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Dapagliflozin, Sacubitril, Ivabradine: Word Scrabble?! A Closer Look at New Heart Failure Therapies

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Learning Objectives



At the end of this session, participants should be able to:

1. Recall mechanisms of action of new heart failure (HF) medications, such as SGLT2 inhibitors, sacubitril/valsartan, vericiguat and ivabradine.
2. Identify the role of these medications in conjunction with traditional HF therapies, including beta-blockers, ACE inhibitors and diuretics.
3. Recognize the clinical evidence supporting the integration of new HF agents into current treatment algorithms.

HF = Heart Failure
SGLT2 = sodium glucose
cotransporter 2
ACE = Angiotensin Conversion
Enzyme



UNDERSTANDING HEART FAILURE

Pathophysiological Approach



Understanding Heart Failure



Heart Failure: condition in which the heart is unable to meet the ongoing circulatory demands of the body's tissues and organs



HF can be an acute or insidious event



Heart Failure with reduced Ejection Fraction (HFrEF) or reduced cardiac output will be the focus of this presentation

CAD = Coronary Artery Disease

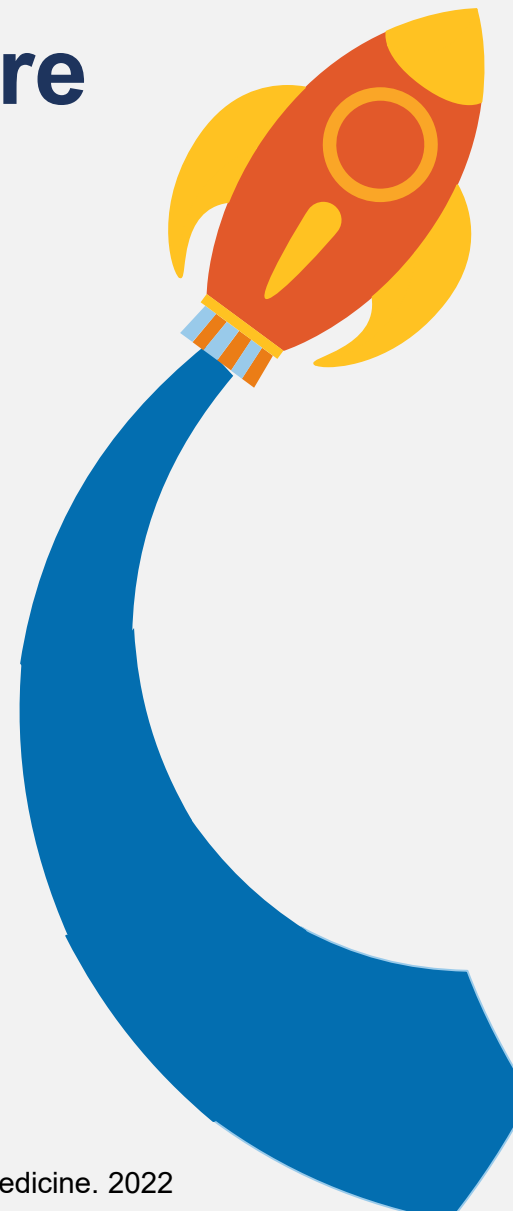
MI = Myocardial Infarction

HTN = Hypertension

COPD = Chronic Obstructive Pulmonary Disease

ETOH = Alcohol

Source: Hassenfuss G, et al. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 2022



Index Events

CAD

MI

HTN

Arrhythmias

COPD

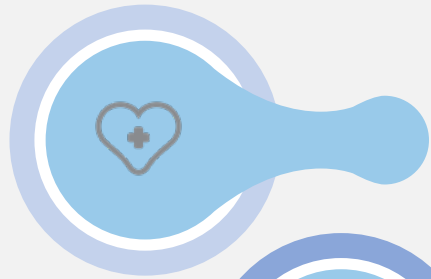
Diabetes

Infections

ETOH
abuse

Drug
abuse

Understanding Heart Failure



Cardiac
Output

Cardiac Output = Heart Rate x Stroke Volume



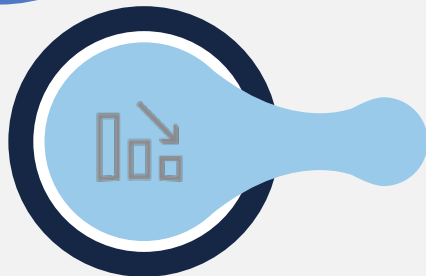
Homeostasis

The body has regulatory mechanisms intended to return to normal physiological parameters



Compensation

Chemoreceptors and baroreceptors that detect a decrease in effective circulating volume activate compensatory mechanisms



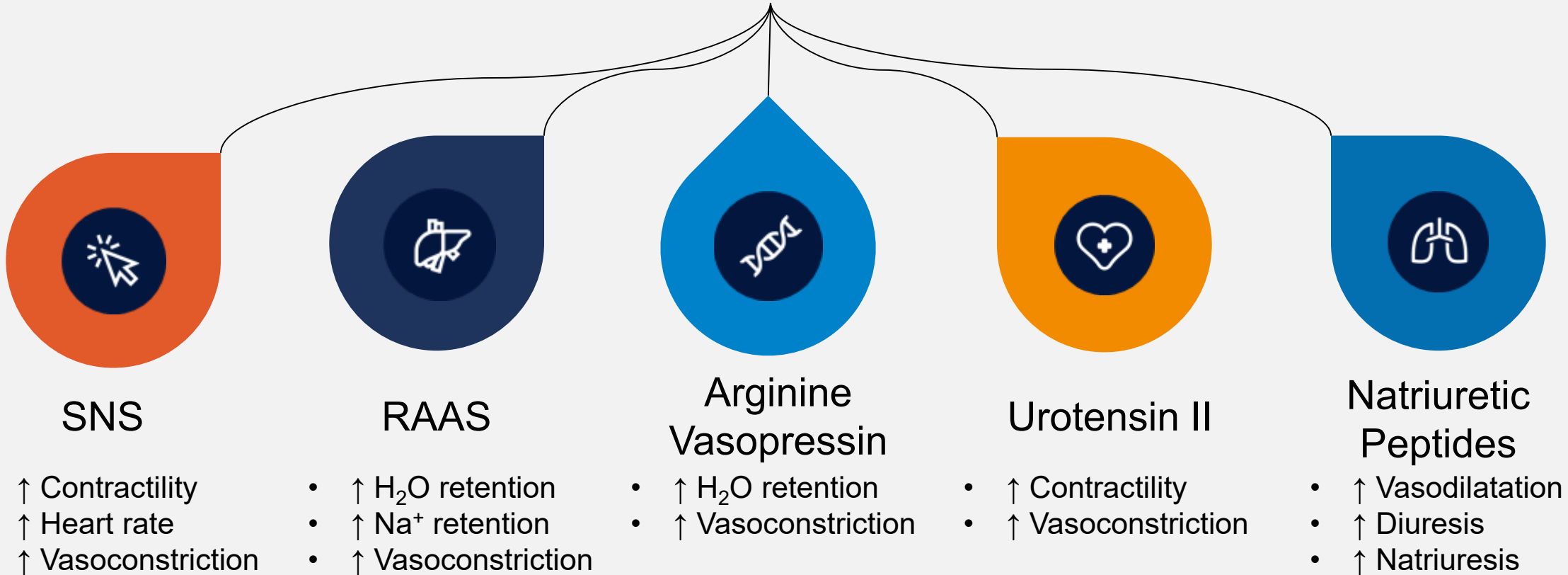
Maladaptive
Process

Compensatory mechanisms important in short term for returning to homeostasis but long term becomes maladaptive

Source: Rogers JG, O'Connor. Goldman-Cecil Medicine. 2024.

