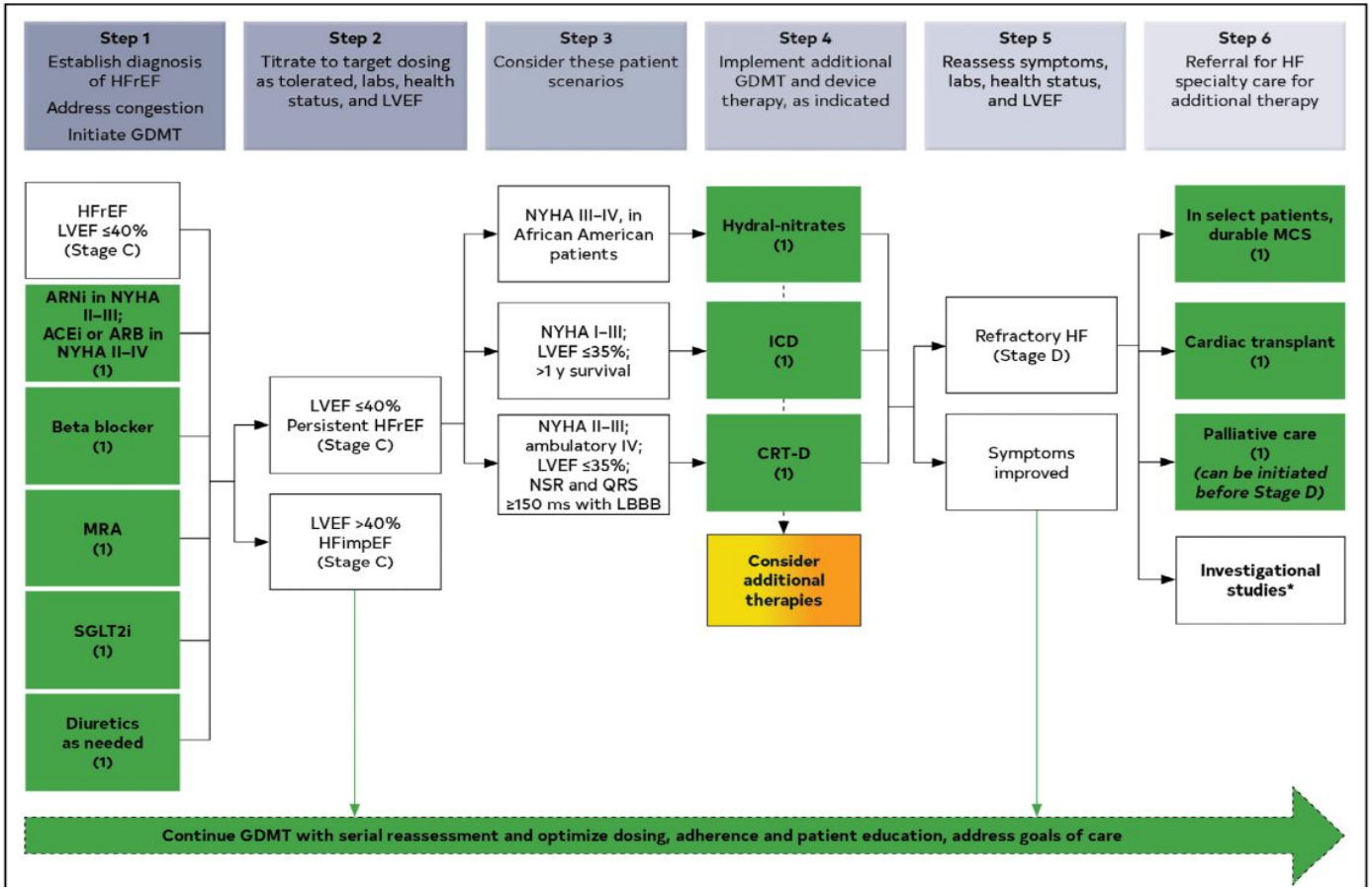
2022 ACC Recommendations:



Circulation. 2022;145(18):e895-e1032.

2022 AHA/ACC/HFSA Guidelines

- Recommendation for SGLT2 Inhibitors
  - For symptomatic chronic HFrEF, SGLT2 inhibitors are recommended to reduce HF hospitalizations and cardiovascular mortality, irrespective of the presence of T2DM (COR 1, LOE A)
- Management of Diabetes with HF
  - For patients with HF and T2DM, SGLT2 inhibitors are recommended for the management of hyperglycemia and to reduce HF-related morbidity and mortality (COR 1, LOE A)

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2022 AHA/ACC/HFSA Guidelines

