BRIGHAM HEALTH
BRIGHAM AND WOMEN'S
Department of Medicine

HARVARD MEDICAL SCHOOL | Postgraduate Medical Education

Recent Advances in Heart Failure

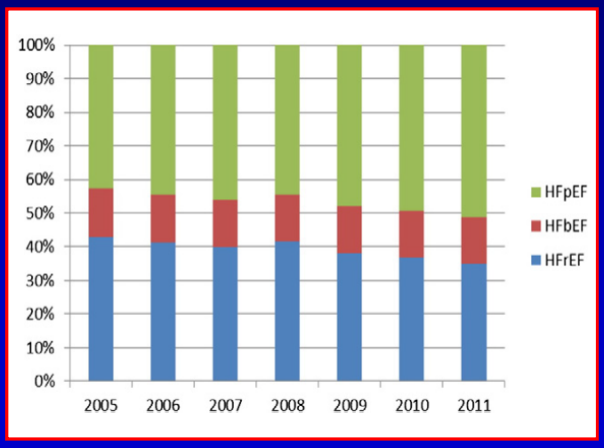
Anju Nohria, MD
Advanced Heart Disease Section
Brigham and Women's Hospital

Disclosures

- Amgen – research support
- Takeda Oncology – consultant
- Astrazeneca – consultant
- Boehringer Ingelheim – consultant

Distribution of EF in Pts. Hospitalized with HF

40,239 Medicare pts enrolled in GWTG-HF from 2005-11



Cheng et al. Am Heart J 2014;168:721-30.e3

HF-pEF vs. HFrEF

- Older
- Female
- HTN
- CKD
- A Fib
- ↓ CAD

HFbEF like HFpEF

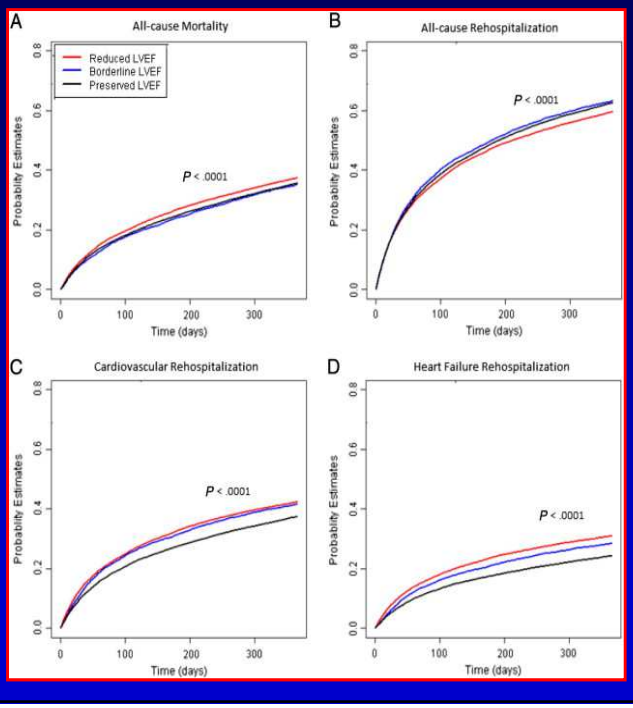
- ↑ CAD

Outcomes after HF Hospitalization, by EF

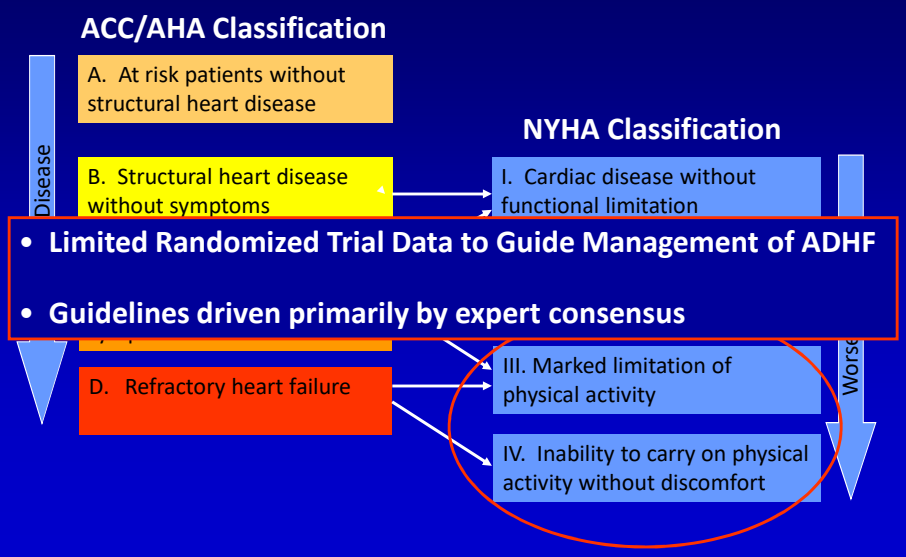
HFrEF vs. HFbEFvs. HFpEF

- **Mortality:**
  - **30d: 9.5% vs. 8.2% vs. 8.5%**
  - **1 yr: 37.5% vs. 35.1% vs. 35.6%**
- **All-cause Readmission:**
  - **30d: 19.7% vs. 20.9% vs. 20.5%**
  - **1 yr: 59.6% vs. 63.2% vs. 62.5%**

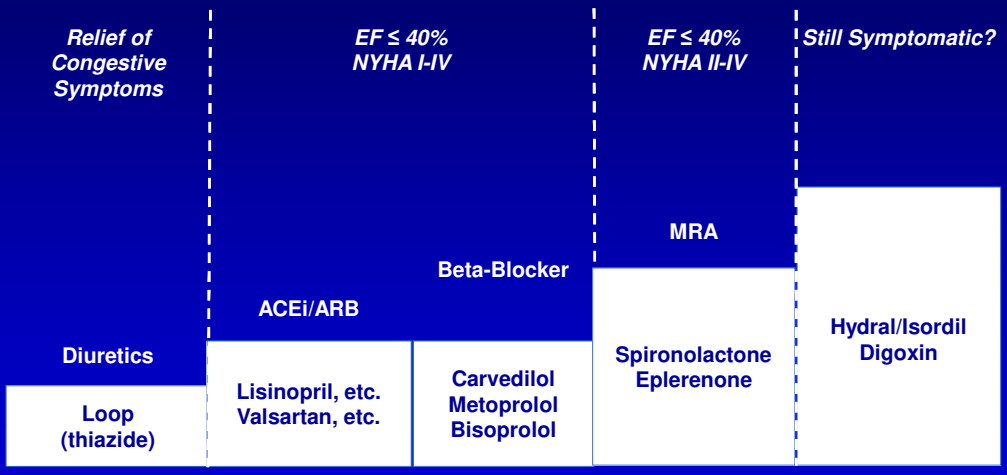
Cheng et al. Am Heart J 2014;168:721-30.e3



Stages of Heart Failure



Guideline-Directed Medical Therapy for HFrEF: 2013



Yancy C, et al. Circulation. 2013;128:e240-e327
McMurray JJV, et al. Eur Heart J. 2012;33:1787-1747

Heart Failure Case

- 53 y.o. man presents for f/u after 2nd admission for ADHF
- Non-ischemic CMP (EF 25%, LVEDD 7.5 cm)
- PAF/VT w/ ICD therapies
- Metoprolol succinate 200 mg daily, losartan 50 mg daily, spironolactone 25 mg daily, digoxin 0.125 mg daily, furosemide 80 mg bid, and apixaban 5 mg bid

