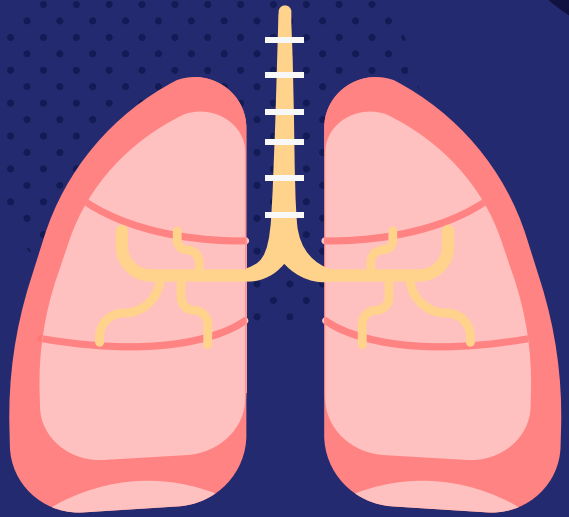


Air We Go Again: COPD Management

Ryan Stewart PharmD/MBA Candidate 2024

Objectives

- Recognize the diagnostic criteria of COPD
- Understand the grading system of COPD based on FEV1
- Describe the signs, symptoms, and common risk factors for COPD
- Analyze the 2023 GOLD guidelines for the pharmacologic management of initial and follow up therapy
- Assess the appropriateness of pharmacologic therapy given a patient case
- Discuss the clinical and economic benefits of triple therapy

Chronic Obstructive Pulmonary Disease (COPD)[1]

- Characterized by chronic respiratory symptoms and airflow limitation due to airway and or alveolar abnormalities that cause persistent and progressive airway obstruction
- Diagnosis
  - Spirometry post-bronchodilator test
    - FEV1/FVC <0.70
  - Persistent airflow limitation

Signs & Symptoms

- Cardinal symptoms
  - Persistent cough or wheezing
  - Dyspnea
  - Sputum production
- Chest tightness
- Activity limitations

Causes & Risk Factors

- Tobacco smoking
- Environmental exposures
  - Air pollution
  - Occupational dusts, fumes, chemicals
  - Gases
- Host factors
  - Abnormal lung development
  - Accelerated lung aging
- Genetic factors[2]
  - Alpha-1 Antitrypsin Deficiency
  - Protein made in the liver which protects the lungs

2023 GOLD Guidelines[1]

GOLD Guidelines

- GOLD Grades
  - Used to classify severity of airflow limitation
    - Based on FEV1 post-bronchodilator test results

Grade	FEV1 (%)	Severity
GOLD 1	≥80%	Mild
GOLD 2	50-79%	Moderate
GOLD 3	30-49%	Severe
GOLD 4	<30%	Very Severe

GOLD Guidelines: Initial Treatment

- GOLD Groups
  - Assessment of COPD symptoms
  - Used for initial pharmacological treatment
  - Based on
    - Exacerbation/hospitalization history
    - Modified Medical Research Council dyspnea questionnaire (mMRC)
    - COPD Assessment Test (CAT)
- mMRC
  - Questionnaire used to measure breathlessness
- CAT
  - Assesses health status of patients with COPD

≥2 moderate exacerbations or ≥1 leading to hospitalization	**Group E** LABA + LAMA Consider LABA + LAMA + ICS if eosinophil ≥300	
0 or 1 moderate exacerbations (not leading to hospital admission)	**Group A** Bronchodilator	**Group B** LABA +LAMA
	mMRC 0-1, CAT <10	**mMRC ≥2,CAT≥10**

GOLD Guidelines: Follow Up

- Maintain initial treatment if patient is stable on regimen
- Before adding or changing regimen, confirm adherence and inhaler techniques
- Consider changing regimen based on if patient is experiencing dyspnea or exacerbations
    - If experiencing both, use exacerbation pathway

Dyspnea

LABA or LAMA

↓

LABA + LAMA

Consider switching inhaler devices
Nonpharm
Investigate and treat other causes of dyspnea

Exacerbations

LABA or LAMA

If eos <300

If eos ≥300

If Eos ≥100

LABA + LAMA → LABA + LAMA + ICS

If Eos <100

Roflumilast
FEV1 <50% & Chronic bronchitis

Azithromycin
Preferentially in former smokers

Celebration of Knowledge

A 48 yo male presents to your pharmacy with a new diagnosis of COPD. He has a CAT score of 13, eosinophils are 275, and no exacerbation history. Based on his this, which of the following is the best medication for his maintenance therapy?

A) Breztri

B) Stiolto

C) Serevent

D) Advair

Celebration of Knowledge

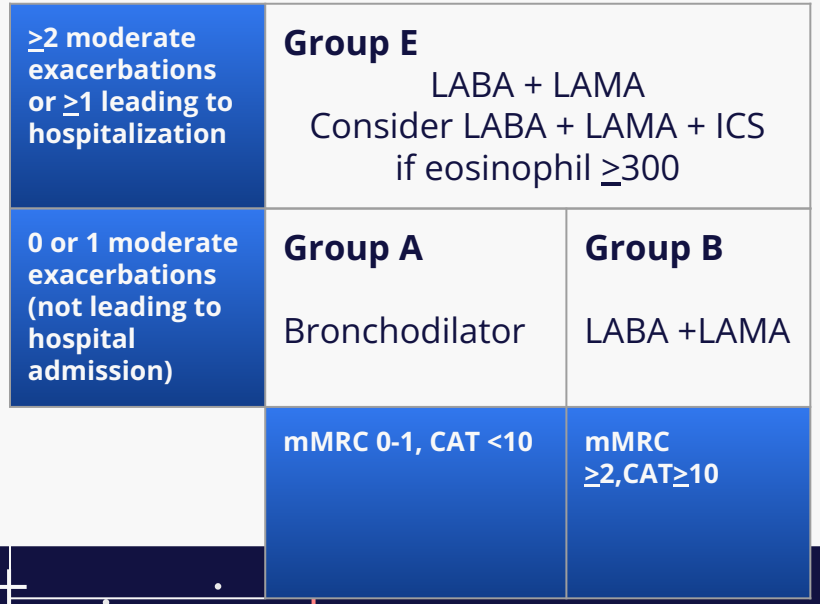
A 48 yo male presents to your pharmacy with a new diagnosis of COPD. He has a CAT score of 13, eosinophils are 275, and no exacerbation history. Based on his this, which of the following is the best medication for his maintenance therapy?

A) Breztri

B) Stiolto

C) Serevent

D) Advair



Bronchodilators

- Stimulate beta$_2$ adrenergic receptors causing bronchodilation
- Short-acting beta$_2$-agonists (SABA)
  - Effects last 4 to 6 hours
  - Generally used as rescue inhaler for immediate symptom relief
    - Every patient with COPD should be prescribed a SABA as a rescue inhaler
    - Overuse of rescue could indicate progression of COPD
  - Albuterol (Proair HFA)
- Long-acting beta$_2$-agonist (LABA)
  - Last 12 hours
  - Used as maintenance inhalers
  - Salmeterol (Serevent Diskus)
  - Formoterol (Perforomist)
  - Olodaterol (Striverdi Respimat)
- SABAs and LABAs can be used together

Bronchodilators

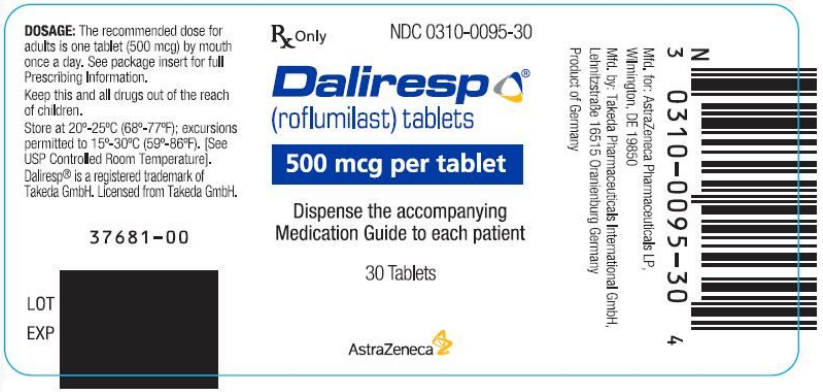
- Long-acting muscarinic antagonist (LAMA)
  - Used in monotherapy in Group A
- LABA + LAMA combinations
  - Used in combination for Group B and E patients
  - Vilanterol + **Umeclidinium** (Anoro Ellipta)
  - Olodaterol + **Tiotropium** (Stiolto)
    - Once daily
  - Formoterol + **Glycopyrrolate** (Bevespi Aerosphere)
  - Formoterol + **Aclidinium** (Duaklir Pressair)
    - Twice daily

Inhaled Corticosteroids

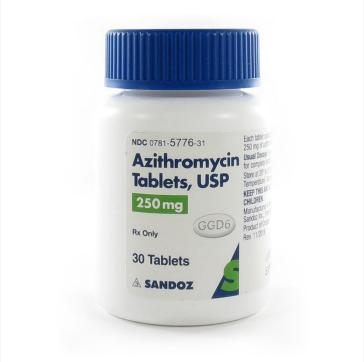
- Inhibit inflammatory response to reduce symptoms and increase lung function
- Important that patients rinse mouth with water after each dose to prevent thrush
- Use of ICS monotherapy in COPD does not prevent decline in FEV1 or improve morbidity/mortality outcomes
- Group B and E
  - Added to regimen if eosinophil count is ≥300 cells/microliter
    - Little to no benefit in patients with low eosinophil counts (<100 cells/μL)
    - ICS benefit increases as eosinophil counts increase
      - Higher eosinophil count represents more inflammation in airway
- LABA + LAMA + ICS
  - **Fluticasone** + Umeclidinium + Vilanterol (Trelegy Ellipta)
  - **Budesonide** + Glycopyrrolate + Formoterol (Breztri Aerosphere)

Roflumilast

- Phosphodiesterase-4 inhibitor
  - Reduces inflammation by inhibiting the breakdown of intracellular cyclic AMP
    - Help reduce proinflammatory cytokines
    - Has no direct bronchodilator activity
  - Used for moderate and severe exacerbations in patients with
    - Chronic bronchitis
    - Severe to very severe COPD
      - GOLD Grades 3 and 4
    - History of exacerbations

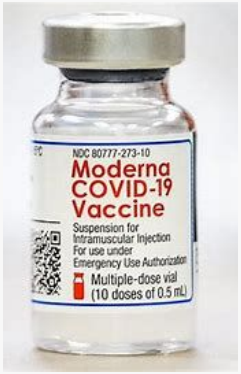


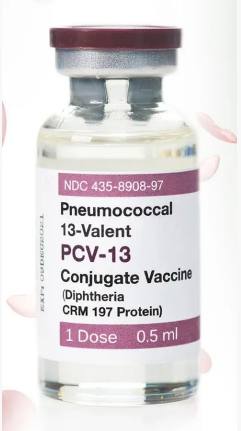
Azithromycin



- Used in COPD to kill bacteria and reduce inflammation in the lungs
  - Can reduce exacerbation risk
  - Reduce COPD symptoms
- Azithromycin 250 mg/day or 500 mg 3x/week for one year
  - Helps to prevent exacerbations in patients prone to exacerbations
  - Greater risk of adverse events
    - Bacterial resistance
    - Hearing impairment
    - QTc prolongation
  - No safety or efficacy data for use of Azithromycin over 1 year
- Former smokers have shown greater benefit and prevention of exacerbations with Azithromycin compared to current smokers

Clinical Pearl: Vaccines





Clinical Pearl: Beta Blockers[3]

Selective Beta-Blockers

- Metoprolol, Atenolol, Bisoprolol
- Selective for beta adrenergic receptor in the heart

Non-Selective Beta-Blockers

- Carvedilol, propranolol, labetalol
- Non-selective for beta adrenergic receptors
  - Bind both beta-1 in the heart and beta-2 in the lungs
  - Risk for COPD/Asthma exacerbations

Celebration of Learning

TH is a 57 yo female who comes to your clinic for follow up on her current regime which includes Anoro 1 puff once daily and Proair PRN. When asked, she tells you she has been been short of breath more often in the last two weeks and relies solely on her albuterol because she feels it working. Which of the following should you do?

A) Increase her Anoro to 2 puffs once daily

B) Change her Anoro to Breztri 1 puff once daily

C) Counsel on adherence

Celebration of Learning

TH is a 57 yo female who comes to your clinic for follow up on her current regime which includes Anoro 1 puff once daily and Proair PRN. When asked, she tells you she has been been short of breath more often in the last two weeks and relies solely on her albuterol because she feels it working. Which of the following should you do?

