10:30 – 11:45 am

Optimizing Outcomes for Heart Failure Patients: Best Practices for Primary Care Clinicians

SPEAKERS

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Presenter Disclosure Information

The following relationships exist related to this presentation:

- Javed Butler, MD, MPH, MBA: Services Provided for Promotional Purposes (Not for CME/CE Services) for Amgen; Bayer; Boehringer Ingelheim Pharmaceuticals, Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Relyspa, Inc.; and ZS Pharma Inc.
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Optimizing Outcomes for Heart Failure Patients: Best Practices for Primary Care Physicians

Educational Objectives

1) Recognize the key signs, symptoms, and comorbidities associated with heart failure (HF).
2) Implement effective management strategies to facilitate transitions in care, self-care patient education, and medication adherence for HF.
3) Integrate current guidelines and evidence-based literature into the management of patients with chronic heart failure (CHF).
4) Assess the efficacy and safety data of emerging therapies for CHF based on results from clinical trials

Defining a role for Primary Care Clinicians in Heart Failure Management: a call to action

Prakash Deedwania, MD
Professor of Medicine, UCSF
Professor of Medicine
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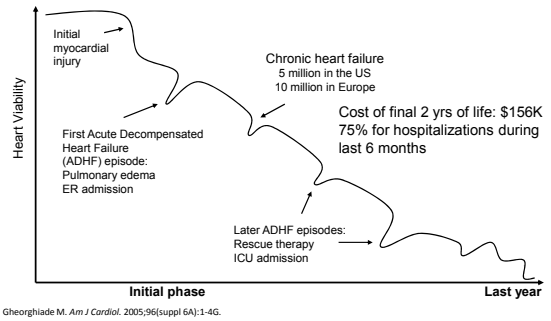
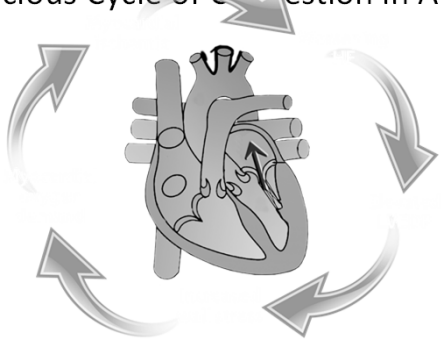
Natural History of Heart Failure



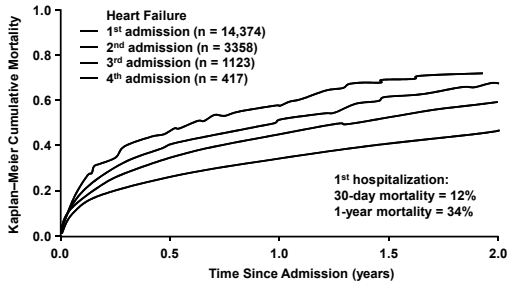
Gheorghiade M. *Am J Cardiol.* 2005;96(suppl 6A):1-4G.

Vicious Cycle of Congestion in AHF



Repeat Hospitalizations Predict Mortality

All-Cause Mortality After Each Subsequent Hospitalization for HF



Reproduced with permission from Setoguchi S, et al. *Am Heart J.* 2007;154:260-266.

Improvement in Heart Failure Assessment and Management is Needed

- **Direct and indirect cost estimates for HF up to $56 billion USD annually**
- **Average HF Admission costs between $7,000 - $13,000 USD/admission**
- **Re-hospitalization rate: 50% within 6 months**
- **ACA has made HF readmission a major focus for improvement**

Berkowitz et al Lippincotts Case Manag. 2005
Schlendorf et al Curr Treat Options in Cardiovasc Med 2011

The global reach of heart failure

- Heart failure is a diagnosis that affects:
  - Patients
  - Families
  - Medical practices
  - Healthcare system
  - You

The role of the PCP in HF care

- You are the captain of the team.
  - Prevention
  - Diagnosis
  - Management of comorbidities
  - Gatekeeper for referral
  - Central role in care transition
  - Advanced care planning

Heart Failure Healthcare Team

- **Primary Care Physician**
- **Cardiologist**
- **Other Physicians**
- **Clinical Nurse Specialists, Nurse Practitioners**
- **Physical and Occupational Therapists**
- **Dietitians**
- **Mental Health Professionals**
- **Social Workers and Case Managers**
- **Pharmacists**

Modifiable/preventable risk factors for HF

- Dyslipidemia leading to CAD
- Previous MI
- Hypertension
- Abnormal heart valves
- Heart muscle disease
- Congenital heart disease
- Severe lung disease
- Diabetes
- Obesity
- Sleep Apnea

Primary Care Physician Diagnosis

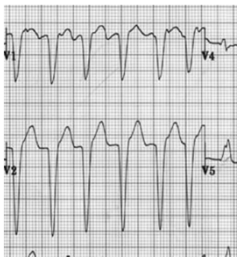
- **EARLY diagnosis and treatment** of HF is important for better clinical outcomes—**including quality and length of life**
- To foster a team approach to care, it is recommended to establish diagnosis whenever possible prior to referring to cardiologist
- In-office diagnosis—identification of signs and symptoms of HF

Clinical History
Common symptoms of heart failure

- Dyspnea
  - Commonly misdiagnosed as asthma, bronchitis, pneumonia
- Orthopnea – most suggestive that heart failure as cause of dyspnea
- Paroxysmal nocturnal dyspnea
- "Bendopnea"
- RUQ pain from hepatic congestion
- Abdominal distention from ascites
- Edema
- Weight Gain*
- Fatigue
- Anorexia/Early satiety/RUQ pain
- Tachycardia

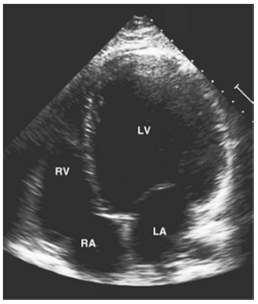
Electrocardiography in HF

- Widely available, rapidly available, inexpensive
- May provide evidence for cause of acute HF decompensation
  - Ischemia
  - Arrhythmia, such as atrial fibrillation
- May inform the substrate for HF
  - Q waves (ischemic)
  - LVH (hypertensive heart disease, aortic stenosis)
  - Low voltage (amyloidosis)



Suh WM, et al. *J Electrocardiol*. 2008;41(1):44-48.