- Stage A (at-risk) with DM
  - In patients with T2DM and CVD or at high CVD risk, SGLT2 inhibitors should be used to prevent hospitalizations for HF (COR 1, LOE A)
- HF with mildly reduced EF (HFmrEF)
  - For HFmrEF, SGLT2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality (COR 2a, LOE B-R)
- HF with preserved EF (HFpEF)
  - For HFpEF, SGLT2 inhibitors can be beneficial in decreasing HF hospitalizations and cardiovascular mortality (COR 2a, LOE B-R)

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Sodium-Glucose Cotransporter Type 2 Inhibitors

- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- *Sotagliflozin (Zynquista)*

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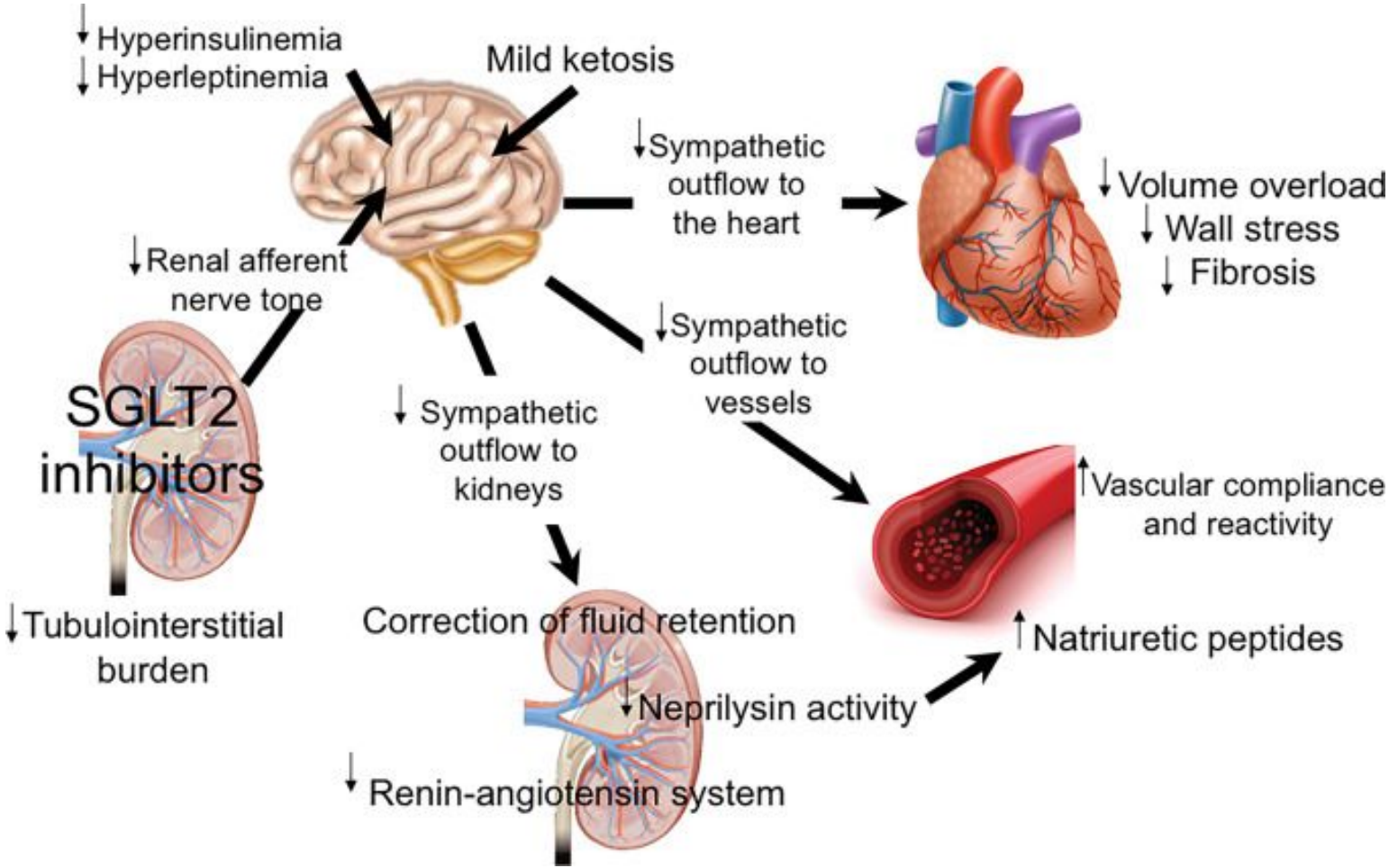

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Sodium-Glucose Cotransporter Type 2 Inhibitors

- Dapagliflozin (Farxiga)
  - SGLT2 activity only
  - **Initial/maintenance dose for HF = 10 mg daily**
  - *Type 2 diabetes, initial dose = 5 mg daily, may increase to 10 mg daily*
  - DAPA-HF trial

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Sodium-Glucose Cotransporter Type 2 Inhibitors

