PHARMACY LEARNING NETWORK 1-DAY REGIONAL MEETINGS

Improving Long Term Outcomes in Heart Failure:

Practical Implications for Pharmacists

ICHP

Presented in partnership with the ICHP Annual Meeting

Faculty

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Disclosure

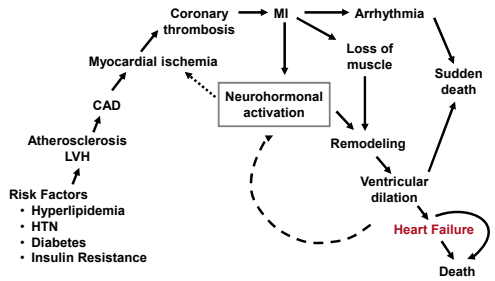
Mark A. Munger, PharmD, FCCP, FACC, FHFSA has no financial relationships to disclose relating to the subject matter of this presentation.

Objectives

- Recognize and classify HF patients according to disease stage and class
- Review current guidelines for the pharmacologic treatment and management of patients with chronic HF
- Assess clinical evidence on existing and emerging treatments in chronic HF to provide personalized therapy toward decreasing hospitalizations and mortality
- Develop strategies to maximize cost-effectiveness of new FDA-approved HF drugs

HF = heart failure; FDA = Food and Drug Administration.

Risk Factors for HF in the Cardiovascular Continuum



HTN = hypertension; LVH = left ventricular hypertrophy; CAD = coronary artery disease; MI = myocardial infarction.
Adapted with permission from Dzau V, Braunwald E. *Am Heart J*. 1991;121(4 Pt 1):1244-1263.

Prevalence and Burden of HF

- HF affects ~5.1 million people in the United States, 26 million worldwide
- The estimated risk for developing HF for individuals ≥40 years of age is ~20%
- ~50% of people who develop HF die within 5 years
- Reported hospitalizations for HF exceed 1 million each year and are associated with a 30-day readmission rate of 25%
- IN 2013, >$30 billion was spent on HF with the reported costs of hospitalizations alone being ≥$23,077/patient

Ponikowski P, et al. Heart failure: preventing disease and death worldwide. https://www.escardio.org/static_file/Escardio/Subspecialty/HFA/WHFA-whitepaper-15-May-14.pdf. Accessed January 29, 2016. Go AS, et al. *Circulation*. 2013;127(1)e6-e245.

Definition of Heart Failure

- Complex, progressive, clinical syndrome
- Results from structural or functional impairment of ventricular filling or contractility
- Major clinical manifestations
  - Dyspnea and fluid retention
  - Fatigue
- Patient presentation is variable
- HFrEF: Heart failure with reduced ejection fraction
- HFpEF: Heart failure with preserved ejection fraction

ACCF/AHA Guidelines. *J Am Coll Cardiol*. 2013;62:e147-e239. Rodriguez JL, et al. *Heart Lung*. 2008; 37:257-265.

Definition of Heart Failure

Patient Perspective

"When you have heart problems, you always worry [that] your next breath is your last one. That's something you never know."

Patient Perspective

"I'm not depressed. ..not really depressed...It's just a low feeling and its not a happy feeling, and you never feel your life's worth anything at times."

Patient Perspective

"I did at times start having queasy feelings and pains in my one side,

And it all happened once or twice while driving. I pulled off the road, but I didn't do anything about it.

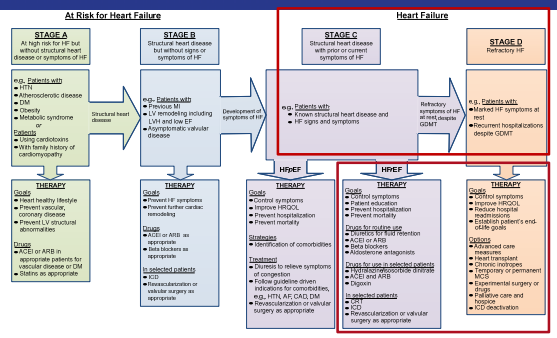
All of a sudden, I was developing sleep apnea or wasn't breathing right but sloughed it off until I could hardly breathe at all the last few days.

I did ignore the original symptoms. The last day I woke up and couldn't breathe well and told my kid to take me to the hospital.