Echocardiography in HF



Echocardiography: pros

- Widely available, portable, and reproducible
- Provides functional information about cardiac size, systolic and diastolic function, valve regurgitation, and filling pressures
- Prognostic

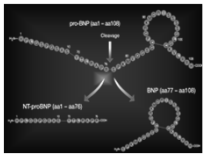
Echocardiography: cons

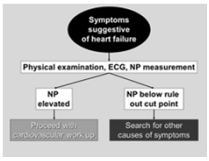
- May be costly
- Requires specialized interpretation
- A high % have preserved LV function or have ambiguous findings

Arques S. *Minerva Cardioangiol*. 2012;60(4):385-394.

NT-proBNP and BNP

- Concentrations of NT-proBNP and BNP are higher in those with heart failure compared to those without.
- Measurement of either is a Class I, level A recommendation for heart failure diagnosis





How to Interpret Elevated B-type Natriuretic Peptide Levels

Know the Differential Diagnosis

Heart failure
LVH
Valvular heart disease
Atrial fibrillation
Advancing age
Myocarditis
ACS
Pulmonary hypertension
Anemia
Pulmonary embolism
Cardiac surgery
Sleep apnea
Critical illness
Sepsis
Burns
Renal failure
Toxic-metabolic insults

Baggish A, et al. *Crit Path Cardiol.* 2004;3:171-176.

How to Interpret Low B-type Natriuretic Peptide Levels:

Know the Differential Diagnosis

Compared to HF with low ejection fraction, the following are all associated with lower than "expected" BNP/NT-proBNP values in patients with HF:

- HF with preserved ejection fraction
- Right heart predominant HF
- Mild or partially treated HF
- Obesity

Baggish A, et al, *Crit Path Cardiol*. 2004;3:171-176.

CHARACTERIZING THE PATIENT WITH HF

Definitions of HFrEF and HFpEF

Classification	Ejection Fraction	Description
1. HF with reduced ejection fraction (HFrEF)	≤40%	• Also referred to as systolic HF • Randomized controlled trials have mainly enrolled patients with HFrEF
2. HF with preserved ejection fraction (HFpEF)	≥50%	• Also referred to as diastolic HF • Several different criteria have been used to further define HFpEF • Diagnosis of HFpEF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF
a. HFpEF, borderline	41%-49%	• These patients fall into a borderline or intermediate group • Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HFpEF
b. HFpEF, improved	>40%	• It has been recognized that a subset of patients with HFpEF previously had HFrEF; these patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF • Further research is needed to better characterize these patients

1. Yancy CW et al. *J Am Coll Cardiol*. 2013;62:e147-e239.

Classification of HF: Stage vs Class

ACCF/AHA Stages of HF		NYHA Functional Classification	
A	High risk for HF but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity
C	Structural heart disease with prior or current symptoms of HF	II	Slight limitation of physical activity; comfortable at rest; ordinary physical activity results in symptoms of HF
		III	Marked limitation of physical activity; comfortable at rest; less than ordinary activity causes symptoms of HF
D	Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without symptoms of HF

1. Yancy CW et al. *J Am Coll Cardiol*. 2013;62:e147-e239.

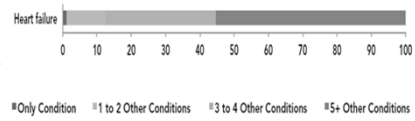
Variables that May Predict Increased Mortality in HF

Age	Diabetes	HBG < 12	NYHA Class IV / Pres
Atrial fibrillation	Duration of symptoms	Heart rate	Peripheral Edema
BNP	Dyspnea category	Hemoglobin	Primary Insurance
Blood urea nitrogen (BUN)	Dyspnea type	HF: Baseline NYHA class	QRS duration >120ms
BUN / Creatinine ratio	Ever smoked	HF: pre-hospital	Qualitative LVEF
CAD	Fatigue	Hyperlipidemia	Race / ethnicity
CAD: Prior myocardial infarction (MI)	First diastolic BP	Hypertension	Rales
CAD: Prior re-vascularization	First height	Hypertensive-SBP >140	Sodium
Cardiac enzymes	First systolic BP	Ischemic Etiology	Stroke / TIA
Congest /1st x-ray	First weight	UNC HF score	Tachycardia >100
Creatinine	Gender	LOS-inpatient	Time in care

Fonarow GC et al. *JAMA* 2005; 293:572-580.

Co-morbidity Burden in Heart Failure

Prevalence of Comorbid Conditions in Medicare Beneficiaries with HF



The majority of Medicare Beneficiaries with heart failure have 5 or more other major conditions present.

CMS: Chronic Conditions Chartbook: 2012 Edition. Available: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/2012ChartBook.html. Accessed: August 12, 2016.

Important Comorbidities in Heart Failure

Cardiovascular

- Hypertension
- Coronary artery disease
- Peripheral vascular disease
- Cerebral vascular disease
- Hyperlipidemia
- Atrial fibrillation

Non-Cardiovascular

- Obesity
- Diabetes
- Anemia
- Chronic kidney disease
- Thyroid disease
- COPD / Asthma
- Smoking
- Sleep disordered breathing
- Liver disease
- Arthritis
- Cancer
- Depression

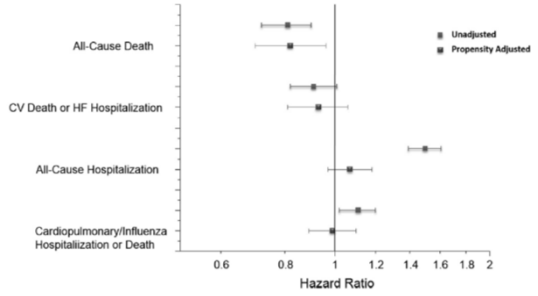
Yancy CW et al. *J Am Coll Cardiol.* 2013;62:1495-1539.

