Recent Advances in Heart Failure

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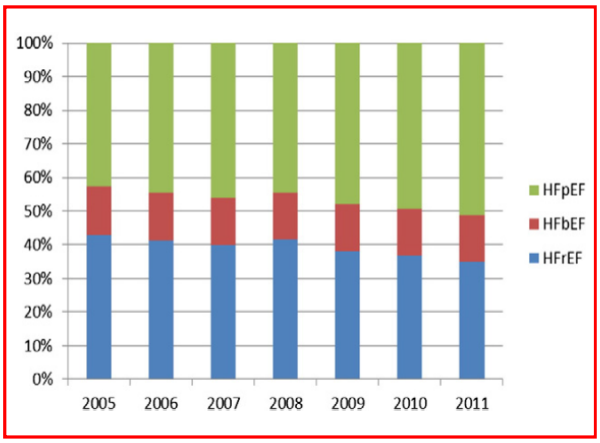
DISCLOSURES

- Research Support: Bristol Myers Squibb
- Consulting Fees: Altathera Pharmaceuticals, AstraZeneca, Bantam Pharmaceuticals, Regeneron Pharmaceuticals, and Takeda Oncology

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

HFpEF vs. HFrEF

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

HFmrEF like HFpEF

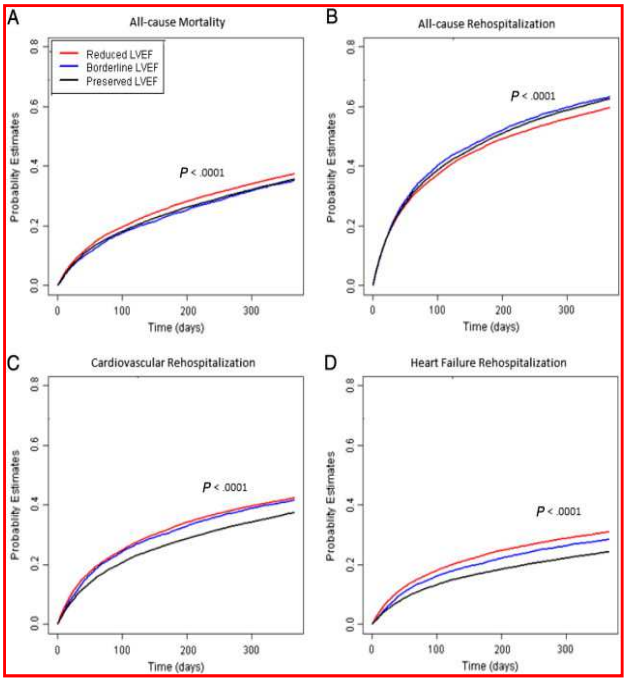
- ↑ CAD

Outcomes after HF Hospitalization, by EF

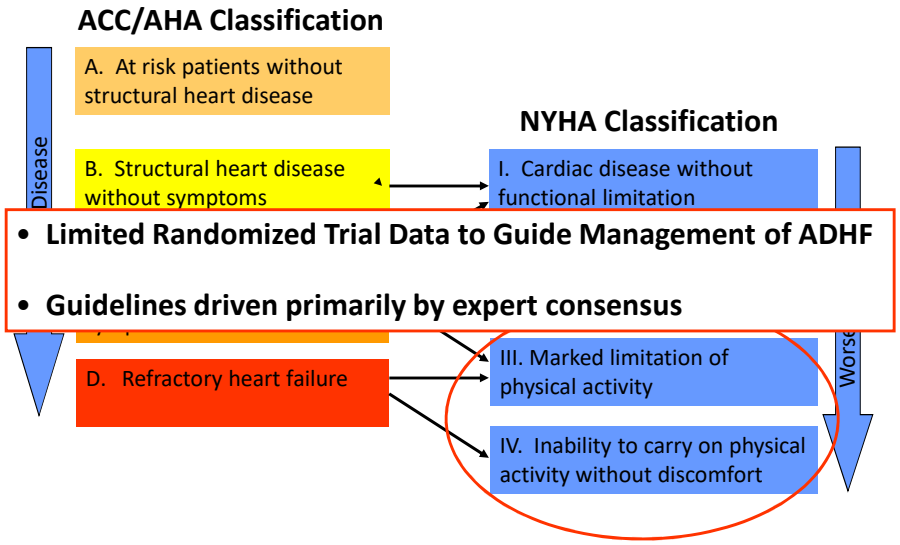
HFrEF vs. HFmrEFvs. HFpEF

- **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%**

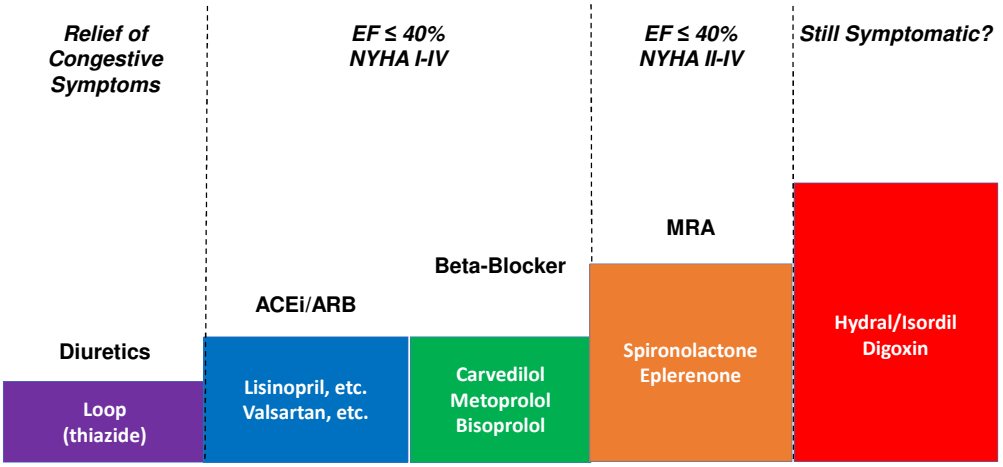
Cheng et al. Am Heart J 2014;168:721-30.e3