A) Increase her Anoro to 2 puffs once daily

B) Change her Anoro to Breztri 1 puff once daily

C) Counsel on adherence

Clinical and Economic Outcomes of Triple Therapy

Early Initiation of Triple Therapy[4]

- Objective:
  - Determine whether or not prompt initiation of triple therapy (ICS+LABA+LAMA) lowers risk of future exacerbations and healthcare costs compared to delayed initiation
- Retrospective observational study (n=24,770)
  - Patients ≥40 yo with COPD, initiated triple therapy after 2 moderate or 1 severe exacerbation in the last year
  - Prompt (≤30 days), delayed (31-180 days), very delayed (181-365)
- Results
  - Every 30 day delay of triple therapy initiation translated to:
    - 7% increase in risk of severe exacerbations, 4.3% increase in number of exacerbations
    - 1.8% increase in all cause cost, 2.1% increase in COPD related cost
- Takeaway
  - Clinicians should consider triple therapy in comparison to LABA+LAMA in patients with COPD exacerbations

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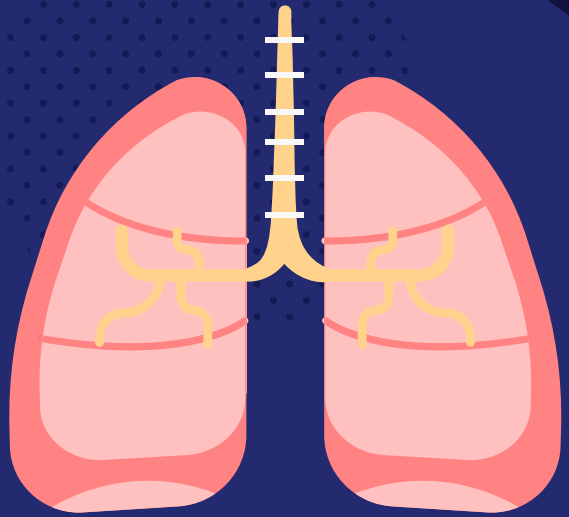
2. Stoller JK, Aboussouan LS. A review of α1-antitrypsin deficiency. Am J Respir Crit Care Med. 2012;185(3):246-259. doi:10.1164/rccm.201108-1428CI
3. Huang YL, Lai CC, Wang YH, Wang CY, Wang JY, Wang HC, Yu CJ, Chen L. Impact of selective and nonselective beta-blockers on the risk of severe exacerbations in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2017 Oct 11;12:2987-2996. doi: 10.2147/COPD.S145913. PMID: 29066880; PMCID: PMC5644571.
4. Tkacz J, Evans KA, Touchette DR, et al. PRIMUS - Prompt Initiation of Maintenance Therapy in the US: A Real-World Analysis of Clinical and Economic Outcomes Among Patients Initiating Triple Therapy Following a COPD Exacerbation. Int J Chron Obstruct Pulmon Dis. 2022;17:329-342. Published 2022 Feb 10. doi:10.2147/COPD.S347735

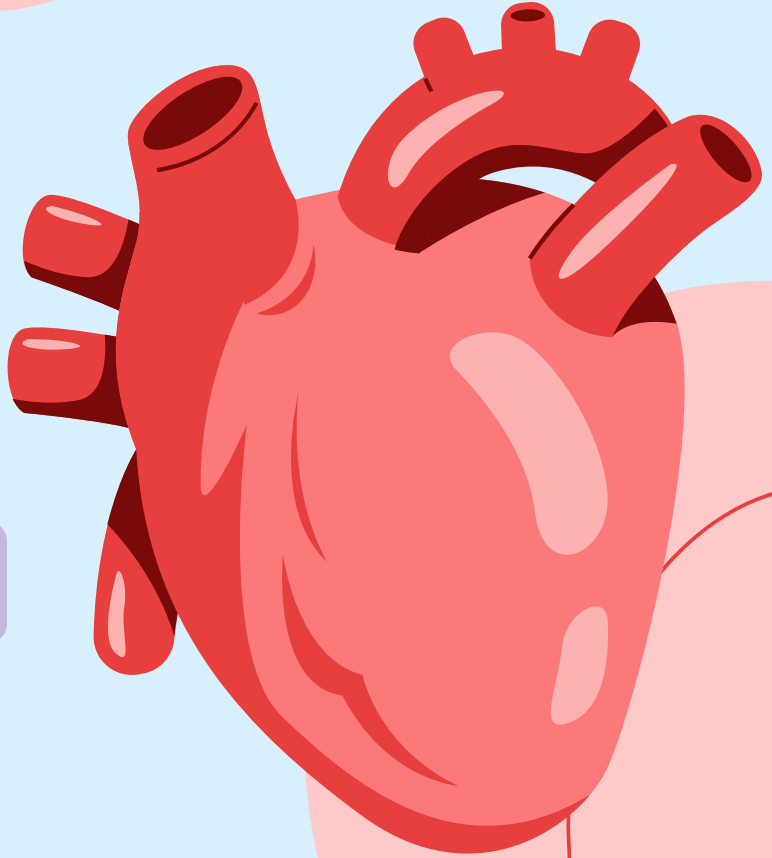


Air We Go Again: COPD Management

Ryan Stewart PharmD/MBA Candidate 2024

ARNi-thing is Possible!

Shannon Brown, PharmD Candidate 2024
Wilkes University Nesbitt School of Pharmacy



Objectives

01

Discuss the background of heart failure and its diagnosis

02

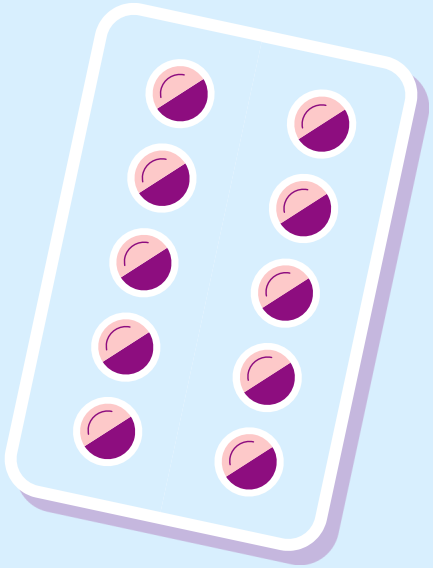
Explain the staging and treatment guidelines for heart failure

03

Understand the place in therapy for ARNis and the evidence surrounding it

01

Disease Background



Heart Failure

- Inability for the heart to adequately fill or eject blood to meet the demands of the body
- Measured by left ventricular ejection fraction (LVEF)
  - Volume of blood ejected from left ventricle during systole
  - 55-70%
- Prevalence
  - 6.2 million Americans suffer from heart failure

Heart Failure

Signs & Symptoms

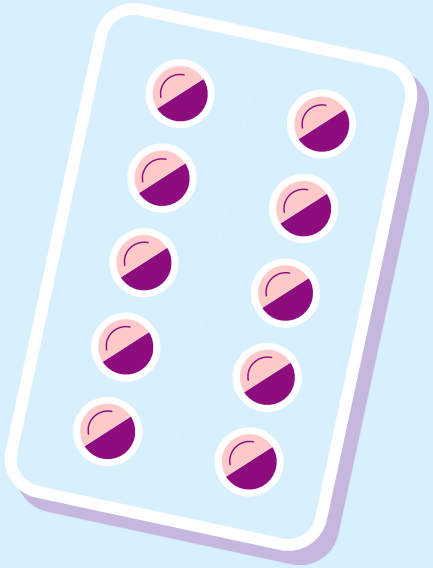
- Chest pain
- Dyspnea upon exertion
- Shortness of breath
- Edema
- Fatigue
- Wheezing and coughing
- Exercise intolerance

Risk Factors

- Coronary artery disease (MI)
- Hypertension
- Excess alcohol
- Diabetes
- Obesity
- Age >60
- Medications
  - DPP-4 inhibitors
  - Non-DHP CCBs
  - TZDs

02

Diagnosis



Heart Failure

Imaging

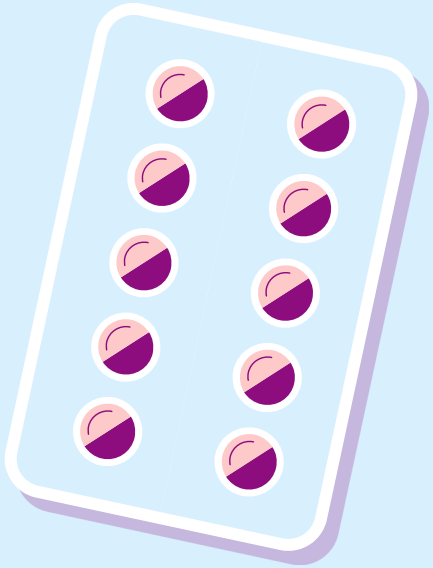
- Echocardiography
  - LVEF ≤40%
- Chest x-ray
  - Heart size
  - Pulmonary congestion
  - Rule out other causes

Labs

- Brain natriuretic peptide (BNP)
  - Released when cardiac wall stretches
  - Indicates volume overload
  - Higher BNP, more severe heart failure
    - RR: <100 pg/mL
- N-terminal proBNP
  - Precursor for BNP
  - Higher NT-proBNP, more work on heart
    - RR: <300 pg/mL

03

Staging



Heart Failure

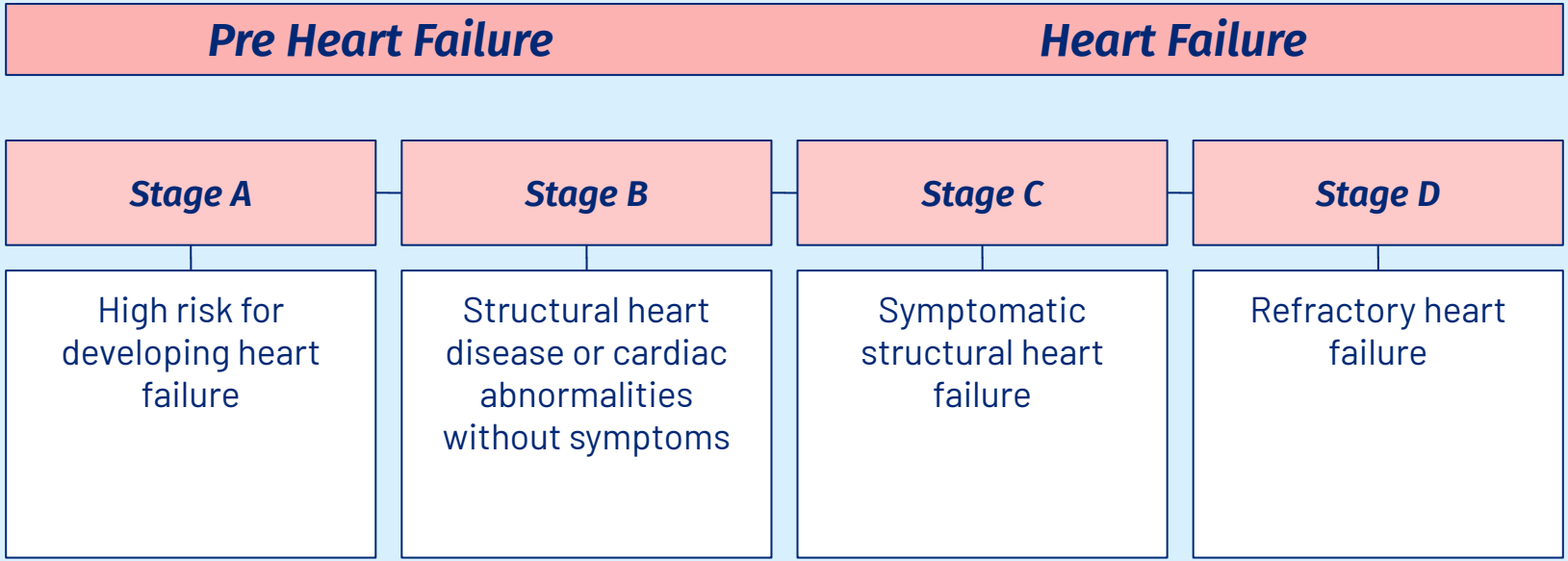
HFpEF

- Heart failure with **preserved** ejection fraction
  - LVEF ≥50%
- Near normal LVEF with symptoms of heart failure
- Diastolic dysfunction
  - “Filling problem”

HFrEF

- Heart failure with **reduced** ejection fraction
  - LVEF ≤40%
- Systolic dysfunction
  - “Pumping problem”

AHA/ACC Heart Failure Staging

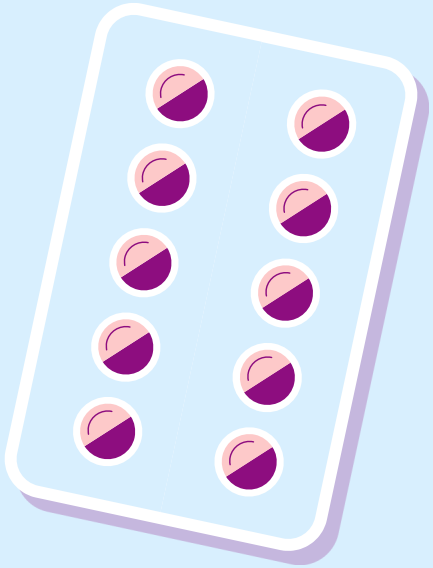


NYHA Functional Classification

Class I	Class II	Class III	Class IV
No symptoms from ordinary daily activities	No symptoms at rest Ordinary daily activities cause symptoms	No symptoms at rest Less than ordinary daily activities cause symptoms	Symptoms at rest Symptoms worsen with ordinary daily activities