Monitoring and Follow-up

- At each visit:
  - Assess ability to perform ADL's
  - Determine volume status and weight
  - Review self care: exercise, diet, sodium intake and fluid restriction.
  - Medication reconciliation: remove 'bad' meds
  - Electrolyte and renal function assessment
  - BNP/NT-proBNP?
- Remember to assess for depression

Circulation 2009, 119:1977-2016 ; JAMA. 2009 Jan 28;301(4):383-92. ; J Card Fail. 2011 Aug;17(8):613-21; Am Heart J. 2009 Sep;158(3):422-30

Influenza vaccination and outcome in HF



Vardeny et al, JACC Heart Failure 2016

Goals of Therapy for Patients with Chronic HF

A	• Risk factor reduction • Prevent ischemic events • Prevent development of LV structural abnormalities
B	• Prevent HF symptoms • Prevent further cardiac remodeling
C	• Control symptoms • Improve health-related quality of life (HRQoL) • Prevent hospitalization • Prevent mortality
D	• Control symptoms • Improve HRQoL • Prevent hospitalizations • Establish end-of-life goals

Yancy CW et al. *Circulation.* 2013 Oct 15;128:e240-327.

Who to Refer?

- New onset heart failure
- Need for an ICD/BiV
- Worsening or refractory symptoms
- Hyponatremia (especially < 125)
- High diuretic requirements (> 1.5mg/kg furosemide)
- Intolerant to guideline based medications
- Worsening renal insufficiency
- Recurrent hospitalizations

Your patient is admitted…

Now what?

Inpatient and Transitions of Care

Throughout the hospitalization as appropriate, before hospital discharge, at the first postdischarge visit, and in subsequent follow-up visits, the following should be addressed:

a. initiation of GDMT if not previously established and not contraindicated;

b. precipitant causes of HF, barriers to optimal care transitions, and limitations in postdischarge support;

c. assessment of volume status and supine/upright hypotension with adjustment of HF therapy, as appropriate;

d. titration and optimization of chronic oral HF therapy;

e. assessment of renal function and electrolytes, where appropriate;

f. assessment and management of comorbid conditions;

g. reinforcement of HF education, self-care, emergency plans, and need for adherence; and

h. consideration for palliative care or hospice care in selected patients.

Yancy CW et al. *Circulation*. 2013 Oct 15;128:e240-327.

Inpatient and Transitions of Care

Multidisciplinary HF disease-management programs are recommended for patients at high risk for hospital readmission, to facilitate the implementation of GDMT, to address different barriers to behavioral change, and to reduce the risk of subsequent rehospitalization for HF.

Scheduling an early follow-up visit (within 7 to 14 days) and early telephone follow-up (within 3 days) of hospital discharge is reasonable.

Use of clinical risk prediction tools and/or biomarkers to identify patients at higher risk for postdischarge clinical events is reasonable.

Yancy CW et al. *Circulation*. 2013 Oct 15;128:e240-327.

Coordinating Care for Patients With Chronic HF

Effective systems of care coordination with special attention to care transitions should be deployed for every patient with chronic HF that facilitate and ensure effective care that is designed to achieve GDMT and prevent hospitalization.

Every patient with HF should have a clear, detailed and evidence-based plan of care that ensures the achievement of GDMT goals, effective management of comorbid conditions, timely follow-up with the healthcare team, appropriate dietary and physical activities, and compliance with Secondary Prevention Guidelines for cardiovascular disease. This plan of care should be updated regularly and made readily available to all members of each patient's healthcare team.

Palliative and supportive care is effective for patients with symptomatic advanced HF to improve quality of life.

Yancy CW et al. *Circulation*. 2013 Oct 15;128:e240-327.

Hospital to Home (H2H) Initiative

- The H2H initiative is a national quality improvement program established by the American College of Cardiology and the Institute of Healthcare Improvement with the goal of improving outcome for patients discharged with HF or AMI. The 3 core concept areas of H2H include:

1) follow-up
2) post-discharge medication management
3) patient recognition of signs and symptoms

American College of Cardiology. H2H Available: http://cvquality.acc.org/en/Initiatives/H2H/About-H2H.aspx. Accessed: March 2, 2016.

H2H Strategies to Reduce HF

- **Provide info about medications --purpose, which were new, which changed in dose/frequency, which were stopped and have pharmacist conduct medication reconciliation at discharge.**
- **Teach patients about self care, and provide patients/caregivers direct contact info for a specific physician (for emergencies)**
- **Arrange an outpatient follow-up appointment before patients leave the hospital (and occurring within 7 days of discharge)**
- **Ensure outpatient physicians are alerted to patient's discharge within 48 hours**
- **Call patients regularly post discharge; follow- up on needs or to provide education.**

American College of Cardiology. H2H Available: http://cvquality.acc.org/en/Initiatives/H2H/About-H2H.aspx. Accessed: March 2, 2016.

H2H: "Mind Your Meds" Success: The Clinician is successful if:

- **HF pts are prescribed appropriate meds, dose, type, and frequency.**
- **Medication reconciliation is performed accurately AND is documented.**
- **Possible external barriers to obtaining prescribed meds are identified in advance, addressed, and documented.**
- **Possible barriers to patients remembering/understanding the need to take meds and taking meds as prescribed are identified in advance, addressed, and documented.**
- **Patient/caregiver is provided with documented instructions and prescriptions for all their meds during the discharge process.**
- **Patient/caregiver can demonstrate they understand the importance of taking their meds, of adhering to their meds as prescribed, and of adhering to any changes to their prescriptions.**
- **Patient/caregiver can demonstrate they understand possible side effects and symptoms that may be related to their medications, and who to call if they have symptoms that may be related to meds.**

American College of Cardiology. H2H Available: http://cvquality.acc.org/en/Initiatives/H2H/About-H2H.aspx. Accessed: March 2, 2016.

H2H: "Mind Your Meds" Success: The Patient is successful if:

- **Patient/caregiver remembers to take all their meds as prescribed (i.e., dose, type, frequency).**
- **Patient/caregiver can demonstrate they understand what each medication does, why the medication is important to take as prescribed, and what potential side effects there may be for meds.**
- **Patient/caregiver brings his/her meds or a medication list to each and every clinic visit.**
- **Patient/caregiver can discuss any challenges, problems, issues, side effects, or questions about meds with the clinician.**

American College of Cardiology. H2H Available: http://cvquality.acc.org/en/Initiatives/H2H/About-H2H.aspx. Accessed: March 2, 2016.