I was unconscious when I got to the hospital."

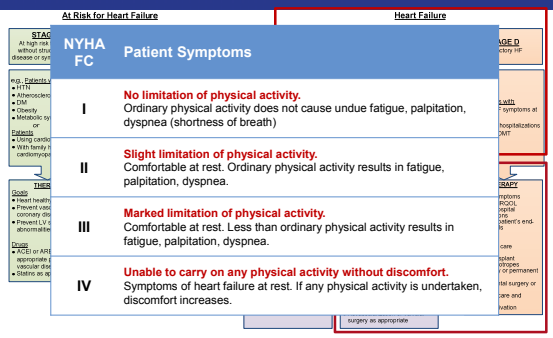
ACCF/AHA Guidelines. *J Am Coll Cardiol*. 2013;62:e147-e239. Rodriguez JL, et al. *Heart Lung*. 2008; 37:257-265.

Stages, Phenotypes and Treatment of HF



ACCF/AHA Guidelines. *J Am Coll Cardiol*. 2013;63:e193.

Stages, Phenotypes and Treatment of HF



ACCF/AHA Guidelines. *J Am Coll Cardiol*. 2013;63:e193.

Common Causes of Heart Failure

Ponikowski P, et al. Heart failure: preventing disease and death worldwide. https://www.escardio.org/static_file/Escardio/Subspecialty/HFA/WHFA-whitepaper-15-May-14.pdf. Accessed January 29, 2016.

Case Study: Background

- 64-year-old female
- Remote history of smoking
- Moderate alcohol consumption
- T2DM (controlled with metformin; HbA1c=6.9%)
- Mild COPD
- Reports increasing dyspnea on exertion over the previous month
- Orthopnea; bilateral pedal edema
- Moderate weight gain despite increased appetite
- Creatinine: 1.4 mg/dL (Creatinine Clearance: 66.3 mL/min)

T2DM = type 2 diabetes mellitus; COPD = chronic obstructive pulmonary disease.

Case Study: Physical Exam and Laboratory Tests

- BP: 130/86 mmHg; HR: 90 bpm; Respirations: 24/minute
- O2 Saturation: 97% on room air
- Lung Sounds: clear
- JVD: 15 cm + + Kussmaul's sign (JVP rise on inspiration-indicative of right-sided heart failure)
- BNP Level: 689 pg/mL
- TSH and Cardiac Enzymes: Normal
- CXR: Mild pulmonary vascular redistribution
- Echo: LVEF 31%; RV mild dysfunction

BP = blood pressure; HR = heart rate; bmp = beats per minute; JVD = jugular venous distention; JVP = jugular venous pressure; BNP = brain natriuretic peptide; TSH = thyroid stimulating hormone; CXR = chest x-ray; LVEF = left ventricular ejection fraction; RV = right ventricle.

Case Question

Based on the findings presented, how would you classify this patient with HF?

1. HFrEF; Stage C, NYHA FC III
2. HFrEF: Stage C, NYHA FC IV
3. HFpEF; Stage C, NYHA FC I
4. HFpEF; Stage C, NYHA FC IV

HFrEF = heart failure with reduced ejection fraction; NYHA FC = New York Heart Association Functional Classification; HFpEF = heart failure with preserved ejection fraction.

Case Question

What is your initial treatment(s)?

1. Start β-adrenergic blocker when euvolemic
2. Start ACEI or ARB unless contraindicated
3. Start loop diuretic for congestive signs and symptoms
4. Low-salt diet
5. All are correct

ACEI = angiotensin converting enzyme inhibitor; ARB = agiotensin receptor blocker.

Guideline-Recommended Pharmacologic Treatments

Therapy for Stage C HFrEF	NYHA Functional Class			
	1	2	3	4
ACEI, ARB	Yes	Yes	Yes	Yes
β-adrenergic blockers	(Yes)	Yes	Yes	(Yes)
Aldosterone Antagonists		(Yes)	Yes	Yes
Diuretics		(Yes)	Yes	Yes
Digoxin			(Yes)	(Yes)
Hydralazine and Isosorbide dinitrate		(Yes)	(Yes)	(Yes)

ACCF/AHA Guidelines. *J Am Coll Cardiol*. 2013;(62):e147-239.