- BP 100/50, HR 85
- JVP 10 cm water, min. HJR
- Clear lungs
- RRR. Nl s1, s2. + Soft MR m
- No HSM
- No edema

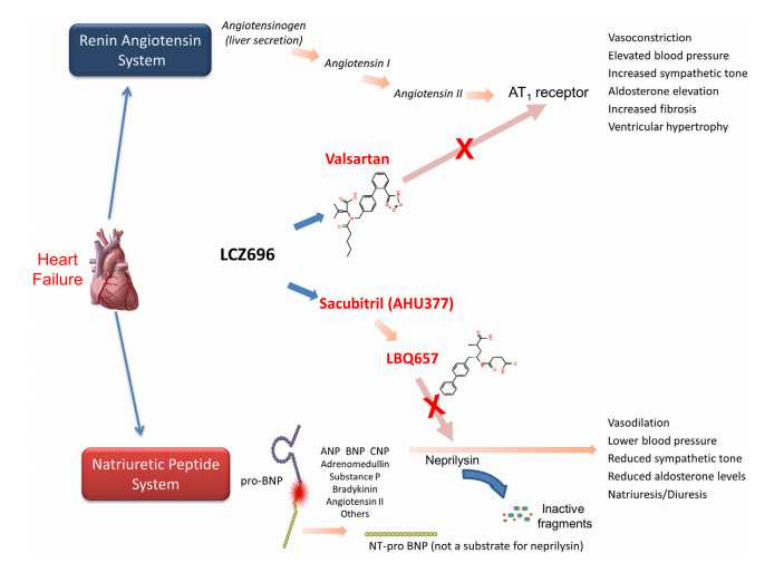
- Na 130, K 4.6, BUN 26, Cr 1.6
- Hb 10, Fe 25, TIBC 150, ferritin 300

Question

- What would be the next best step to lower his risk of HF hospitalization?

A. Change metoprolol to carvedilol
B. Change losartan to sacubitril-valsartan
C. Add ivabradine
D. Give IV iron infusions

Sacubitril/Valsartan: Mechanism of Action



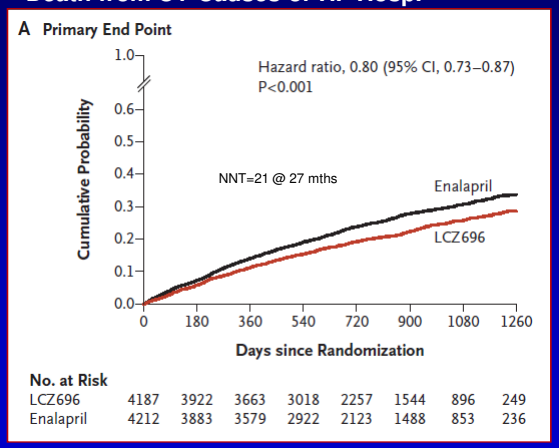
Vardeny O et al. JACC: Heart Failure 2014;2:663-70.

PARADIGM-HF

- N=8,442
- RCT:
  - Enalapril 10mg bid vs. LCZ696 200mg bid
- Inclusion Criteria:
  - EF ≤ 40% → 35%
  - NYHA II-IV
  - BNP ≥ 150, NT-BNP ≥ 600
  - BNP ≥ 100 if hosp w/in 12 mths
  - On optimal Rx
  - SBP ≥ 95
  - eGFR > 30 ml/min
  - K < 5.4

McMurray et al. NEJM 2014; 371:993-1004.

Death from CV Causes or HF Hosp.



- Increased hypotension, less renal dysfunction.
- No increase in hyperkalemia, angioedema, or cough.

Guideline Update

COR	LOE	Recommendations
I	B-R	ACEi OR ARB OR ARNI in conjunction with beta-blockers + MRA (where appropriate) is recommended for patients with chronic HFrEF to reduce morbidity and mortality.
I	B-R	In patients with chronic, symptomatic HFrEF NYHA class II or III who tolerate and ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality
III	B-R	ARNI should NOT be administered concomitantly with ACEi or within 36 hours of last ACEi dose
III	C=EO	ARNI should NOT be administered to patients with a history of angioedema

- Ensure 36 hrs off ACEi
- Adequate BP
- eGFR ≥ 30 ml/min/1.73 m^2

→

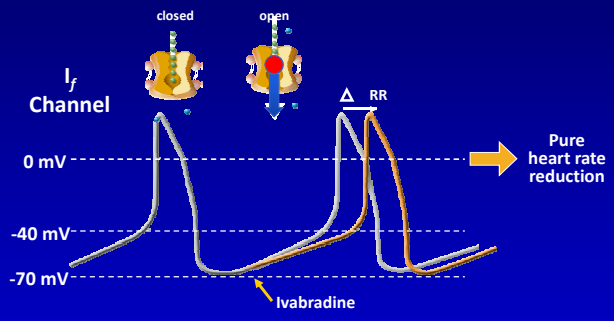
Population	Initial Dose
Enalapril > 10 mg/d or Valsartan > 160 mg/d	49/51 mg twice daily
Low dose ACE-I/ARB	24/26 mg twice daily
ACE-I/ARB naïve	
eGFR<=30 mL/min/m^2	
Moderate Hepatic Impairment (Child-Pugh Class B)	
Elderly	

→

- Assess tolerability
- Up-titrate in step-wise fashion to 97/103 mg bid
- Re-assess BP, K and Cr after each dose increase

Yancy et al. Circulation 2016; Yancy et al. JACC 2018;71(2):201-30.

Ivabradine: A Selective I_f Inhibitor

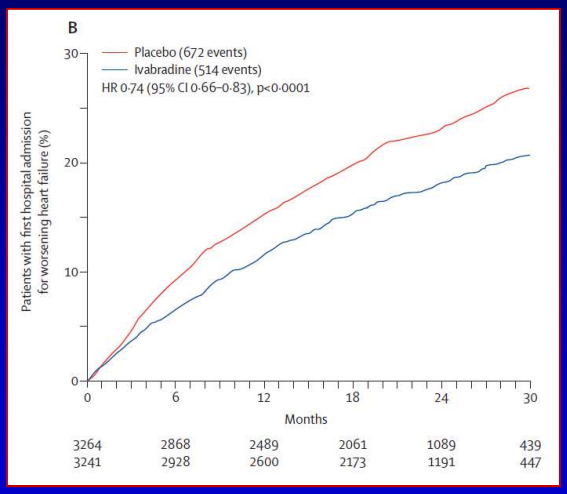


I_f inhibition reduces the diastolic depolarization slope, thereby lowering heart rate
No effect on myocardial contractility or relaxation
Use-dependent block = low risk of bradycardia

Thollon et al. Br J Pharmacol. 1994;112:37-42.

SHIFT: Ivabradine (I_f inhibitor in SA node)

- N=6,558
- EF ≤ 35%, NYHA II-IV
- Resting HR ≥ 70 bpm on max tolerated BB
- Ivabradine: 5 bid → 7.5 bid
- Average HR: 64 vs. 75 bpm @1 yr
- Greater benefit w/ greater reduction in HR
- Side effects
  - Symptomatic bradycardia: 5 vs 1%
  - Phosphenes: 3 vs 1%



Swedberg et al. Lancet 2010;376:875-85.