Advanced care planning

- **Primary care physicians have a pivotal position in the care team for managing patients with heart failure.**
  - **Though difficult, the discussion about end-of-life is not only important, patients and caregivers say they want this (Kaiser Family Foundation 9/2015 poll).**
  - **Medicare is now paying for voluntary ACP.**
- **End-of-life decisions are a team effort.**
  - **Consider involvement of Palliative Care at this crucial moment in the patient journey.**

Summary

- PCPs play a crucial role in the care of patients with heart failure:
  - Prevention
  - Diagnosis
  - Management of comorbidities
  - Gatekeeper for referral
  - Central role in care transitions
  - Advanced care planning

Improving Outcomes in Chronic Heart Failure Treatment

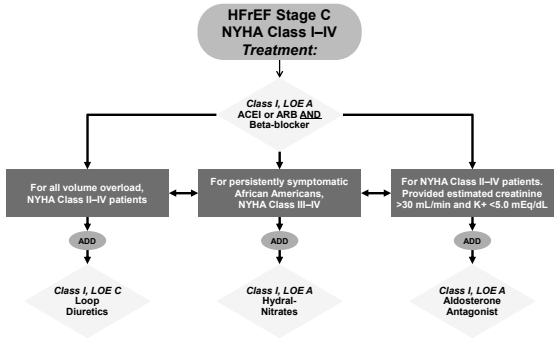
Javed Butler, MD, MPH, MBA
Professor of Medicine
Professor of Physiology and Biophysics
Stony Brook University

Guideline-Recommended Pharmacologic Treatments for HFrEF[1] (also referred to as systolic HF)

Therapy	NYHA Class			
	I	II	III	IV
ACE inhibitor, ARB	✓	✓	✓	✓
Beta blockers	(✓)	✓	✓	✓
Mineralocorticoid receptor antagonists		(✓)	✓	✓
Diuretics		(✓)	✓	✓
Digoxin			(✓)	(✓)
Hydralazine and isosorbidedinitrate		(✓)	(✓)	(✓)

(✓) For select patients.
1. ACCF/AHA Guidelines. *J Am Coll Cardiol*. 2013;62:e147-e239.

Pharmacologic Treatment for Stage C HFrEF



NYHA = New York Heart Association; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; LOE = level of evidence.
Yancy CW, et al. *J Am Coll Cardiol*. 2013;62:1495-1539.

ACEI/ARB in Heart Failure

- Indicated for all patients with asymptomatic LV dysfunction and for Class I to IV heart failure (contraindications: hyperkalemia, angioedema, pregnancy).
- Titrate to target doses (i.e., enalapril 10 mg bid, lisinopril 20 qd, ramipril 10 mg qd, benazepril 40 qd, valsartan 160 mg bid, candesartan 32 mg qd).
- Monitor serum potassium and renal function. Advise checking chemistry panel 1–2 weeks after first dose.
- Use of ACEI together with ARB reserved as a consideration only in patients not candidates for aldosterone antagonist.

LV = left ventricular; qd = every day

Yancy CW, et al. *J Am Coll Cardiol.* 2013;62:1495-1539.

Aldosterone Antagonists in Heart Failure

- Indicated for patients with mild, moderate, or severe HF due to LVD (LVEF ≤0.40).
  - Spironolactone 12.5 mg PO qd starting dose (or 6.25 mg in higher-risk patients) or eplerenone 25 mg PO qd (or 12.5 mg in higher-risk patients).
  - Decrease potassium supplementation and loop diuretic dose at time of initiation.
- Critical to very closely monitor serum potassium and renal function. Advise checking chemistry panel at 72 hours, 1 week, and 4 weeks.
- Advance spironolactone dose at 4 weeks to 25 mg PO qd or eplerenone 50 mg, which is the target dose. Avoid higher doses due to risk of hyperkalemia.
- Contraindicated if hyperkalemia or Cr >2.5 mg/dL in men and >2.0 mg/dL in women.

LVEF = left ventricular ejection fraction; PO = by mouth; Cr = creatinine.

Yancy CW, et al. *J Am Coll Cardiol.* 2013;62:1495-1539.

Beta-Blocker Therapy in Heart Failure

- Indicated for all patients with asymptomatic LV dysfunction and for Class I to IV HF with LVEF ≤0.40.
- Contraindications: cardiogenic shock, severe reactive airway disease, 2/3rd-degree HB.
- Use of one of the 3 evidence-based beta-blockers in HF: e.g., carvedilol, metroprolol succinate, bisoprolol.
- Start at very low HF doses and up-titrate to target doses at two-week intervals or highest dose short of target dose that is well tolerated.
- Monitor HR and BP.

HB = heart block; HR = heart rate; BP = blood pressure

Yancy CW, et al. *J Am Coll Cardiol.* 2013;62:1495-1539.

Beta-Blockers Differ in Their Long-Term Effects on Mortality in HF

Beta-Blocker	Long-Term Effect
Bisoprolol[1]	Beneficial
Bucindolol[2]	No effect
Carvedilol[3–5]	Beneficial
Metoprolol tartrate[6]	Not well studied
Metoprolol succinate[7]	Beneficial
Nebivolol[8]	No effect
Xamoterol[9]	Harmful

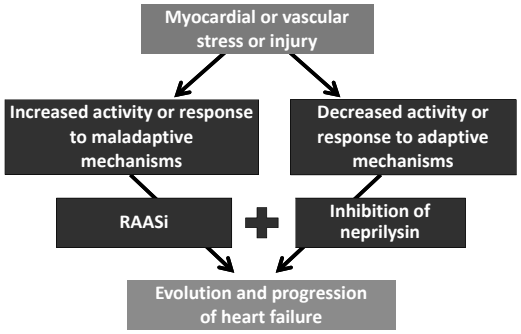
1. CIBIS II Investigators and Committees. *Lancet.* 1999;353:9-13. 2. The BEST Investigators. *N Engl J Med.* 2001; 344:1659-1667. 3. Colucci WS, et al. *Circulation.* 1996;94:2800-2806. 4. Packer M, et al. *N Engl J Med.* 2001;344:1651-1658. 5. The CAPRICORN Investigators. *Lancet.* 2001;357:1385-1390. 6. Waagstein F, et al. *Lancet.* 1993;342:1441-1446. 7. MERIT-HF Study Group. *Lancet.* 1999;353:2001-2007. 8. SENIORS Study Group. *Eur Heart J.* 2005; 26:215-225. 9. The Xamoterol in Severe Heart Failure Study Group. *Lancet.* 1990;336:1-6.