Ten Commandants of HFrEF

1. Maintain patient on 2- to 3-g sodium diet. Follow daily weight. Monitor standing blood pressures in the office, as these patients are prone to orthostasis.
2. Determine target/ideal weight, which is not the dry weight. In order to prevent worsening azotemia, some patients will need to have some edema. Achieving target weight should mean no orthopnea or paroxysmal nocturnal dyspnea. Consider home health teaching.
3. Avoid all nonsteroidal anti-inflammatory drugs because they block the effect of ACEIs and diuretics.
4. Use ACEIs in all heart failure patients unless they have an absolute contraindication or intolerance. Use doses proven to improve survival and back off if they are orthostatic. In those patients who cannot take an ACEI, use an ARB.

ACCF/AHA Guidelines. J Am Coll Cardiol. 2013;(62):e147-239.

Ten Commandants of HFrEF

5. Use loop diuretics (like furosemide) in most NYHA class II through IV patients in dosages adequate to relieve pulmonary congestive symptoms. Double the dosage (instead of giving twice daily) if there is no response or if the serum creatinine level is >2.0 mg/dL.
6. For patients who respond poorly to large dosages of loop diuretics, consider adding 5 to 10 mg of metolazone one hour before the dose of furosemide once or twice a week as tolerated.

ACCF/AHA Guidelines. *J Am Coll Cardiol*. 2013;(62):e147-239.

Ten Commandants of HFrEF

7. Consider adding 25 mg spironolactone in most class III or IV patients. Do not start if the serum creatinine level is >2.5 mg/dL (220 µmol/L).
8. Use metoprolol, carvedilol, or bisoprolol in all class II and III heart failure patients unless there is a contraindication. Start with low doses and work up.
   Do not start if the patient is decompensated (excessively dry or wet).
9. Use digoxin in some symptomatic heart failure patients.
10. Encourage a graded exercise program.

ACCF/AHA Guidelines. *J Am Coll Cardiol*. 2013;(62):e147-239.

Objectives

- Assess clinical evidence on emerging treatments in chronic HF to provide personalized therapy toward decreasing hospitalizations and mortality
- Develop strategies to maximize cost-effectiveness of new FDA-approved HF drugs

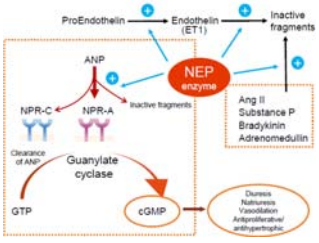
Emerging Therapies for the Treatment of HFrEF

- **Angiotensin Receptor-Neprilysin Inhibitor (ARNI) (Entresto®)**
  - Combines ARB with inhibition of nephrilysin, inhibiting RAAS and augmenting natiuretic peptide activity
  - Approved in July 2015 for patients with chronic HF (NYHA FC II-IV) with reduced ejection fraction
- **Ivabradine (Corlanor®)**
  - Selectively inhibits the sinus node If (funny channel)-reduces SA node pacemaker activity thereby decreasing HR, no effect on contractility or blood pressure
  - Approved in April, 2015 for patients with stable, symptomatic HF, with LVEF ≤35% and in sinus rhythm with resting HR ≥70 bpm and on maximally tolerated dose of β-adrenergic blocker or with contraindications to β-adrenergic blocker

King JB, et al. *Pharmacotherapy*. 2015;35:823-837. DiFrancesco D. *Heart Rhythm*. 2012;9(2):299-301 Rosa GM, et al. *Expert Opin Drug Metab Toxicol*. 2014;10(2):279-291.