Stages of Heart Failure

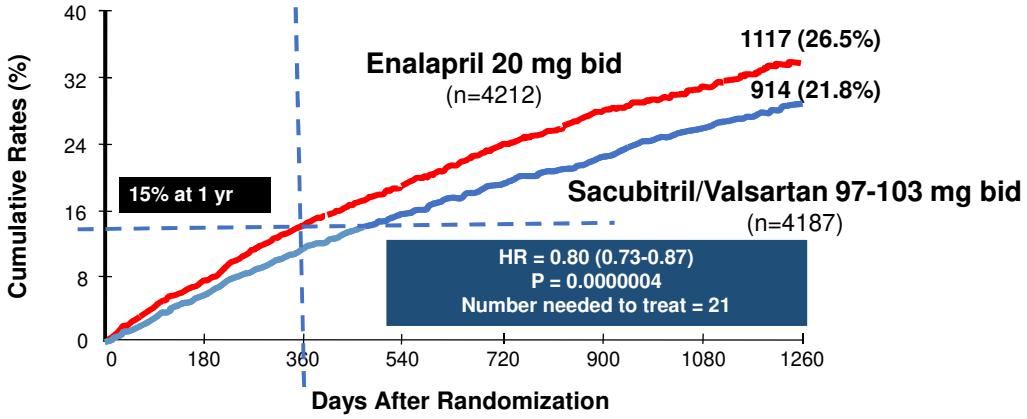


Guideline-Directed Medical Therapy for HFrEF: 2013



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

PARADIGM-HF: Primary Endpoint CV Death or HF Hospitalization



Major Side Effects: Hypotension, hyperkalemia, angioedema, renal dysfunction

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

LIFE: Primary Endpoint NT-proBNP AUC

- N=335 pts, NYHA Class IV, EF ≤ 35%, BNP ≥ 250 or NT-proBNP ≥ 800 pg/ml, 3 mths of GDMT or intolerance, 1 sign of advanced HF (inotropes, EF ≤ 25%, ≥ 1 HF hospitalization, VO2 < 55% predicted, 6 min walk < 300 m)
- Exclusions: SBP < 90, eGFR < 20, K > 5.5

End point	Median (25th to 75th) Sacubitril/valsartan (n = 167)	Valsartan (n = 168)	R, OR, or difference between groups (95% CI)[b]	*P* value
Primary efficacy end point				
NT-proBNP AUC, median (IQR)	1.08 (0.75 to 1.60)	1.19 (0.91 to 1.64)	0.95 (0.84 to 1.08)	.45
No.	155	158	NA	NA
Secondary efficacy end points				
Days alive, out of hospital, and free from HF events, median (IQR)[c]	147.0 (9.0 to 164.0)	157.0 (53.5 to 164.0)	−11.2 (−26.4 to 4.0)	.15

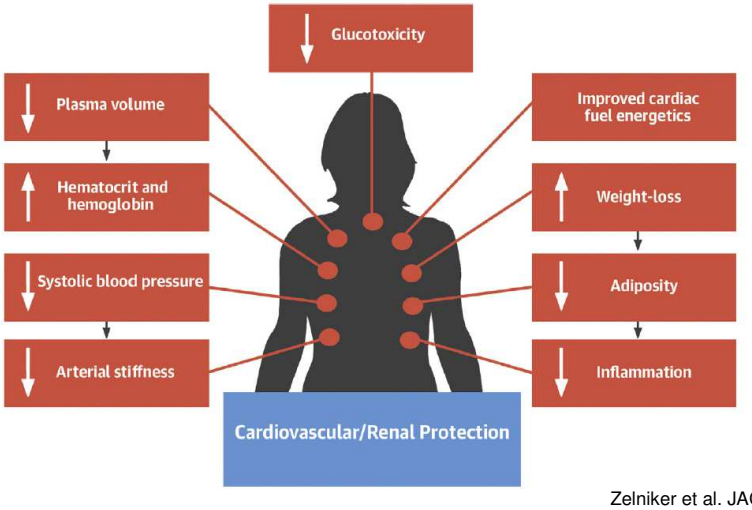
Mann et al. JAMA Cardiol. 2022;7(1):17-25.

Guideline Update

COR	LOE	Recommendations
1	A	1. In patients with HFrEF and New York Heart Association (NYHA) class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality.[7–11]
1	A	2. In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible.[12–19]
1	A	3. In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEi because of cough or angioedema and when the use of ARNi is not feasible, the use of ARB is recommended to reduce morbidity and mortality.[20–24]
1	B-R	4. In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, replacement by an ARNi is recommended to further reduce morbidity and mortality.[7–11]

Heidenreich et al. Circulation 2022;145:e876-894.

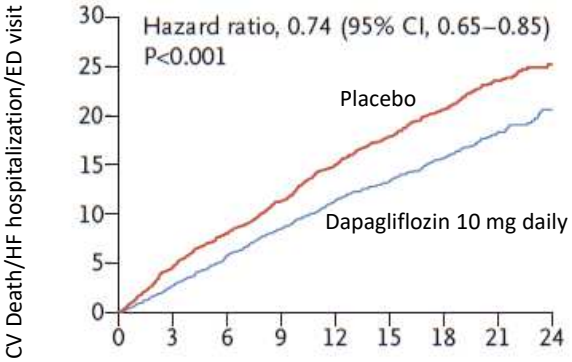
Potential Mechanisms for Cardiorenal Benefits of SGLT2i



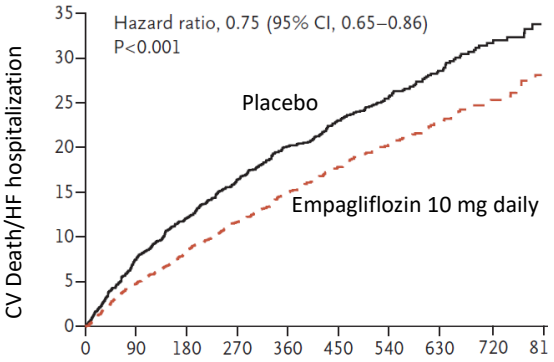
Zelniker et al. JACC 2020;75(4):422

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

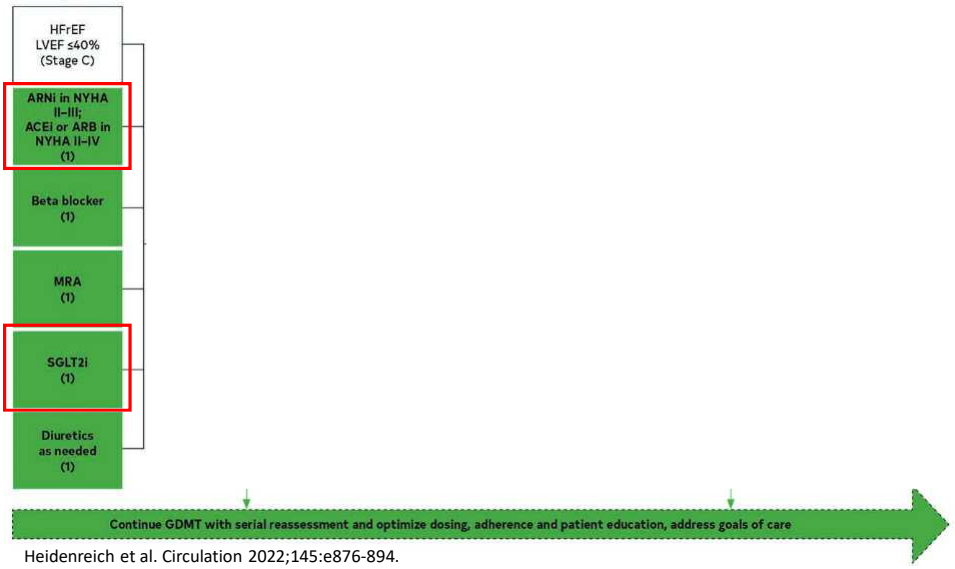
McMurray et al. NEJM 2019;381(21):1995; Packer et al. NEJM 2020;383:1413-24.