New and Emerging Therapies for the Treatment of HF With Novel Mechanisms of Action

Agent	Mechanism of Action	FDA Approval Status
Sacubitril/valsartan	Combines angiotensin receptor blockade with inhibition of neprilysin,[a] inhibiting RAAS and augmenting NP activity	Approved in July 2015 for patients with • Chronic HF (NYHA II-IV) • Reduced ejection fraction
Ivabradine	Selectively inhibits the sinus node I_f channel, decreasing HR	Approved in April 2015 for patients with • Stable, symptomatic HF • LVEF ≤35% • In sinus rhythm with RHR ≥70 bpm On maximally tolerated dose of beta blocker or with contraindications to beta blockers

[a] The metallopeptidase neprilysin hydrolyzes natriuretic peptides.

Mechanism of Progression of HF and Potential Therapeutic Options



PARADIGM-HF: Entry Criteria[1]

- NYHA class II-IV heart failure
- LVEF ≤40%
- BNP ≥150 (or NT-proBNP ≥600), but one-third lower if hospitalized for heart failure within 12 months
- Any use of ACE inhibitor or ARB, but able to tolerate stable dose equivalent to at least enalapril 10 mg daily for at least 4 weeks
- Guideline-recommended use of beta blockers and mineralocorticoid receptor antagonists
- Systolic BP ≥95 mmHg, eGFR ≥30 mL/min/1.73 m^2, and serum K^+ ≤5.4 mEq/L at randomization

1. McMurray JJ et al. *N Engl J Med.* 2014;371:993-1004.

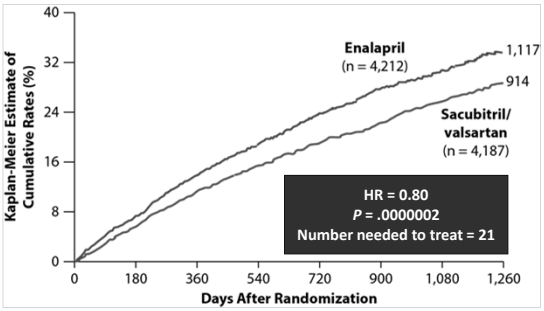
PARADIGM-HF Was Designed to Show Incremental Effect on Cardiovascular Death[1]

Primary endpoint was cardiovascular death or hospitalization for heart failure, but PARADIGM-HF was designed as a cardiovascular mortality trial

- The sample size of the trial was determined by effect on **cardiovascular mortality**, not the primary endpoint
- The Data Monitoring Committee was allowed to stop the trial only for a compelling effect on **cardiovascular mortality** (in addition to the primary endpoint)
- **Difference in cardiovascular mortality of 20%** between sacubitril/valsartan (200 mg BID) and enalapril (10 mg BID) was prospectively identified as being clinically important (n = 8,000 yielded 80% power)

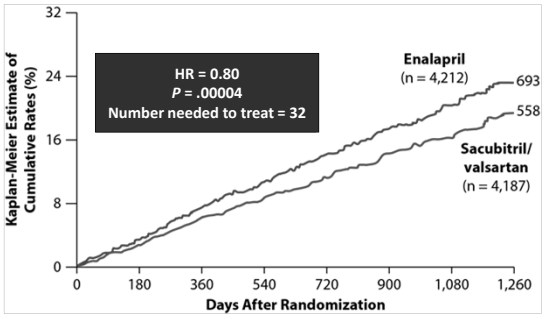
1. McMurray JJ et al. *N Engl J Med.* 2014;371:993-1004.

PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)[1]



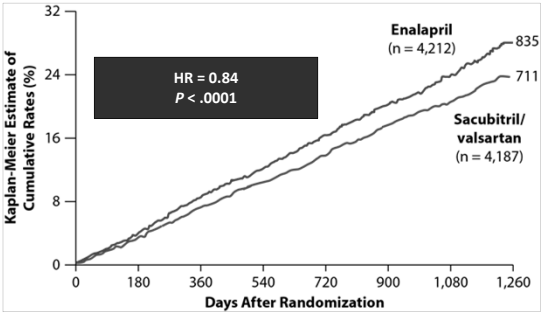
1. McMurray JJ et al. *N Engl J Med.* 2014;371:993-1004.

PARADIGM-HF: Cardiovascular Death[1]



1. McMurray JJ et al. *N Engl J Med.* 2014;371:993-1004.

PARADIGM-HF: All-Cause Mortality[1]



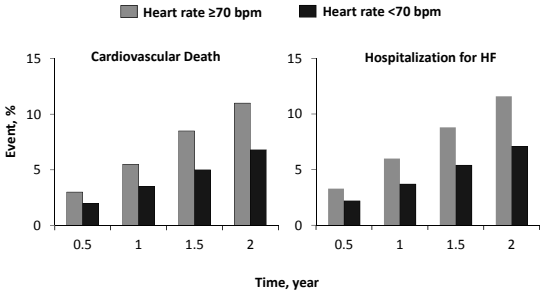
1. McMurray JJ et al. *N Engl J Med.* 2014;371:993-1004.