03

AHA/ACC Guidelines



Celebration of Knowledge

1. Which medications are part of the “backbone” for the treatment of heart failure with reduced ejection fraction?

Celebration of Knowledge

1. Which medications are part of the “backbone” for the treatment of heart failure with reduced ejection fraction?

    a. ACEi/ARB/ARNi
    b. Beta-blockers
    c. SGLT2i
    d. MRA
    e. Loop Diuretics as needed

Celebration of Knowledge

2. Select all that apply: Which beta-blockers have evidence for reducing morbidity and mortality in heart failure?

    a. Metoprolol tartrate
    b. Metoprolol succinate
    c. Atenolol
    d. Labetalol
    e. Bisoprolol
    f. Carvedilol

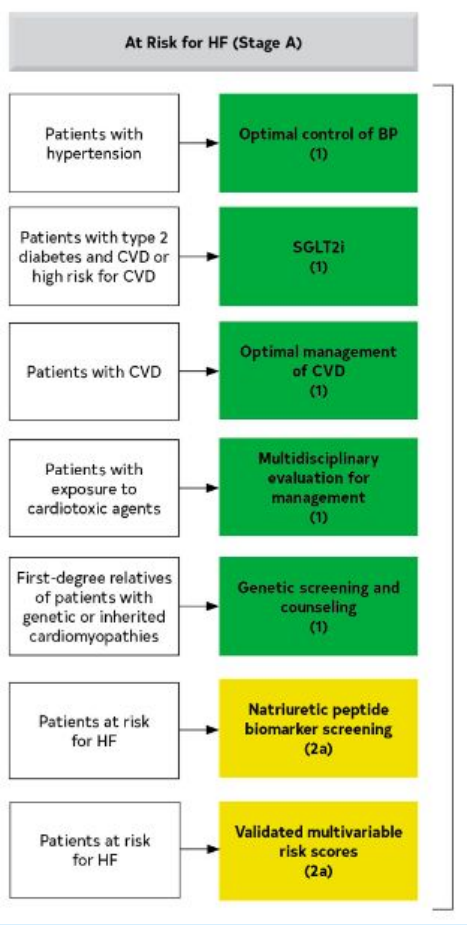
Celebration of Knowledge

2. Select all that apply: Which beta-blockers have evidence for reducing morbidity and mortality in heart failure?

    a. Metoprolol tartrate
    b. Metoprolol succinate
    c. Atenolol
    d. Labetalol
    e. Bisoprolol
    f. Carvedilol

Stage A

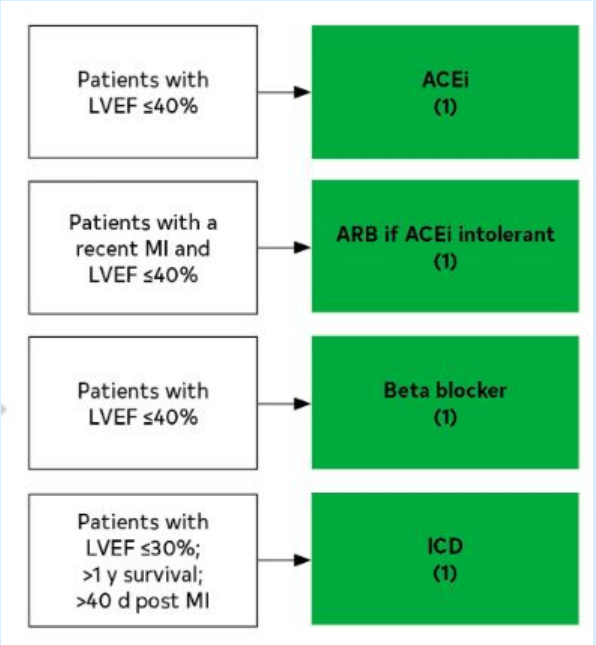
- **Goal:** Manage underlying conditions
- Hypertension
  - Optimize drug therapy
  - <130/80
- Type 2 Diabetes & ASCVD risk
  - SGLT2i
- Diet and lifestyle
  - Sodium <2300 mg/day
  - Exercise
  - Immunizations
  - Smoking cessation



Paul A. Heidenreich et al. J Am Coll Cardiol 2022; 79:1757-1780

Stage B

- **Goal:** slow progression to symptomatic heart failure
- ACEi
  - Greatest benefit seen in LVEF ≤40%
- Statins
  - Prevents additional CV events
  - Benefits shown in patients with MI
- Beta-blockers
  - Benefit shown in patients with asymptomatic heart failure with MI history



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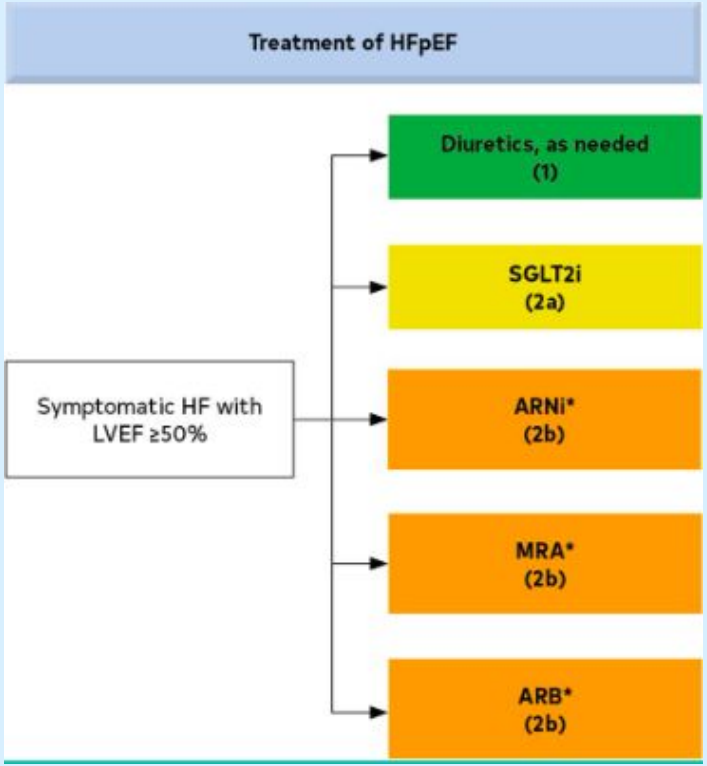
Stage C HFpEF

- **Goal:** manage symptoms and preserve LVEF
- Hypertension
  - Optimize drug therapy
- Diuretics
  - Reduce congestions
  - Improve symptoms
- SGLT2i
  - Decreased hospitalization and morbidity
- ARNi/MRA/ARB
  - Benefit shown in patients with LVEF closer to 50%



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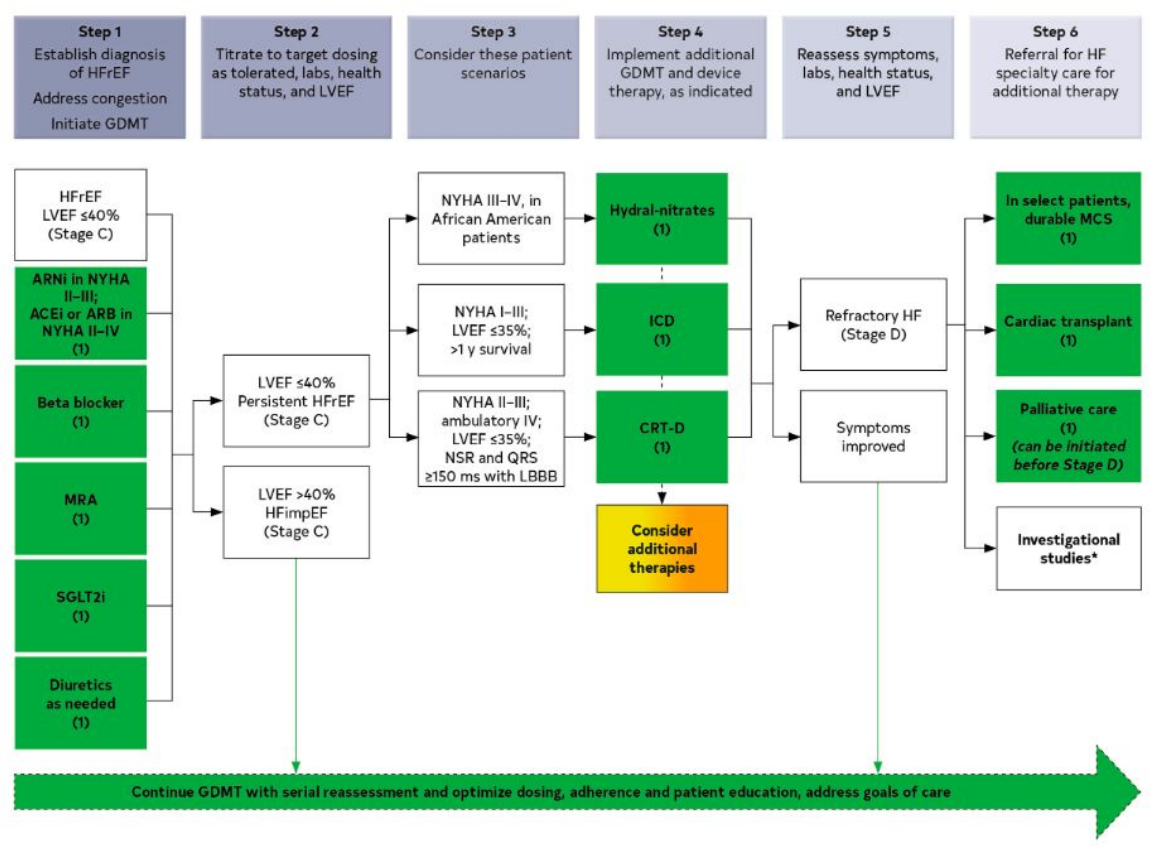
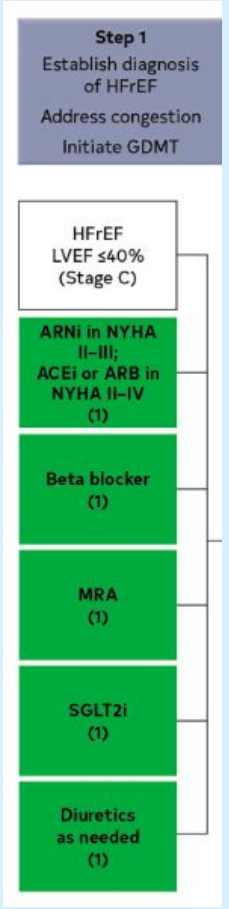
HFrEF



Paul A. Heidenreich et al. J Am Coll Cardiol 2022; 79:1757-1780

Stage C HFrEF

- **Goal:** manage symptoms and prevent decompensation
- Want patients to be on each medication at maximally titrated or tolerated dose, even if stabilized on lower doses
  - Improves outcomes
- Backbone initiation
  - Start all medications at once at low dose
  - Start one medication at a time
    - Order of initiation up to clinical discretion
    - Do not have to max out a medication before starting the next
    - Titrate doses as frequently as every 1-2 weeks



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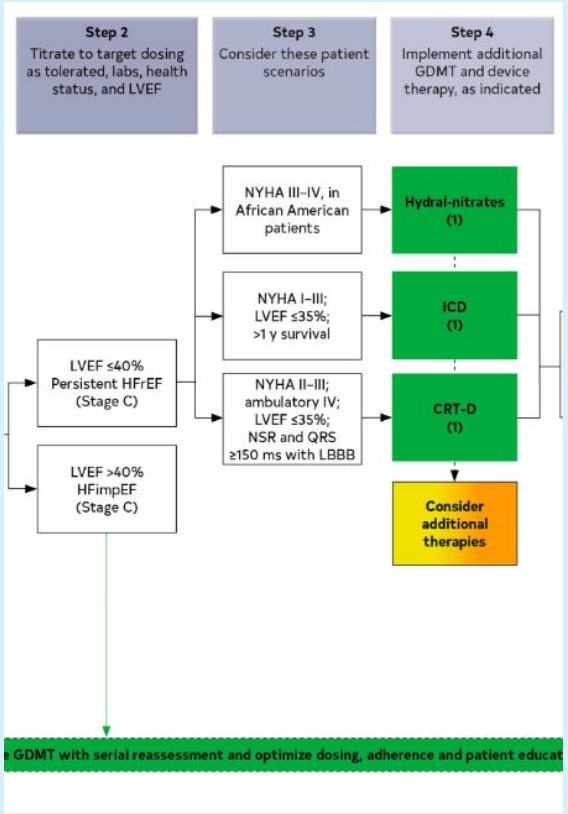
Stage C HFrEF