Guideline Update

COR	LOE	Recommendation
1	A	1. In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes.[31,32]

Heidenreich et al. Circulation 2022;145:e876-894.

Stage C HF: Symptomatic HF



Heidenreich et al. Circulation 2022;145:e876-894.

Heart Failure Case

- 53 y.o. black man presents for f/u after 1st admission for ADHF
- Non-ischemic CMP (EF 25%, LVEDD 6.5 cm)
- Metoprolol succinate 200 mg daily, losartan 50 mg daily, spironolactone 25 mg daily, and furosemide 80 mg bid

- BP 120/50, HR 85
- JVP 10 cm water, mild HJR
- Clear lungs
- Nl s1, s2. + Soft MR m
- No hepatosplenomegaly
- No edema

- Na 135, K 4.6, BUN 26, Cr 1.4
- HbA1c 5.4%

Question

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

A. Change metoprolol succinate to carvedilol
B. Change losartan to sacubitril/valsartan
C. Add hydralazine and isordil
D. Do not add SGLT-2i since he is not a diabetic

Heart Failure Case

- 53 y.o. black man presents 1 month later w/ ↑ SOB
- Non-ischemic CMP (EF 25%, LVEDD 6.5 cm)
- Metoprolol succinate 200 mg daily, sacubitril/valsartan 24-26 bid, spironolactone 25 mg daily, dapagliflozin 10 mg daily, and furosemide 80 mg bid

- BP 100/50, HR 90
- JVP < 10 cm water
- Clear lungs
- Irregularly, irregular. Nl s1, s2. II/VI sys m
- No HSM
- No edema

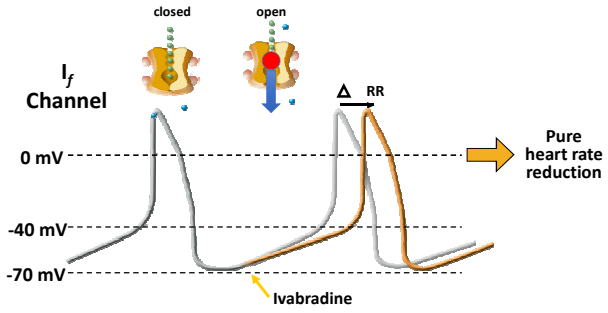
- Na 135, K 4.6, BUN 26, Cr 1.6
- Hb 10, Fe 25, TIBC 150, ferritin 300

Question

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

A. Add ivabradine
B. Give IV iron infusions
C. Add vericiguat
D. Start apixaban and plan for cardioversion in 3-4 weeks

Ivabradine: A Selective I_f Inhibitor



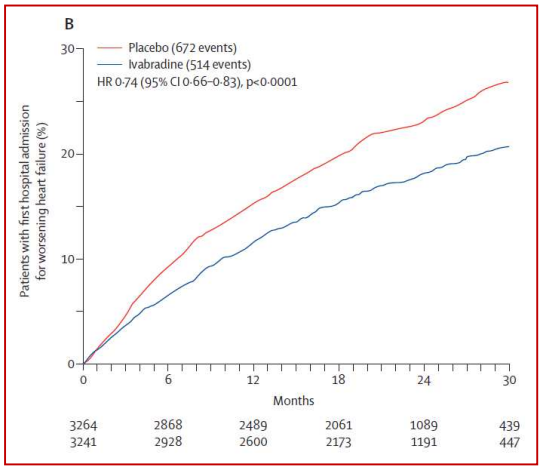
I_f inhibition reduces the diastolic depolarization slope, thereby lowering heart rate
No effect on myocardial contractility or relaxation
Use-dependent block = low risk of bradycardia

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
- 1° Endpt: CV death or HF hospitalization

- Side effects
  - Symptomatic bradycardia: 5 vs 1%
  - Phosphenes: 3 vs 1%



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

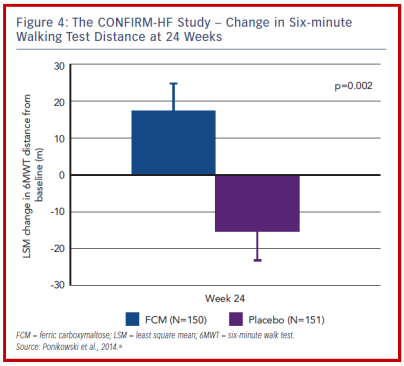
Guideline Update

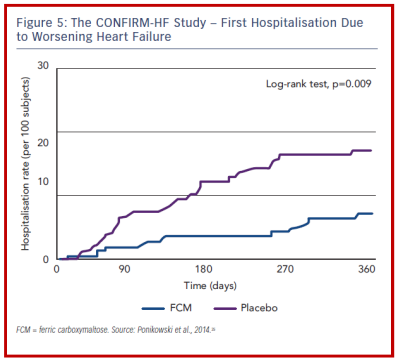
COR	LOR	
IIa	**B-R**	**For patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤ 35%) who are receiving GDMT, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of ≥ 70 bpm at rest, ivabradine can be beneficial to reduce HF hospitalization and cardiovascular death.**

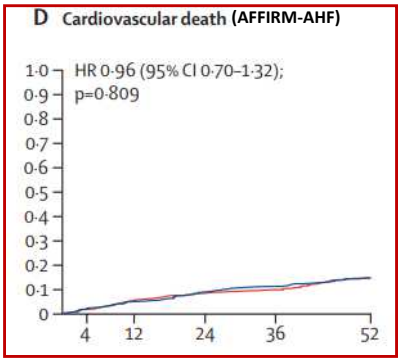
Heidenreich et al. Circulation 2022;145:e895-1032.