PARADIGM-HF: Adverse Events[1]

	Sacubitril/ Valsartan (n = 4,187)	Enalapril (n = 4,212)	*P*
Prospectively identified adverse events, % of patients			
Symptomatic hypotension	14.0	9.2	<.001
Serum potassium >6.0 mmol/L	4.3	5.6	.007
Serum creatinine ≥2.5 mg/dL	3.3	4.5	.007
Cough	11.3	14.3	<.001
Discontinuation for adverse event	**10.7**	**12.2**	**.02**
Discontinuation for hypotension	0.9	0.7	NS
Discontinuation for hyperkalemia	0.3	0.4	NS
Discontinuation for renal impairment	0.7	1.4	.001
Angioedema (adjudicated)			
Medications; no hospitalization	0.2	0.2	NS
Hospitalized; no airway compromise	0.1	0.1	NS
Airway compromise	0	0	----

1. McMurray JJ et al. *N Engl J Med.* 2014;371:993-1004.

Heart Rate as a Predictor of Cardiovascular Death and Hospitalization for HF[1]



1. Fox K et al. *Lancet*. 2008;372:817-821.

Mechanism of action and indications of drugs with HR-lowering effects in chronic HF

Drug	Mechanism of action	HF indication
Beta-blockers	Blocks adrenergic activity; slows sinus rate and prolongs AV conduction.	HF-rEF with sinus rhythm or AF; HF-pEF with AF
Ivabradine	Selective inhibition of the pacemaker modulating 'f' current (I_f) in the sinoatrial node; slows sinus rate. No effect on AV node.	HF-rEF with sinus rhythm
Digoxin	Increases vagal tone; inhibits sympathetic nervous system activity; slows sinus rate and prolongs AV conduction.	HF-rEF with sinus rhythm or AF; HF-pEF with AF
Verapamil	Blocks high voltage calcium channels; slows sinus rate and prolongs AV conduction.	HF-pEF with sinus rhythm or AF
Amiodarone	Blocks potassium channels; antiadrenergic effects; slows sinus rate and prolongs AV conduction.	HF-rEF with AF

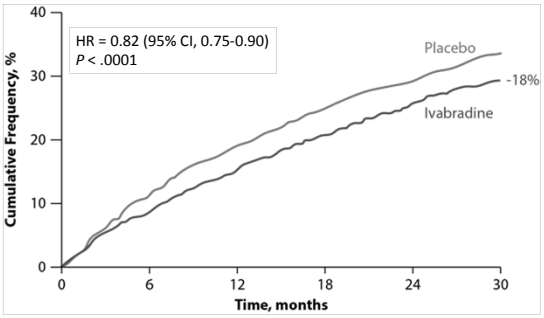
Dobre D et al. Eur J Heart Fail. 2014;16:76-85.

SHIFT Study Trial Design

- Randomized, double-blind, placebo-controlled trial in 6,505 patients to test the hypothesis that heart rate slowing with funny current inhibitor ivabradine improves cardiovascular outcomes in patients with
  - Moderate to severe chronic HF
  - Hospitalization for worsening HF within 12 months prior to randomization
  - LVEF ≤35%
  - Sinus rhythm and heart rate ≥70 bpm
  - Receiving guidelines-based background HF therapy, including maximally tolerated dose of a beta blocker, unless beta blocker is contraindicated
  - Ivabradine dose: 5 mg BID, then titrate to 7.5 mg BID if HR still >60 bpm, or down titrate to 2.5 mg BID if HR <50 bpm

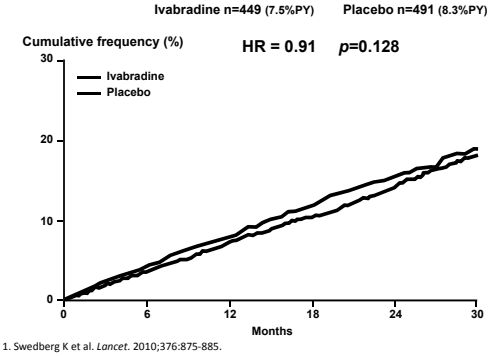
1. Swedberg K et al. *Lancet*. 2010;376:875-885.

Primary Endpoint: Composite of CV Death or Hospitalization for Heart Failure (Time-to-First Event Analysis)[1]



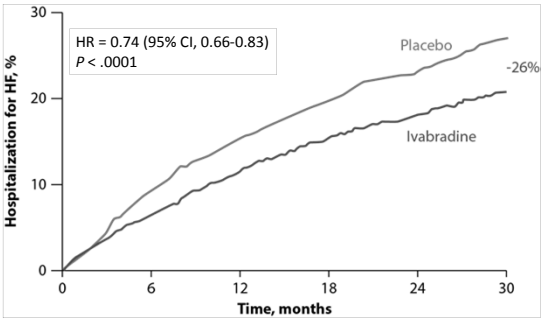
1. Swedberg K et al. *Lancet*. 2010;376:875-885.

Cardiovascular death[1]



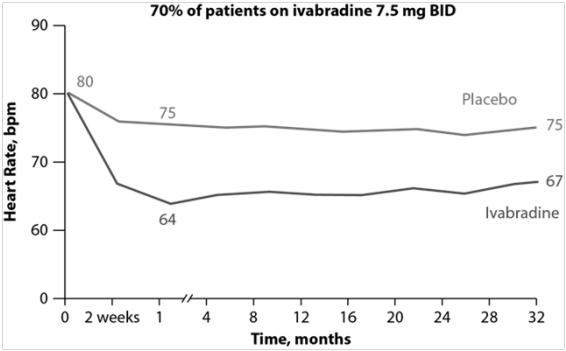
1. Swedberg K et al. *Lancet*. 2010;376:875-885.

