Advances in the Treatment of Heart Failure: Medical Therapy and Beyond

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CARDIAC CLINICAL CARE

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Today's Objectives

- Discuss advances in the pharmacologic therapy for:
  - Heart failure with reduced ejection fraction (HFrEF)
  - Heart failure with preserved ejection fraction (HFpEF)

- Describe the potential benefits of implantable hemodynamic monitoring in patients with heart failure and identify patients who may benefit from this technology.

- Understand the role of percutaneous mitral valve therapy in the treatment of patients with heart failure.

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Advances in pharmacologic therapy for HFrEF

ARNI

Ivabradine

SGLT-2 Inhibitors

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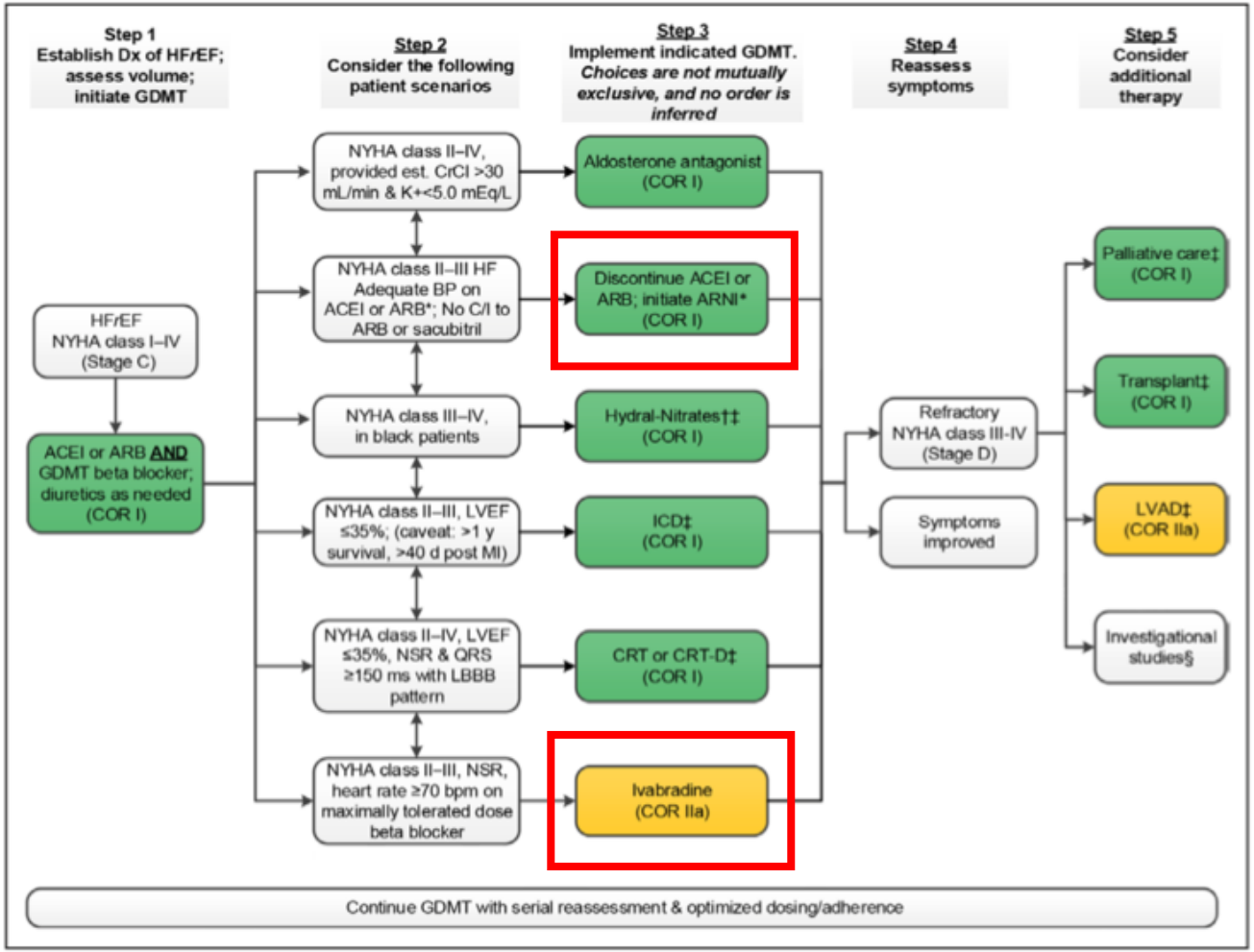
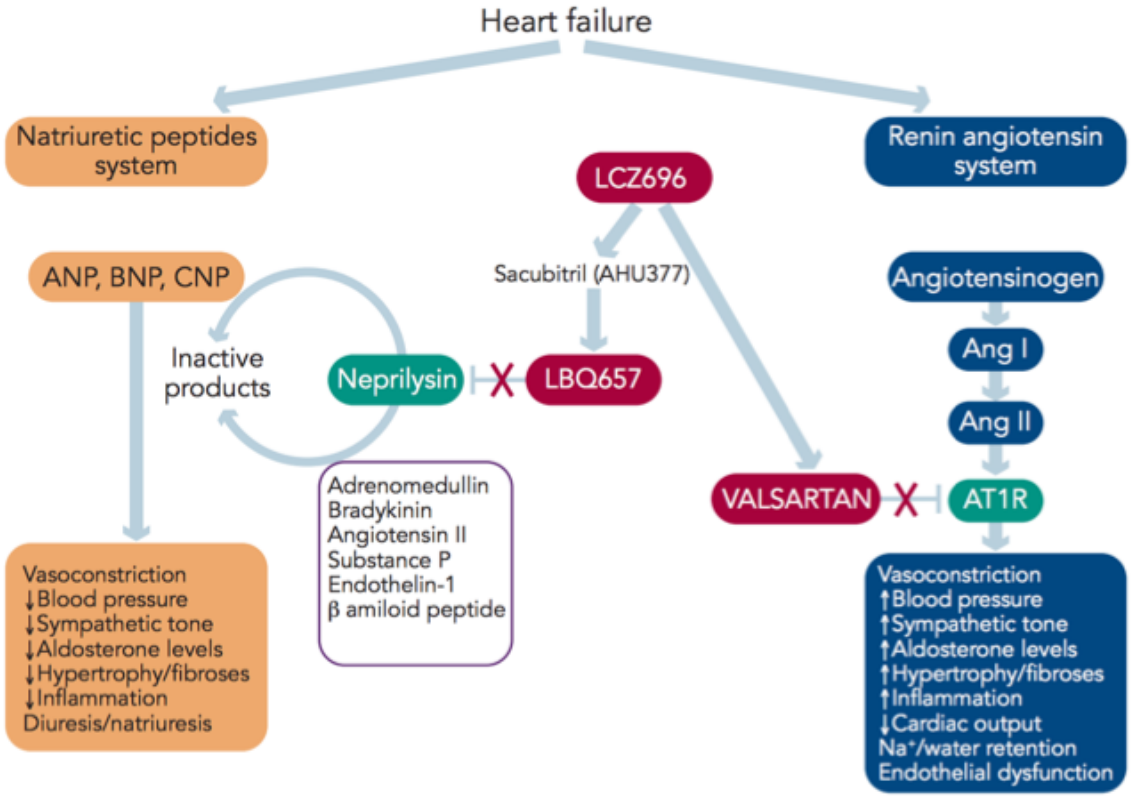


ACC/AHA Guidelines. Circulation. 2017.