Guideline Update

COR	LOR	
IIa Moderate	**B-R**	**Ivabradine may be beneficial to reduce HF hospitalization for patients with symptomatic stable chronic HFrEF who are receiving GDMT, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of ≥ 70 bpm at rest.**

- Ensure that b-blockers maximized
- Assess eligibility for ivabradine

→

Age ≥ 75	Ivabradine 2.5 mg bid
Age ≤ 75	Ivabradine 5 mg bid

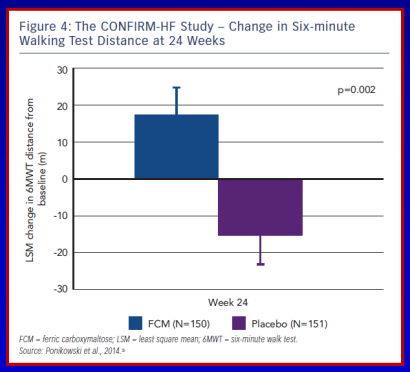
→

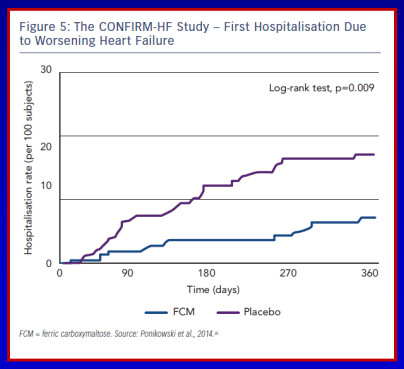
HR < 50	Reduce to 2.5 mg bid or stop
HR 50-60	Continue 5 mg bid
HR > 60	Increase to 7.5 mg bid

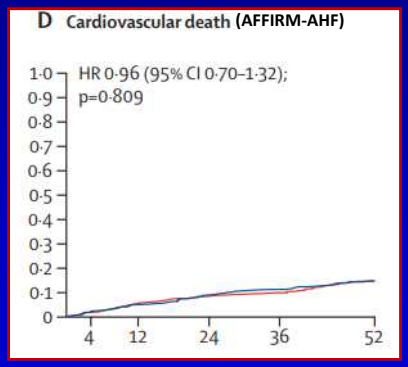
Yancy et al. Circulation 2016; Yancy et al. JACC 2018;71(2):201-30.

Iron Repletion in HF

- 50% HF patients have iron deficiency, with or without anemia
- Iron deficiency in HF is associated with ↑ mortality, independent of anemia
- No improvement in all-cause mortality and HF hospitalization with darbopoeitin
- No improvement in functional capacity or QOL with oral iron







Ponikowski et al. Eur Heart J 2015;36(11):657; Ponikowski et al. Lancet 2020;396(10266):1895.

Guideline Update

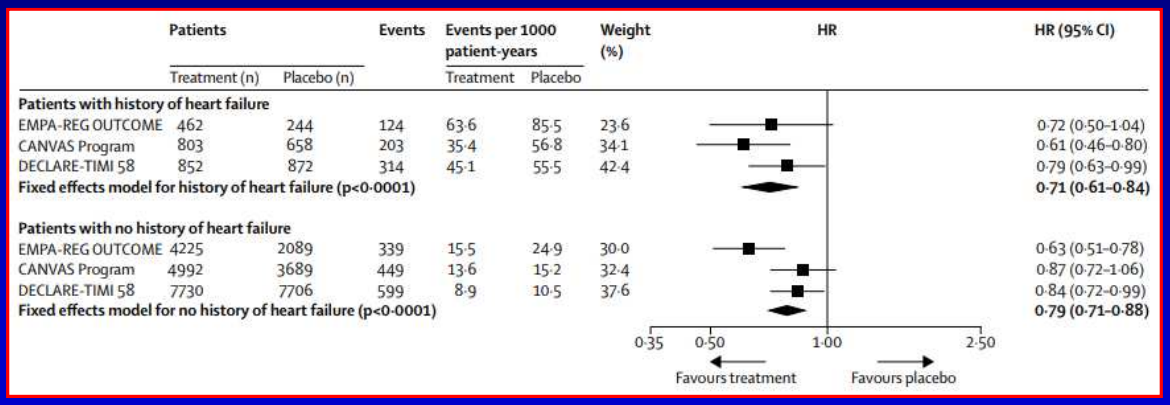
Recommendations for Anemia

COR	LOE	Recommendations
IIb	B-R	In patients with NYHA class II and III HF and iron deficiency (ferritin <100 ng/mL or 100 to 300 ng/mL if transferrin saturation is <20%), intravenous iron replacement might be reasonable to improve functional status and QoL(173, 174).
See Online Data Supplement D.		
III: No Benefit	B-R	In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality (176).
See Online Data Supplement D.		

Yancy et al. Circulation 2017. DOI:10.1161/CIR0000000000000509

SGLT-2i Reduce HF Hospitalizations in Type II DM

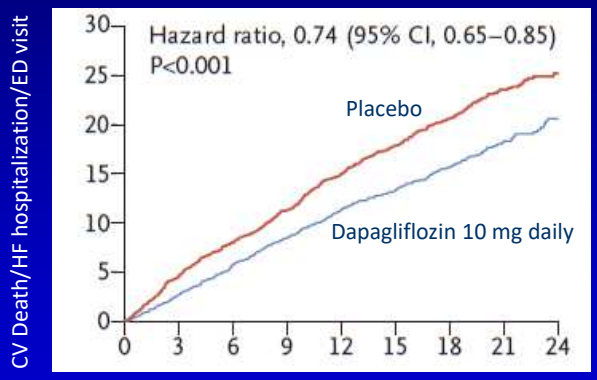
- 34,322 pts w/ established CVD or at high-risk for CVD + Type II DM
- Meta-analysis of 3 RCTs of SLGT-2i vs. placebo



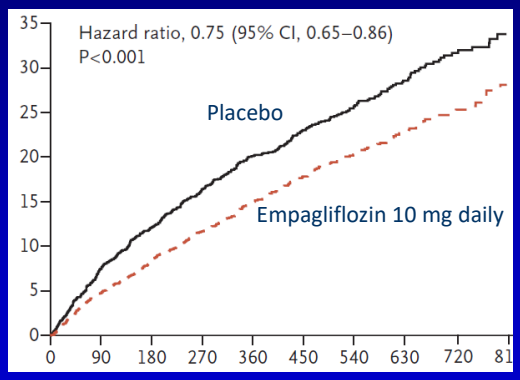
Zeniker et al. Lancet 2019;393:31-9.

SGLT-2i in HFrEF

DAPA-HF:
N=4744, EF≤40% ± DM II, NYHA II-IV



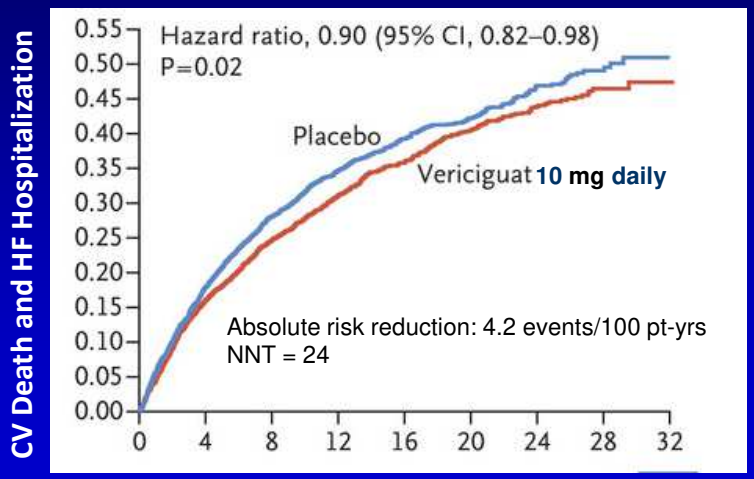
EMPEROR-REDUCED:
N=3730, EF≤40% ± DM II, NYHA II-IV



Also lower rate of decline of eGFR; Side Effects: Hypovolemia, UTI (Fungal), Balanitis, DKA

McMurray et al. NEJM 2019;381(21):1995; Packer et al. NEJM 2020;383:1413-24.