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







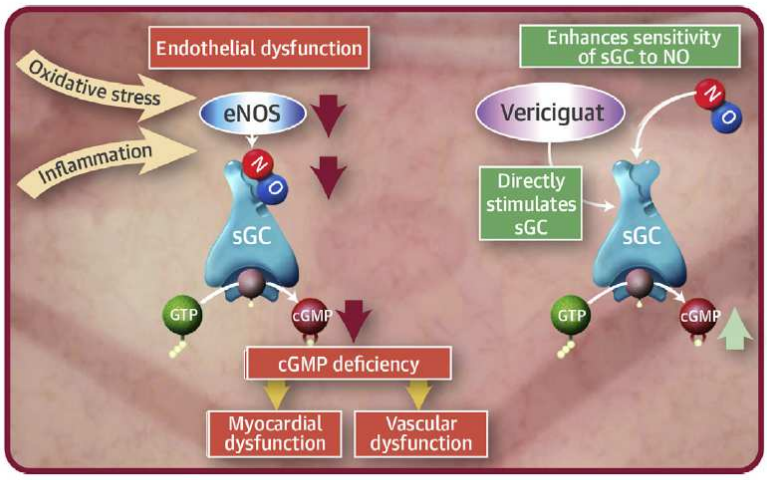
Ponikowski et al. Eur Heart J 2015;36(11):657; Ponikowski et al. Lancet 2020;396(10266):1895.

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.		

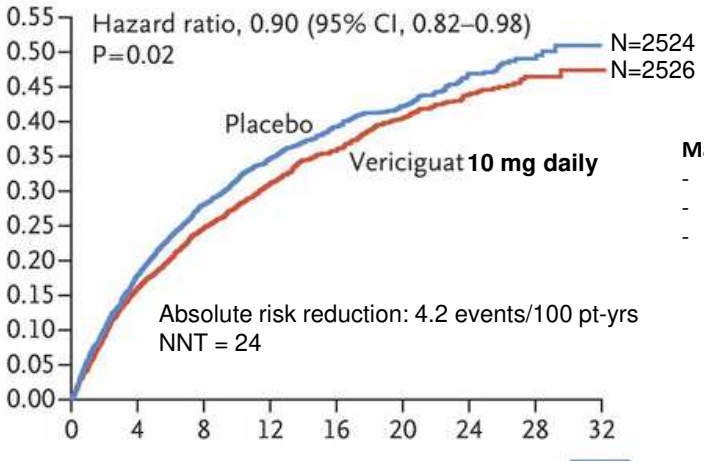
Yancy, et al. Circulation 2017;136:e137-161

Vericiguat: Mechanism of Action



Armstrong, P.W. et al. J Am Coll Cardiol HF. 2018;6(2):96-104.

VICTORIA: Primary Endpoint
CV Death and HF Hospitalization



Major Side Effects:
- Hypotension
- Syncope
- Anemia

Armstrong et al. N Engl J Med 2020;382(20):1883-93

VICTORIA: Individual Endpoints

Outcome	Vericiguat (N=2526)		Placebo (N=2524)		Hazard Ratio (95% CI)†	P Value‡
	no. (%)	*events/100 patient-yr*	*no. (%)*	*events/100 patient-yr*		
Primary composite outcome and components						
Death from cardiovascular causes or first hospitalization for heart failure	897 (35.5)	33.6	972 (38.5)	37.8	0.90 (0.82–0.98)	0.02
Death from cardiovascular causes§	206 (8.2)		225 (8.9)			
Hospitalization for heart failure	691 (27.4)		747 (29.6)			
Secondary outcomes						
Death from cardiovascular causes	414 (16.4)	12.9	441 (17.5)	13.9	0.93 (0.81–1.06)	
Hospitalization for heart failure	691 (27.4)	25.9	747 (29.6)	29.1	0.90 (0.81–1.00)	
Total hospitalizations for heart failure¶	1223	38.3	1336	42.4	0.91 (0.84–0.99)	0.02
Secondary composite outcome and components						
Death from any cause or first hospitalization for heart failure	957 (37.9)	35.9	1032 (40.9)	40.1	0.90 (0.83–0.98)	0.02
Death from any cause§	266 (10.5)		285 (11.3)			
Hospitalization for heart failure	691 (27.4)		747 (29.6)			
Death from any cause	512 (20.3)	16.0	534 (21.2)	16.9	0.95 (0.84–1.07)	0.38

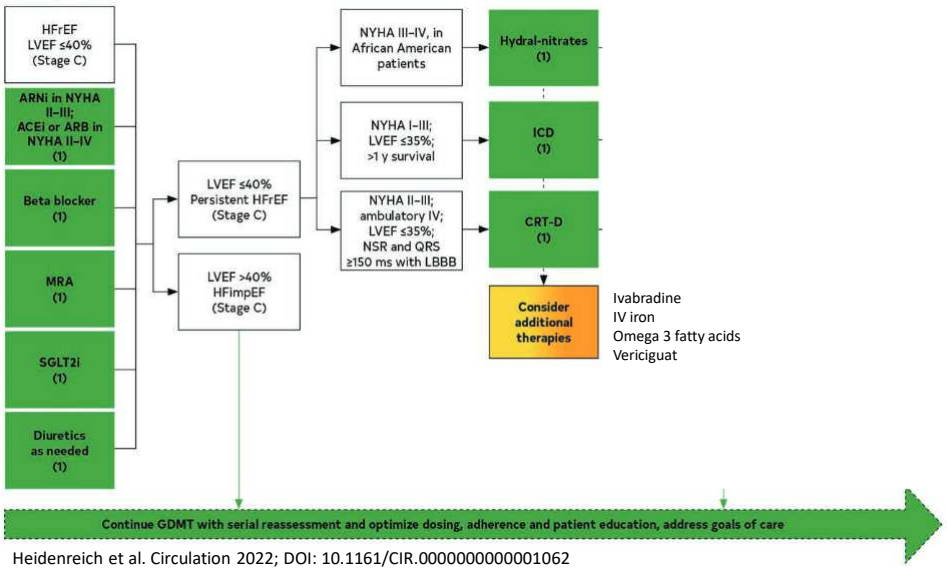
Armstrong et al. N Engl J Med 2020;382(20):1883-93

Guideline Update

COR	LOE	Recommendations
2b	**B-R**	**In selected high-risk patients with HFrEF and recent worsening of HF already on GDMT, an oral soluble guanylate cyclase stimulator (vericiguat) may be considered to reduce HF hospitalization and cardiovascular death.**

Heidenreich et al. Circulation 2022;145:e895-1032.