Neprilysin (neutral endopeptidase 24.11; NEP)

Role in Natriuretic Peptide Degradation
Metabolism of ANP and Other Peptide Hormones by NEP

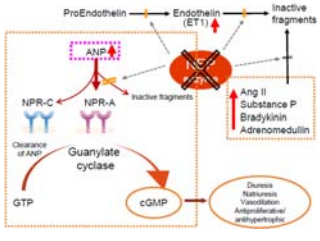


- NEP is the major enzyme responsible for degrading the NPs (ANP, BNP, CNP)
- NEP catalyzes the degradation of other vasoactive peptides:
  - Vasodilating peptides
    - substance P
    - bradykinin
  - Vasoconstrictor peptides
    - ET-1
    - Ang II
- NEP converts big ET-1 to the active vasoconstrictor peptide ET-1

Erdos, Skidgel. *FASEB J*. 1989;3:145-51. Levin, et al. *N Engl J Med*. 1998;339:321-8. Stephenson, et al. *Biochem J*. 1987;243:183-7. Lang, et al. *Clin Sci*. 1992;82:619-23. Kenny, et al. *Biochem J*. 1993;291:83-8. Skidgel, et al. *Peptides*. 1984;5:769-76. Abassi, et al. *Metabolism*. 1992;41:683-5. Murphy, et al. *Br J Pharmacol*. 1994;113:137-42. Jiang, et al. *Hypertens Res*. 2004;27:109-17.

Neprilysin Inhibition

Effects on Natriuretic Peptides
Metabolism of ANP and Other Peptide Hormones by NEP

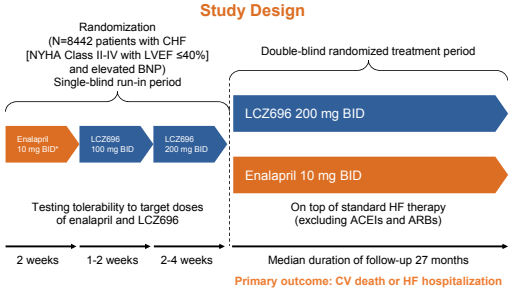


- Neprilysin (NEP) is the major enzyme responsible for degrading NPs
  - BNP, not NT-proBNP, is a NEP substrate
- Inhibition of NEP enhances the effects of NPs
- Studies suggest the potential effects of NEP inhibitors may be offset by an increase in ANG II levels

Erdos, Skidgel. *FASEB J*. 1989;3:145-51. Levin, et al. *N Engl J Med*. 1998;339:321-8. Murphy, et al. *Br J Pharmacol*. 1994;113:137-42. Jiang, et al. *Hypertens Res*. 2004;27:109-17. Ferro, et al. *Circulation*. 1998;97:2323-30. Martinez-Rumayor, et al. *Am J Cardiol*. 2008;101[suppl]:3A-8A. Richards, et al. *Hypertens*. 1993;11:407-16.

PARADIGM-HF

Study Design



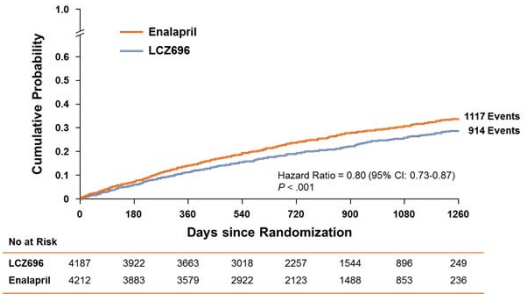
Primary outcome: CV death or HF hospitalization

***Enalapril 5 mg BID for 1-2 weeks followed by enalapril 10 mg BID as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEI.**

McMurray, et al. Eur J Heart Fail. 2013;15:1062-73. McMurray, et al. Eur J Heart Fail. 2014;16:817-25. McMurray, et al. N Engl J Med. 2014;epub ahead of print:DOI:10.1056/NEJMoa1409077.

PARADIGM-HF

Primary Endpoint: Death from CV Causes of First Hospitalization for HF



No at Risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

McMurray, et al. *N Engl J Med*. 2014;ePub ahead of print:DOI:10.1056/NEJMoa1409077.

PARADIGM-HF

Prospectively Defined Safety Events

Event, n (%)	LCZ696 (n=4187)	Enalapril (n=4212)	*P*-Value
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	< .001
Symptomatic with SBP <90 mmHg	112 (2.7)	59 (1.4)	< .001
Elevated serum creatinine			
≥2.5 mg/dL	139 (3.3)	188 (4.5	.007
≥3.0 mg/dL	63 (1.5)	83 (2.0)	.10
Elevated serum potassium			
>5.5 mmol/L	674 (16.1)	727 (17.3)	.15
>6.0 mmol/L	181 (4.3)	236 (5.6)	.007
Cough	474 (11.3)	601 (14.3)	< .001
Angioedema *(adjudicated by a blinded expert committee)*			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	.19
Catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	.52
Hospitalized without airway compromise	3 (0.1)	1 (<0.1)	.31
Airway compromise	0	0	—

Fewer patients in the LCZ696 group than in the enalapril group stopped their study medication because of an AE (10.7% vs 13.3%, P=.03)

McMurray, et al. *N Engl J Med*. 2014;ePub ahead of print:DOI:10.1056/NEJMoa1409077.