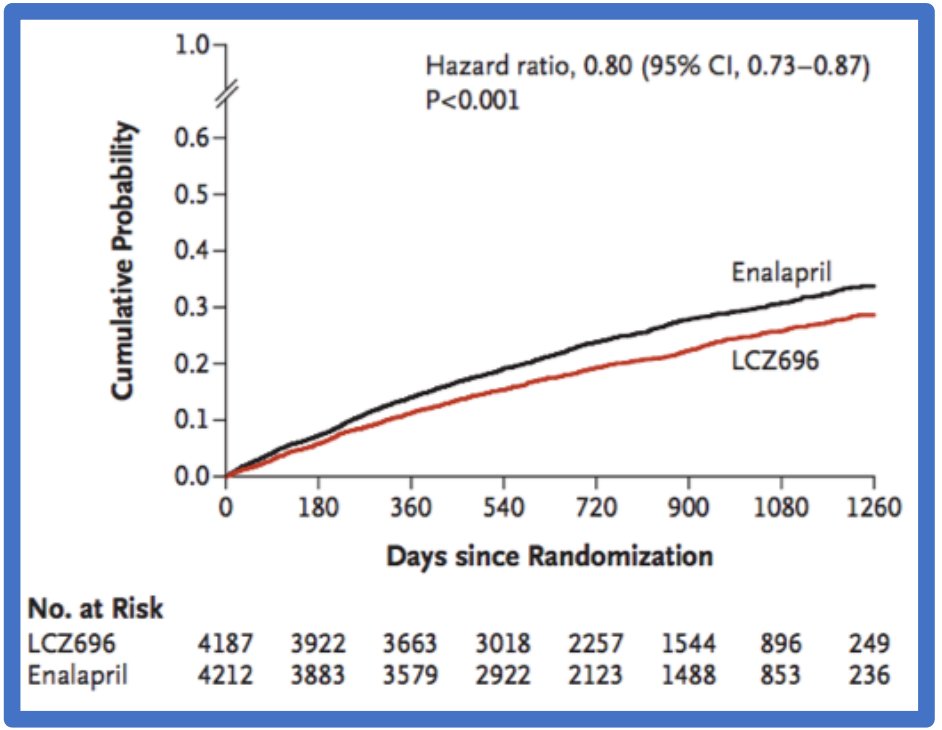
Angiotensin Receptor Neprilysin Inhibitor (ARNi)



Menendez JT. *Cardiac Failure Review* 2016;2:40-46

Sacubitril Valsartan- PARADIGM HF

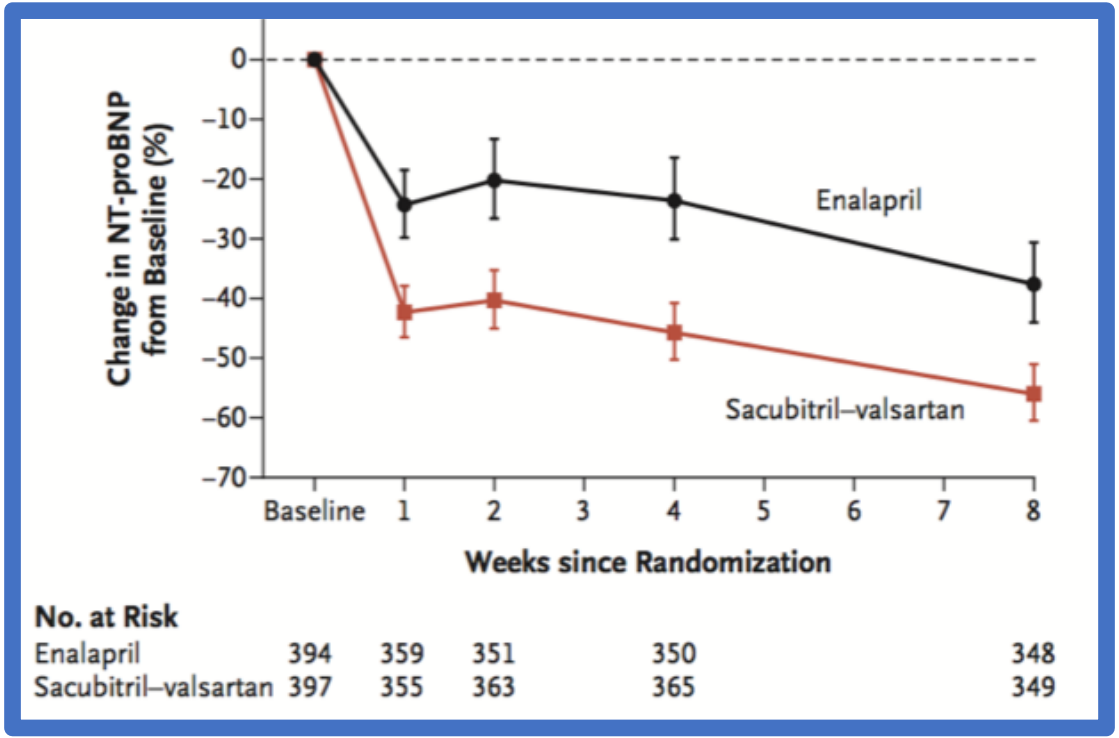
- EF < 40% → < 35%
- Class II or higher
- Elevated BNP/HF hospitalization
- Run in period
- Excluded: SBP < 100 mmHg → < 95 mmHg, GFR < 30, elevated KCL, angioedema
- Primary end point: Death from CV cause or hospitalization for HF