Stage C HF: Symptomatic HF



Heidenreich et al. Circulation 2022; DOI: 10.1161/CIR.0000000000001062

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, 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

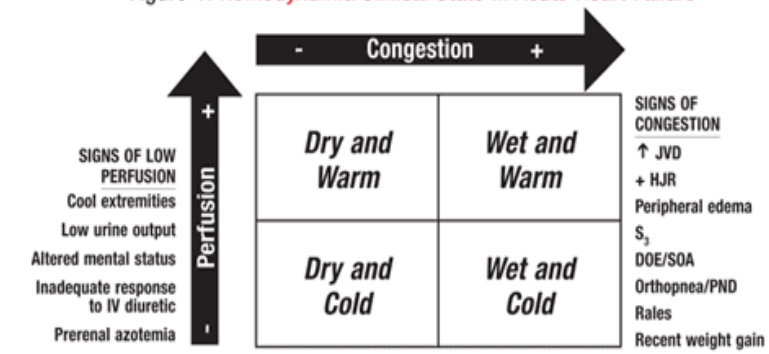
- Address precipitating factors
- Optimize volume status and perfusion
- Optimize oral heart failure regimen
- Manage Related Risks (e.g. SCD, VTE)
- Patient Education
- Initiate Longitudinal Disease Management

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.

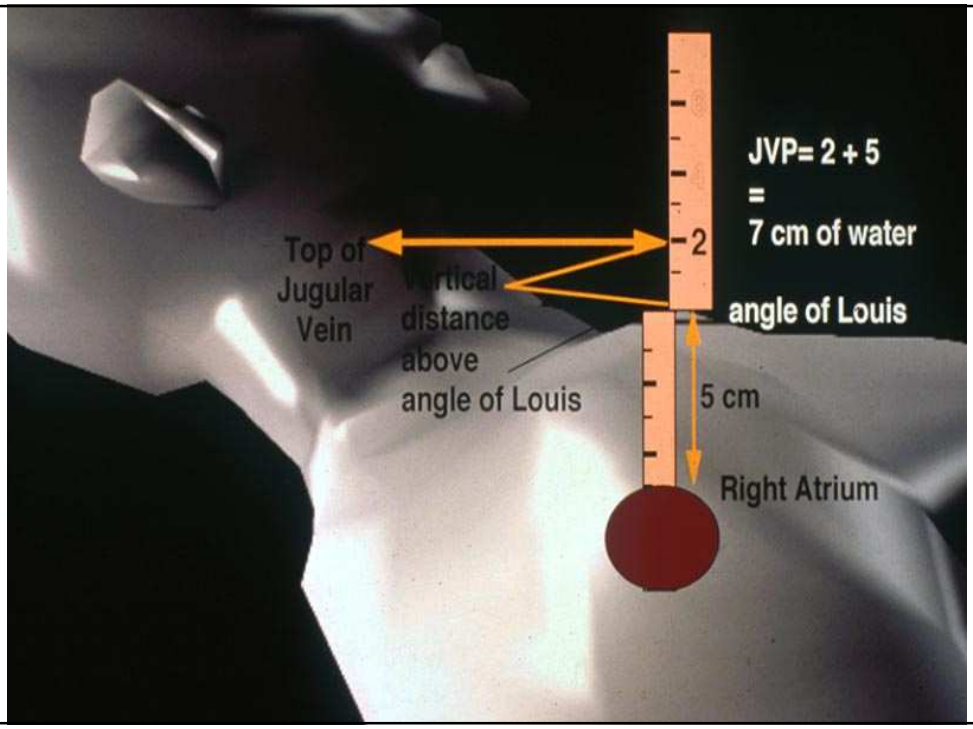
Nohria et al. JACC 2003;41:1797-1804.

Accuracy of Physical Findings for Elevated LV Filling Pressure

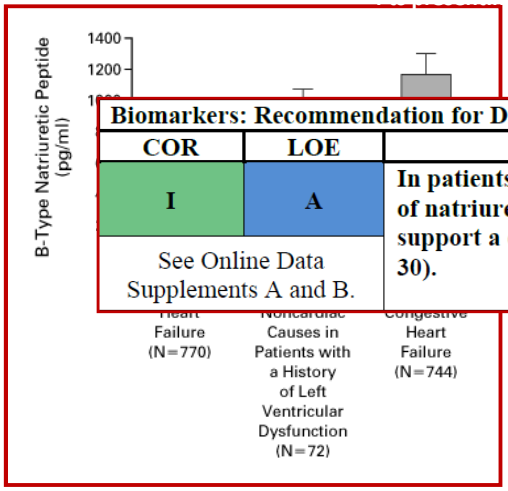
Finding	Sensitivity	Specificity
Orthopnea (≥2 pillows)	85%	24%
Rales (≥1/3 lungs fields)	15 %	89%
S3	63%	34%
Edema (>1+)	41%	67%
Elevated JVP (>10 cm)	67%	72%

Sensitivity and specificity for predicting PCWP > 22 mm Hg

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



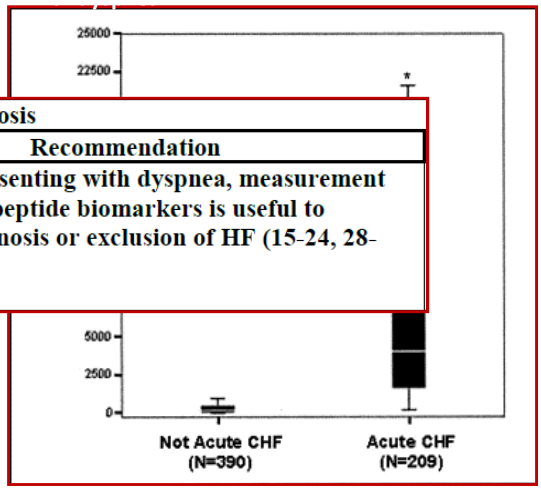
BNP to Assist Diagnosis of HF



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
- **Measurement of NPs is most useful when there is diagnostic uncertainty or for prognostic indications**
- Only NT-proBNP predictive w/ Valsartan-Sacubitril

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

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

BOLUS vs. CONTINUOUS Diuretic Infusion

- No difference in any outcomes

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

ADVOR Trial

- N=519 pts, ADHF (≥ 1 sign of HF and elevated NPs), no prior Rx w/ acetazolamide or SGLT-2i
- IV Lasix twice daily + 500 mg IV acetazolamide daily vs. placebo x 3 days or until decongestion

Variable	Placebo (N=259)	Acetazolamide (N=256)	Treatment Effect (95% CI)	P Value
Primary end point				
Successful decongestion within 3 days after randomization — no. (%)†	79 (30.5)	108 (42.2)	Risk ratio, 1.46 (1.17–1.82)	<0.001
Secondary end points				
Duration of hospital stay (95% CI) — days‡	9.9 (9.1–10.8)	8.8 (8.0–9.5)	0.89 (0.81–0.98)	
Death from any cause or rehospitalization for heart failure during 3 mo of follow-up — no. (%)	72 (27.8)	76 (29.7)	Hazard ratio, 1.07 (0.78–1.48)	

Mullens et al. NEJM 2022;387:1185-95.

