Heart Failure - Medical Management

Ajay Vallakati, MD, MPH
Assistant Professor of Internal Medicine
Heart Failure & Cardiac Transplant Program
Division of Cardiovascular Diseases
The Ohio State University Wexner Medical Center

Objectives

- Discuss pharmacological management of heart failure
- Recognize new heart failure therapies including sacubitril-valsartan and ivabradine and understand their role in treating heart failure
- Review the signs of advanced heart failure and understand when to refer to a heart failure specialist

Heart Failure Statistics

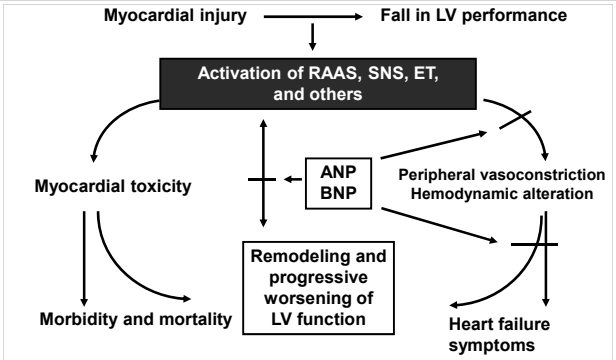
- Incidence is 10 per 1000 cases > age 65
- At age 40, lifetime risk is 1 in 5
- Mortality rate in large population studies remains 50% at 5 years.
- Over 1.1 million HF hospitalizations per year.
- With each HF hospitalization, survival goes down

Benjamin, et al. Circulation 2017.
AHA Statistics 2011

Heart Failure Definitions

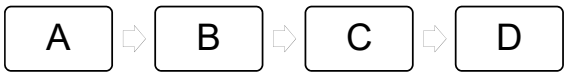
- HFrEF ("systolic HF"): LVEF ≤ 40%
- HFpEF ("diastolic HF"): LVEF ≥ 40%

Heart Failure Pathophysiology



Fonarow GC. *Rev Cardiovasc Med.* 2001;2:7-12.

Stages of Heart Failure



A	B	C	D
High risk for developing HF	**Asymptomatic HF**	**Symptomatic HF**	**Refractory end-stage HF**
• HTN • CAD • Diabetes mellitus • Family history	• Previous MI • LV systolic dysfunction • Asymptomatic valvular disease	• Known structural heart disease • Shortness of breath • Reduced exercise tolerance	• Marked symptoms at rest despite maximal medical therapy (eg, those who are recurrently hospitalized

Goldberg, L.R. and M. Jessup, Circulation, 2006. 113(24): p. 2851-60.

2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary

A Report of the American College of Cardiology Foundation/
American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American College of Chest Physicians, Heart Rhythm Society, and International Society for Heart and Lung Transplantation

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation

WRITING COMMITTEE MEMBERS

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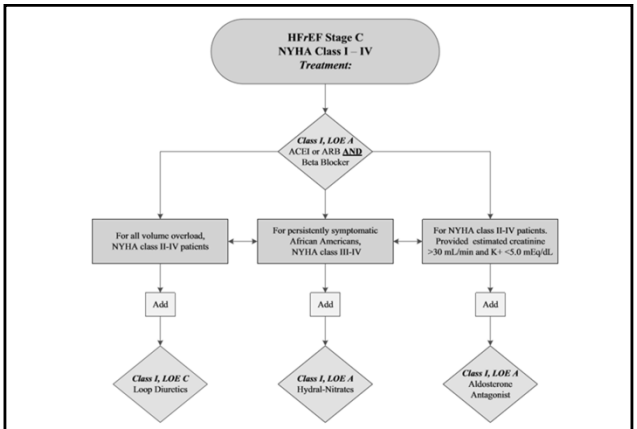
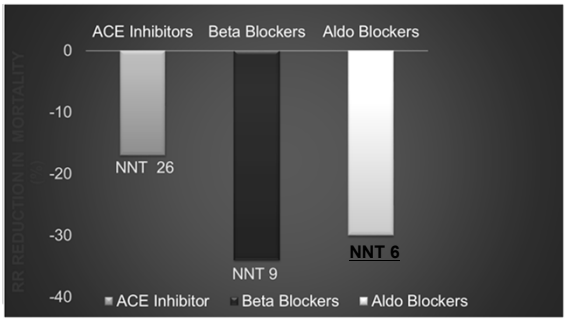