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

Sacubitril Valsartan- PIONEER HF

- Acute decompensated HF
- EF < 40%
- Elevated BNP
- 24 hours to 10 days after presentation
- SBP > 100 mmHg
- No IV vasodilators or inotropes x 24 hours



Velazquez, et al. NEJM. 2019; 380: 539-48.

Sacubitril Valsartan- PIONEER HF

Exploratory Clinical Outcome: Re-hospitalization for Heart Failure

Sacubitril Valsartan: n = 35 (8.0%)
Enalapril: n = 61 (13.8%)
HR 0.56 (0.37, 0.84)

Key Safety Outcomes: No difference

Worsening renal function
Hyperkalemia
Symptomatic hypotension
Angioedema

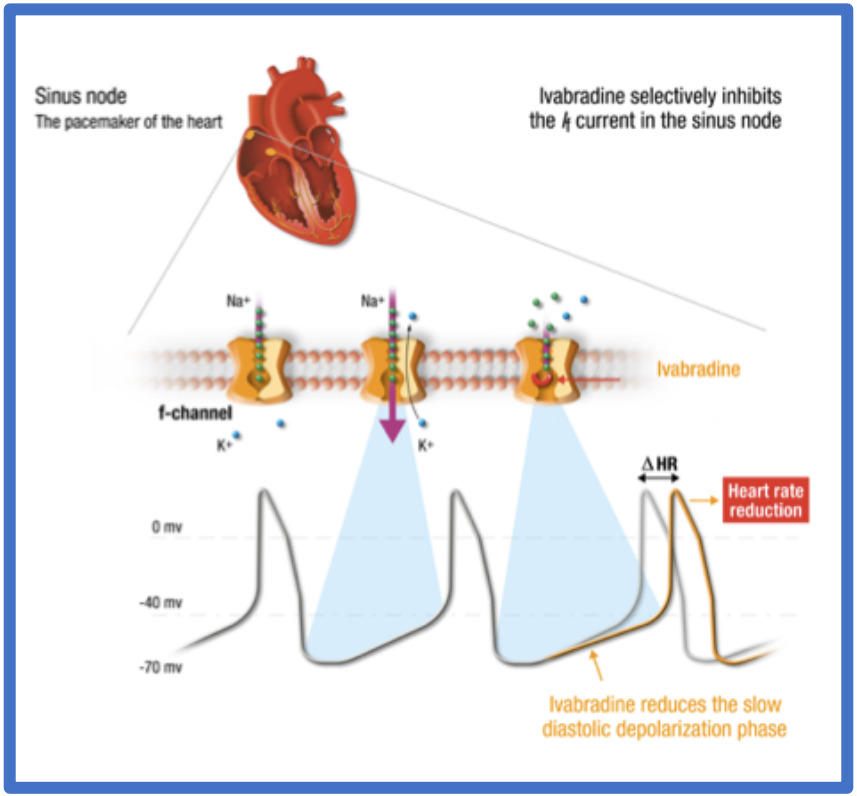
Velazquez, et al. NEJM. 2019; 380: 539-48.