- DAPA-HF
  - 4744 patients with HFrEF
  - Dapagliflozin superior to placebo in preventing cardiovascular-related deaths and HF events

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Sodium-Glucose Cotransporter Type 2 Inhibitors

- Empagliflozin (Jardiance)
  - SGLT2 activity only
  - **Initial/maintenance dose for HF = 10 mg daily**
  - *Type 2 diabetes, initial dose = 10 mg daily, may increase to 25 mg daily*
  - EMPEROR-Reduced trial

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Sodium-Glucose Cotransporter Type 2 Inhibitors

- EMPEROR-Reduced
  - 3730 patients with HFrEF
  - Empagliflozin reduced the risk and total number of inpatient and outpatient worsening HF events compared to placebo

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Sodium-Glucose Cotransporter Type 2 Inhibitors

- Sotagliflozin (Zynquista)
  - Dual SGLT1 and SGLT2 activity
  - Phase 3 study: Initial dose for HF = 200 mg daily; 400 mg if tolerated
  - *Not currently FDA-approved*
  - SOLOIST-WHF trial

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Sodium-Glucose Cotransporter Type 2 Inhibitors

- SOLOIST-WHF
  - 1222 patients with T2DM recently hospitalized for HF symptoms
  - Sotagliflozin resulted in a lower number of deaths from cardiovascular causes and hospitalizations/urgent visits for HF compared to placebo

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What about Canagliflozin?

- Canagliflozin
  - CHIEF-HF trial (February 2022)
  - 476 patients with HFrEF or HFpEF
  - Participants who received canagliflozin reported significantly greater improvements in their heart failure symptoms compared to placebo

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What about Canagliflozin?

- Approved indications:
  - Adjunct to diet/exercise to improve glycemic control in adults with T2DM
  - To reduce the risk of major adverse cardiovascular events in adults with T2DM and established CVD
  - **To reduce the risk** of ERSD, doubling of serum creatinine, cardiovascular death, and **hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy** with albuminuria greater than 300 mg/day

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SGLT2 Inhibitor Safety and Monitoring

- Renal function thresholds for initiating therapy
  - Dapagliflozin - eGFR ≥ 25 mL/min/1.73m^2
  - Empagliflozin - eGFR ≥ 20 mL/min/1.73m^2
  - *If already stable on SGLT2 inhibitor, no adjustment needed for eGFR below threshold*
- Volume status - potential contribution to volume depletion (diuretics)
- Mycotic genital infections, urinary tract infections
- Fournier's gangrene
- Euglycemic diabetic ketoacidosis

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Financial Considerations of SGLT2 Inhibitors

- **Brand name only**
- Farxiga (dapagliflozin) = $21.95 per tablet
- Januvia (empagliflozin) = $22.82 per tablet

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Patient Case

- 63 yo male with established HFrEF, T2DM, HTN, HLD, and CKD presents to the cardiology office after a recent hospitalization for a HF-related exacerbation. At baseline, he has NYHA Class II symptoms and occasionally becomes lightheaded upon standing. He had 4 separate hospitalizations related to HF in the past 12 months.

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Patient Case

- Home medications:
  - Metoprolol succinate 100mg daily
  - Sacubitril/valsartan 49mg/51mg twice daily
  - Eplerenone 25mg daily
  - Aspirin 81mg daily
  - Atorvastatin 80mg daily
  - Sitagliptin/metformin 50mg/500mg twice daily

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Patient Case

- Physical examination:
  - Pulse = 69 bpm
  - BP = 95/60 mmHg
  - Lungs clear to auscultation
- Labs:
  - eGFR = 45 mL/min/1.73m^2
  - ProBNP = 252 pg/mL
  - A1C = 7.9%
- Echocardiography:
  - LVEF = 35%
  - Mildly dilated left ventricle

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Patient Case

Which of the following is the best option to reduce the patient's risk for future HF exacerbations and hospitalizations?

A. Start loop diuretic
B. Refer for left ventricular assist device implantation
C. Start SGLT2 inhibitor
D. Further evaluate for proteinuria
E. Increase current sacubitril/valsartan dose

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Patient Case

Which of the following is the best option to reduce the patient's risk for future HF exacerbations and hospitalizations?

A. Start loop diuretic

B. Refer for left ventricular assist device implantation

C. Start SGLT2 inhibitor

D. Further evaluate for proteinuria

E. Increase current sacubitril/valsartan dose

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Patient Case

Which of the following regimens is appropriate for this patient?

A. Canagliflozin 300mg twice daily

B. Empagliflozin 10mg daily

C. Dapagliflozin 300mg daily

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Patient Case

Which of the following regimens is appropriate for this patient?

A. Canagliflozin 300mg twice daily

B. Empagliflozin 10mg daily

C. Dapagliflozin 300mg daily

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