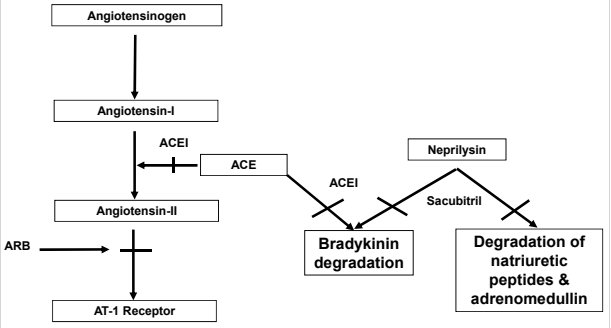
American Heart Association. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. Yancy et al. Circulation, 2013:128(16): 1810-52.

Magnitude of Benefit in RCTs

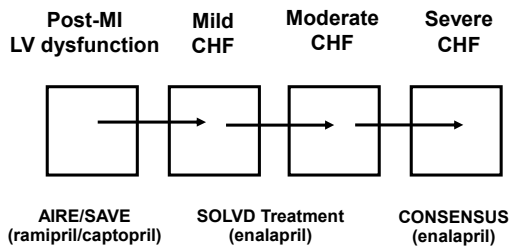


Yancy et al. Circulation, 2013:128(16): 1810-52.

Renin-Angiotensin Pathway



Renin Angiotensin Antagonism



Managing Heart Failure with ACE Inhibitors

- Indication – Symptomatic/asymptomatic pts with EF ≤ 40%
- No difference among ACEI regarding Sx / survival.
- When initiating therapy, start at low dose and optimize volume status.
- Change in salt/water balance will exaggerate or attenuate clinical response.
- Expect early rise in creatinine of 10-20%; greater initial increase in creatinine in CRI.
- Creat. increase > 0.3 mg/dl seen in 15-30% with severe HF;
- 5-15% with mild-moderate HF.

ACE Inhibitors – Adverse Effects

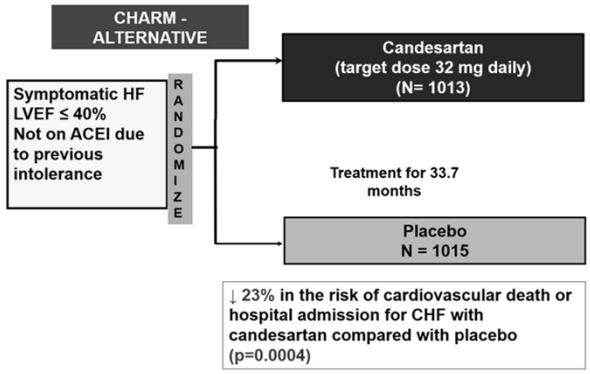
Related to angiotensin suppression:

- ***Hypotension*** – severe postural symptoms, worsening renal function, blurred vision, syncope.
- ***Worsening renal function*** –
  - 5-10% mild to moderate HF, 15-30% severe HF.
  - Risks greater with NSAID's, RAS.
  - Try to reduce diuretic first.
- ***Potassium retention*** – seen frequently in those with renal disease and DM

Related to kinin production:

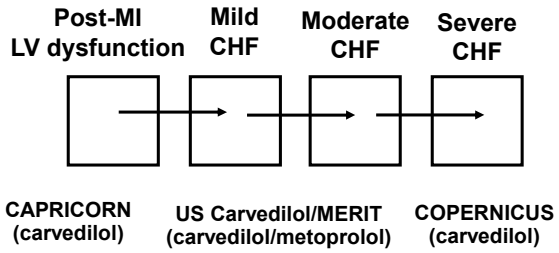
- ***Cough*** (5-10%)
- ***Angioedema*** (1%)

ARBS in Patients Not Taking ACE Inhibitors:



Granger et al. Lancet 2003: 362: 772-776

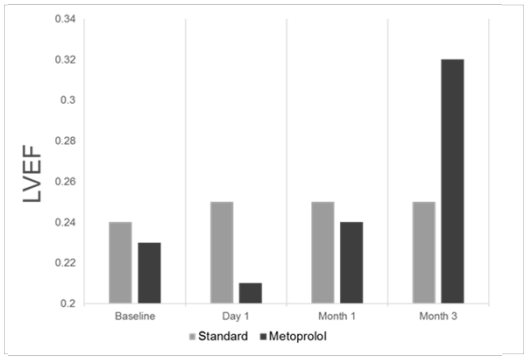
Beta- receptor Antagonism



Not all β- Blockers improve survival

Study	Drug	Target Dosage(mg)	Outcome
CIBIS 2	Bisoprolol	10 QD	↓34% mortality
MERIT-HF	Metoprolol succinate	200 QD	↓34% mortality
COPERNICUS	Carvedilol	25 BID	↓35% mortality
BEST	Bucindolol	100 BID	Not significant
SENIORS	Nebivolol	10 QD	Not significant