- **Goal:** manage symptoms to prevent progression and decompensation
- Hydralazine/Isosorbide
  - Recommend adding to optimized backbone regimen if persistent HFrEF
  - Consider adding to regimen for patients unable to take a first line agent
    - Morbidity and mortality outcomes uncertain
- Digoxin
  - Increases CO
  - Decreases hospitalizations



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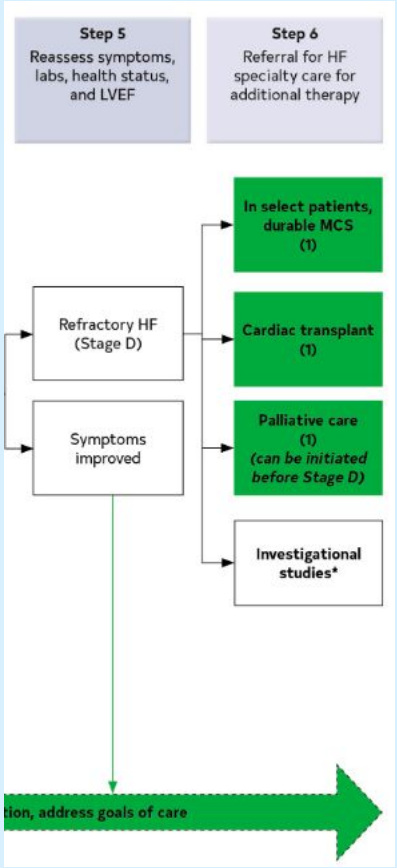
Stage D HFrEF

- **Goal:** continue symptom management and palliation
- Guidelines recommend referral to heart failure specialist



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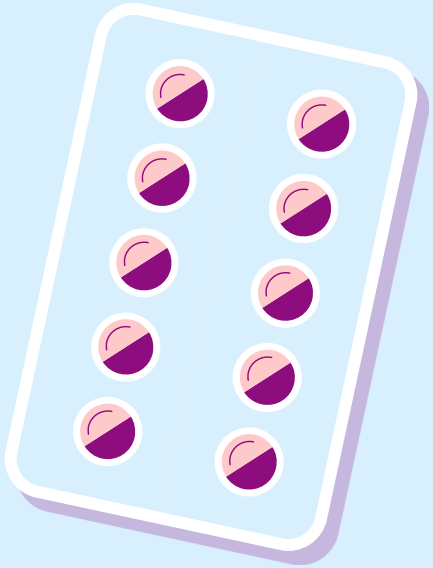
05

ARNi Background



Celebration of Knowledge

3. A patient with heart failure brings a new prescription for Entresto to the pharmacy. He was instructed to stop lisinopril, but is unsure of when to start the new medication. How long after the last lisinopril dose should the patient wait before starting Entresto?

    a. 12 hours
    b. 18 hours
    c. 24 hours
    d. 36 hours
    e. 48 hours

Celebration of Knowledge

3. A patient with heart failure brings a new prescription for Entresto to the pharmacy. He was instructed to stop lisinopril, but is unsure of when to start the new medication. How long after the last lisinopril dose should the patient wait before starting Entresto?

    a. 12 hours
    b. 18 hours
    c. 24 hours
    d. 36 hours
    e. 48 hours

Mechanism of Action

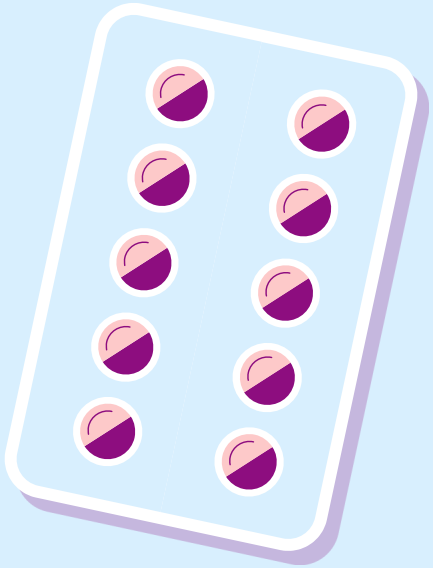
- Entresto (sacubitril/valsartan)
  - Valsartan: angiotensin II receptor blocker (ARB)
    - Angiotensin II: hormone that causes vasoconstriction
    - ARBs block angiotensin II at its receptor site to cause vasodilation
  - Sacubitril: neprilysin inhibitor
    - Neprilysin: enzyme that breaks down vasoactive peptides
    - Sacubitril increase the levels of these peptides
      - Natriuretic peptides: vasodilation, diuresis, natriuresis
    - Decreases blood pressure, fluid retention
    - Improves cardiac function in heart failure patients

Place in Therapy

- Recommended to use an ARNi over ACEi/ARB for patients in NYHA class II to III symptoms
  - Patients tolerating an ACEi/ARB should be switched to ARNi
  - Evidence for further morbidity and mortality improvement
- Recommended to use an ACEi for patients that cannot take an ARNi
  - Cost
- Recommended to use ARB for patients that cannot tolerate an ACEi
  - Cough

05

ARNi Efficacy



Angiotensin-neprilysin inhibition versus enalapril in heart failure

Design	• Double-blind, RCT including 8442 patients with class II, III, or IV NYHA symptoms and HFrEF (EF ≤40%) • 4187 participants received Entresto 200 mg BID and 4212 received enalapril 10 mg BID
Primary Outcome	• Death from cardiovascular causes and hospitalizations from heart failure • Difference in rate of death from cardiovascular causes between the two groups.
Results	• Trial was stopped early at 27 months • Death from cardiovascular causes or hospitalization for heart failure occurred in 21.8% of those in the Entresto group and 26.7% receiving enalapril • Entresto reduced the risk of hospitalization by 21%
Conclusion	• Entresto was superior to enalapril in reducing the risk of death and hospitalization for heart failure • Supports the use of Entresto over ACEi/ARBs in heart failure

McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077

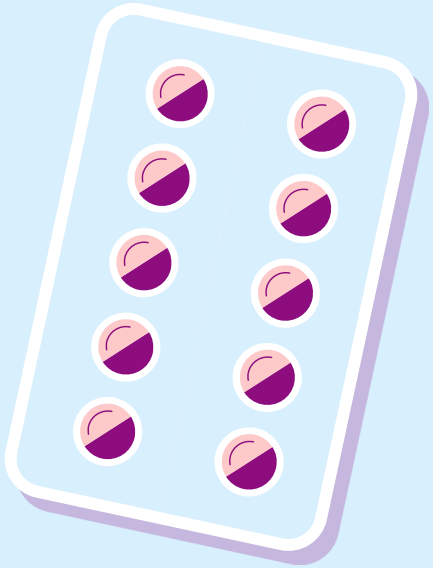
Effects of the Angiotensin-Receptor Neprilysin Inhibitor on Cardiac Reverse Remodeling: Meta-Analysis

Design	• Meta-analysis to searching PubMed, EMBASE, and the Cochrane Library to find studies published between 2010 to 2019 that focused on cardiac remodeling in ARNis, ACEi, ARBs. This included 20 studies with a total of 10,175 participants
Objective	• Assess the impact of ARNis on cardiac reverse remodeling compared to ACEi and ARBs
Results	• ARNis presented a significant improvement in the left ventricular size and hypertrophy compared to ACEi and ARBs. A greater benefit from cardiac reverse remodeling was seen in ARNis
Conclusion	• Entresto showed a greater improvement in the structure and function of the heart over ACEi and ARBs, supporting their use in heart failure

Wang Y, Zhou R, Lu C, Chen Q, Xu T, Li D. Effects of the Angiotensin-Receptor Neprilysin Inhibitor on Cardiac Reverse Remodeling: Meta-Analysis. J Am Heart Assoc. 2019;8(13):e012272. doi:10.1161/JAHA.119.012272

05

ARNi Safety



Safety

- Boxed Warning
  - Risk of injury or death to fetus
  - Avoid in pregnancy
  - Discontinue as soon as pregnancy detected
- Contraindications
  - Use within 36 hours of ACEi
  - Angioedema from ACEi
- Side effects
  - Hyperkalemia
  - Hypotension
  - Renal impairment
- Monitoring
  - Blood pressure
  - Potassium
  - Renal function

Dosing

- Starting dose
  - 24/26 mg BID
- If patient is already on a moderate to high ACEi or ARB
  - Start at 49/51 mg BID
- Target dose
  - 97/103 mg BID

Cost Comparison

Entresto
$13.76 per tablet
$412.80 per 30 day supply

Valsartan
$0.25 - $0.37 per tablet
$7.50 - $11.10 per 30 day supply

Lisinopril
$0.01 - $0.65 per tablet
$0.30 - $19.50 per 30 day supply

Bottomline

- Entresto has shown superiority compared to ACEi/ARBs for reduction of morbidity and mortality in HFrEF
  - However, significant cost associated with Entresto
  - ACEi/ARBs are appropriate alternatives with evidence supporting their use in HFrEF

References

1. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18). doi:https://doi.org/10.1161/cir.0000000000001063
2. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. Circulation. 2020;141(9):e139-596.
3. Ng TH, Yeung SL. Heart Failure. In: Chisholm-Burns MA, Schwinghammer TL, Malone PM, Kolesar JM, Bookstaver P, Lee KC. eds. Pharmacotherapy Principles & Practice 6e. McGraw Hill; 2022. https://ppp.mhmedical.com/content.aspx?bookid=3114s&sectionid=261459687
4. Heart Failure - Diagnosis | NHLBI, NIH. www.nhlbi.nih.gov. Published March 24, 2022. https://www.nhlbi.nih.gov/health/heart-failure/diagnosis
5. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004. doi:10.1056/NEJMoa1409077
6. Wang Y, Zhou R, Lu C, Chen Q, Xu T, Li D. Effects of the Angiotensin-Receptor Neprilysin Inhibitor on Cardiac Reverse Remodeling: Meta-Analysis. J Am Heart Assoc. 2019;8(13):e012272. doi:10.1161/JAHA.119.012272
7. Entresto (sacubitril/valsartan) [package insert]. East Hanover, NJ: Novartis Pharmaceutical Corp.;2015.
8. Lexidrugs: Entresto https://online-lexi-com.wilkes.idm.oclc.org/lco/action/doc/retrieve/docid/patch_f/5725052?cesid=aLnWaguQ4Xb&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dentresto%26t%3Dname%26acs%3Dfalse%26acq%3Dentresto

Thank you!

What questions do you have?

Shannon.brown1@wilkes.edu

The Skinny on GLP-1 RAs in Obesity

Dominic Maneval
PharmD Candidate 2024
Wilkes University

CONTROVERSY

- GLP-1 RAs are typically used to treat type 2 diabetes
- Many celebrities and others began to use them for weight loss
- Used as off-label indication
- Created a drug shortage for those with the labeled indication
- Diabetes drugs are once again available
    - Intermittent shortages of Wegovy at present
- FDA warns not to use off-brand compounded versions
    - Reports of adverse events
    - Compounders may use salt forms of semaglutide

Medications containing semaglutide. U.S. Food and Drug Administration. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/medications-containing-semaglutide-marketed-type-2-diabetes-or-weight-loss.

LEARNING OBJECTIVES

1. Describe Obesity Disease State and Management to Providers
2. Discuss GLP-1 RA Obesity Medication Characteristics
3. Examine Current Literature of GLP-1 RA Usage for Obesity
4. Formulate Conclusions about GLP-1 RAs in Obesity Patients

1. DESCRIBE OBESITY DISEASE STATE AND MANAGEMENT TO PROVIDERS

WHAT BMI IS CLASSIFIED AS OBESITY?

WHAT BMI IS CLASSIFIED AS OBESITY?