Secondary Pre-Specified Endpoint: Hospitalization for Heart Failure (Time-to-First Event Analysis)[1]



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

Changes in Mean HR With Ivabradine[1]



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

Ivabradine Treatment Discontinuation[1]

	Patients With an Adverse Event, Leading to Withdrawal		
	Ivabradine, % (N = 3,232)	Placebo, % (N = 3,260)	*P*
All adverse events	14	13	.051
Symptomatic bradycardia	1	<1	.002
Asymptomatic bradycardia	1	<1	<.0001
Atrial fibrillation	4	3	.137
Phosphenes	<1	<1	.224
Blurred vision	<1	<1	1

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

Elevated Heart Rate in Heart Failure--Summary

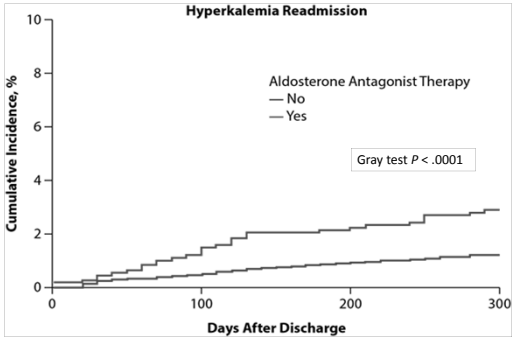
- Elevated resting heart rate (HR) is associated with an increased risk of mortality in HFrEF.[1]
- HR reduction is a treatment target for HFrEF.[1]
- Beta blockers remain underutilized and underdosed in clinical practice (and in trials).[1] Given the well-proven mortality benefits of beta blocker therapy, it is important to initiate and uptitrate these agents to target doses, as tolerated, before assessing the resting heart rate for consideration of ivabradine initiation.[2]
- Ivabradine reduces the risk of HF hospitalization for patients with HFrEF who are receiving a beta blocker at maximum tolerated dose, and who are in sinus rhythm with HR ≥ 70 bpm at rest.[3]

1. Kitai T and Tang W. *Curr Treat Options Cardiovasc Med*. 2016;18:13.
2. Yancy et al. *Circulation*. 2016;134:[ePub ahead of print].
3. Swedberg K et al. *Lancet*. 2010;376:875-885.

Hyperkalemia in Heart Failure

- Guidelines state to limit RAASi use in HF patients exhibiting hyperkalemia
- Current RAASi prescribing labels restrict use in patients with potassium levels >5.0 mEq/L
- Novel HF therapies excluded hyperkalemic patients from their clinical trials
- Even with precaution, HF patients on emerging therapies will struggle with potassium-elevating side effects

Association Between Aldosterone Antagonist Therapy and Risk of Readmission Among HFrEF Patients[1]

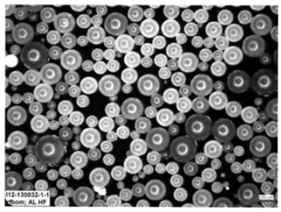


1. Hernandez AF et al. *JAMA*. 2012;308:2097-2107.

Patiromer for Oral Suspension[1]

Patiromer

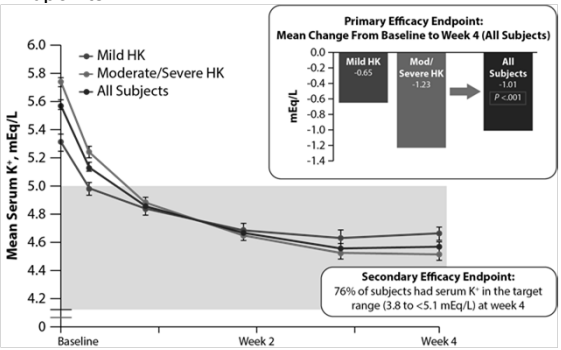
- Free-flowing powder of small spherical beads (~110 µm)
- Calcium (rather than sodium) is exchanged for potassium
- Site of action is the GI tract, mainly in the lumen of the colon
  - K^+ is the most abundant cation
  - Residence time of the polymer is the longest



Light microscopy image

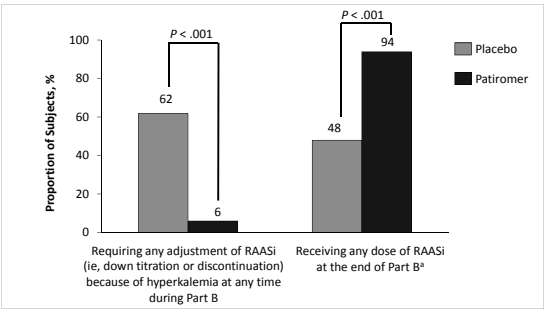
1. Adapted from: Juurlink DN et al. *N Engl J Med*. 2004;351:543-551.

Phase 3 Part A: Primary and Secondary Efficacy Endpoints[1]



1. Weir MR et al. *N Engl J Med*. 2015;372:211-221.

Control of Hyperkalemia Enables More Patients to Stay on RAASi Therapy[1]



[a] End of Part B could be at final visit (Week 8) or earlier if subject discontinued; includes RAASi discontinuation for any reason.

1. Weir MR et al. *N Engl J Med*. 2015;372:211-221.

Adverse Events While on Patiromer in ≥2%of Subjects[1]

Adverse Events During the Initial Treatment Phase and Through the Safety Follow-up Period for That Phase[a]

Adverse Event	No. of Patients, %
≥1 adverse event	114 (47)
Constipation	26 (11)
Diarrhea	8 (3)
Hypomagnesemia	8 (3)
Nausea	8 (3)
Anemia	7 (3)
Chronic renal failure	7 (3)
≥1 serious adverse event[b]	3 (1)

Events are listed if they occurred in at least 3% of the 243 patients overall

Adverse Events During the Randomized Withdrawal Phase and Through the Safety Follow-up Period for That Phase[a]

Adverse Event	Placebo (N = 52)	Patiromer (N = 55)
	No. of Patients, %	
≥1 adverse event[b]	26 (50)	26 (47)
Headache	4 (8)	2 (4)
Supraventricular extrasystoles	1 (2)	2 (4)
Constipation	0	2 (4)
Diarrhea	0	2 (4)
Nausea	0	2 (4)
≥1 serious adverse event	1 (2)[c]	0

Adverse events are listed if they occurred in at least 4% of patients in the patiromer group

[a] The safety follow-up period was 1 to 2 weeks after discontinuation of the study drug. [b] The serious adverse events included atrial fibrillation (in one patient), enterococcal endocarditis (in one), escherichia bacteremia (in one), urinary tract infection (in one), subtherapeutic anticoagulant blood levels (in one), and chronic renal failure (in one).
[c] Mesenteric vessel thrombosis leading to death occurred in one patient.