Pathophysiological Response

Neurohormonal Response Mechanisms



Source: Hassenfuss G, et al. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 2022

Na⁺ = Sodium
H₂O = Water

SNS = Sympathetic Nervous System
RAAS = Renin Angiotensin
Aldosterone System

Inotropic Effects

- Contractility

Chronotropic Effects

- Heart Rate

Volume Effects

- Diuresis/Natriuresis
- H₂O & Na⁺ retention

Vasodilatation

Lusitropic Effects

- Cardiac remodeling

Portfolio of Compensatory Mechanisms



Compensatory mechanisms augment cardiac output & perfusion acutely

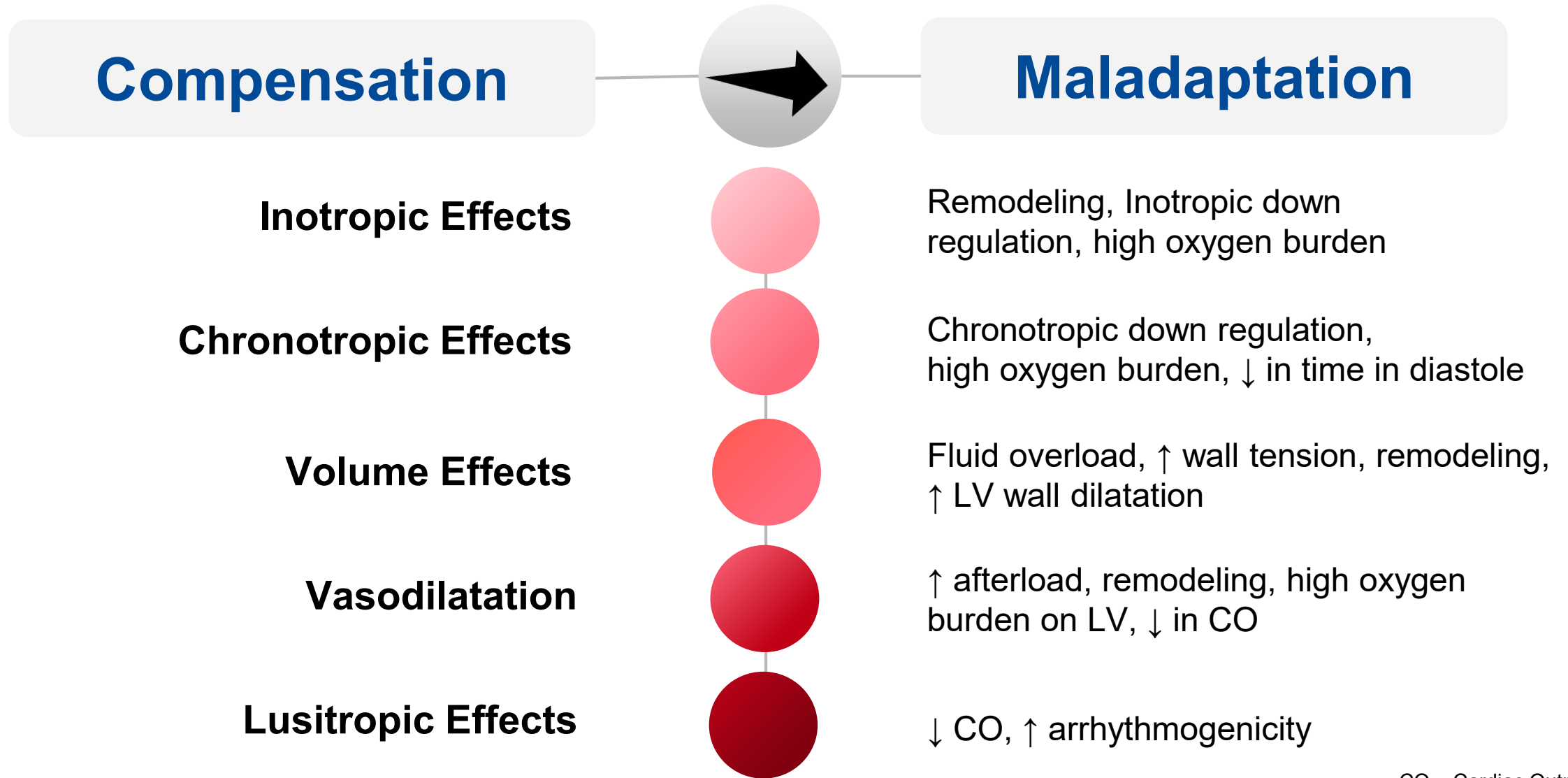


Ongoing compensatory support of cardiac output & perfusion leads to decompensation



Medications target overexpression of compensatory mechanisms that lead to maladaptation

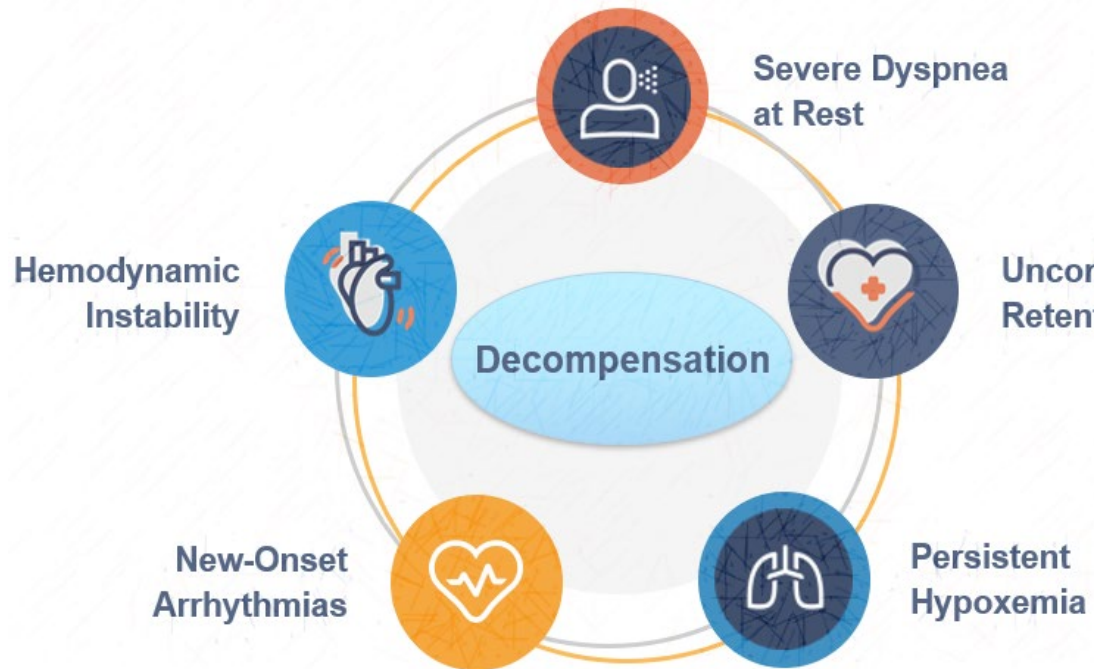
Maladaptive Processes in Heart Failure



Heart Failure Symptomology



...& Goals of Therapy



Reduce symptom severity



Decrease the risk of mortality & morbidity



Attenuate or possibly reverse the process of adverse remodeling of the LV

Source: Mann DL, et al. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 2022

10 | **CE Credit Deadline: 09/30/24**

LV = Left Ventricle

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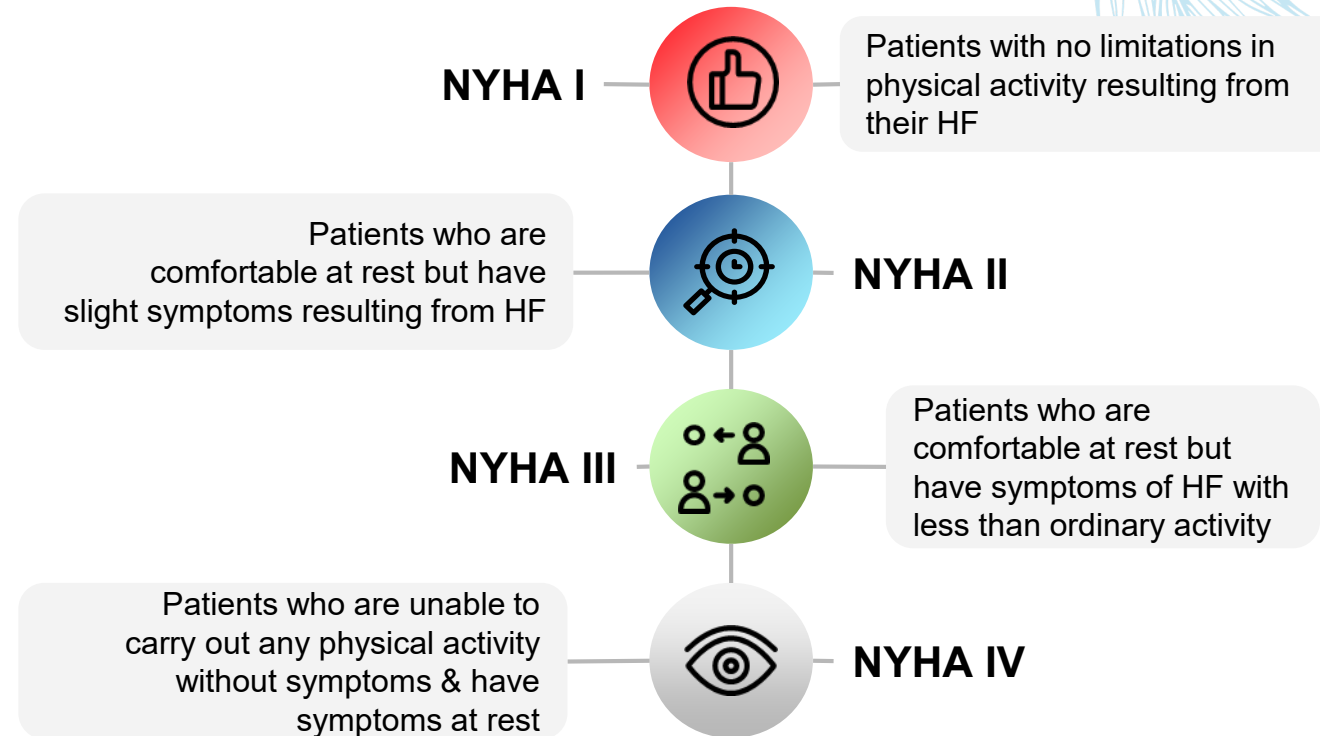
Heart Failure Classification