Vericiguat: Soluble Guanylate Cyclase Stimulator/Sensitizer (VICTORIA)



Major Side Effects:
- Hypotension
- Syncope
- Anemia

Armstrong et al. N Engl J Med 2020;382:1883-93.

Heart Failure Case

- 53 y.o. man presents for f/u after 2nd admission for ADHF
- Non-ischemic CMP (EF 25%, LVEDD 7.5 cm)
- PAF/VT w/ ICD therapies
- Metoprolol succinate 200 mg daily, sacubitril/valsartan 24-26 bid, spironolactone 25 mg daily, digoxin 0.125 mg daily, furosemide 80 mg bid, and apixaban 5 mg bid

- BP 100/50, HR 85
- JVP 10 cm water, min. HJR
- Clear lungs
- RRR. Nl s1, s2. + Soft MR m
- No HSM
- No edema

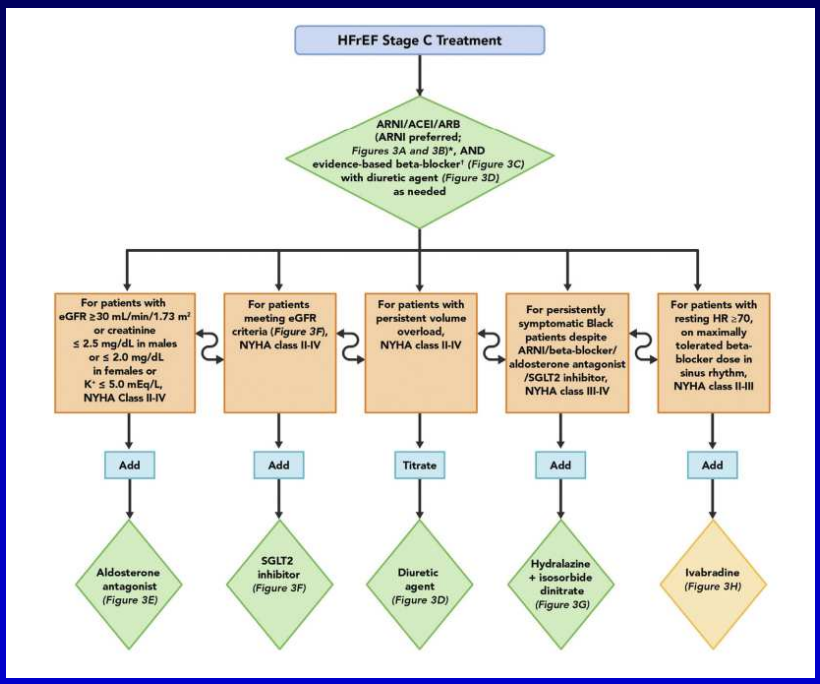
- Na 130, K 4.6, BUN 26, Cr 1.6
- Hb 10, Fe 25, TIBC 150, ferritin 300

Question

- What would be the next best step in his management?

A. Change metoprolol to carvedilol
B. Add dapagliflozin
C. Add ivabradine
D. Give IV iron infusions

Algorithm for GDMT in Stage C HFrEF



Maddox et al. JACC 2021;77(6):772-810.

Heart Failure Case

- He presents 3 mths later w/ dyspnea w/ minimal exertion and 10 lb weight gain despite doubling of diuretic dose
- Metoprolol succinate 200 mg daily, sacubitril/valsartan 24-26 bid, spironolactone 25 mg daily, dapagliflozin 10 mg daily, digoxin 0.125 mg daily, furosemide 160 mg bid, and apixaban 5 mg bid

- BP 90/70, HR 90
- JVD to angle of jaw
- Clear lungs
- RRR. Nl s1, s2. + s3, MR, TR
- Liver edge 2 cm below costal margin
- Trace edema, lukewarm to touch, 2+ distal pulses

- Na 128, K 4.6, BUN 30, Cr 1.8

Treatment Goals in ADHF

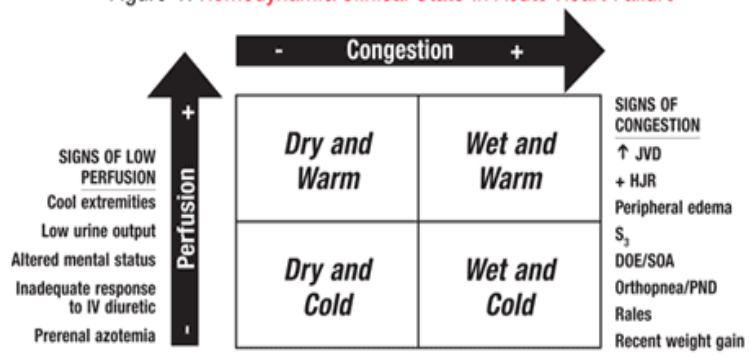
- Address precipitating factors
- Optimize volume status and perfusion
- Optimize oral heart failure regimen
- Manage Related Risks (e.g. SCD, VTE)
- Patient Education
- Initiate Longitudinal Disease Management

Precipitating Factors

- Acute coronary syndromes/coronary ischemia
- Uncontrolled hypertension
- Atrial or ventricular arrhythmias
- Acute Infection (e.g. URI, pneumonia, UTI)
- Medications (e.g. NSAIDs, steroids, TZDs, L-type CCBs)
- Nonadherence (eg. sodium and fluid restriction, medications)
- Excessive alcohol intake or illicit drug use
- Hypo/hyperthyroidism
- Other cardiac dz (acute endocarditis, acute dissection, acute myopericarditis)

Symptomatic HF is a Clinical Diagnosis

Figure 1. Hemodynamic/Clinical State in Acute Heart Failure



↑: increased; +: positive; -: negative; DOE: dyspnea on exertion; HJR: hepatojugular reflux; JVD: jugular venous distention; PND: paroxysmal nocturnal dyspnea; S_3: ventricular filling murmur; SOA: shortness of air.
Source: References 10, 11.