Impact of Beta-blocker on Ejection Fraction



Hall et al JACC 1995: 25(5): 1154-1161

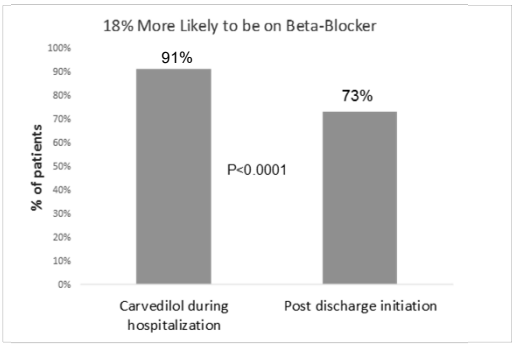
Managing Heart Failure with Beta-blockers

- Indication – Symptomatic/asymptomatic pts with EF ≤ 40%
- Initiate at low dose when patient is stable
- Use drugs shown to be beneficial in studies
- Up-titrate gradually, generally ≥ 2 week intervals
- Goal is target dose achieved in clinical trials
- Start in the hospital if intravenous inotropic or vasoactive medications were not used

Beta-blockers -Contraindications

- Decompensated patient
- Cardiogenic shock
- Fluid overload
- Symptomatic bradycardia/ high degree heart block (without pacemaker)
- Symptomatic hypotension

IMPACT-HF - Beta blocker at 60 days



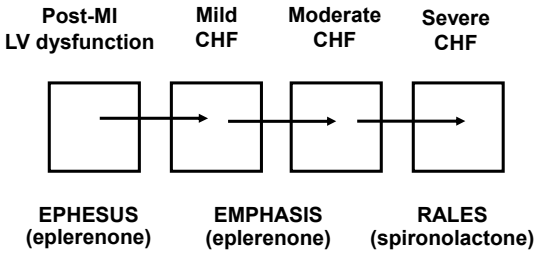
Gattis et al. JACC 2004: 43(9): 1534-1541

Aldosterone Antagonism

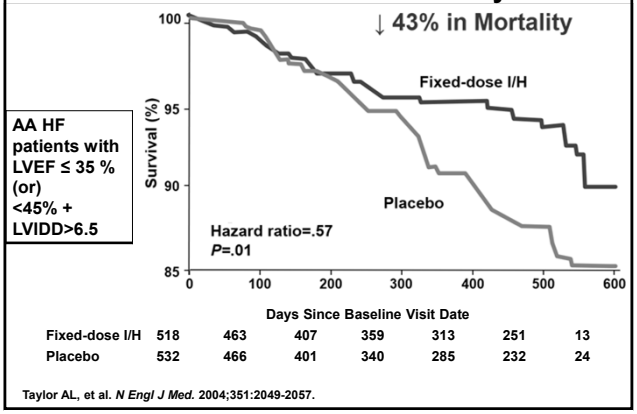
Study	Drug	Patient description	Outcome
RALES	Spironolactone	NYHA FC III-IV	↓30% mortality
EPHESUS	Eplerenone	Post MI HF	↓15% mortality
EMPHASIS	Eplerenone	NYHA FC II	↓24% mortality

Pitt et al. NEJM 1999
Pitt et al. NEJM 2003
Zannad et al. NEJM 2011

Aldosterone Antagonism



Hydralazine/Isosorbide Dinitrate A-HeFT All Cause Mortality



Taylor AL, et al. *N Engl J Med.* 2004;351:2049-2057.