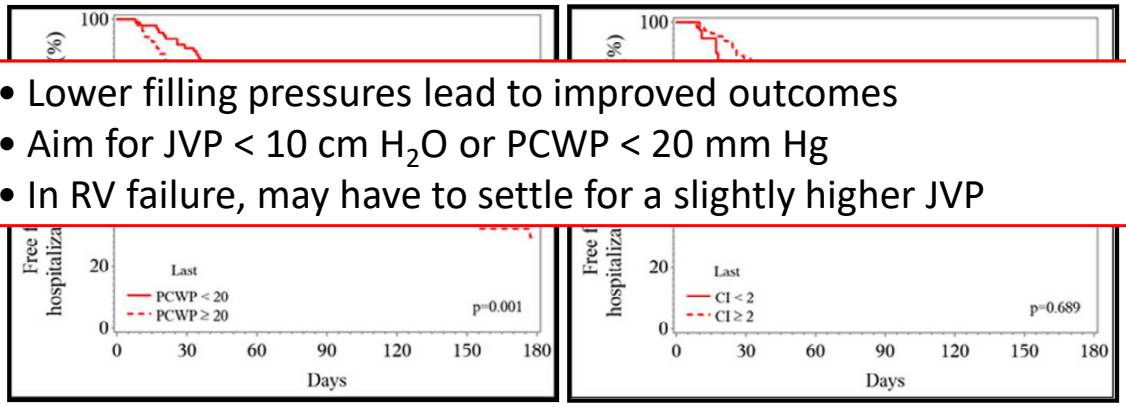
TRANSFORM-HF: Torsemide vs. Furosemide

N=2859, HF hospitalization, LVEF < 40% or ↑ Natriuretic peptides

Variable	Torsemide (n = 1431) No. (%)	Torsemide (n = 1431) Events per 100 patient-years	Furosemide (n = 1428) No. (%)	Furosemide (n = 1428) Events per 100 patient-year	Risk reduction (95% CI)[a]	HR (95% CI)[b]	*P* value[b]
Primary outcome							
All-cause mortality	373 (26.1)	17.0	374 (26.2)	17.0	0.12 (−2.85 to 3.14)	1.02 (0.89 to 1.18)	.76
Secondary outcomes							
All-cause mortality or all-cause hospitalization (over 12 mo)	677 (47.3)	99.2	704 (49.3)	107.6	1.99 (−1.79 to 5.56)	0.92 (0.83 to 1.02)	
Total hospitalizations (over 12 mo)	940	106.3	987	111.9		RR, 0.94 (0.84 to 1.07)	
All-cause mortality or all-cause hospitalization (over 30 d)	149 (10.4)	147.2	157 (11.0)	157.5	0.58 (−1.80 to 2.75)	0.94 (0.75 to 1.18)	

Mentz et al. JAMA 2023;329 (3):214-223.

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



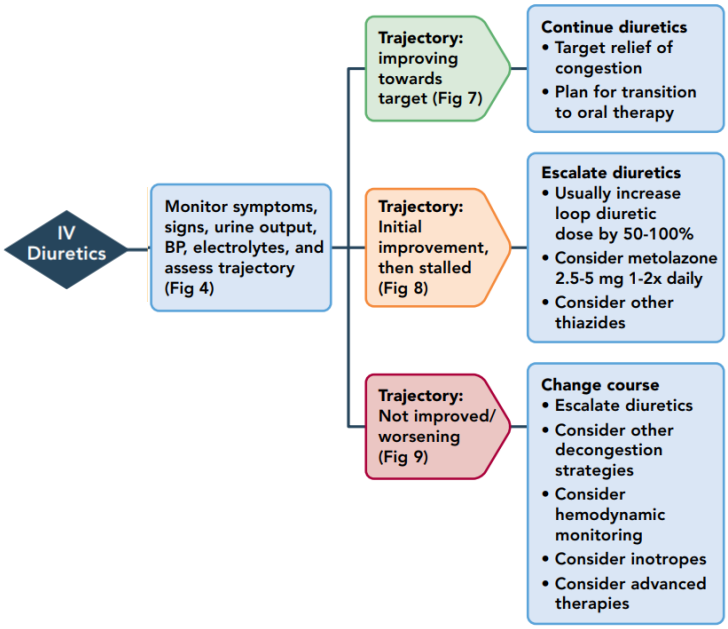
- Lower filling pressures lead to improved outcomes
- Aim for JVP < 10 cm H_2O or PCWP < 20 mm Hg
- In RV failure, may have to settle for a slightly higher JVP

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



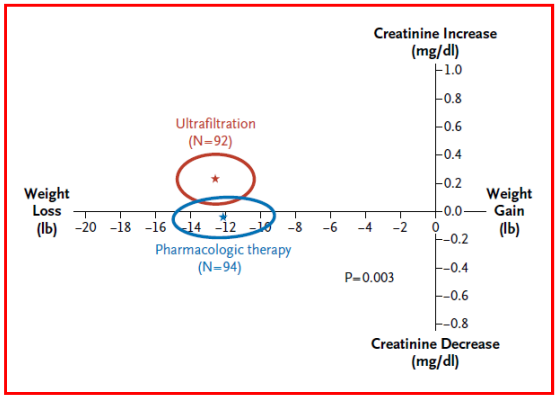
Hollenberg et al. JACC 2019;74(15):1966-2011

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: Ultrafiltration 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^{o} 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

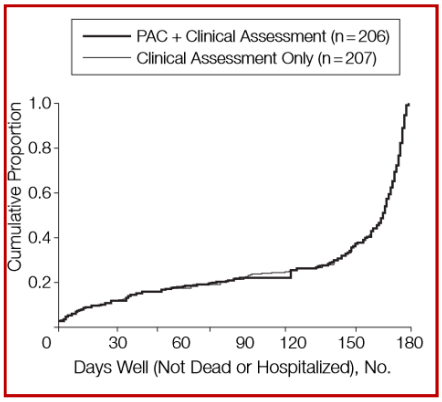
Table 2. Coprimary End Points: Effect of Low-Dose Dopamine vs Placebo or Low-Dose Nesiritide vs Placebo on Cumulative Urine Volume During 72 Hours and Change in Cystatin C Level From Baseline to 72 Hours

	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?