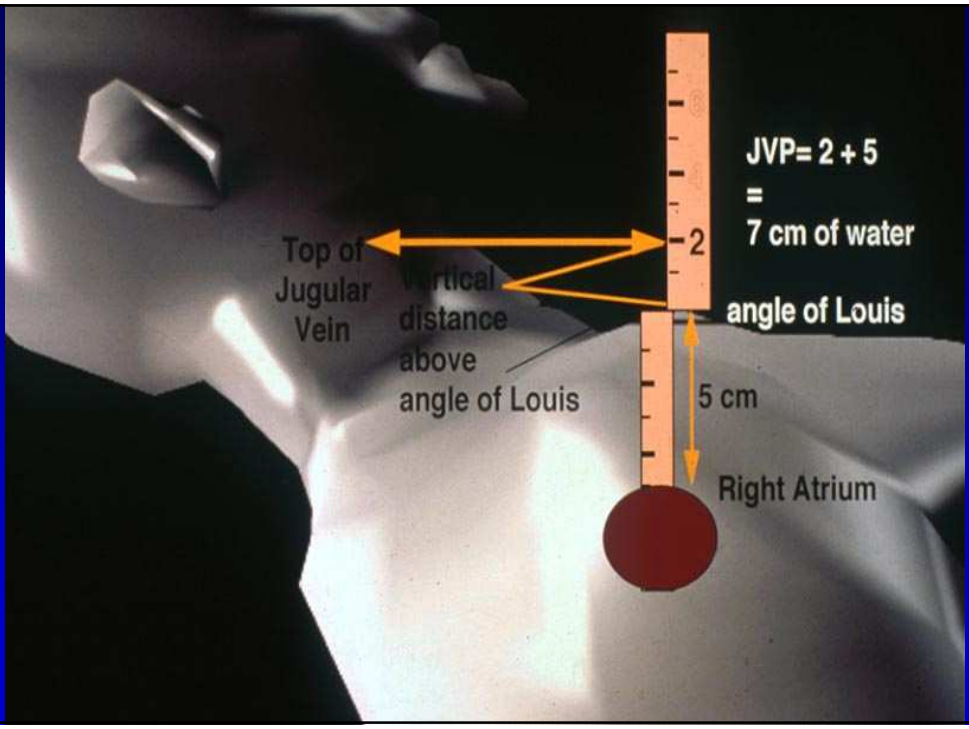
Nohria et al. JACC 2003;41:1797-1804.

Accuracy of Physical Findings for Elevated LV Filling Pressure

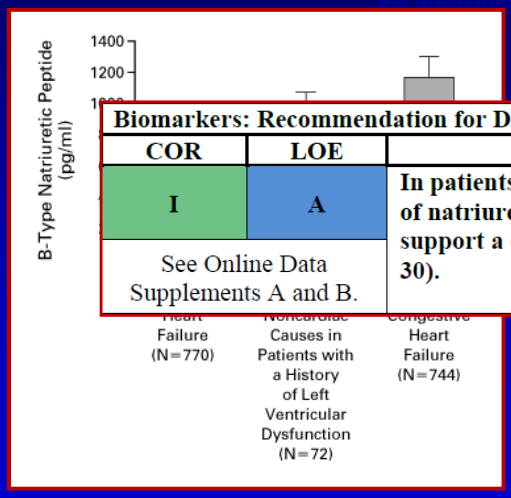
Finding	Sensitivity	Specificity
Orthopnea (≥2 pillows)	85%	24%
Rales (≥1/3 lungs fields)	15 %	89%
S3	63%	34%
Edema (>1+)	41%	67%
Elevated JVP (>10 cm)	67%	72%

Sensitivity and specificity for predicting PCWP > 22 mm Hg

Drazner M et al. Circ Heart Fail 2008;1:170

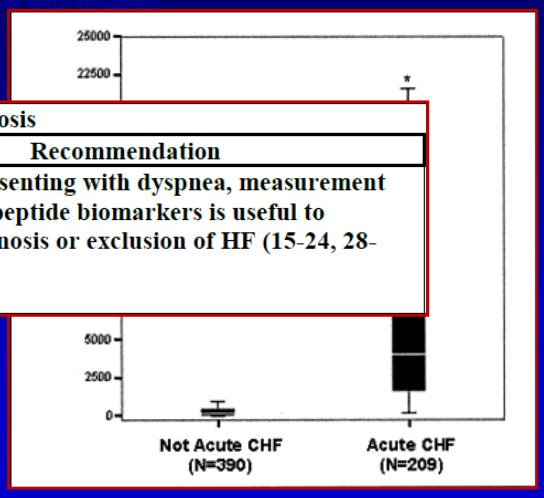


BNP to Assist Diagnosis of HF



Biomarkers: Recommendation for Diagnosis

COR	LOE	Recommendation
I	A	In patients presenting with dyspnea, measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclusion of HF (15-24, 28-30).
See Online Data Supplements A and B.		



Maisel AS, et al. NEJM 2002;347:161; Januzzi J et al. Am Heart J 2005;149:744.

Diagnostic Limitations of Natriuretic Peptides

- Imperfect surrogate for filling pressures
  - Levels increase with age, female gender, pressure overload, renal failure
- [illegible]
- [illegible]
- Levels can be elevated in diseases other than HF
- Only NT-proBNP predictive w/ Valsartan-Sacubitril

Measurement of NPs is most useful when there is diagnostic uncertainty or for prognostic indications

Redfield et al., JACC 2002; Raymond et al. Heart 2003; McCullough et al., AJKD 2003; Wang et al., Circulation 2004; Januzzi et al. Am J Cardiol 2005; Maisel et al., NEJM 2002; Wu et al. Eur J Heart Failure 2003; Shah et al. J Card Fail 2011.

Diuresis in ADHF

- Loop diuretics: IV bolus or continuous infusion
  - Furosemide, torsemide, bumetanide
    - 80 mg po furosemide = 40mg IV furosemide = 20 mg po/IV torsemide = 1 mg po/IV bumetanide
- Initiate diuretics rapidly at dose ≥ oral regimen
  - i.e. if home dose 80 mg p.o. furosemide, give 80 mg I.V. furosemide
  - Give at frequent intervals
    - At least b.i.d. or t.i.d.
  - Give higher doses in pts with elevated BUN
- ***Aldosterone antagonists are weak diuretics and used mostly for K-sparing and neurohormonal effects***

DOSE Trial

- N=308 pts with ADHF, < 24 hrs admission

HIGH vs. LOW DOSE Diuretics

- ↑ improvement in dyspnea @ 72 hrs
- ↑ net diuresis and weight loss @ 72 hrs
- ↑ proportion w/ WRF (↑Cr > 0.3 mg/dL)
- No diff in death, re-hospitalization, or ED visits @ 60d

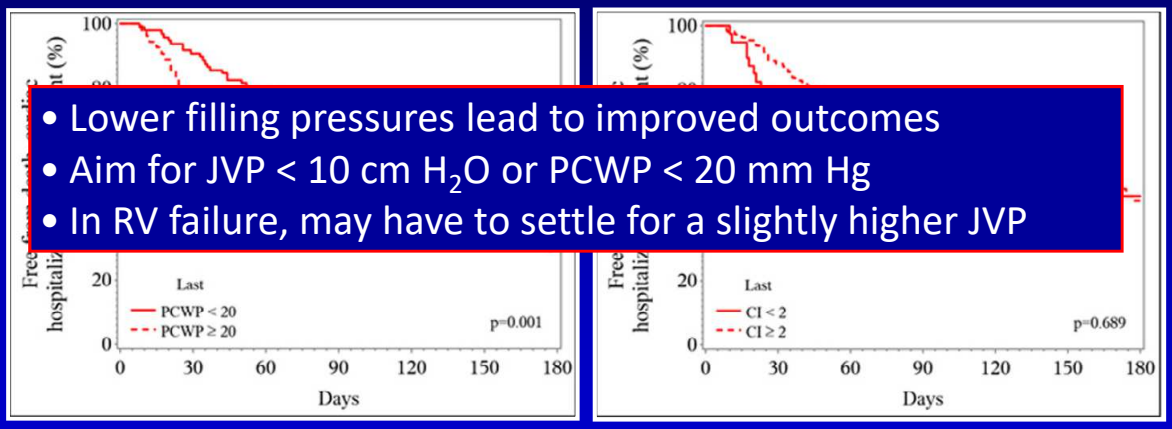
BOLUS vs. CONTINUOUS Diuretic Infusion

- No difference in any outcomes

	Low Dose	High Dose
Q12 Bolus	1X oral	2.5X oral
Continuous	1X oral	2.5X oral

Felker et al. NEJM 2011;364:797-805.