$\geq 30\ \mathrm{kg/m^2}$

OBESITY OVERVIEW

Definition	• BMI ≥ 30 kg/m^2
Epidemiology	• 2015: 12% prevalence in adults worldwide • 2013-2016: prevalence 36.5% in men and 40.8% in women in the US

DynaMed. Obesity in Adults. EBSCO Information Services. Accessed June 20, 2023. https://www.dynamed.com/condition/obesity-in-adults

ETIOLOGY

- Cause: positive energy imbalance
  - Increased energy intake or decreased energy expenditure
  - Long-term imbalance factors: behavioral, sociocultural, environmental, genetic, and physiological
  - Results in weight gain
- Determinants of imbalance:
  - Pleasure of consuming foods
  - Role of leptin in fasting and weight loss
    - Signals nutritional depletion and triggers changes to maintain homeostasis
    - Could also have anorectic effects

DynaMed. Obesity in Adults. EBSCO Information Services. Accessed June 20, 2023. https://www.dynamed.com/condition/obesity-in-adults

ETIOLOGY

- Appetite regulated by many brain areas
  - Hypothalamus
  - Dorsal vagal complex of brainstem
  - Reward mediating brain areas
- Hormones with anorectic effects
  - **Glucagon-like peptide (GLP-1)**
  - Insulin
  - Peptide tyrosine tyrosine (PYY)
  - Pancreatic polypeptide (PP)
  - Oxyntomodulin (OXM)
  - Glucagon
  - Cholecystokinin (CCK)
  - Amylin

DynaMed. Obesity in Adults. EBSCO Information Services. Accessed June 20, 2023. https://www.dynamed.com/condition/obesity-in-adults

DIAGNOSIS

- BMI parameters
- BMI does not directly measure adiposity
  - Sex, race, fluid status, muscularity, waist circumference
- Tests to rule out secondary causes
  - Thyroid function test
  - Endocrine evaluation: growth hormone assessment
  - Genetic testing
- Tests to rule out complications
  - Lipid profile: HLD
  - HbA1c: prediabetes, diabetes, or metabolic syndrome
  - Polysomnography: OSA
  - Testosterone deficiency if hypogonadism suspected

Classification by BMI	
30-34.9	Class 1: Mild
35-39.9	Class 2: Moderate
≥ 40	Class 3: Severe
≥ 50	"Super Obesity"

DynaMed. Obesity in Adults. EBSCO Information Services. Accessed June 20, 2023. https://www.dynamed.com/condition/obesity-in-adults

RISK FACTORS

- Lower socioeconomic status
- Genetic predisposition
- Highly processed diet with added sugar
- Physical inactivity
- Stress or depression
- Insufficient sleep
- Pregnancy

DynaMed. Obesity in Adults. EBSCO Information Services. Accessed June 20, 2023. https://www.dynamed.com/condition/obesity-in-adults

COMPLICATIONS

Increased risk of overall mortality

Lifetime impact of disability and morbidity

Orthopedic issues: low back pain, disk degeneration, hip replacement, knee osteoarthritis

Weight stigma: social devaluation of individuals due to excess body weight

Increased risk of:

- Cancer
- Cardiovascular disease
- Type 2 diabetes
- Dementia in middle aged adults
- GI disease
- Pregnancy complications

DynaMed. Obesity in Adults. EBSCO Information Services. Accessed June 20, 2023. https://www.dynamed.com/condition/obesity-in-adults

MANAGEMENT

- American Association of Clinical Endocrinologists / American College of Endocrinology
  - Make available a structured lifestyle intervention program consisting of a healthy meal plan, physical activity, and behavioral interventions
- Weight loss diets need caloric expenditure to exceed caloric intake
- Exercise may promote weight loss, especially when added to dietary change
- Behavioral strategies
- Acupuncture
- Surgery – bariatric surgery and liposuction
- Weight loss medication may be used as an adjunct to diet, behavioral therapy, and exercise

DynaMed. Obesity in Adults. EBSCO Information Services. Accessed June 20, 2023. https://www.dynamed.com/condition/obesity-in-adults

FDA APPROVED MEDICATIONS

- Options
  - Orlistat (Xenical)
  - Naltrexone plus Bupropion ER(Contrave)
  - Phentermine plus topiramate ER (Qsymia)
  - Setmelanotide (Imcivree)
  - **Liraglutide (Saxenda)**
  - **Semaglutide (Wegovy)**
- Off-label use of meds can involve penalties
  - Ohio – can be felony or loss of medical license

DynaMed. Obesity in Adults. EBSCO Information Services. Accessed June 20, 2023. https://www.dynamed.com/condition/obesity-in-adults

GUIDELINES

American Association of Clinical Endocrinologists / American College of Endocrinology (AACE/ACE) Recommendations:

- Offer approved meds for chronic management of obesity and use weight loss meds only as an adjunct to lifestyle therapy including diet modification, physical activity, and behavioral interventions (AACE/ACE Grade A, Best evidence level 1)
  - Drug therapy in addition to lifestyle changes results in greater weight loss compared to lifestyle alone
- When choosing medication, consider patient factors, efficacy, adverse effects, and warnings
  - No recommendations for step care approach
  - Recommended to use FDA approved meds or can use others if there is enough safety and efficacy data to analyze benefit to risk ratio

DynaMed. Obesity in Adults. EBSCO Information Services. Accessed June 20, 2023. https://www.dynamed.com/condition/obesity-in-adults

GUIDELINES

Endocrine Society Recommendations on Pharmacological Management of Obesity

- Use medications only as an adjunct to a comprehensive, long-term management program that includes diet modification, physical activity, and behavior therapy (Endocrine Society Strong recommendation, Moderate-quality evidence)
  - In patients with BMI ≥ 30 without concomitant risk factors
  - In patients with BMI ≥ 27 with concomitant risk factors
    - HTN, dyslipidemia, CAD, T2DM, and OSA
  - Only continue if weight loss tolerated and ≥ 5% in 3 months

DynaMed. Obesity in Adults. EBSCO Information Services. Accessed June 20, 2023. https://www.dynamed.com/condition/obesity-in-adults

2.DISCUSS GLP-1 RA OBESITY MEDICATION CHARACTERISTICS

WHICH IS NOT A MECHANISM OF GLP-1 RA'S?

a. Promote satiety and slow gastric emptying
b. Reduce tubular glucose reabsorption
c. Decrease Hepatic glucose production
d. Stimulate glucose dependent insulin release

WHICH IS NOT A MECHANISM OF GLP-1 RA'S?

a. Promote satiety and slow gastric emptying
b. **Reduce tubular glucose reabsorption**
c. Decrease Hepatic glucose production
d. Stimulate of glucose dependent insulin release

MECHANISM

- Glucagon-like peptide 1 receptor agonists
- GLP1 is a gastrointestinal peptide involved in glucose homeostasis
  - An incretin hormone linking absorption of nutrients from GI tract with pancreatic hormone secretion
  - Released after ingestion of glucose, protein, and fat
- Binds to specific GLP1 receptor and exerts main effect by stimulating glucose dependent insulin release from pancreatic islets
  - Decreases glucagon production and hepatic glucose production
  - Slows gastric emptying and promotes satiety
  - Feel full faster and longer = less food consumption

Dungan K, DeSantis A. Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus. UpToDate. May 4, 2023. Accessed June 22, 2023. https://www.uptodate.com/contents/glucagon-like-peptide-1-based-therapies-for-the-treatment-of-type-2-diabetes-mellitus#references.

WEGOVY (SEMAGLUTIDE)

- Dosing: subcutaneous once weekly
  - Weeks 1-4: 0.25 mg
  - Weeks 5-8: 0.5 mg
  - Weeks 9-12: 1 mg
  - Weeks 13-16: 1.7 mg
- maintenance dose: 2.4 mg
  - Max T2DM dose: 2 mg
- If increase not tolerated, consider delaying escalation for 4 weeks
- May temporarily reduce dose to 1.7 mg to improve tolerance but for no longer than 4 weeks
  - If not able to tolerate max dose, discontinue
- Approved 12 years or older with max dose of 1.7 mg once weekly

(Semaglutide). In: Merative Micromedex® DRUGDEX® (electronic version). Merative Healthcare Solutions/EBSCO Information Services, Greenwood Village, Colorado; Cambridge, Massachusetts, USA. Available at: https://www.dynamed.com (cited: June 23, 2023)

LIRAGLUTIDE (SAXENDA)

- Dosing: subcutaneous daily
  - Titration
    - 0.6 mg daily for 1 week
    - Increase weekly in 0.6 mg increments until maintenance dose of 3 mg reached
    - Can delay escalation for a week if needed
  - Continue on max tolerated dose even if < 3 mg
  - Discontinue at 16 weeks if at least 4% weight loss not observed
  - Max T2DM dose: 1.8 mg daily

(Liraglutide). In: Merative Micromedex® DRUGDEX® (electronic version). Merative Healthcare Solutions/EBSCO Information Services, Greenwood Village, Colorado; Cambridge, Massachusetts, USA. Available at: https://www.dynamed.com (cited: June 23, 2023)

ADVERSE EFFECTS

- Hypoglycemia
- GI: abdominal pain, constipation, diarrhea, nausea, and vomiting
  - Higher incidence with weight management versus diabetes
- Headache
- Upper respiratory infection (Saxenda)

(Liraglutide). In: Merative Micromedex® DRUGDEX® (electronic version). Available at: https://www.dynamed.com (cited: June 23, 2023)
(Semaglutide). In: Merative Micromedex® DRUGDEX® (electronic version). Available at: https://www.dynamed.com (cited: June 23, 2023)

CONTRAINDICATIONS

- Black Box Warning for thyroid C-cell tumors including medullary thyroid carcinoma (MTC)
  - Only seen in rodents
  - Contraindicated in patients with personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2)
- Liraglutide contraindicated in pregnancy in patients treated for obesity
  - Not recommended for semaglutide

(Liraglutide). In: Merative Micromedex® DRUGDEX® (electronic version). Available at: https://www.dynamed.com (cited: June 23, 2023)
(Semaglutide). In: Merative Micromedex® DRUGDEX® (electronic version). Available at: https://www.dynamed.com (cited: June 23, 2023)

ADMINISTRATION

- Inject in abdomen, thigh, or upper arm
- Wegovy
  - Missed dose: if more than 2 days from next dose, administer as soon as possible. If not, do not administer
  - Same day each week at any time of day
- Saxenda
  - Missed dose: do not double up
    - If missed 3 days in a row, reinitiate at 0.6 mg daily
  - Administer at any time of day independent of meals

(Liraglutide). In: Merative Micromedex® DRUGDEX® (electronic version). Available at: https://www.dynamed.com (cited: June 23, 2023)
(Semaglutide). In: Merative Micromedex® DRUGDEX® (electronic version). Available at: https://www.dynamed.com (cited: June 23, 2023)

ADDITIONAL BENEFITS

ASCVD

- **Semaglutide**
- **Liraglutide**
- Dulaglutide

Renal

- **Semaglutide**
- **Liraglutide**
- Dulaglutide

Heart failure: neutral

American Diabetes Association. Section 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2023. Individual manufacturer product labels.

TRUE OR FALSE: PATIENTS ARE MORE LIKELY TO EXPERIENCE GI ADVERSE EFFECTS OF GLP-1 RA'S WHEN BEING TREATED FOR DIABETES VERSUS OBESITY.

TRUE OR FALSE: PATIENTS ARE MORE LIKELY TO EXPERIENCE GI ADVERSE EFFECTS OF GLP-1 RA'S WHEN BEING TREATED FOR DIABETES VERSUS OBESITY.

False

3. EXAMINE CURRENT LITERATURE OF GLP-1 RA USAGE FOR OBESITY

EFFECTIVENESS OF GLP-1 RA IN WEIGHT LOSS

- Meta-analysis form PubMed, Embase, and Cochrane Library for RCTs in adults with overweight and obesity
- GLP-1 RAs associated with a greater reduction in % BW and higher likelihood of weight loss ≥ 5% in people without diabetes compared with lifestyle modification alone
- GLP-1 RAs and phentermine/topiramate may increase weight loss compared to most other medications but may increase adverse events compared to lifestyle modification alone
  - Compared agents: lifestyle modification alone, levocarnitine, metformin, naltrexone / bupropion, orlistat, pramlintide, SGLT2i
    - All effective compared to lifestyle modification alone except levocarnitine
- Post-hoc analysis: semaglutide showed substantially larger weight loss with similar risk of AE when compared to other GLP1s

Shi Q, Wang Y. Lancet. 2022 Jan 15;399(10321):259-269. doi: 10.1016/S0140-6736(21)01640-8.

WEGOVY TRIAL

- Population: obese patients without diabetes
- Participants lost a mean 14.9% in study group vs 2.4% weight loss in placebo group after 68 weeks
- Patients receiving Wegovy also had improvement in cardiometabolic risk factors
- Nausea and diarrhea most common AE
  - Typically transient and mild to moderate severity
  - 4.5% of patients discontinued due to this

Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF, STEP 1 Study Group. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021;384:989.

SAXENDA TRIAL

- Population: obese patients without diabetes
- Participants lost a mean 6% screening weight during run-in
- Randomization to week 56
  - Liraglutide group lost an additional mean 6.2%, placebo lost additional 0.2%
  - More participants receiving liraglutide maintained the run-in weight loss
- Most common side effects: nausea and vomiting
- Produced small but statistically significant improvements in cardiometabolic risk factors compared to placebo

Wadden TA, Hollander P, Klein S, Niswender K, Woo V, Hale PM, Aronne L; NN8022-1923 Investigators. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: The SCALE maintenance randomized study. Int J Obes (Lond) 2013;37:1443–1451.