Controlling Costs with Entresto®

- 2 million patients are eligible for taking Entresto® over the next 5 years
  - Cost: $4,600/year, $12.50/day
  - Total Cost to Health Care: $9.2 billion (Entresto® – ACEi ($50/year) or ARB ($150-200/year) ~ $8.9 billion/5 years
- Projected mortality benefit of Entresto® is 1-2 years of increased life expectancy and survival free from heart failure
- New Dx Patient: Patient-provider discussion with about morbidity and mortality difference between ACEi/ARB compared to Entresto® (with additional co-pay tier)
- Hospitalized HFrEF Patient on ACEI or ARB: "Treatment Failure" if patient adherent, on target doses, and no other identifiable reason for heart failure hospitalization. Start Entresto®

McMurray JJV, et al. *N Engl J Med*. 2014;373:993-1004. Claggett B. *N Engl J Med*. 2015;373:2289-2290. FiercePharma. Novartis priced Entresto on par with results, new cost watchdog says. http://www.fiercepharma.com/story/novartis-priced-entresto-par-results-new-cost-watchdog-says/2015-09-14. Accessed January 29, 2016. Modern Healthcare. Entresto's cost-effectiveness questioned. http://www.modernhealthcare.com/article/20150911/NEWS/150919974. Accessed January 29, 2016. Medicaid. Pharmacy Drug Pricing. https://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Pharmacy-Pricing.html. Accessed January 29, 2016.

Ivabradine for Moderate-to-Severe HF and LV Systolic Dysfunction: SHIFT Study

- Randomized, double-blind, placebo-controlled (Ivabradine)
- 6505 NYHA FC II-IV Subjects
  - Male (77%), Caucasian (89%), LVEF <35%, HR >70 bpm
  - Admission for HF in previous 2 months
  - On optimal medical management (90% BB, 84% on ACEi/ARBs, 60% ARAs)
- Primary Endpoint: Composite of CV death or hospital admission for HF

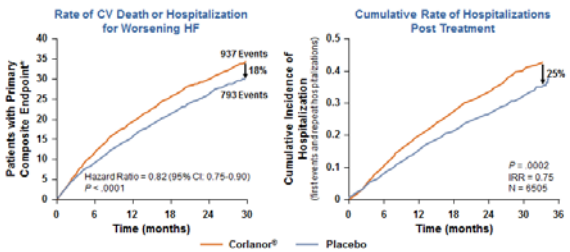
Heart Rate	# of Events (CV Death or Hospital Admission	Hazard Ratio (55% CI) vs Lowest HR group	*P*-value
70 to <72	92	1.00	—
72 to <75	157	1.15 (0.88-1.48)	.308
75 to <80	197	1.33 (1.03-1.70)	.027
80 to <87	205	1.80 (1.40-2.31)	< .001
> 87	286	2.34 (1.84-2.98)	< .001

Borer JS, et al. *Eur Heart J*. 2012;33(22):2813-2820. Swedberg K et al. *Lancet*. 2010;376(9744):875-885.

Corlanor® Significantly Reduced Risk of CV Death or Hospitalization for Worsening Heart Failure

Corlanor® in combination with SOC is associated with an additional 18% risk reduction in primary composite end point of CV mortality or hospitalization for worsening HF

In all patients with HR ≥70 bpm, Corlanor® demonstrated 25% fewer hospitalizations due to worsening HF



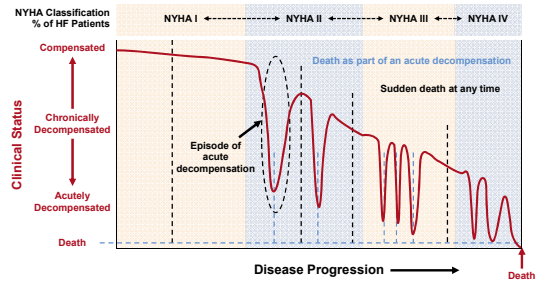
*Primary Composite Endpoint: Time to CV Death or First Hospitalization for Worsening HF

Swedberg K, et al. *Lancet*. 2010;376:875-885.