PCWP, not CI, Predicts Outcomes After HF Hospitalization: ESCAPE Trial



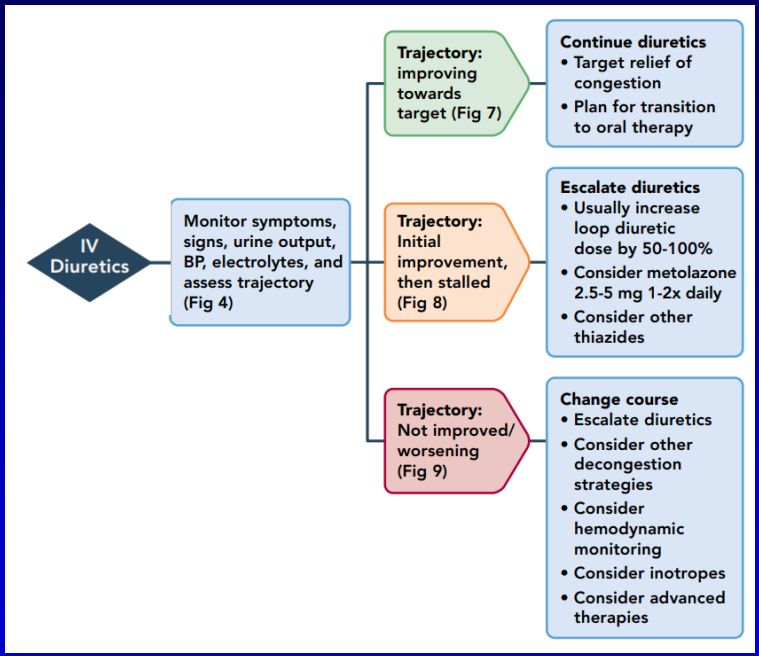
- Lower filling pressures lead to improved outcomes
- Aim for JVP < 10 cm H_2O or PCWP < 20 mm Hg
- In RV failure, may have to settle for a slightly higher JVP

Cooper LB et al. J Cardiac Fail. 2016;22;182-9.

Hospital Course

- **Day 1:**
  - **200 mg IV furosemide b.i.d.**
  - **Net urine output 1000 ml**
- **Day 2:**
  - **200 mg IV furosemide b.i.d.**
  - **Net urine output 300 ml**
  - **BUN/Cr 30/1.8 → 40/2.2**

Diuretic Therapy in Different Clinical Trajectories



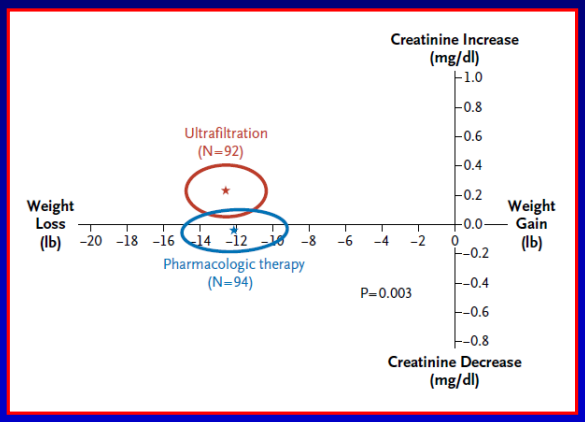
Hollenberg et al. JACC 2019;74(15):1966-2011

Hospital Course

- Day 3:
  - IV furosemide drip @ 20 mg/h + metolazone 5 mg x 1
  - Net urine output 1000 ml
  - BUN 50, Cr 3.1
  - Transient drop in SBP to 75 mm Hg
- Day 4:
  - Weaned off metoprolol w/out improvement
- Day 5:
  - Stopped valsartan-sacubitril w/out improvement

CARESS: UF vs. IV Diuretics

- N=188
- HFrEF or HFpEF
- ≥ 2 signs of ADHF
- ↑ SCr ≥ 0.3, 12 wk prior to or 10 d after admit
- No IV vasoactive meds
- SCr < 3.5 mg/dL
- 1° End-pt: Δ in weight and Cr @ 96 hr



Bart et al. NEJM 2012;367:2269-304

ROSE-AHF

- 360 pts admitted with ≥ 1 symptom and sign of ADHF (HFrEF or HFpEF)
- eGFR 15-60 ml/min
- Randomized to nesiritide, dopamine, or placebo within 24 hrs
- Primary end-points: urine volume and change in cystatin C at 72 hrs

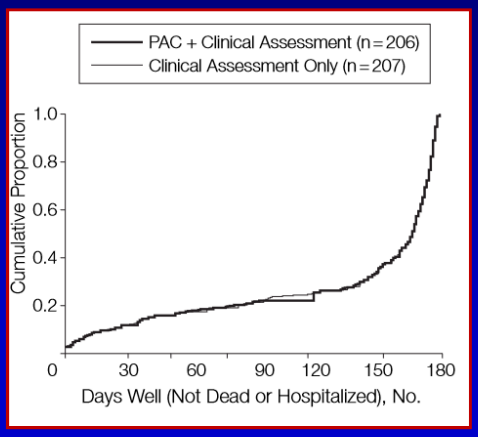
Table 2. Coprimary End Points: Effect of Low-Dose Dopamine vs Placebo or Low-Dose Nesiritide vs Placebo on Cumulative Urine Volume During 72 Hours and Change in Cystatin C Level From Baseline to 72 Hours

	Mean (95% CI)			
	Placebo	Drug	Treatment Difference	*P* Value
Dopamine strategy	**Placebo (n = 119)**	**Dopamine (n = 122)**		
Cumulative urine volume from randomization to 72 h, mL	8296 (7762 to 8830)	8524 (7917 to 9131)	229 (−714 to 1171)	.59
Change in cystatin C level from randomization to 72 h, mg/L	0.11 (0.06 to 0.16)	0.12 (0.06 to 0.18)	0.01 (−0.08 to 0.10)	.72
Nesiritide strategy	**Placebo (n = 119)**	**Nesiritide (n = 119)**		
Cumulative urine volume from randomization to 72 h, mL	8296 (7762 to 8830)	8574 (8014 to 9134)	279 (−618 to 1176)	.49
Change in cystatin C level from randomization to 72 h, mg/L	0.11 (0.06 to 0.16)	0.07 (0.01 to 0.13)	−0.04 (−0.13 to 0.05)	.36

JAMA. 2013;310(23):2533-2543

When to consider PA Catheter?