Selecting an ACE inhibitor

Selecting a diuretic

Sacubitril-Valsartan (ARNi)

Brent C. Lampert, DO, FACC
Associate Professor
Heart Failure & Cardiac Transplant Program
The Ohio State University Wexner Medical Center

Neprilysin

- Enzyme that degrades several endogenous vasoactive compounds
  - Natriuretic peptides
  - Bradykinin
  - Adrenomedullin
- Inhibition of neprilysin increases levels of these substances
  - Vasodilation
  - Natriuresis
  - Diuresis

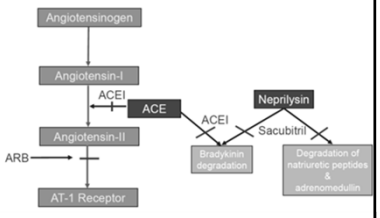
Neprilysin

- Inhibiting neprilysin was a therapeutic target for several other compounds
- Combination neprilysin and ACE inhibitor (Omapatrilat)
  - Promising, but associated with severe angioedema
  - Angioedema d/t inhibition of 3 enzymes involved in bradykinin degradation
    - ACE
    - Neprilysin
    - Aminopeptidase P

Fryer RM, et al. Br J Pharmacol 2008

Sacubitril-valsartan

- **Combo of neprilysin inhibitor sacubitril and ARB valsartan**
- **Designed to minimize risk of angioedema by only blocking 1 bradykinin degrading enzyme**



PARADIGM-HF

- **8442 patients**
- **LVEF ≤ 40%**
- **NYHA II-IV**
- **Randomized to sacubitril-valsartan (200 mg – equivalent to valsartan 160 mg BID) or enalapril 10 mg BID**
- **Primary outcome was composite CV death or first HF hospitalization**
- **Stopped early (median follow up 27 months) because of benefit seen in interim analysis**

McMurray J, et al. NEJM 2014

PARADIGM-HF: Baseline Characteristics

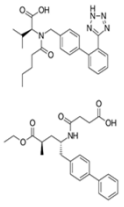
	LCZ696 (n=4187)	Enalapril (n=4212)
Age (years)	63.8 ± 11.5	63.8 ± 11.3
Women (%)	21.0%	22.6%
Ischemic cardiomyopathy (%)	59.9%	60.1%
LV ejection fraction (%)	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class II / III (%)	71.6% / 23.1%	69.4% / 24.9%
Systolic blood pressure (mm Hg)	122 ± 15	121 ± 15
Heart rate (beats/min)	72 ± 12	73 ± 12
N-terminal pro-BNP (pg/ml)	1631 (885-3154)	1594 (886-3305)
B-type natriuretic peptide (pg/ml)	255 (155-474)	251 (153-465)
History of diabetes	35%	35%
Digitalis	29.3%	31.2%
Beta-adrenergic blockers	93.1%	92.9%
Mineralocorticoid antagonists	54.2%	57.0%
ICD and/or CRT	16.5%	16.3%

PARADIGM-HF: Results

- **Sacubitril-valsartan reduced primary endpoint by 20%**
  - **NNT = 21**
- **Secondary endpoints**
  - **20% reduction in CV death**
  - **21% reduction in HF hospitalization**
  - **16% reduction in all cause mortality**

Sacubitril-Valsartan

- Approved by the FDA July 7, 2015
- "Entresto"
- NYHA Class II-IV
- EF ≤ 40%
- Used in place of ACE or ARB
- Guidelines: IB indication for patients with HFrEF to reduce morbidity and mortality



By Vaccinationist - Own work, Public Domain, https://commons.wikimedia.org/w/index.php?curid=41435503

Sacubatril-Valsartan: Contraindications

- Patients with history of angioedema due to ACE or ARB
- Pregnancy
- Do not use concurrently with ACE - hold for 36 hours after switching from ACE
- Avoid using with another ARB (i.e. avoid dual ARB therapy)

Sacubitril-Valsartan: Dosing

- Patients previously taking equivalent > 10 mg/day enalapril or > 160 mg/day valsartan
  - Starting dose 49/51 mg BID
  - Double dose (as tolerated) after 2-4 weeks to target dose 97/103
- Patients previously taking low dose (or no) ACE or ARB
  - Starting dose 24/26 mg BID
  - Double dose (as tolerated) q 2-4 weeks to target 97/103

Sacubitril-Valsartan: Dosing

- Severe renal impairment (eGFR < 30mL/min/1.73m^2)
  - Starting dose 24/26 mg BID and titrate as tolerated
- Moderate hepatic impairment (Child-Pugh B)
  - Starting dose 24/26 mg BID and titrate as tolerated
- Severe hepatic impairment
  - Use not recommended

PIONEER-HF

- Initiation of sacubitril-valsartan in ADHF hospitalized pts
- 881 patients randomized: sacubitril-valsartan or enalapril
  - LVEF ≤ 40%
  - NT pro-BNP ≥1600 pg/mL or BNP ≥400 pg/mL
  - Enrolled within 24 hrs-10 days of presentation
  - Hemodynamically stable (no increase in diuretics or use of inotropes)
- Primary outcome: Change in the NT-proBNP concentration from baseline through weeks 4 and 8