COMPARATIVE TRIALS

- Randomized double-blind controlled trial
  - Semaglutide and liraglutide compared, semaglutide given at various doses
  - Mean bodyweight reductions for at least 0.2 mg daily semaglutide versus liraglutide were all significant
    - 11.3% to 13.8% versus 7.8% at week 52
- Randomized trial
  - Once weekly semaglutide 2.4 mg vs once daily liraglutide 3 mg
  - Weight loss at 68 weeks
    - 15.8% with semaglutide versus 6.4% with liraglutide
  - GI AE: semaglutide 84.1% versus liraglutide 82.7%
- Both studies in patients without diabetes

O'Neil PM. Lancet. 2018 Aug 25;392(10148):637-649. doi: 10.1016/S0140-6736(18)31773-2.
Rubino DM. JAMA. 2022 Jan 11;327(2):138-150. doi: 10.1001/jama.2021.23619.

INSURANCE COVERAGE

- Medicare does not cover obesity medications
- Medicaid and private insurance coverage may vary
  - Likely may require prior authorization
- $1,349.02 per package
  - Both manufactured by Novo Nordisk
- Savings offers and coupons available

Saxenda® (liraglutide) injection 3mg list Price & https://www.novocare.com/obesity/products/saxenda/explaining-list-price.html.
Wegovy® (semaglutide) injection 2.4 mg list price & https://www.novocare.com/obesity/products/wegovy/let-us-help/explaining-list-price.html.

4. FORMULATE CONCLUSIONS ABOUT GLP-1 RAS IN OBESITY PATIENTS

CONCLUSIONS

- Obesity is a disease state with many causes and complications
- Medications should be used as an adjunct to diet modification, physical activity, and behavioral interventions
- Approved GLP-1 RAs for obesity include Wegovy and Saxenda
- Both have proven weight loss benefit, but Wegovy may be superior
- These medications are often expensive and not covered by insurance

The Skinny on GLP-1 RAs in Obesity

Dominic Maneval
PharmD Candidate 2024
Wilkes University

My Heart Can't Go On: A Lighthearted Look at a newer Heart Failure Treatment

By: Andrew Dean
PharmD Candidate 2024
Wilkes University
June 27, 2023

Formal Topic Discussion Presentation
Internal Medicine APPE Rotation

Learning Objectives

1. Explain the role of therapy for myosin activators in heart failure
2. Classify the drugs in the myosin activator class
3. Implement the therapy of myosin activators when applicable
4. Question whether or not Myosin Activators should be part of the gold standard of therapy in heart failure

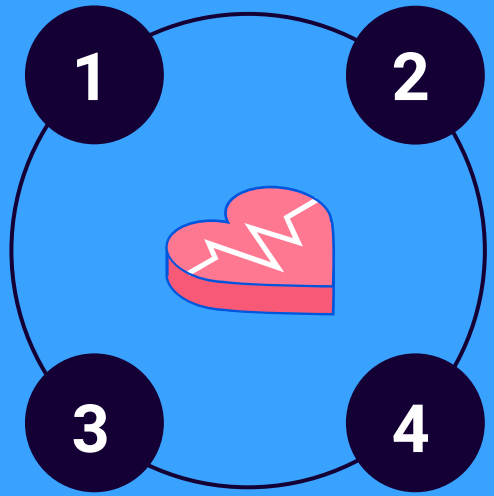


Table of Contents

01

Introduction

Definition

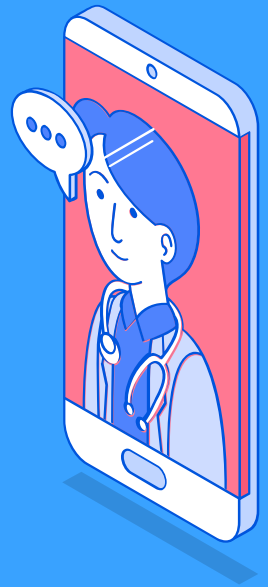
Definition

- In the simplest of terms, heart failure is when the heart has trouble pumping blood to the body
  - Problem filling and ejecting blood
    - Can be reminiscent of a contusion with the structure or function of the heart
  - Three types
    - Left Sided Heart Failure
    - Right Sided Heart Failure
    - High-output Heart Failure

Professional CC medical. Congestive heart failure: What does it mean? Cleveland Clinic. Accessed June 26, 2023. https://my.clevelandclinic.org/health/diseases/17069-heart-failure-understanding-heart-failure#:~:text=Types%20of%20congestive%20heart%20failure%20include%3A,High%2Doutput%20heart%20failure.

Definition cont.

- Two subcategories
  - Heart Failure with Reduced Ejection Fraction (HFrEF)
    - Systolic Problem
    - Ejection Fraction of ≤ 40%
  - Heart Failure with Preserved Ejection Fraction (HFpEF)
    - Diastolic Problem
    - Ejection Fraction of ≥ 50%



Parker RB, Rodgers J. Chronic Heart Failure. In: DiPiro JT, Yee GC, Michael Posey LL, Haines ST, Nolin TD, Ellingrod VL. eds. DiPiro: Pharmacotherapy A Pathophysiologic Approach, 12e
. McGraw Hill; 2021. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=267924089

Epidemiology

Epidemiology

1/3

Of heart failure patients are hospitalized within 30 days of diagnosis

44.6%

Of heart failure patients experience an all-cause rehospitalization

1,000,000+

Americans are diagnosed with heart failure annually

$30,700,000,000

Is the amount it cost the nation to treat heart failure in 2012

Heart failure. Centers for Disease Control and Prevention. January 5, 2023. Accessed June 26, 2023. https://www.cdc.gov/heartdisease/heart_failure.htm.

Etiology/Pathophysiology

Etiology/Pathophysiology

- Formula
  - Cardiac Output (CO) = Heart Rate (HR) x Stroke Volume (SV)
- Compensatory Actions
  - This is the bodies way of trying to make up for the lack of something else due to a precipitating event
  - How it's related to HF
    - CO goes down therefore a compensatory action takes place with hoping for a good outcome to occur but instead a bad outcome usually happens which makes CO decline more

Parker RB, Rodgers J. Chronic Heart Failure. In: DiPiro JT, Yee GC, Michael Posey LL, Haines ST, Nolin TD, Ellingrod VL. eds. DiPiro: Pharmacotherapy A Pathophysiologic Approach, 12e
. McGraw Hill; 2021. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=267924089

Etiology/Pathophysiology cont.

- Why are we worried about compensatory actions?
  - The drug class I will be covering today specifically works on this
- Cardiac hypertrophy and cardiac remodeling
  - The body is trying to have a good outcome by reducing heart wall stress, volume, and pressure
  - The two bad outcomes of this though are;
    - Cardiac remodeling
      - Change in size and structure which in turn will make the heart work less efficient ultimately causing an increase in CO
    - Ventricular hypertrophy
      - Increase in muscle mass which increases myocardial oxygen (O2) demand therefore increasing work for the heart

Parker RB, Rodgers J. Chronic Heart Failure. In: DiPiro JT, Yee GC, Michael Posey LL, Haines ST, Nolin TD, Ellingrod VL. eds. DiPiro: Pharmacotherapy A Pathophysiologic Approach, 12e
. McGraw Hill; 2021. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=267924089

Clinical Presentation

Clinical Presentation

- General presentation
  - Shortness of breath
    - While at rest or while lightly active
  - Chest pain
  - Heart palpitations
  - Swelling in your ankles, legs, abdomen
    - Unwanted weight gain
  - Loss of appetite
    - Nausea
  - Fatigue at rest or while lightly active

Parker RB, Rodgers J. Chronic Heart Failure. In: DiPiro JT, Yee GC, Michael Posey LL, Haines ST, Nolin TD, Ellingrod VL. eds. DiPiro: Pharmacotherapy A Pathophysiologic Approach, 12e
. McGraw Hill; 2021. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=267924089

Diagnosis

Diagnosis

- In Chronic heart failure (CHF) there are three categories and two subcategories that we look at and diagnose patients with

- Before we even get to that though we have to run tests and do assessments
  - Echocardiogram
    - Get ejection fraction
    - Heart size
  - Chest X-ray
    - Heart size
    - Pulmonary edema

Parker RB, Rodgers J. Chronic Heart Failure. In: DiPiro JT, Yee GC, Michael Posey LL, Haines ST, Nolin TD, Ellingrod VL. eds. DiPiro: Pharmacotherapy A Pathophysiologic Approach, 12e
. McGraw Hill; 2021. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=267924089

Diagnosis cont.

- Brain natriuretic peptide (BNP) test
  - Indicates how much BNP is in your bloodstream
  - Produced in ventricles and are released as the cardiac wall stretches
  - Higher concentrations correlate to a higher degree of HF
- Left, right, or high-output?
  - Left refers to pulmonary congestion due to slacking left ventricle
  - Right refers to systemic congestion due to slacking right ventricle
  - High-output refers to the heart pumping a higher than normal amount of blood

Important note: Having any of these do not affect therapy!!

- HFrEF or HFpEF
  - Reserved EF characterized by ≤ 40%
  - Preserved EF characterized by ≥ 50%

Parker RB, Rodgers J. Chronic Heart Failure. In: DiPiro JT, Yee GC, Michael Posey LL, Haines ST, Nolin TD, Ellingrod VL. eds. DiPiro: Pharmacotherapy A Pathophysiologic Approach, 12e . McGraw Hill; 2021. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=267924089

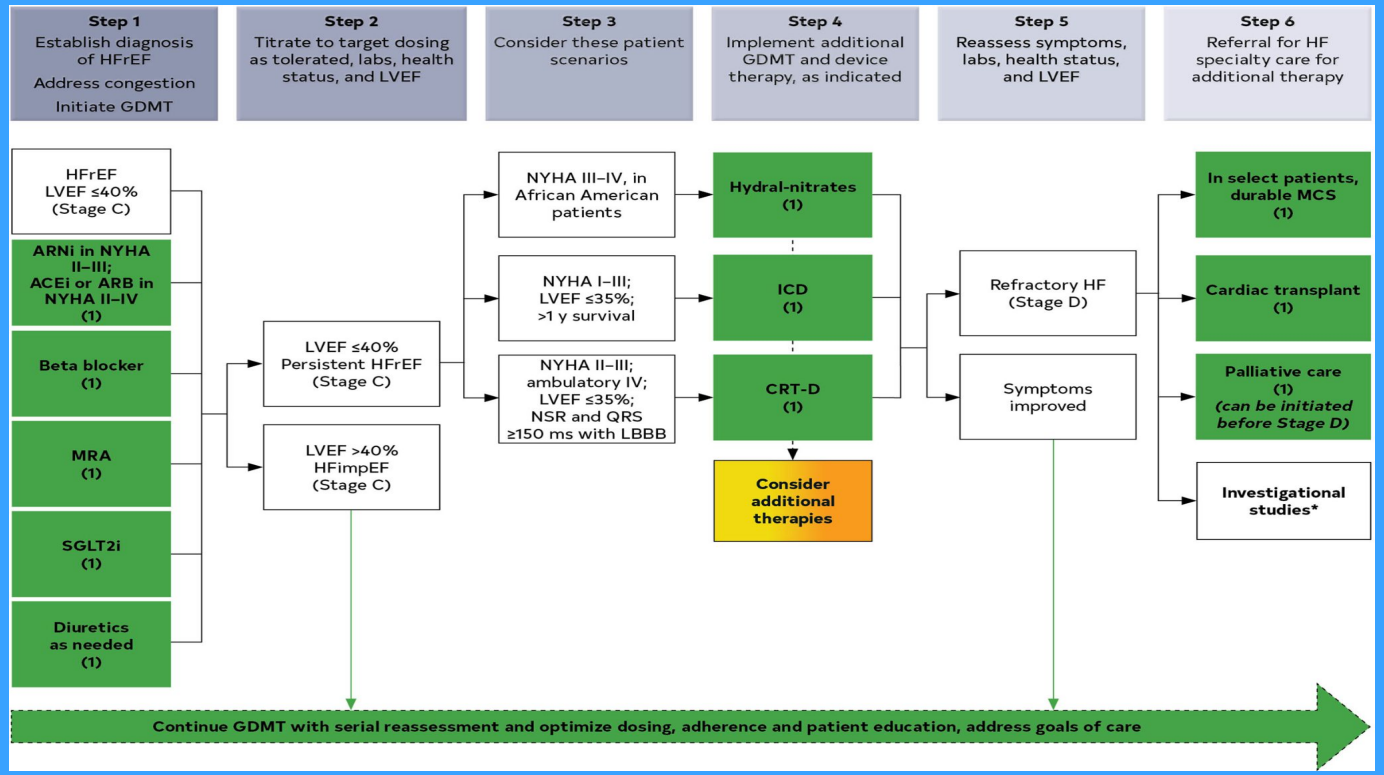
Diagnosis cont.