Classification of HF by Left Ventricular Ejection Fraction (LVEF)

	LVEF ≤40%	LVEF 41% - 49%	LVEF ≥ 50%
HF_rEF HF with reduced EF	LVEF ≤40%		
HF_{imp}EF HF with improved EF	Previous LVEF ≤40% and a follow-up measurement of LVEF >40%		
HF_{mr}EF HF with mildly reduced EF		LVEF 41%–49% ↑ LV filling pressures	
HF_pEF HF with preserved EF			≥ 50% ↑ LV filling pressures

New York Heart Association (NYHA) functional classification



Source: Heidenreich PA, et al., AHA Journal. 2022



GUIDELINE DIRECTED MEDICAL THERAPY (GDMT)

Heart Failure



Guideline Directed Medical Therapy



GDMT

GDMT refers to the optimal pharmacological & non-pharmacological treatments recommended in clinical practice guidelines for heart failure



Well Studied

These therapies have been extensively studied & shown to improve outcomes in patients with heart failure



Cornerstone

Considered the backbone of therapy for heart failure, specifically heart failure with reduced ejection fraction



HFrEF

Heart Failure with Reduced Ejection Fraction

Source: GDMT = Guideline Directed Medical Therapy

13 | **CE Credit Deadline: 09/30/24**

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Multimodal Approach to Heart Failure

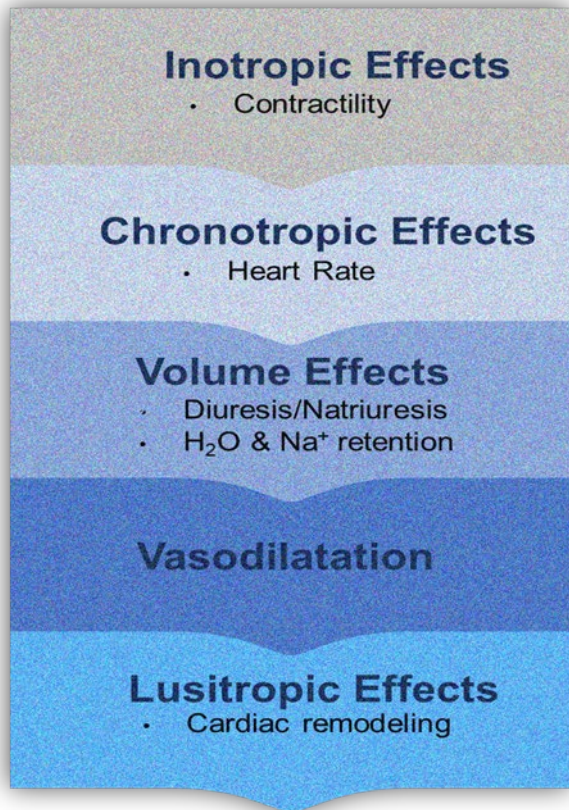


Hand Holding One Wood Block Out Of Four Blank, illustration. Nora Carol Photography. July 15, 2022. Accessed June 2024. Getty Images. Used with permissions

- GDMT consist of **4** “pillars” of medical therapy in the treatment of HFrEF
- The four classes of medication for GDMT are unique, overlapping & synergistic
- GDMT consists of:
 - Renin-angiotensin-aldosterone system inhibitors (RAASI)
 - Beta blockers
 - Mineralocorticoid receptor antagonists (MRA)
 - Sodium-glucose cotransporter-2 inhibitors (SGLT2i)

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Renin-Angiotensin-Aldosterone System Inhibitors in Heart Failure



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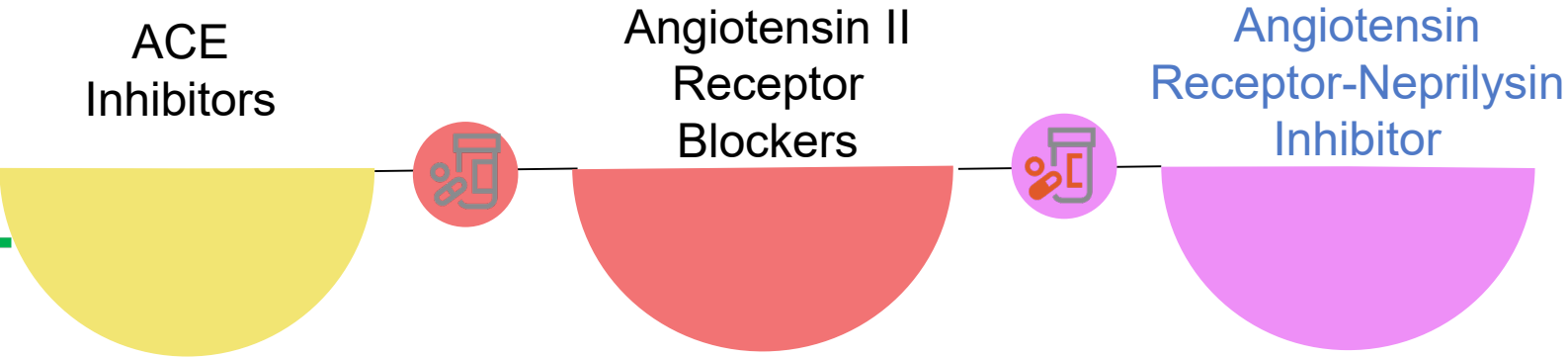
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3 Medication Classes



Source: Felker GM, Teerlink JR. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 2022.

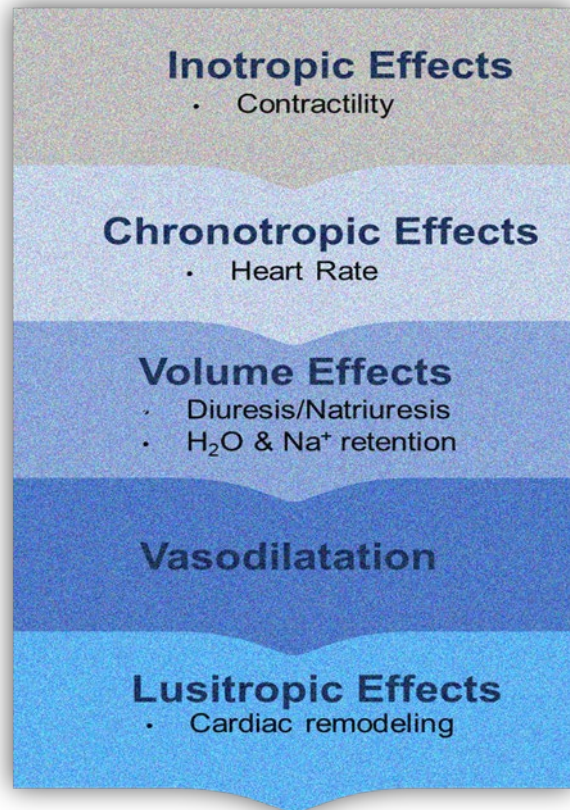
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ACE= Angiotensin Converting Enzyme
H₂O = Water
Na⁺ = sodium

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Evidence-based Beta Blockers in Heart Failure



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Carvedilol

COPERNICUS

Metoprolol Succinate

MERIT- HF

Bisoprolol

CIBIS – I & II

H₂O = Water
Na⁺ = sodium

Sources: Eichhorn EJ. et al. Curr Control Trials Cardiovasc Med. 2001
Hjalmarson A. et al. JAMA. 2000
Krumholz HM. Lancet. 1999
Lechat PH. Circulation. 1994

Mineralocorticoid Receptor Antagonists in Heart Failure



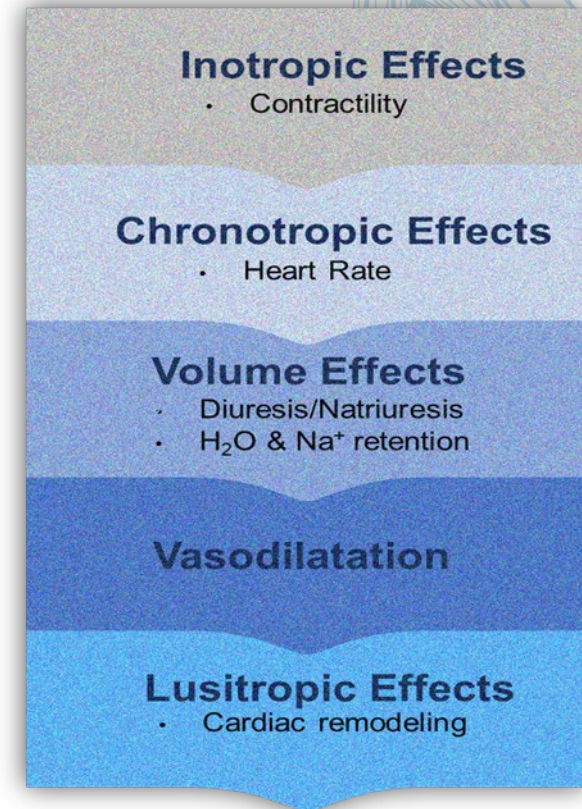
Spironolactone



Eplerenone

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Source: Felker GM, Teerlink JR. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 2022.