Velazquez EJ, et al. NEJM 2019

PIONEER-HF

- Baseline characteristics
  - Mean age 61
  - 72% male
  - 36% black
  - First diagnosis of HF: 34.4%
  - 52% not on ACE/ARB at admission
  - Median SBP: 118 mmHg
  - Median hospitalization 5.2 days

PIONEER-HF

- Greater BNP reduction in sacubitril-valsartan group
  - % change: −46.7% vs. −25.3%
  - Ratio of change with sacubitril–valsartan vs. enalapril 0.71; 95% CI, 0.63 to 0.81; P<0.001
  - Reduction evident as early as 1 week

PIONEER-HF

- Rates of worsening renal function, hyperK, and symptomatic hypotension did not differ significantly between groups
- 1 angioedema in sacubitril-valsartan vs 6 in enalapril group (all in black patients)
- Rate of drug discontinuation d/t adverse events did not differ

UK HARP III Trial

- United Kingdom Heart and Renal Protection-II
- 414 pts with eGFR 20-60 ml/min/1.73 m^2 randomized to sacubitril/valsartan 97/103 vs irbesartan 300
- Primary outcome: measured GFR at 12 months

Haynes R, et al. Circulation 2018

UK HARP III Trial

- Results
  - Baseline GFR: 34.0 and 34.7
  - At 12 months, no difference in GFR (29.8 and 29.9)
  - No difference in urinary albumin:creatinine ratio
  - Sacubitril/valsartan reduced
    - SBP by 5.4 mmHg
    - DBP by 2.1 mmHg
    - Troponin I by 16%
    - BNP by 18%

Haynes R, et al. Circulation 2018

PRIME Study

- 118 pts with chronic functional MR
- Randomized to sacubitril/valsartan or valsartan (in addition to standard GDMT)
- Primary endpoint: change in effective regurgitant orifice area at 12 months
- Results:
  - EROA -0.058 in sacubitril/valsartan vs -0.018 in valsartan (P=0.032)
  - Regurg volume decreased (mean difference -7.3 mL, P=0.009)
  - No significant difference in change in BP btwn groups

Kang DH, et al. Circulation 2019

Sacubitril-Valsartan

- Effect on ventricular arrhythmias
- 120 patients, NYHA II-IV, EF ≤ 40%, remote monitoring
  - For 9 months received ACE/ARB, bblocker, and aldosterone antagonist
  - ACE/ARB then changed to ARNI and followed 9 months
  - ARNI
    - ↓ NSVT (5.4 ± 0.5 vs 15 ± 1.7 in ACE/ARB; *P* <.002)
    - ↓ sustained VT and ICD shocks (0.8% vs 6.7% in ACE/ARB; *P* <.02)
    - ↓ PVCs/hr (33 ± 12 vs 78 ± 15 in ACE/ARB; *P* <.0003)
    - ↑ biventricular pacing (95%±6% to 98.8%±1.3%; *P* <.02)

De Diego, et al. Heart Rhythm 2017

Ivabradine

- **Selective inhibitor of sinoatrial pacemaker modulating "f-current" (If)**
- **Slows the sinus heart rate**
- **Mechanism of ivabradine in HFrEF likely due to heart rate reduction**

Dobre D, et al. Eur J Heart Fail 2014

SHIFT Trial

- **6558 patients**
- **LVEF ≤ 35%**
- **Sinus rhythm and resting HR ≥ 70 bpm**
- **Randomized to ivabradine or placebo**
- **Primary endpoint: composite CV death or HF hospitalization**
- **Median follow-up 23 months**

Swedberg K, et al. Lancet 2010

SHIFT Trial: Baseline Characteristic

	Ivabradine N=2052	Placebo N=2098
Mean age, years	60	60
Male, %	77	77
BMI, kg/m^2	28	28
Mean HF duration, years	3.4	3.4
HF, ischemic cause, %	66	65
NYHA Class III, %	50	51
NYHA Class IV, %	2	2
Mean LVEF, %	28.7	28.5
Mean HR, bpm	84.3	84.6