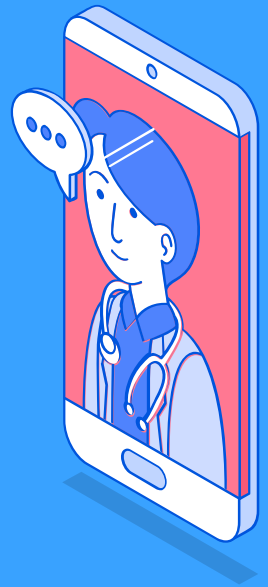
NYHA Class	Level of Clinical Impairment
I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

Lorenzini M. New York Heart Association (NYHA) heart failure symptom classification ... 2016. Accessed June 26, 2023. https://www.researchgate.net/figure/New-York-Heart-Association-NYHA-Heart-Failure-Symptom-Classification-System_fig1_303031519.

Current Therapies

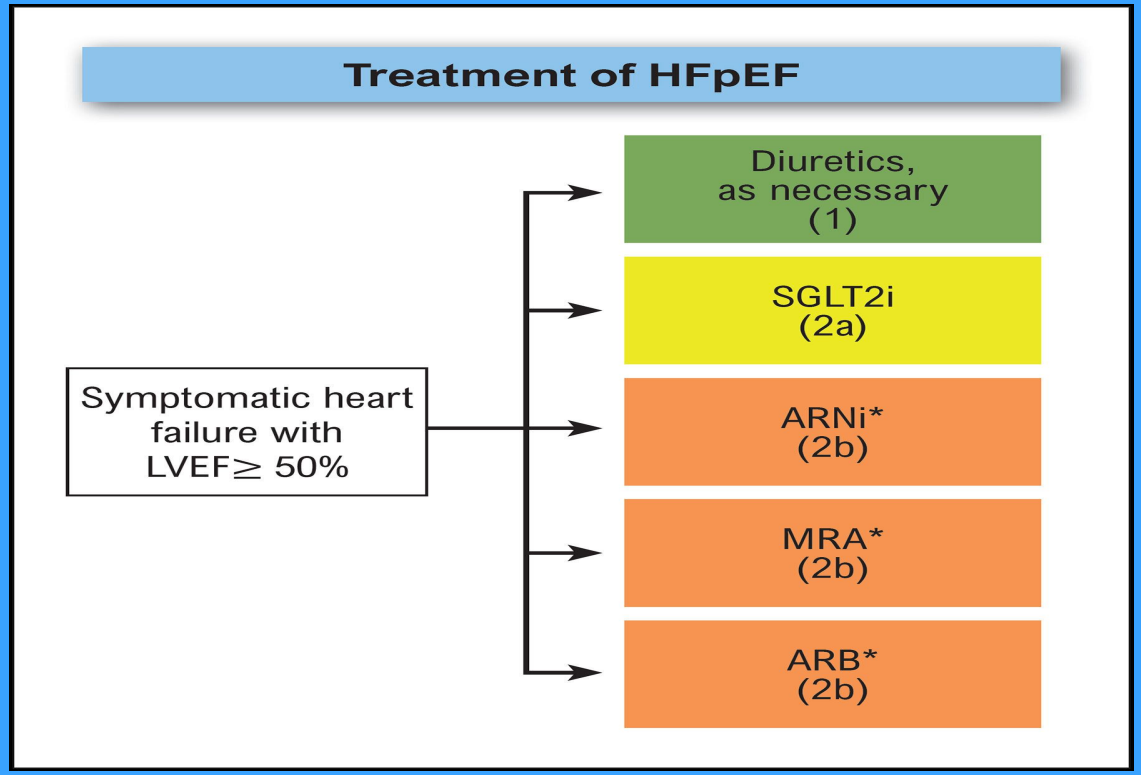
Known Therapies





Heidenreich P. 2022 AHA/ACC/HFSA guideline for the management of heart failure ... 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. 2022. Accessed June 26, 2023. https://www.ahajournals.org/doi/10.1161/CIR.0000000000001062.

Known Therapies cont.



Heidenreich P. 2022 AHA/ACC/HFSA guideline for the management of heart failure ... 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. 2022. Accessed June 26, 2023. https://www.ahajournals.org/doi/10.1161/CIR.0000000000001062.

Myosin Activator

Myosin Activator Background

- Originally designed to treat hypertrophic obstructive cardiomyopathy (HOCM)
  - Further testing has shown its benefits in preventing the progression of HF in reducing cardiac remodeling and ventricular hypertrophy
- Agents
  - Mavacamten (Camzyos)
    - Only one FDA approved (4/28/2022)
    - Mainly used for (HOCM)
  - Omecamtiv mecarbil
    - Has been denied by FDA due to inconclusive results
    - Focuses on the secondary benefits
  - Aficamten
    - Still in Phase II and III trials
    - Not a lot of literature out there on medication

Day SM, Tardiff JC, Ostap EM. Myosin modulators: Emerging approaches for the treatment of Cardiomyopathies and heart failure. The Journal of Clinical Investigation. March 1, 2022. Accessed June 26, 2023. https://www.jci.org/articles/view/148557.

Medication Dosing

Medication Dosing

- Mavacamten Dosing (Initial)

Hypertrophic cardiomyopathy with left ventricular outflow tract obstruction

Hypertrophic cardiomyopathy with left ventricular outflow tract obstruction:

Note: Only initiate therapy in patients with left ventricular ejection fraction (LVEF) ≥55%. If LVEF falls to <50% at any point, interrupt therapy (see "Dosing: Adjustment for Toxicity: Adult"). Recheck LVEF regularly and at least 4 weeks after dose adjustments. Delay dose increases or consider interrupting therapy when there is a concurrent illness or arrhythmia present that may impair systolic function.

Oral:

Initiation phase:

Initial: 5 mg once daily, only if LVEF is ≥55%; further titration is based on Valsalva left ventricular outflow tract (LVOT) gradient and LVEF reassessment every 4 weeks.

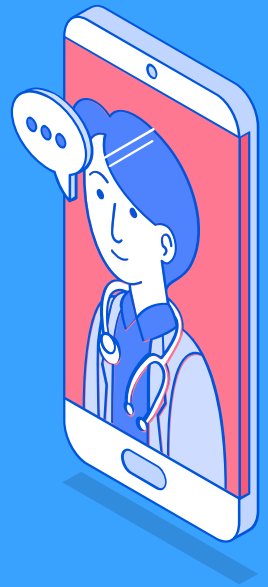
Week 4 assessment**:** If Valsalva LVOT gradient is <20 mm Hg, reduce dose to 2.5 mg once daily. If Valsalva LVOT gradient is ≥20 mm Hg, continue 5 mg once daily.

Week 8 assessment, **patients on 2.5 mg once daily**: If Valsalva LVOT gradient is <20 mm Hg, interrupt therapy and reassess at week 12. If Valsalva LVOT gradient is ≥20 mm Hg, continue 2.5 mg once daily.

Week 8 assessment, **patients on 5 mg once daily**: If Valsalva LVOT gradient is <20 mm Hg, reduce dose to 2.5 mg once daily. If Valsalva LVOT gradient is ≥20 mm Hg, continue 5 mg once daily.

Week 12 assessment, **patients who needed to interrupt therapy at week 8**: If LVEF is ≥50%, restart 2.5 mg once daily and continue for the next 12 weeks unless LVEF falls <50%.

Week 12 assessment, **patients on 2.5 mg or 5 mg once daily:** See “Maintenance phase” below.



Lexicomp. Mavacamten (Lexi-Drugs). 2022. Accessed 2023. https://online-lexi-com.wilkes.idm.oclc.org/lco/action/doc/retrieve/docid/patch_f/7219055?cesid=9grcYH7Cnsz&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dmavacamten%26t%3Dname%26acs%3Dtrue%26acq%3Dmava#pha.

Medication Dosing cont.

- Mavacamten Dosing (Maintenance)

Maintenance phase:

LVEF <50% at any time: Interrupt therapy and see "Dosing: Adjustment for Toxicity: Adult."

LVEF 50% to 55%, regardless of Valsalva LVOT gradient: Maintain current dose and reassess in 12 weeks.

LVEF >55% and Valsalva LVOT gradient <30 mm Hg: Maintain current dose and reassess in 12 weeks.

LVEF ≥55% and Valsalva LVOT gradient ≥30 mm Hg: Increase dose to the next higher daily dosage level after being on the same dose for 12 weeks (eg, 2.5 mg once daily increased to 5 mg once daily, or 5 mg once daily increased to 10 mg once daily, or 10 mg once daily increased to 15 mg once daily). A maximum dose is not specifically noted in the prescribing information, but it does not mention titrating beyond 15 mg once daily, and the clinical trial did not titrate beyond 15 mg once daily (Olivotto 2020).

Lexicomp. Mavacamten (Lexi-Drugs). 2022. Accessed 2023. https://online-lexi-com.wilkes.idm.oclc.org/lco/action/doc/retrieve/docid/patch_f/7219055?cesid=9grcYH7Cnsz&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dmavacamten%26t%3Dname%26acs%3Dtrue%26acq%3Dmava#pha.

Medication Dosing cont.

- Omecamtiv mecarbil
  - No approved dosing besides the clinical trial dosing
- Aficamten
  - No approved dosing besides the clinical trial dosing

Question #1

What are the three names of the current myosin modulators? (Select all that apply)

A) Omecamtiv mecarbil
B) Aficamten
C) Mavacamten
D) Dilcamten
E) Mecamtiv

Question #1

What are the three names of the current myosin modulators? (Select all that apply)

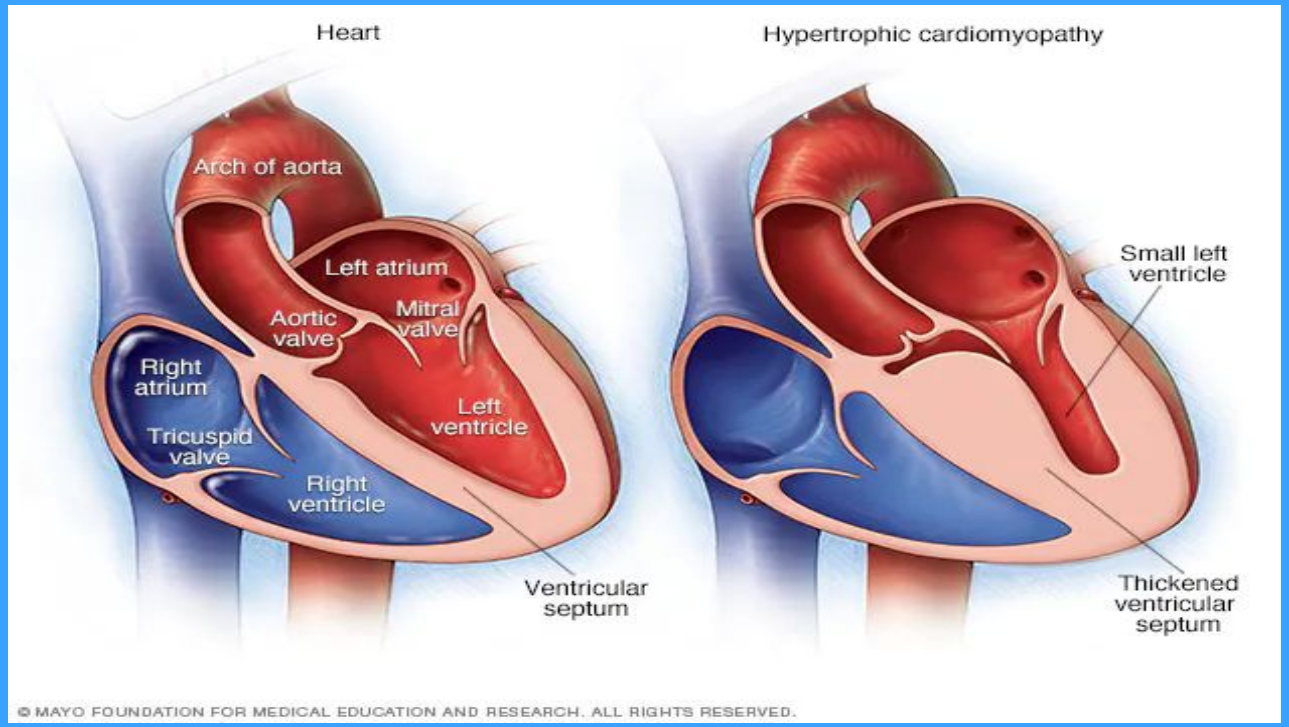
A) Omecamtiv mecarbil
B) Aficamten
C) Mavacamten
D) Dilcamten
E) Mecamtiv