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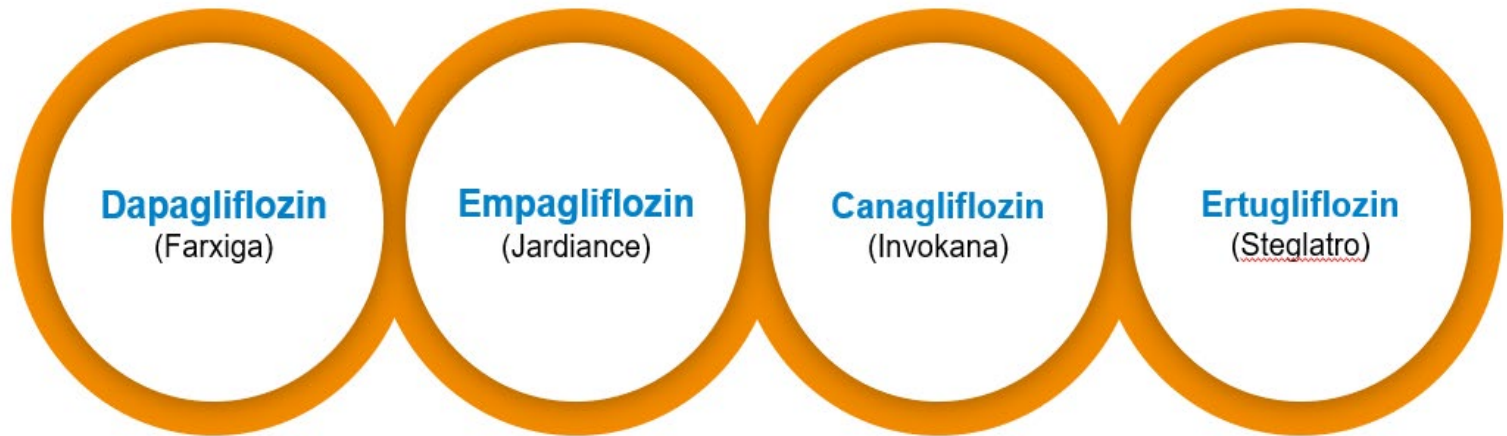
H₂O = Water
Na⁺ = sodium



OVERVIEW OF NEW MEDICATION THERAPIES



Sodium Glucose Co –Transporter - 2 (SGLT2) Inhibitors in Heart Failure



Doctor gives medication instructions to patients, illustration. SDI Productions. February 07, 2020. Accessed June 2024. Getty Images. Used with permissions

Sodium Glucose Co –Transporter (SGLT2) Inhibitors in Heart Failure

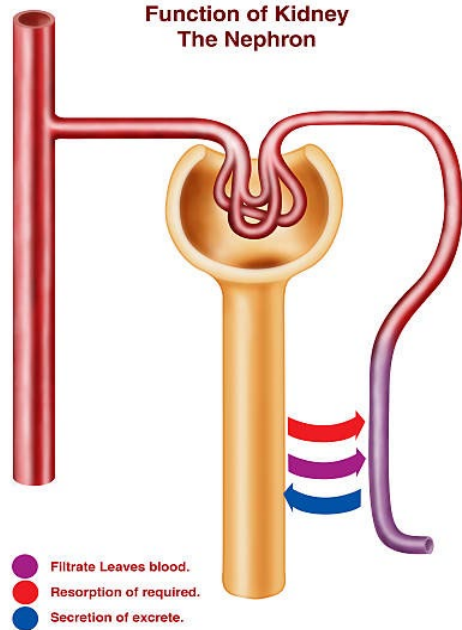
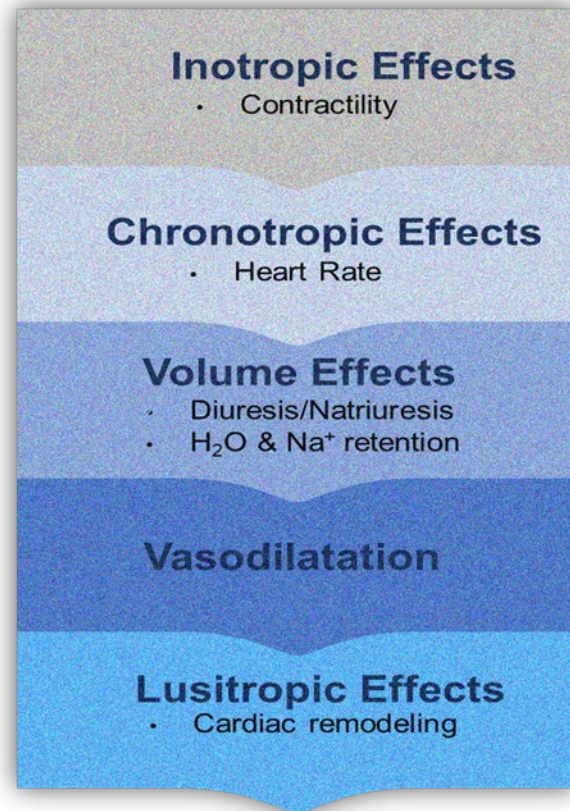


Diagram of a nephron, the functional unit of excretion in the human kidney, illustration. Stocktrek Images. Nov 13, 2023. Accessed June 2024. Getty Images. Used with permissions



H₂O = Water
Na⁺ = sodium

Mechanisms

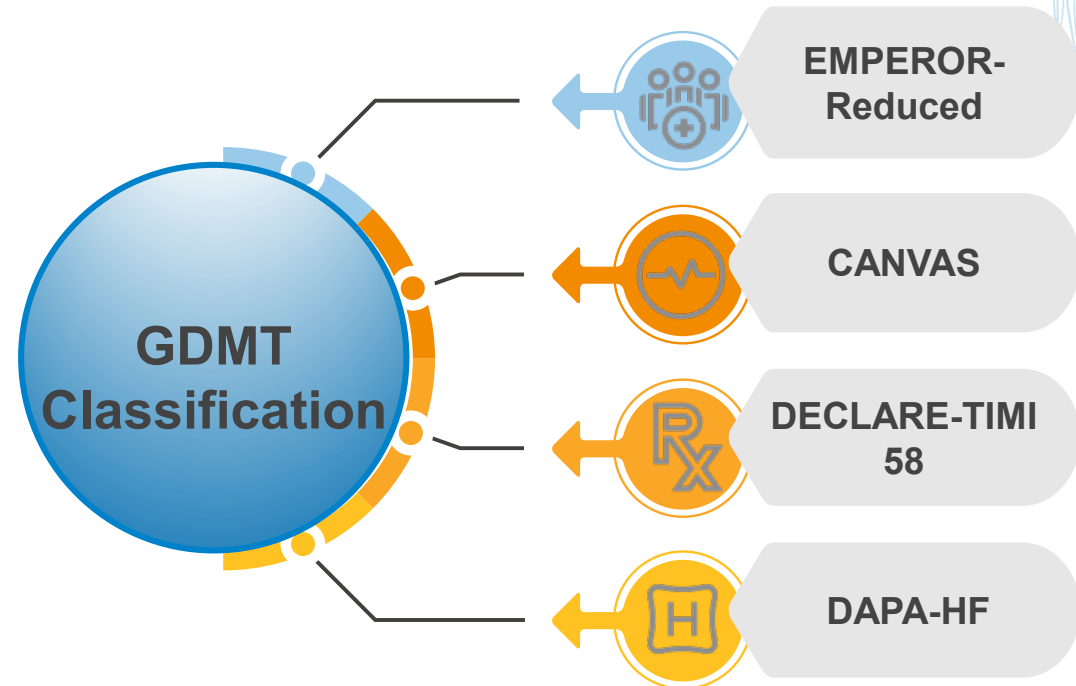
- Volume reduction
- Blood pressure reduction
- Reduced arterial stiffness
- Improvements in myocardial energetics
- Anti-inflammatory effects
- Sympatholytic effects
- Improved myocardial efficiency