1. Weir MR et al. *N Engl J Med*. 2015;372:211-221.

FDA-Approved Sacubitril/Valsartan

	Sacubitril/Valsartan
Brand name	Entresto
Indication	The fixed-dose combination of the neprilysin inhibitor sacubitril and the ARB valsartan is indicated to reduce the risk of CV death and HF hospitalization in patients with HF with reduced ejection fraction.
Dosage	Start with 49/51 mg twice daily. Double the dose after 2–4 weeks as tolerated to maintenance dose of 97/103 mg twice daily.
Renal/hepatic impairment	For patients not currently taking an ACEI or ARB, or for those with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or moderate hepatic impairment, start with 24/26 mg twice daily.
Switching from an ACE inhibitor	**Stop ACE inhibitor for 36 hours before starting treatment.**
Contraindications	History of angioedema related to previous ACE inhibitor or ARB, concomitant use of ACE inhibitors, concomitant use of aliskiren in patients with diabetes. WARNING – pregnancy, hyperkalemia.
Side effects	Hypotension, hyperkalemia, cough, dizziness, renal failure, and angioedema (0.5% Sac/Val vs. 0.2% Enalapril).

http://www.pdr.net/full-prescribing-information/entresto?druglabelid=3756. Accessed October 20, 2015.

2016 ACC/AHA/HFSA Heart Failure Guideline Update

Pharmacological Treatment for Stage C HF*r*EF

Recommendations for RAS Inhibition With ACE Inhibitor or ARB or ARNI		
COR	**LOR**	**Recommendations**
I	ACE: A ARB: A ARNI: B-R	The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors *(Level of Evidence: A)*, OR ARBs *(Level of Evidence: A)*, OR ARNI *(Level of Evidence: B-R)* (19) in conjunction with evidence-based beta blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HF*r*EF to reduce morbidity and mortality.
I	ARNI: B-R	In patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.
III: Harm	B-R	ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor.
III: Harm	C-EO	ARNI should not be administered to patients with a history of angioedema.

COR = class of recommendation; LOR = level of recommendation; ARNI = angiotensin receptor blocker and neprilysin inhibitor.
Yancy et al. *Circulation*. 2016;134:[ePub ahead of print].

FDA-Approved Ivabradine

	Ivabradine
Brand name	Corlanor
Indication	To reduce the risk of hospitalization for worsening HF in patients with stable, symptomatic chronic HF with LVEF ≤35% who are in sinus rhythm with resting HR ≥70 bpm and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.
Dosage	Start with 5 mg twice daily. After 2 weeks of treatment, adjust dose based on HR. Max is 7.5 mg twice daily. In patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise, start with 2.5 mg twice daily.
Contraindications	Acute decompensated HF; BP <90/50 mmHg; sick sinus syndrome or third-degree AV block, unless a functioning demand pacemaker is present; resting HR < 60 bpm prior to treatment; severe hepatic impairment; pacemaker dependence. WARNING – fetal toxicity.
Side effects	Occurring in ≥1% of patients are bradycardia, hypertension, atrial fibrillation, and luminous phenomena (phosphenes).

http://www.pdr.net/full-prescribing-information/corlanor?druglabelid=3713. Accessed October 20, 2015.

2016 ACC/AHA/HFSA Heart Failure Guideline Update

Pharmacological Treatment for Stage C HF*r*EF

Recommendation for Ivabradine		
COR	**LOR**	**Recommendations**
IIa	B-R	Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HF*r*EF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (37-40).

COR = class of recommendation; LOR = level of recommendation; GDEM = guideline-directed evaluation & management.
Yancy et al. *Circulation*. 2016;134:[ePub ahead of print].

Conclusions: Impact of New and Emerging Therapies on HF Management

- Sacubitril/valsartan is shown to reduce the risk of CV death and HF hospitalization in symptomatic HFrEF patients by 20% more as compared with ACEI
- Ivabradine added to patients who have resting HR >70 and LVEF ≤35%, despite maximally tolerated beta blocker dose, reduces the risk of HF hospitalization
- New potassium binding agents are highly effective in reducing K^+ and should help increase the safety of RAASi, particularly in high-risk patients
- Optimal management of chronic HF requires that treatment be individualized accordingly

Case

Mr. Roberts is a 73 year old man with a history of coronary artery disease, COPD, hypertension, chronic kidney disease, and prior bypass surgery. In 2014, he had a stress echo performed for shortness of breath, which showed no evidence for inducible ischemia, however his left ventricular ejection fraction was 48%.

He now presents to your office with a chief complaint of fatigue, shortness of breath on exertion, and difficulty sleeping; he states that he now needs to sleep in a recliner next to his bed due to inability to breathe due to "post nasal drip".

Medications include verapamil, aspirin and rosuvastatin.

On physical examination, his blood pressure is 142/70, and his heart rate is 90. His neck veins are difficult to appreciate. His lungs show poor air entry. He has a soft heart murmur on examination and 1+ edema.

Case

NT-proBNP is markedly elevated at 5000 pg/mL. Mr. Roberts is sent for an echocardiogram, which shows his left ventricular ejection fraction is now 30%. He is referred to the hospital for admission.

During hospitalization, he has a heart catheterization, but no targets for revascularization are found. He is started on furosemide 80 mg daily, carvedilol 6.25 mg twice daily, and enalapril 10 mg twice daily. He is feeling better and is ready to return home.

You visit him on the day of discharge.

Case

You see Mr. Roberts in the office several weeks later. His post-hospital course has been uneventful. He is only mildly short of breath with exertion, but he is exercising and is no longer struggling with congestive symptoms.

He is still taking furosemide 80 mg daily, carvedilol 6.25 mg twice daily, and enalapril 10 mg twice daily, and his cardiologist added spironolactone 12.5 mg daily.

His blood pressure is 120/70 and his heart rate is 88. Recent laboratory investigations show his potassium is 4.0 (normal is up to 5.0), his blood urea nitrogen is 16 (normal is up to 20) and his creatinine is 1.5 (normal is up to 1.4).

Case

Two months later, Mr. Roberts has been titrated to maximum dose sacubitril/valsartan, and is feeling better. His cardiologist also attempted to up-titrate his carvedilol, but this was met with severe fatigue and depression.

His blood pressure is 108/60 and his heart rate is 89.