Considerations with Ivabradine

- Improvement in NYHA FC and outcomes
- Limited Side Effect Profile (phosphenes-sudden change in brightness of light-2%) and lowers atrial fibrillation threshold (1%+) (208 treated/1 case Afib)
- Effect largely contingent on basal HR
- Is not a β-adrenergic blocker and is "add-on" therapy
- "Personalized" medicine based on HR?
  - Estimated Population: 1.4 Million persons
- Cost: $375.00 (WAC)/month [5mg and 7.5mg] $4500/year
- Cost-Effectiveness: 9-18,000 Euros ($9.8-$19.5) [UK Cost: 42.1 Euros/month]

Heart Failure Progression, Morbidity, and Mortality



Mozaffarian D, et al. *Circulation*. 2015;131(4):e29-e322. Gheoghiade M, et al. *Am J Cardiol*. 2005;96(6A): 11G-17G. Muntwyler J, et al. *Eur Heart J*. 2002;23(23):1861-6. Ahmed A, et al. *J Card Fail*. 2008;14(3): 211-8. Gheoghiade M, et al. *JACC*. 2009;53(7):557-73. McCullough PA, et al. *JACC*. 2002;39(1):60-9. McMurray JJ, et al. *Eur Heart J*. 2012;33(14):1787-1847. Roger VL, et al. *JAMA*. 2004;292(3):344-50.

Case Study: Background

- 54-year-old male
- Four previous hospital admissions for worsening HF over 2 years
- Non-obstructive CAD on cardiac catherization at time of initial diagnosis
- LVEF 26%, PAS 55 mmHg, EDD 6.7 cm
- Chronic bilateral edema of legs, has difficulty bathing and dressing, no PND, no orthopnea
- BP 106/78 mmHg; HR 82 bpm (sinus rhythm), +S4
- Creatinine: 2.0 mg/dL (CrCl ~ 32 mL/min)
- Meds: lisinopril 20mg qday, carvedilol 25mg qday (max tolerated dose), furosemide 40mg qday, Spironolactone 12.5mg qday, ICD

To Add or Not to Add?

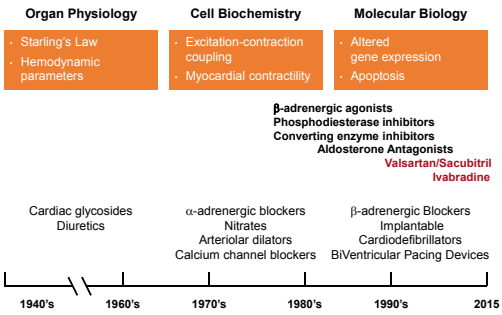
Which of the following treatment options is best after bolus dosing of loop diuretics with vasodilator therapy in-hospital over 24 hours?

1. Up-titrate furosemide to 80mg qday and follow weights on outpatient basis, no other changes to medications
2. Start ivabradine 5mg BID (with up-titration furosemide)
3. Start sacubitril/valsartan 24/26mg BID, D/C lisinopril
4. Discharge patient on outpatient therapy at admission, follow-up in 1 week with cardiologist

To Add or Not to Add?

- Up-titrate furosemide to 80mg qday and follow weights on outpatient basis, no other changes to medications
  - Patient admitted 4 times in past 2 years
- Start Ivabradine 5mg BID (with up-titration furosemide)
  - Patient eligible: YES, cost-effective, YES through reduction in hospitalizations, no all-cause mortality benefit
- Start sacubitril/valsartan 24/26mg BID, D/C lisinopril
  - Patient eligible: YES, cost-effective, YES through reduction in hospitalization and reduction in mortality (+ 2years)
- Discharge patient on outpatient therapy at admission, follow-up in 1 week with cardiologist
  - Patient admitted 4 times in past 2 years

Changing Treatment Strategies in Heart Failure



Questions?