Source: Marx N, et al. Braunwald's Heart Disease 2022

Sodium Glucose Co –Transporter - 2 (SGLT2) Inhibitors



- SGLT2 inhibitors have found to have cardiovascular benefit with or without patients with T2DM
- Beneficial in decreasing cardiovascular mortality in HFpEF, HFmrEF, HFimpHF, HFrEF
- In patients with HFrEF
 - SGLT2 inhibitors is should be initiated as part of GDMT
 - GDMT agents can be added together or sequentially, in patients with T2DM adding early in course of HFrEF preferred



HFpEF = Heart Failure with Preserved Ejection Fraction
HFmrEF = Heart Failure with Mildly Reduced Ejection Fraction
HFimpEF = Heart Failure with Improved Ejection Fraction
HFrEF = Heart Failure with Reduced Ejection Fraction
T2DM = Type 2 Diabetes Mellitus

Sodium Glucose Co –Transporter (SGLT2) Inhibitors



Target
Dose: 10
mg BID
(dapa, empa)

Clinical Pearls



SGLT2 inhibitors can cause euglycemic DKA (rare). Recognizing symptoms of DKA (e.g., nausea, vomiting, abdominal pain, confusion & fatigue) is important while patients are on SGLT2 inhibitors

For patients with T2DM and HFrEF, SGLT2Is should be considered in managing T2DM due lower incidence of hypoglycemia. Hypoglycemia stimulates the SNS & has deleterious effects on HF



Pearl, illustration. Loops7. August 25, 2011. Accessed June 2024. Getty Images. Used with permissions

Source: Marx N, et al. Braunwald's Heart Disease 2022

Dapa = Dapagliflozin
Empa = Empagliflozin
DKA = Diabetes Ketoacidosis

T2DM = Type 2 Diabetes
SNS = Systemic Nervous System
HF = Heart Failure

Question 1



SGLT2 inhibitors and sacubitril/valsartan should be used in which of the following patient scenarios?

- A. Dual therapy for HFpEF without beta blockers or mineralocorticoid receptor antagonists (MRA)
- B. As add-on therapy after device placement
- C. Refractory HFpEF after GDMT backbone therapy has been established
- D. As part of the backbone of GDMT with beta blockers and MRA



Uncertainty, illustration. Crispin la valiente. May 08, 2021. Accessed June 2024. Getty Images. Used with permissions

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Uncertainty, illustration. Crispin la valiente. May 08, 2021. Accessed June 2024. Getty Images. Used with permissions

Sacubitril / Valsartan



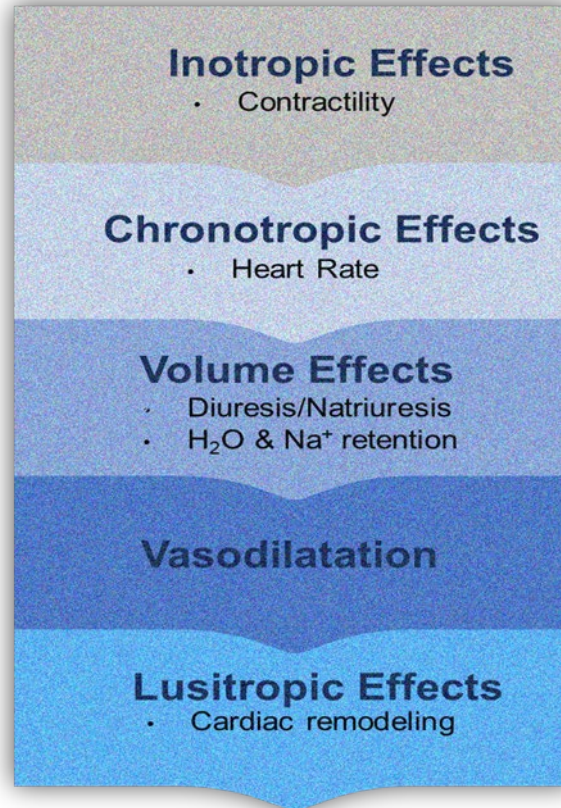
Top view of blood pressure machine on table, Romania, illustration. Malaeru Florentina / 500px. April 21, 2023. Accessed June 2024. Getty Images. Used with permissions

Mechanisms

 Nephilysin Inhibition

 Angiotensin II Receptor Blockade

Source: Felker GM, Teerlink JR. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 2022. 25 | **CE Credit Deadline: 09/30/24**

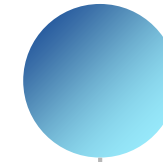


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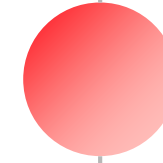
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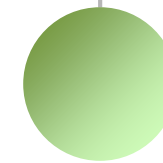
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Improved Hemodynamics



Enhanced Diuretic Effects



Greater Vasodilatation

H₂O = Water
Na⁺ = sodium

Sacubitril / Valsartan



Place in Therapy

PARADIGM-HF trial

- Clinical trials have demonstrated that sacubitril/valsartan is superior to traditional therapy with ACE inhibitors
- Sacubitril/valsartan has shown improved outcomes for the following in HFrEF:
 - Reducing the risk of cardiovascular death
 - Heart failure hospitalizations
- This trial led to a paradigm shift in the management of HFrEF, establishing sacubitril/valsartan as a first-line therapy.

Source: McMurray, et al. N Engl J Med. 2019

ACE = Angiotensin Converting Enzyme
HFrEF = Heart Failure reduced Ejection Fraction

26 | **CE Credit Deadline: 09/30/24**



Getty Images: used with the permission of HealthTrust. Accessed June 2024

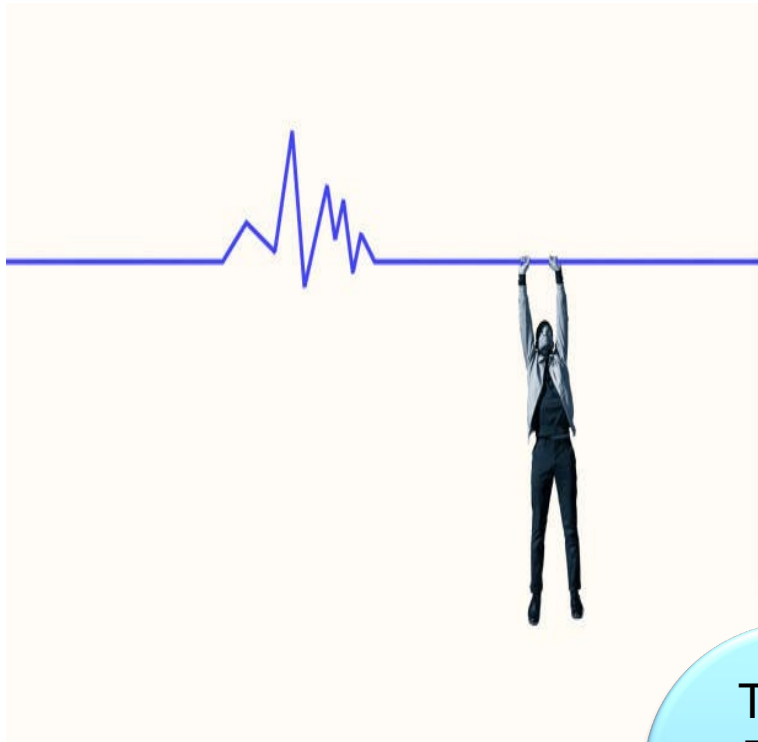
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Sacubitril/Valsartan



Clinical Pearls

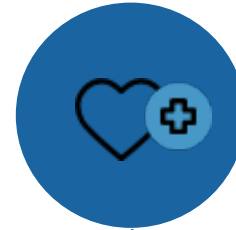


Man hanging from blue line graph for survival, illustration. Klaus Vedfelt. May 27, 2020. Accessed June 2024. Getty Images. Used with permission.