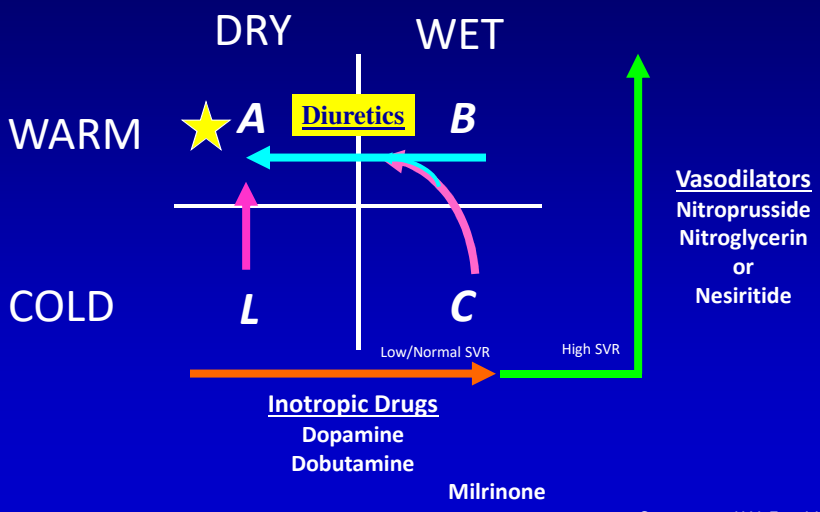
ESCAPE Trial



Binanay et al. 2005;294(13):1625-1633.

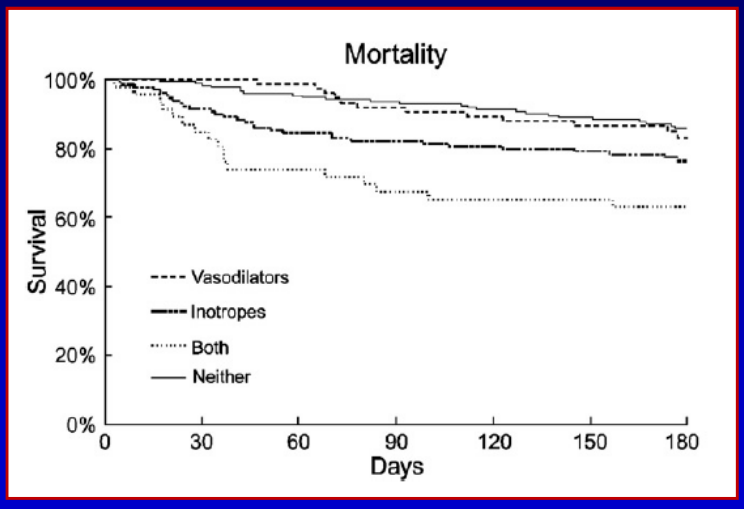
- Hypotension or worsening renal function with empiric therapy
- Presumed cardiogenic shock
- Apparent inotrope dependence or refractory symptoms
- Evaluation for VAD or transplant candidacy
- Evaluation of pulmonary arterial hypertension

Treatment of Acute Decompensated Heart Failure



Stevenson LW. Eur J Heart Failure 1999

Inotropes Increase Mortality in ADHF: ESCAPE



Elkayam et al. Am Heart J 2007;153:98-104.

Hospital Course

- PA catheter: RA 16, PCW 34, CI 1.5, SVR 1800
- Did not tolerate IV nitroprusside due to hypotension
- Started on IV milrinone with improved urine output and renal function
- Attempts to wean milrinone unsuccessful
- Plans to discharge on home IV milrinone

High Risk Features In Hospitalized Pts

At Admission	During Hospitalization	At Discharge
Advanced age Co-morbidities Frailty Cachexia Number of prior hospitalizations Non-adherence RV dysfunction NYHA Class IV symptoms Low SBP Renal Dysfunction Hyponatremia Higher NP levels	Low spot urine after 1st IV diuretic Diuretic resistance Discontinuation of ACEi/ARB/ARNI for hypotension or renal dysfunction Resuscitation or intubation Need for IV inotropes Troponin Elevation	Residual Congestion < 30% reduction in NP levels from admission Need for IV inotropes Low SBP High BUN Hyponatremia Discharge without ACE/ARB/ARNI or beta-blockers

- Discuss prognosis/goals of care
- Consider referring to HF specialist for consideration of advanced therapies

Hollenberg et al. JACC 2019;74(15):1966-2011

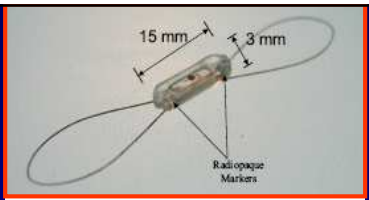
Hospital Discharge

- Ensure adequate decongestion (JVP < 10 cm H_2O)
- Institute evidence-supported therapies prior to d/c
- Careful discharge planning, including written instructions for
  - Discharge medications
  - Diet (2 gm Na and 2 L fluid restriction)
  - Weight monitoring
  - What to do if symptoms worsen
  - Follow-up appointment with 1 week of discharge
- Disease Management Program

Impact of Various Transitional Care Interventions on HF Outcomes

Intervention	Outcome at 3–6 Months	N Studies	N Subjects	Finding	Relative Risk (95% CI)
Home-visiting programs	All-cause readmission	9	1563	⇩	0.75 (0.68 to 0.86)
	HF-specific readmission	1	282	⇩	0.51 (0.31 to 0.82)
	Composite endpoint**	4	824	⇩	0.78 (0.65 to 0.94)
	Mortality	8	1693	⇩	0.77 (0.60 to 0.997)
	Number of hospital days at readmission	3	403	⇩	WMD, -1.17 (-2.44 to 0.09)
Structured telephone support	All-cause readmission	8	2166	⇔	0.92 (0.77 to 1.10)
	HF-specific readmission	7	1790	⇩	0.74 (0.61 to 0.90)
	Composite endpoint	3	977	⇔	0.81 (0.58 to 1.12)
	Mortality	7	2011	⇩	0.74 (0.56 to 0.97)
	Number of hospital days at readmission	5	1189	⇩	WMD, -0.95 (-2.43 to 0.53)
Telemonitoring	All-cause readmission	3	434	⇔	1.11 (0.87 to 1.42)
	HF-specific readmission	1	182	⇔	1.70 (0.82 to 3.51)
	Mortality	3	564	⇔	0.93 (0.25 to 3.48)
Multidisciplinary-HF clinic	All-cause readmission	2	336	⇩	0.70 (0.55 to 0.89)
	HF-specific readmission	1	106	–	0.70 (0.29 to 1.70)
	Composite endpoint	2	306	⇔	0.80 (0.43 to 1.01)
	Mortality	3	536	⇩	0.56 (0.34 to 0.92)
Nurse-led HF clinic	All-cause readmission	2	264	⇔	0.88 (0.57 to 1.37)
	HF-specific readmission	1	158	–	0.95 (0.68 to 1.32)
	Composite endpoint	1	106	–	0.66 (0.43 to 1.01)
	Mortality	2	264	⇔	0.59 (0.12 to 3.03)
Primarily educational interventions	All-cause readmission	1	200	–	1.14 (0.84 to 1.54)
	HF-specific readmission	1	223	–	0.53 (0.31 to 0.90)
	Composite endpoint	2	423	⇔	0.92 (0.58 to 1.47)
	Mortality	2	423	⇔	1.20 (0.52 to 2.76)