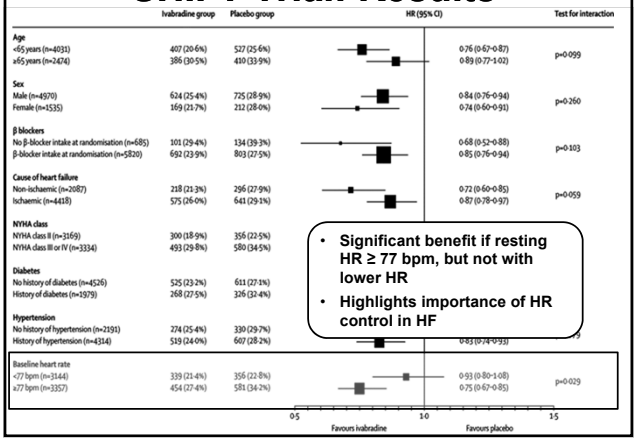
SHIFT Trial: Baseline Characteristics

GDMT	Ivabradine N=2052	Placebo N=2098
B-blocker, %	**87**	**87**
At least ½ target dose	55	56
At target dose	26	26
ACEi / ARB, %	**77**	**77**
Diuretis, %	**28**	**28**
Aldosterone antagonists, %	**3.4**	**3.4**

SHIFT Trial: Results

- Heart rate reduction
  - 28 days: HR ↓ 10.9 bpm
  - 1 yr: HR ↓ 9.1 bpm
  - Study end: HR ↓ 8.1 bpm
- 24% reduction in primary end-point in ivabradine group
- Results largely d/t ↓ HF hospitalization (HR 0.74, 95% CI 0.66-0.83) and ↓ HF death (HR 0.74, 95% CI 0.58-0.94)

SHIFT Trial: Results



- Significant benefit if resting HR ≥ 77 bpm, but not with lower HR
- Highlights importance of HR control in HF

Ivabradine

- Approved by the FDA on April 15, 2015
- "Corlanor"
- Stable HF with LVEF ≤ 35%
- Sinus rhythm with resting HR ≥ 70 bpm
- Either on max tolerated dose of β-blocker or have contraindication to β-blockers
- Not a full or partial substitute for β-blockade
- Guidelines: IIA indication in HFrEF patients on max GDMT with HR > 70

Ivabradine: Contraindications

- Acute decompensated heart failure
- Hypotension (BP < 90/50)
- Sick sinus syndrome, sinoatrial block, or 3rd degree AV block
- Patients who are pacemaker dependent
- Severe hepatic impairment
- In combo with strong CYP34A inhibitors

Other Ivabradine Data in HF

- **ETHIC-AHF**
  - **Early co-administration of ivabradine and BB versus BB alone in hospitalized HFrEF pts**
  - **71 pts**
  - **Ivabradine added 24-48 hrs after admission**
    - **Significant reduction in HR at 28 days and 4 months**
    - **Lower BNP levels**
    - **Lower # of pts documented to have advanced HF functional class**

Hidalgo FJ, et al. Int J Cardiol 2016

Other Ivabradine Data in HF

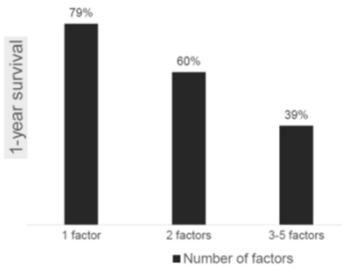
- **PRIME-HF (Predischarge Initiation of Ivabradine in the Management of Heart Failure)**
  - **Designed to enroll 450 pts; stopped early d/t difficulty with enrollment**
  - **104 pts: age 57.5 yrs, 36% women, 64% black**
  - **6 months post hospitalization**
    - **Greater HR reduction: 10 bpm vs 0.7 bpm**
    - **No significant reduction in b-blocker dose**
    - **No hypotension or bradycardia**
  - **31% pts had difficulty getting initial Rx and 58% had difficulty at some point: price, insurance decline, physician stopping drug**

Metz, RJ, et al. Circulation 2019

Identifying Advanced Heart Failure

High risk HF patients

Criteria for referral of patients < 80 years to HF specialist
• SBP< 90 mmHg
• Creatinine ≥ 1.6
• Hb ≤ 12
• No RAS antagonist
• No β-blocker



Thorvaldsen, et al. JACC 2014.

Patient referral to HF specialist I-NEED-HELP

- I: IV inotropes
- N: NYHA IIIB/IV or persistently elevated natriuretic peptides
- E: End-organ dysfunction
- E: Ejection fraction ≤ 35%
- D: Defibrillator shocks
- H: Hospitalizations > 1
- E: Edema despite escalating diuretics
- L: Low blood pressure, high heart rate
- P: Prognostic medication – progressive intolerance or down-titration of GDMT

Yancy, et al. JACC 2017