The addition of SGLT2i may have a greater effect on reducing mortality in HFrEF than does an increase in dose of RAAS inhibitor or Beta Blocker

Target Dose:
97/103 mg
BID



Sacubitril-valsartan should not be administered to patients who have taken an ACE inhibitor within the previous 36 hours



RAAS-neprilysin inhibitor agent & beta blocker undergo titration together

RAAS = Renin Angiotensin Aldosterone System
SGLT2i = Sodium Glucose Cotransporter 2 inhibitor
ACE = Angiotensin Converting Enzyme
BID = Twice Daily

Source: Mann DL, et al. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 2022

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Vericiguat | “ver-i-SIG-you-at”



Inotropic Effects

- Contractility

Chronotropic Effects

- Heart Rate

Volume Effects

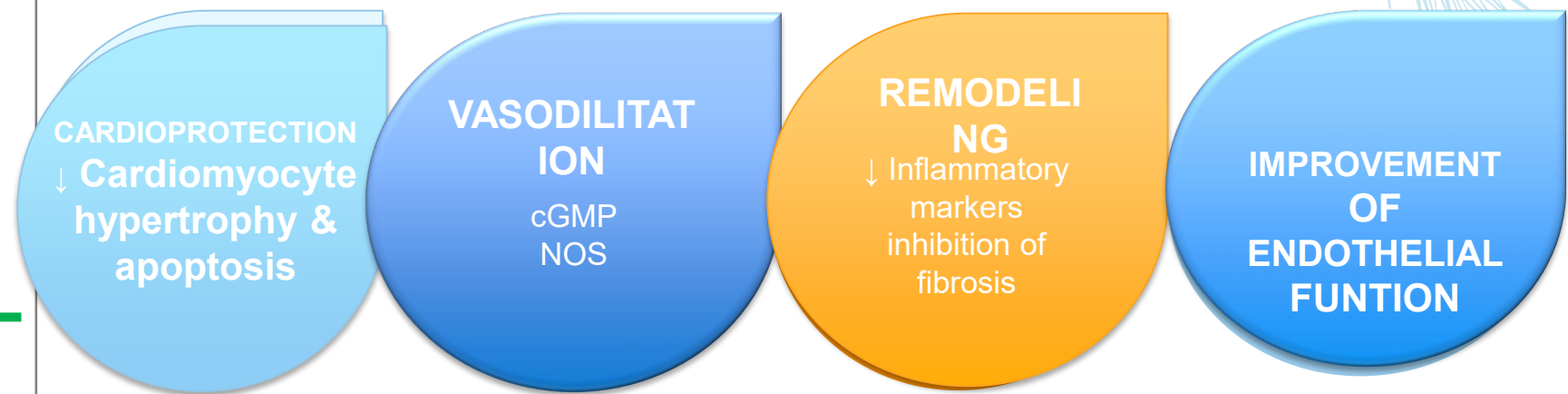
- Diuresis/Natriuresis
- H₂O & Na⁺ retention

Vasodilatation

Lusitropic Effects

- Cardiac remodeling

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Source: Mann DL, et al. Braunwald’s Heart Disease: A Textbook of Cardiovascular Medicine. 2022

cGMP = Guanosine 3',5'-cyclic monophosphate
 NOS = Nitric Oxide Synthase
 H₂O = Water
 Na⁺ = sodium

Vericiguat



Vericiguat Global Study in subjects with Heart Failure with reduced Ejection Fraction

Adjunctive Therapy HFrEF

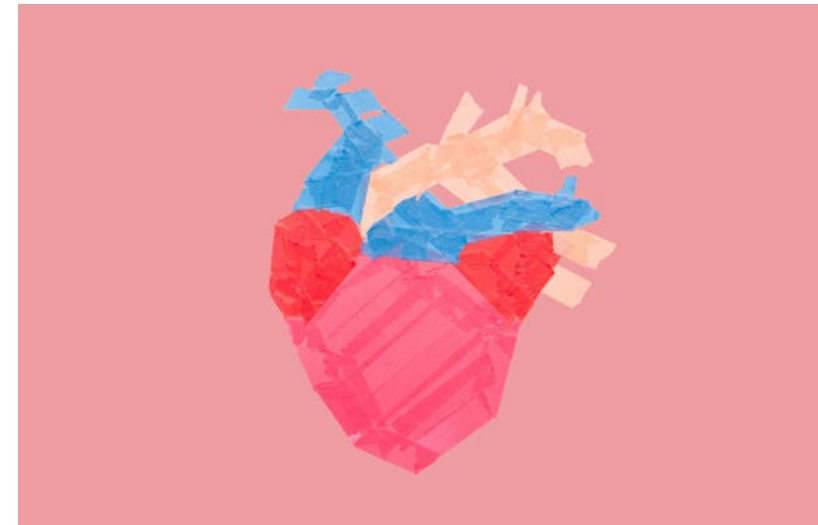


Add-on Therapy: Add-on therapy to GDMT

High-Risk Patients: High risk of recurrent hospitalizations or those who have recently been hospitalized for heart failure exacerbation



Patients with Advanced Disease: Additional therapeutic option to manage HF symptoms



Human heart made of adhesive tape., illustration. Malorny. May 05, 2023. Accessed June 2024. Getty Images. Used with permission.

Source: Armstrong PW, et al. N Engl J Med. 2020

29 | **CE Credit Deadline: 09/30/24**

GDMT = Goal-directed Medical Therapy

HF = Heart Failure

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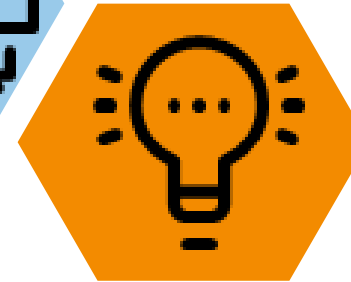
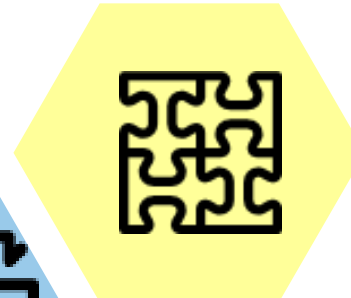
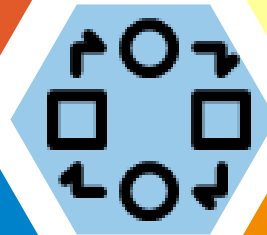
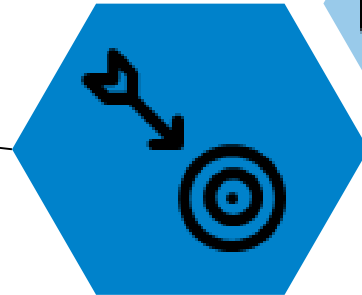
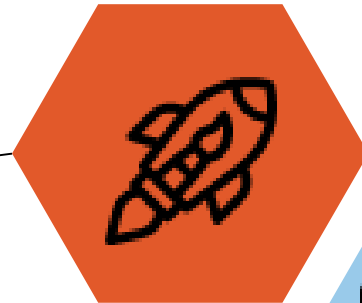


Vericiguat



Clinical Pharmacy Pearls

Target maintenance dose of 10 mg once daily



Patients with persistent symptoms of HF despite GDMT optimized AND diuretic therapy before initiation

Minimum 2-week dosing titrations schedule. Dose should be doubled with every interval as tolerated

Vericiguat should be taken with food to enhance absorption

Source: Mann DL, et al. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 2022