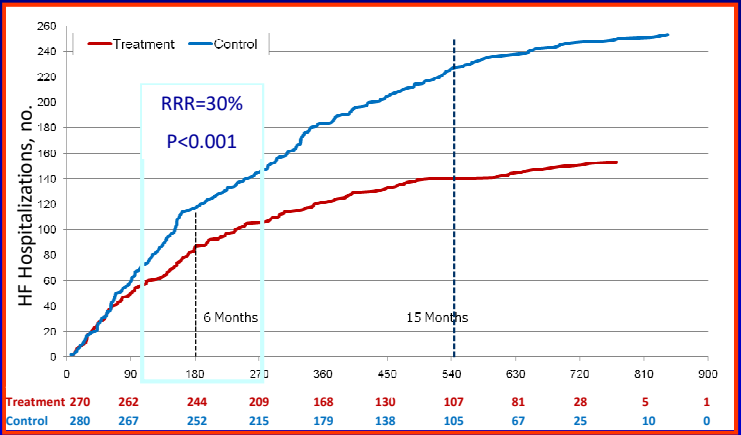
AHRQ Pub. No. 14(15) – EHC021-3-EF Oct. 2015



PA pressure Sensor

CHAMPION

Heart Failure Management Guided by Implantable PA pressure Sensor vs. Usual Care (N=550)



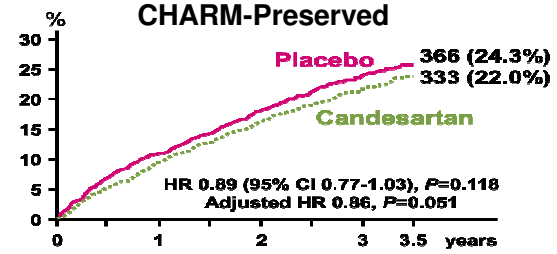
Abraham WT, et al. *Lancet* 2011; 377: 658–66

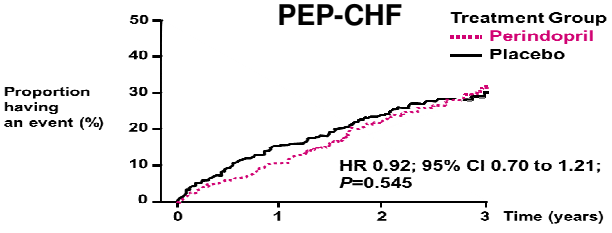
2017 Guideline Update for HFpEF

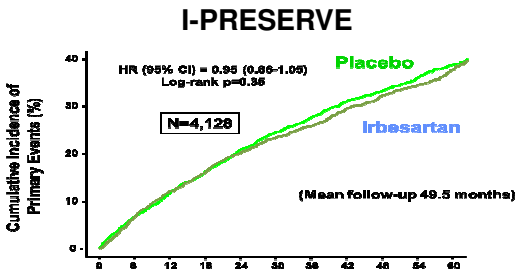
COR	LOE	Recommendation
I	B	SBP and DBP should be controlled according to guidelines
I	C	Diuretics for relief of symptoms, volume overload
I	C-LD	Persistent HTN after diuresis? Rx to SBP < 130
IIa	C	Coronary revascularization if evidence of significant CAD and symptoms/ischemia despite GDMT
IIa	C	Management of AF according to published guidelines
IIa	C	Beta-blockers, ACE-I, ARBs to Rx HTN
IIb	B-R	Spironolactone to reduce HF hospitalization if EF>45%, GFR>30, creatinine<2.5, and K+<5.0
IIb	B	ARBs to reduce HF hospitalization
III	B-R	PDE5i and nitrates are **ineffective** for QOL, physical activity

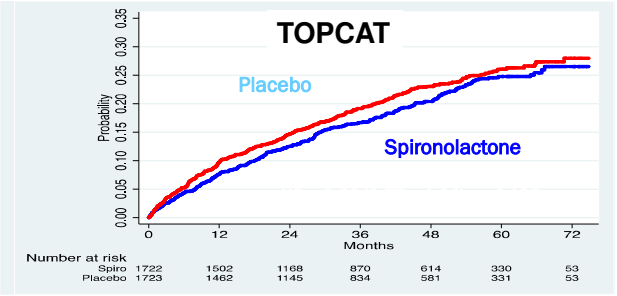
Yancy, et al. Circulation 2017;136:e137-161

RAAS Antagonists in HFpEF





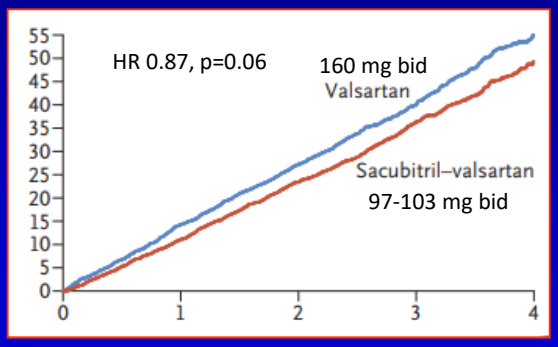


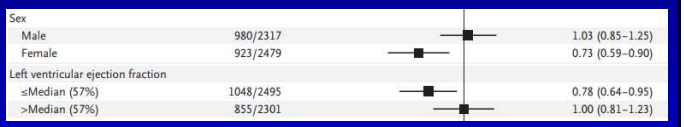


PARAGON-HF

- N=4,822 pts, age ≥ 55 yrs, EF ≥ 45%, NYHA II-IV, LAA or LVH on echo, HF hosp. w/in 9 mths or elevated NT-proBNP

HF Hospitalizations + CV Death

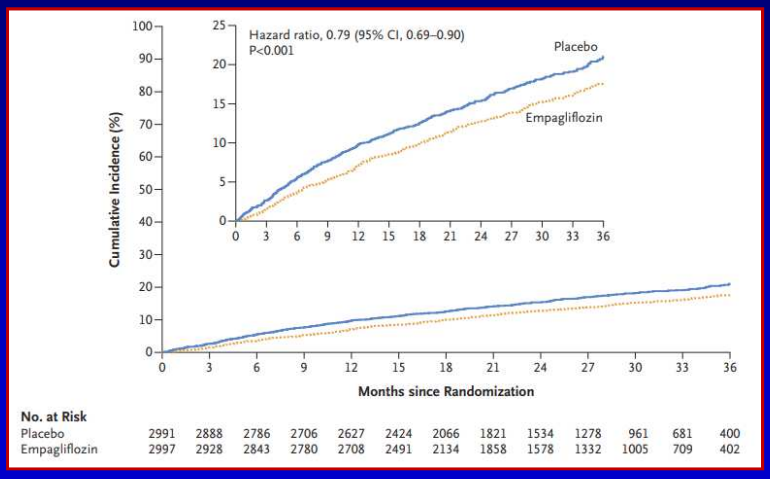




Solomon et al. DOI: 10.1056/NEJMoa1908655

EMPEROR PRESERVED

- N=5,988 pts, EF > 40%, NYHA II-IV, elevated NT-proBNP



CV Death: HR 0.91 (95% CI 0.76-1.09)
HF Hosp: HR 0.71 (95% CI 0.60-0.83)

Anker et al. NEJM 2021
DOI:10.1056/NEJMoa2107038

Summary

- Optimize GDMT to improve outcomes, including consideration of ARNI and SGLT-2i
- ADHF is a clinical diagnosis, but BNP can be useful when there is diagnostic uncertainty
- Treatment of HF should be targeted at optimization of volume status
- Patients should be diuresed to JVP < 10 cm H_2O when possible and routine use of inotropes should be avoided
- Initiate lifesaving therapies prior to hospital discharge and coordinate longitudinal follow-up
- Consider ivabradine and IV iron to reduce HF hospitalization
- Patients with refractory/recurrent symptoms that are resistant to standard therapy or those with high risk features should be referred to HF specialist
- Therapy for HFpEF remains limited but SGLT-2i reduce hospitalizations