02

Review of Therapy

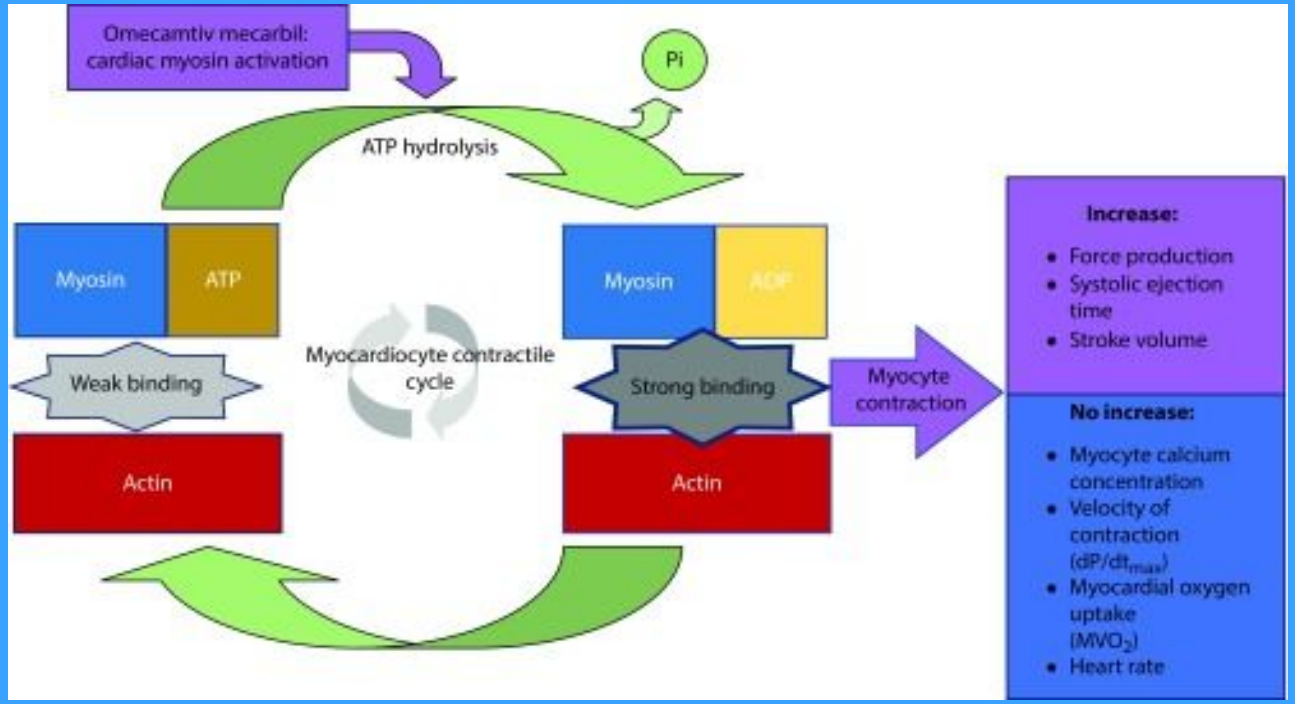
Mechanism of Action

Mechanism of Action



Hypertrophic cardiomyopathy. Mayo Clinic. May 11, 2023. Accessed June 26, 2023. https://www.mayoclinic.org/diseases-conditions/hypertrophic-cardiomyopathy/diagnosis-treatment/drc-20350204.

Mechanism of Action cont.



Kaplinsky E, Mallarkey G. Cardiac myosin activators for heart failure therapy: Focus on Omecamtiv Mecarbil. Drugs in context. April 23, 2018. Accessed June 26, 2023. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5916097/.

Side Effects

Side Effects

- Mavacamten
  - Dizziness
  - Nausea (noted in VALOR study)
  - Still being tested for more
- Omecamtiv mecarbil
  - Fatigue
  - Dizziness
- Aficamten
  - Fatigue
  - Dizziness

Lexicomp. Mavacamten (Lexi-Drugs). 2022. Accessed 2023. https://online-lexi-com.wilkes.idm.oclc.org/lco/action/doc/retrieve/docid/patch_f/7219055?cesid=9grcYH7Cnsz&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dmavacamten%26t%3Dname%26acs%3Dtrue%26acq%3Dmava#pha.

General Information

Clinical Pearls (Mavacamten)

Really Expensive, $8,220 for 30 day supply

Only a branded drug as of right now

Does not need to be renally adjusted

Requires a REMS program

Lexicomp. Mavacamten (Lexi-Drugs). 2022. Accessed 2023. https://online-lexi-com.wilkes.idm.oclc.org/lco/action/doc/retrieve/docid/patch_f/7219055?cesid=9grcYH7Cnsz&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dmavacamten%26t%3Dname%26acs%3Dtrue%26acq%3Dmava#pha.

Contraindications

- Concomitant use of CYP2C19 Inhibitors
  - Amitriptyline, clomipramine, fluconazole
- Concomitant use of CYP3A4 Inducers
  - Clarithromycin, diltiazem, ketoconazole
- Concomitant use of CYP3A4 Inhibitors
  - Phenytoin, phenobarbital, st.john's wort
- Pregnancy is currently being studied
  - Does have evidence that Mavacamten can harm fetus
  - No literature for aficamten and omecamtiv mecarbil
- Lactation
  - No data to support Mavacamten's use
  - No literature for aficamten and omecamtiv mecarbil

Lexicomp. Mavacamten (Lexi-Drugs). 2022. Accessed 2023. https://online-lexi-com.wilkes.idm.oclc.org/lco/action/doc/retrieve/docid/patch_f/7219055?cesid=9grcYH7Cnsz&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dmavacamten%26t%3Dname%26acs%3Dtrue%26acq%3Dmava#pha.

Black Box Warnings

- Mavacamten
  - Risk of heart failure
    - Can reduce left ventricular ejection fraction (LVEF) and cause heart failure due to systolic dysfunction
    - If falls under 50%, stop this agent immediately
- Omecamtiv mecarbil and aficamten have not tested been that thoroughly and do not have a black box warning at this time

Lexicomp. Mavacamten (Lexi-Drugs). 2022. Accessed 2023. https://online-lexi-com.wilkes.idm.oclc.org/lco/action/doc/retrieve/docid/patch_f/7219055?cesid=9grcYH7Cnsz&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dmavacamten%26t%3Dname%26acs%3Dtrue%26acq%3Dmava#pha.

Question 2

Which of the following are contraindicated with concomitant use of a myosin modulator? (Select all that apply)

A) CYP2C19 Inducers
B) CYP3A4 Inhibitors
C) CYP450 Inducers
D) CYP3A4 Inducers
E) CYP3A4 Substrates

Question 2

Which of the following are contraindicated with concomitant use of a myosin modulator? (Select all that apply)

A) CYP2C19 Inducers
B) CYP3A4 Inhibitors
C) CYP450 Inducers
D) CYP3A4 Inducers
E) CYP3A4 Substrates

03

Discussion

Mavacamten

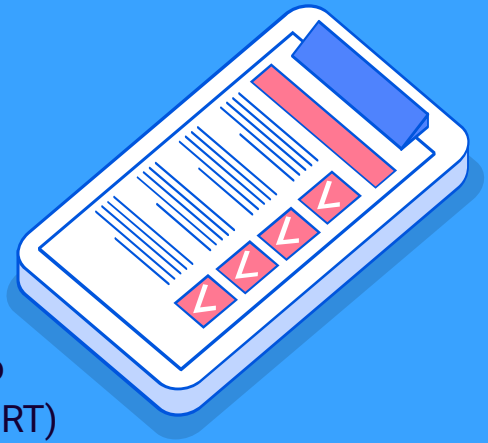
Literature

- EXPLORER-HCM study
  - Goal included testing the efficacy against current therapies of hypertrophic cardiomyopathy (HCM)
  - Double-blinded, parallel, randomized, placebo, prospective
  - Phase III study
  - Showed mavacamtem was superior to placebo
  - Proved to be 20% more effective than placebo at reaching primary endpoints
    - Increase in mixed venous oxygen pressure (pVO2)
    - Class improvement or no change in New York Heart Association (NYHA) classification
  - Showed to be well tolerated with no long term adverse effects reported
  - Improved cardiac exercise
  - Proved to significantly reduce post workout left ventricular output tract (LVOT) gradient

Bavry A. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy. American College of Cardiology. April 4, 2023. Accessed June 26, 2023. https://www.acc.org/Latest-in-Cardiology/Clinical-Trials/2020/08/28/16/14/EXPLORER-HCM.

Literature cont.

- VALOR-HCM study
  - Goal was to test safety and efficacy of mavacantem against the maximum tolerated therapies for HCM
  - Randomized, double blinded, prospective, multicentered, placebo
  - Phase III study
  - Showed a 42% more reduction in NYHA class than placebo
  - Compared to placebo, mavacamten showed a 0% incidence rate of nonsustained ventricular tachycardia
  - Showed at the end of a 16 week study that 17.9% of patients who were on mavacamten proceeded with septal reduction therapy (SRT) while 76.8% of patients who were on placebo proceeded with SRT



Kumbhani D. Mavacamten in adults with symptomatic obstructive HCM who are eligible for septal reduction therapy. American College of Cardiology. April 10, 2023. Accessed June 26, 2023. https://www.acc.org/Latest-in-Cardiology/Clinical-Trials/2022/04/01/02/42/VALOR-HCM.

Omecamtiv mecarbil

Literature

- Went from ATOMIC-HCM to COSMIC-HCM to GALACTIC-HCM
  - All focuses on the same things but galactic was a phase III trial while atomic was a phase I and cosmic phase II
- GALACTIC-HCM
  - Global, double blinded, randomized, placebo
  - Goal was to evaluate the safety and efficacy of omecamtiv mecarbil for patients with HF
  - Cardiovascular death and a HF event occured in 2% less patients on omecamtiv mecarbil than placebo
  - All cause death were identical between both groups
  - Cardiovascular death was very similar between groups

Mefford M. Representativeness of the galactic-hf clinical trial in patients having ... Representativeness of the GALACTIC-HF Clinical Trial in Patients Having Heart Failure With Reduced Ejection Fraction2022. 2022. Accessed June 27, 2023. https://www.ahajournals.org/doi/10.1161/JAHA.121.023766.

Aficamten

Literature

- REDWOOD-HCM
  - Multicentered, double blinded, placebo, randomized
  - Two different cohorts
    - Cohort #1 was dosed at 5 mg and ended at 10 mg
    - Cohort #2 was dosed at 10 mg and ended at 14 mg
  - Cohort #1 showed a 12% improvement in NYHA classification compared to placebo
  - Cohort #2 showed a 33% improvement in NYHA classification compared to placebo
  - At 10 mg, both cohorts showed a significant LVOT gradient decrease
  - Showed a reduction in BNP
  - Aficamten was well tolerated and no serious adverse effects
- Currently has a phase III trial underway named as the SEQUOIA-HCM trial
  - Hopefully it will show good safety and efficacy outcomes against other forms of therapy

Maron M. Study of aficamten for obstructive hypertrophic cardiomyopathy. American College of Cardiology. January 3, 2023. Accessed June 26, 2023. https://www.acc.org/Latest-in-Cardiology/Journal-Scans/2023/01/03/19/29/phase-2-study-of-aficamten.

Question #3

- Which of the following trials showed their studied drug to be 20% more effective than the tested placebo?
  A) ATOMIC-HCM
  B) GALACTIC-HCM
  C) REDWOOD-HCM
  D) VALOR-HCM
  E) EXPLORER-HCM

Question #3

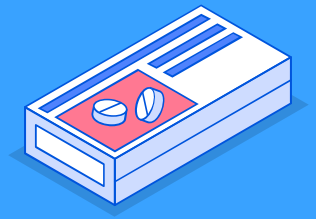
- Which of the following trials showed their studied drug to be 20% more effective than the tested placebo?
  A) ATOMIC-HCM
  B) GALACTIC-HCM
  C) REDWOOD-HCM
  D) VALOR-HCM
  E) EXPLORER-HCM

04

Conclusion

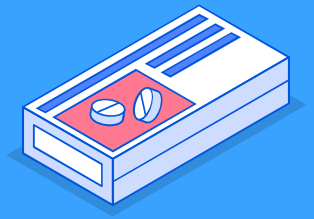
Key Takeaways

- What is really the important stuff?
  - These agents can be very useful in future therapy and have potential to decrease mortality in HF patients
  - Most of this class is still in phase II and phase III trials
  - Requires the REMS program to obtain mavacamten
  - Only studied in patients who have an appropriate drug therapy for their respected HF



My Perspective

- We need more time
  - This class is brand new
    - Had its first agent FDA approved a year ago
  - Longer outcomes need to be studied
    - Long term safety and efficacy needs to be monitored
- Mavacamten trials showed promise
  - Inclusion and exclusion criteria was very appropriate
  - Has great success over current therapies in improving disease oriented outcomes
    - Reducing LVOT
    - Reducing NYHA class
- Omecamtiv mecarbil and aficamten
  - Have potential but need to be further researched to prove their effectiveness and safety



My Heart Can’t Go On: A Lighthearted Look at a Heart Failure Treatment

By: Andrew Dean
PharmD Candidate 2024
Wilkes University
June 27, 2023
APPE Internal Medicine Rotation

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Thanks!

Do you have any questions?

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