30 | **CE Credit Deadline: 09/30/24**

MG = milligram

HF = Heart Failure

GDMT = Goal-directed Medical Therapy

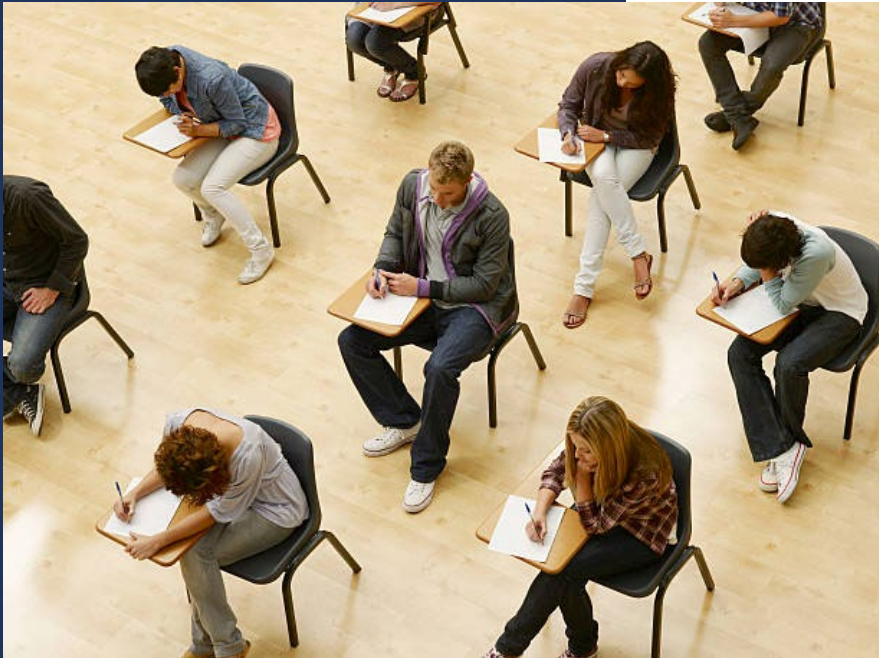


Question 2



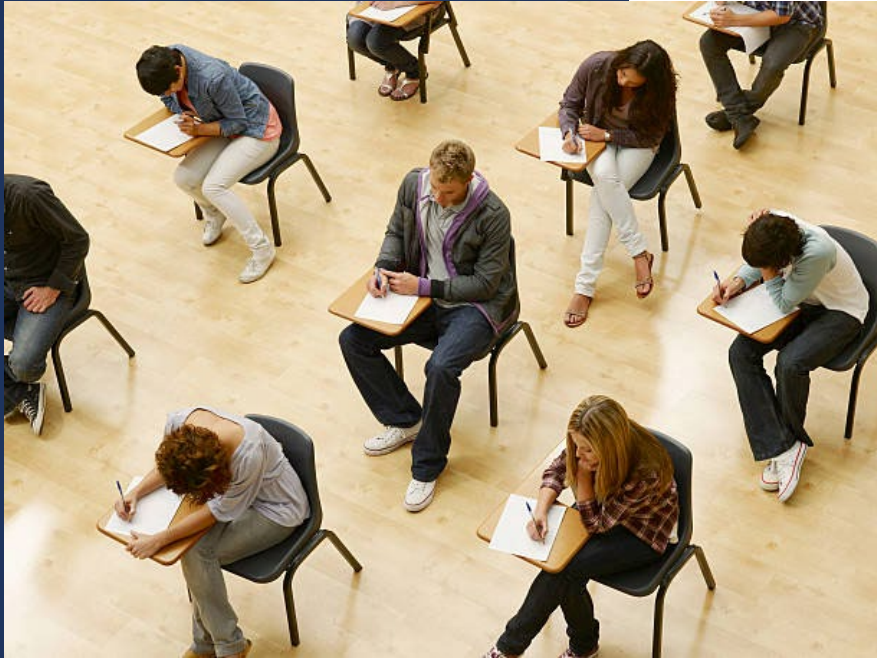
Which of the following is an associated mechanism of action for sacubitril/valsartan?

- A. Sinoatrial (SA) Node inhibition
- B. Neprilysin Inhibition
- C. Stimulates guanylate cyclase (sGC)
- D. Reduces the reabsorption of glucose in the proximal tubule
- E. Prevents the conversion of Angiotensin I to Angiotensin II



College students taking test in classroom, illustration. Chris Ryan. February 15, 2013 Accessed June 2024. Getty Images. Used with permission.

Answer: Question 2



College students taking test in classroom, illustration. Chris Ryan. February 15, 2013 Accessed June 2024. Getty Images. Used with permission.

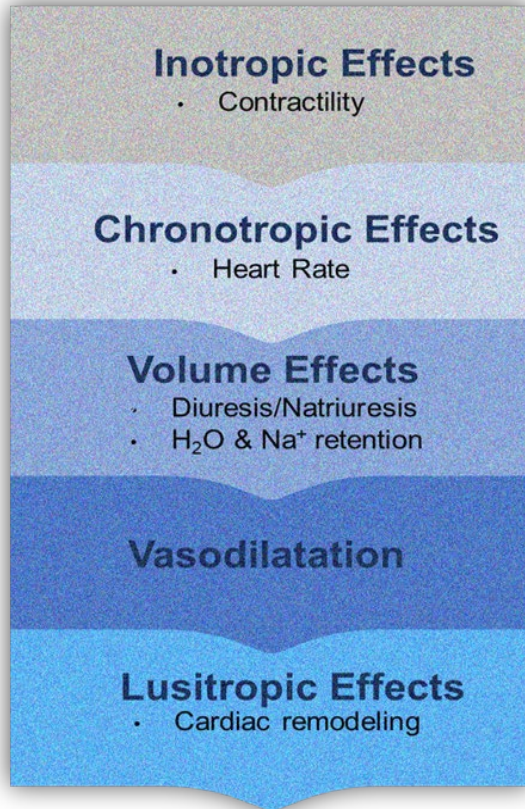
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Ivabradine