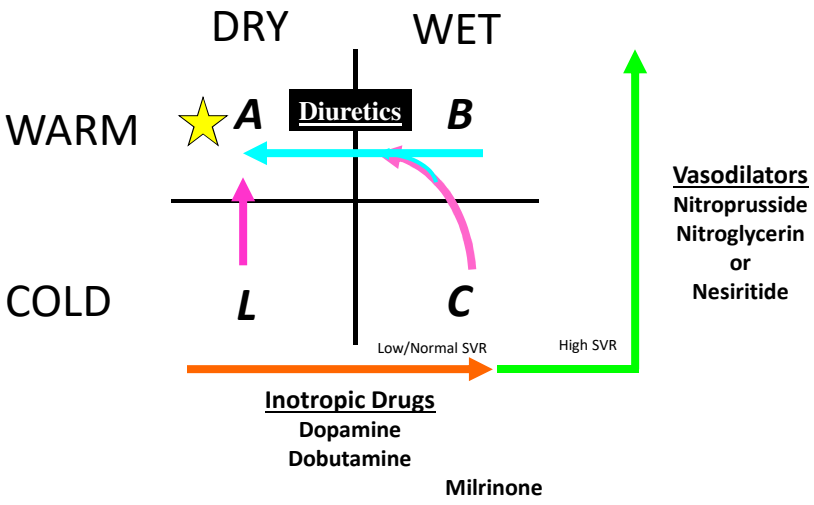
ESCAPE Trial



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

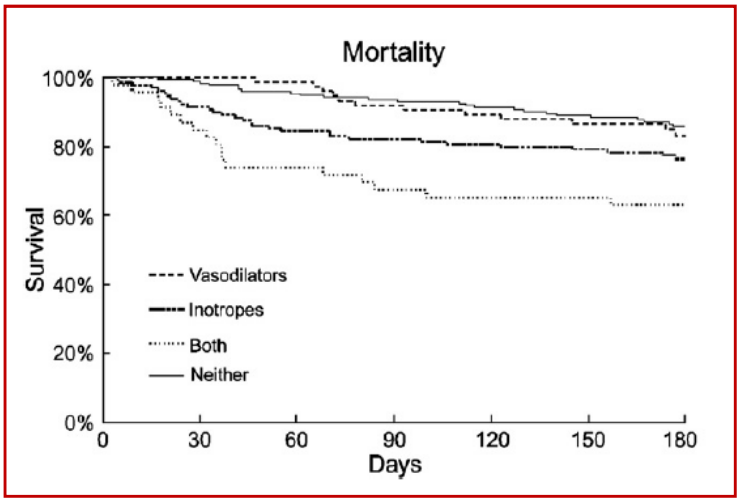
- Hypotension or worsening renal function with empiric therapy
- Presumed cardiogenic shock
- Apparent inotrope dependence or refractory symptoms
- Evaluation for VAD or transplant candidacy
- Evaluation of pulmonary arterial hypertension

Treatment of Acute Decompensated HF



Stevenson LW. Eur J Heart Failure 1999

Inotropes Increase Mortality in ADHF



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)

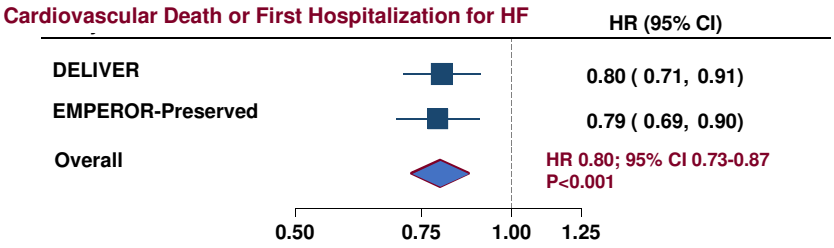
AHRQ Pub. No. 14(15) – EHC021-3-EF Oct. 2015

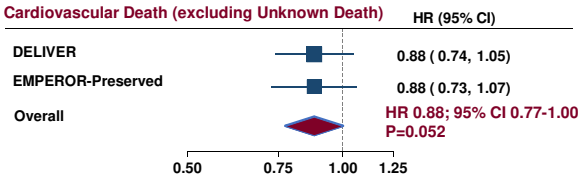
Guideline Update for HFpEF

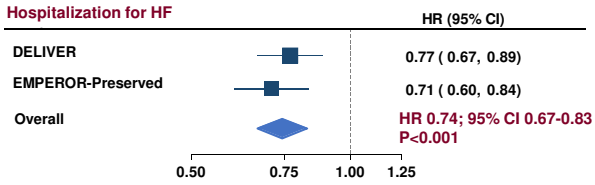
COR	LOE	Recommendations
1	C-LD	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity.[44–46]
2a	C-EO	2. In patients with HFpEF, management of AF can be useful to improve symptoms.
2a	B-R	1. In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality.[33]
2b	B-R	2. In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[38,42,43]
2b	B-R	3. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[35,40]
3: No Benefit	B-R	4. In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life is ineffective.[49,50]

Heidenreich et al. Circulation 2022;145:e876-894

DELIVER and EMPEROR-Preserved Meta-Analysis:



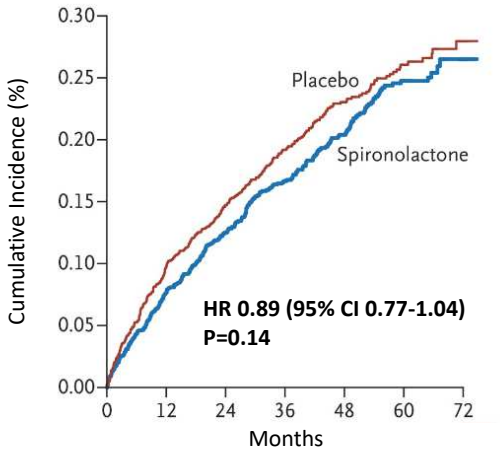


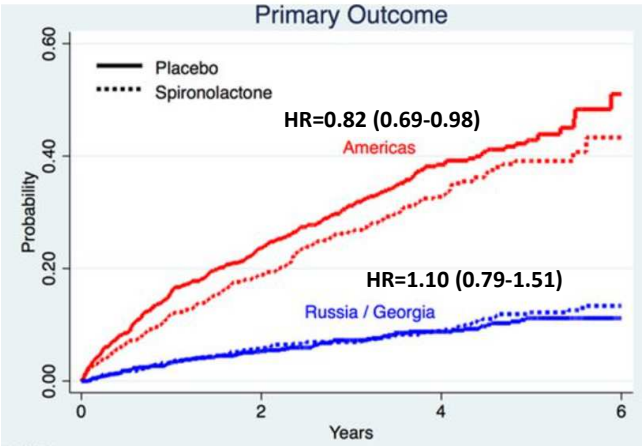


Vaduganathan M, et al. Lancet 2022

$P_{heterogeneity} > 0.10$ for all endpoints

TOPCAT: Spironolactone in HFpEF

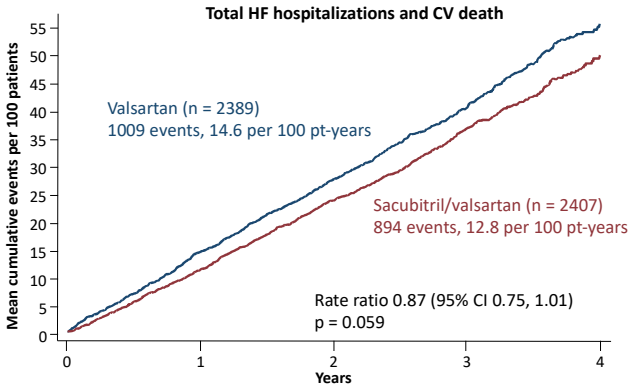




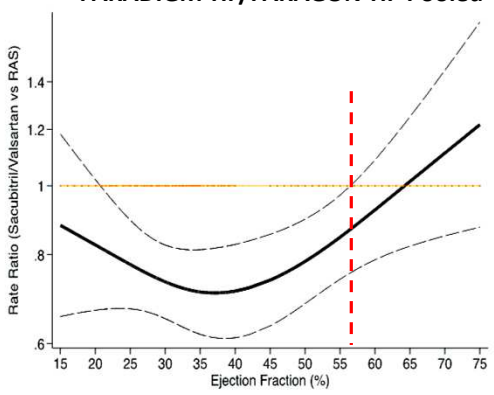
Pitt et al. NEJM 2014; 370:1383-1392; Pfeffer et al. Circulation 2015;131:34-42.

ARNI in HF with HFmrEF or HFpEF

PARAGON-HF Primary Results



PARADIGM-HF/PARAGON-HF Pooled

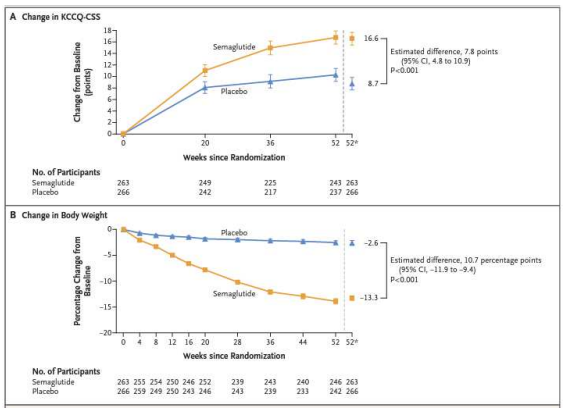


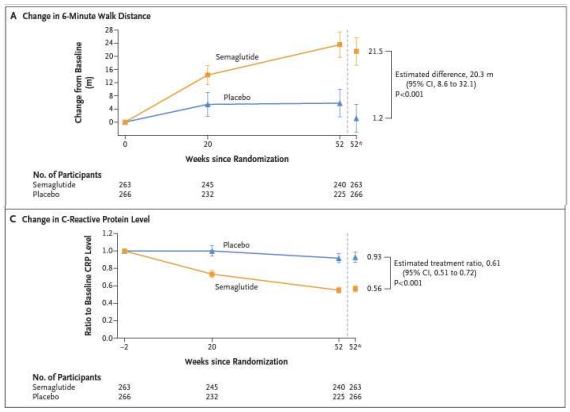
Feb 2021 US FDA approval for sacubitril/valsartan in expanded population, emphasizing benefits in EF 'below normal'

Solomon SD, et al. N Engl J Med 2019; Solomon SD, Circulation 2020

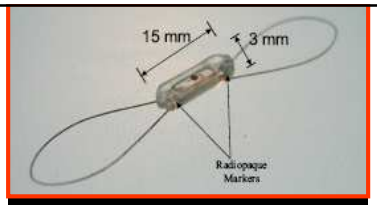
GLP-1 agonists in HFpEF

N=529 pts, symptomatic HFpEF (EF ≥ 45%), BMI ≥ 30
RTC: Semaglutide 2.4 mg weekly vs. placebo X 52 weeks





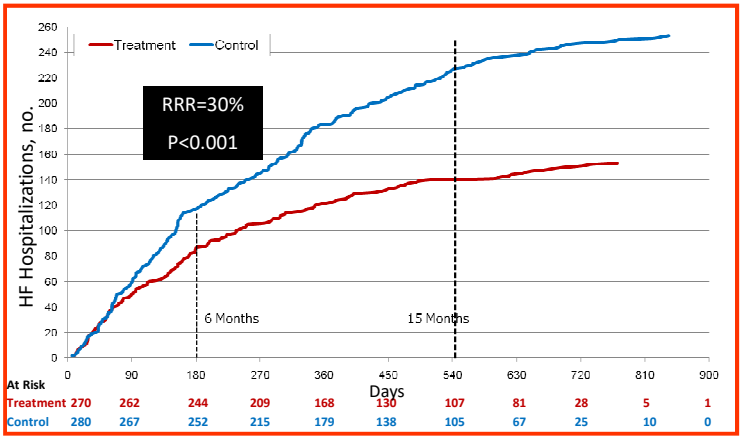
Kosiborod et al. N Engl J Med 2023;389:1069-84.



PA pressure Sensor

CHAMPION

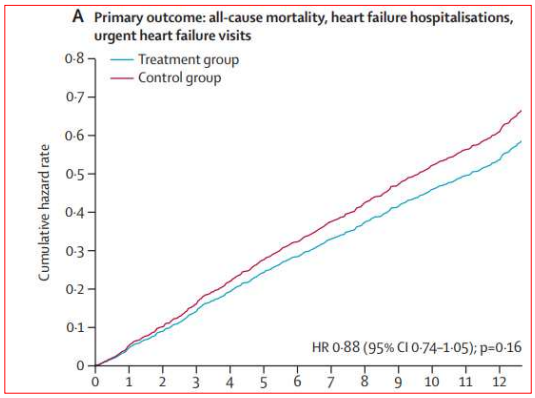
Heart Failure Management Guided by Implantable PA pressure Sensor vs. Usual Care (N=550)



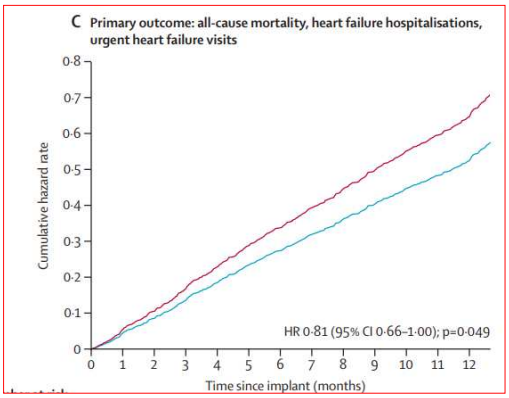
Abraham WT, et al. *Lancet* 2011; 377: 658–66

GUIDE-HF Trial

Primary Analysis



Pre-COVID Analysis



Lindenfeld et al. Lancet 2021;398:991-1001.

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, IV iron and vericiguat 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
- GLP-1 agonists result in weight loss and improve QOL in obese pts with HFpEF