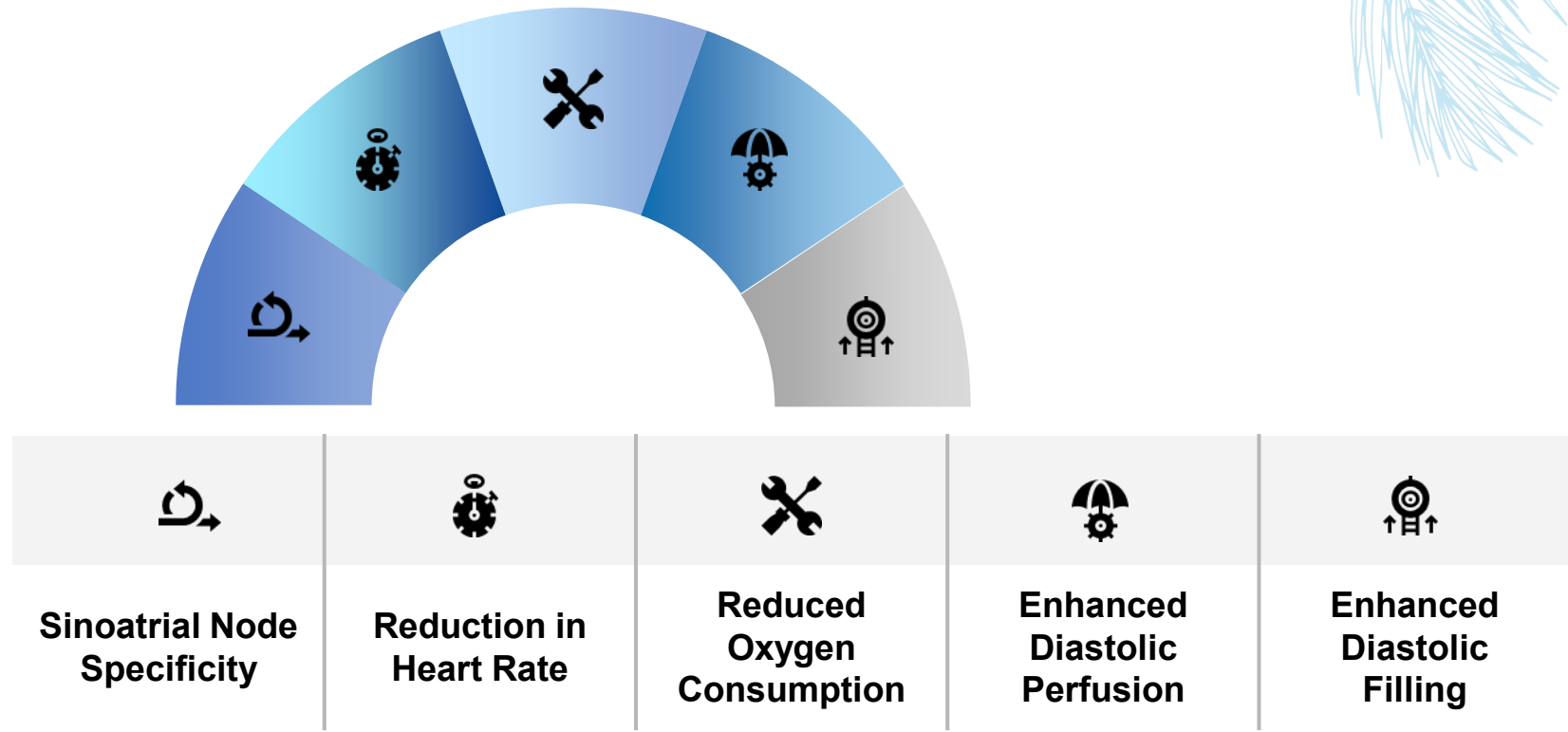


Mechanisms



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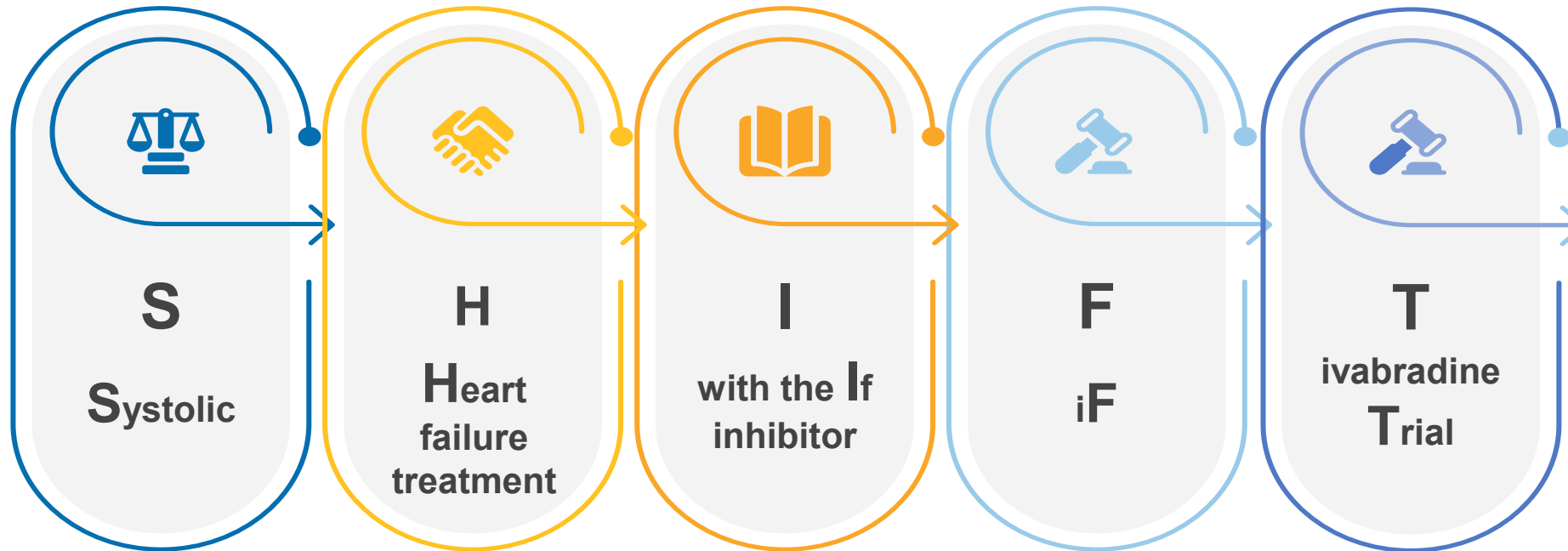
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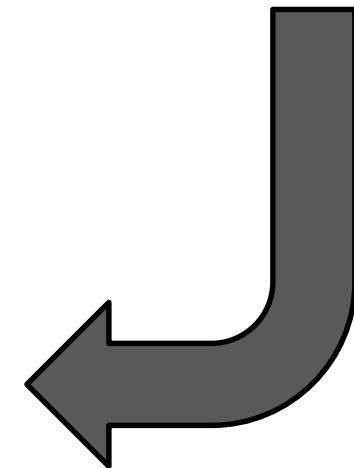
H₂O = Water
Na⁺ = sodium

Source: Felker GM, Teerlink JR. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 2022.

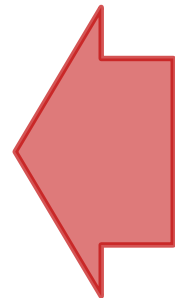
Ivabradine



Position in Therapy



Adjunct to Beta-Blockers



Optimizing Heart Rate Control
Beta-Blocker Intolerance

Source: Swedberg K, et al. Lancet. 2010

34 | **CE Credit Deadline: 09/30/24**

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Ivabradine



Clinical Pharmacy Pearls



Beta blocker regimen should be optimized prior to initiation



Not recommended in patients who do not have evidence of decompensated HF



Most appropriate for patients in sinus rhythm with HR ≥ 70

Source: Mann DL, et al. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 2022

35 | **CE Credit Deadline: 09/30/24** BID = Twice Daily



Target
Dose:
7.5mg BID

Doctor in hospital. Dennis Degnan. April 21, 2016. Accessed June 2024. Getty Images. Used with permission.

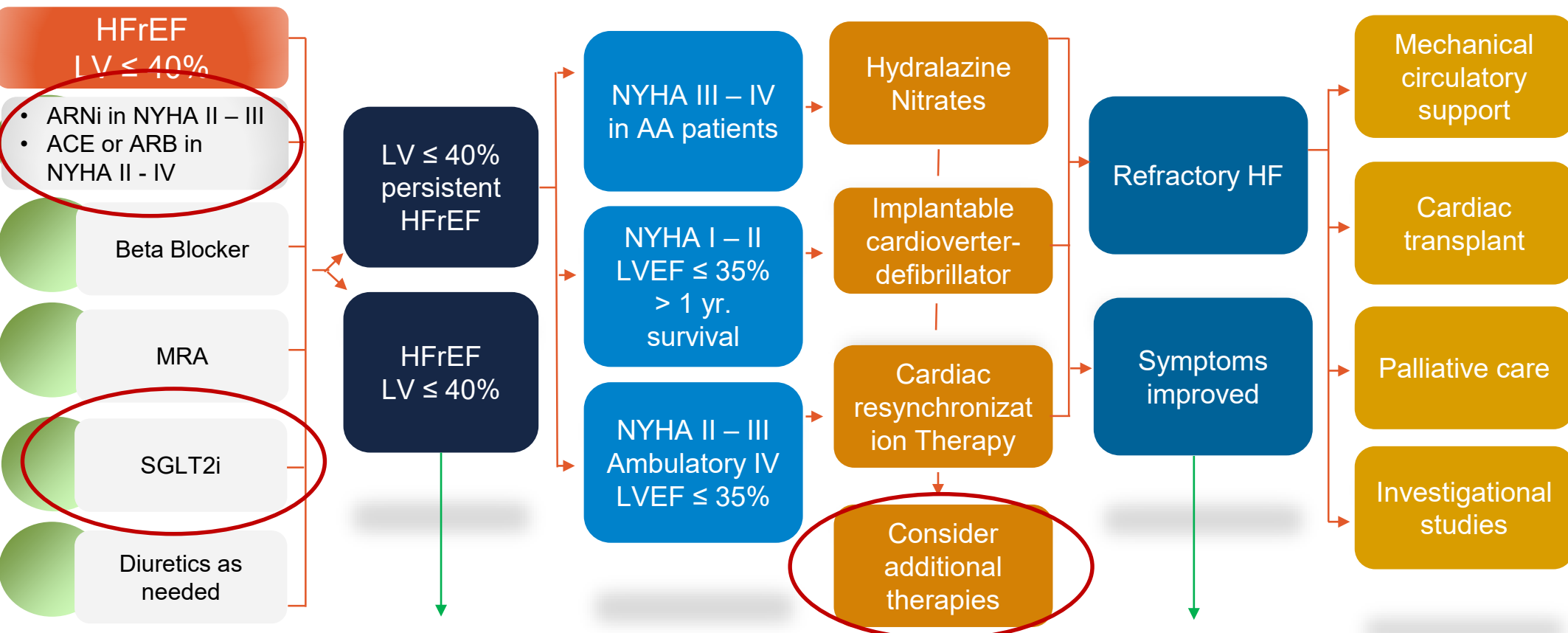
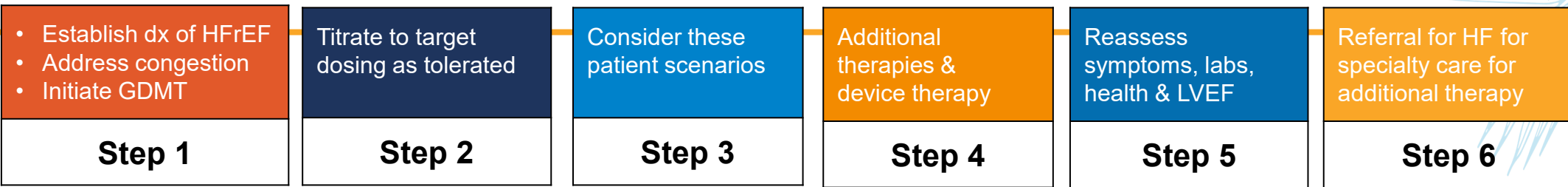


INTEGRATION WITH TRADITIONAL THERAPIES

Reviewing the Evidence



Integration With Traditional Therapies



- HFrEF = Heart Failure reduced Ejection Fraction
- Dx = Diagnosis
- ARNI = Angiotensin Receptor-Neprilysin Inhibitor
- NYHA = New York Heart Association
- ACE = Angiotensin Converting Enzyme
- ARB = Angiotensin Receptor Blocker
- MRA = Mineralocorticoid Receptor Antagonist
- SGLT2i – Sodium Glucose Cotransporter2 inhibitor
- LVEF = Left Ventricular Ejection Fraction
- HF = Heart Failure
- AA = African American

37 | Continue GDMT with serial assessment & optimize dosing, adherence & patient education, address goals of care

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Question 3



Which of the following statements are TRUE about ivabradine & vericiguat?

- A. Evidence and guidelines support the use of ivabradine & vericiguat as first line agents for HFrEF
- B. Ivabradine & vericiguat should be initiated before GDMT medications for HFrEF are optimized
- C. Ivabradine & vericiguat are best suited for patients for NYHA I classification of heart failure
- D. Evidence suggests that ivabradine or vericiguat should be considered when patient remain symptomatic after GDMT & diuretics have been optimized



Source: Getty Images. Used with permission.

Question 3



Which of the following statements are TRUE about ivabradine & vericiguat?

- A. Evidence and guidelines support the use of ivabradine & vericiguat as first line agents for HFrEF
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References



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Thank You

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