Sacubitril Valsartan- Practical Tips

More to come….

Make the change!

Ivabradine



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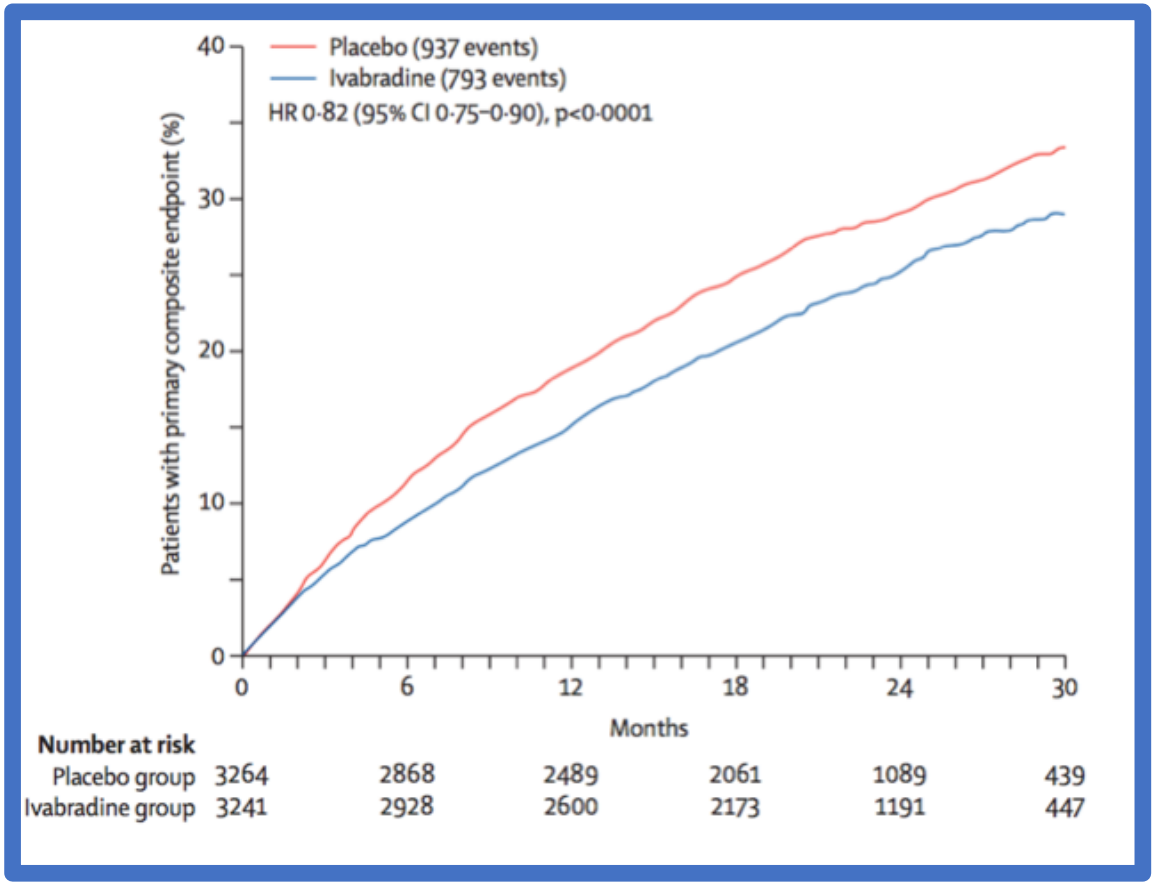
Ivabradine- SHIFT

- EF < 35% , HF hospitalization
- Sinus rhythm > 70 bpm
- Class II or higher
- Few Class IV patients
- 25% of patients on optimal beta blocker
- Primary end point: Death from CV cause or HF hospitalization



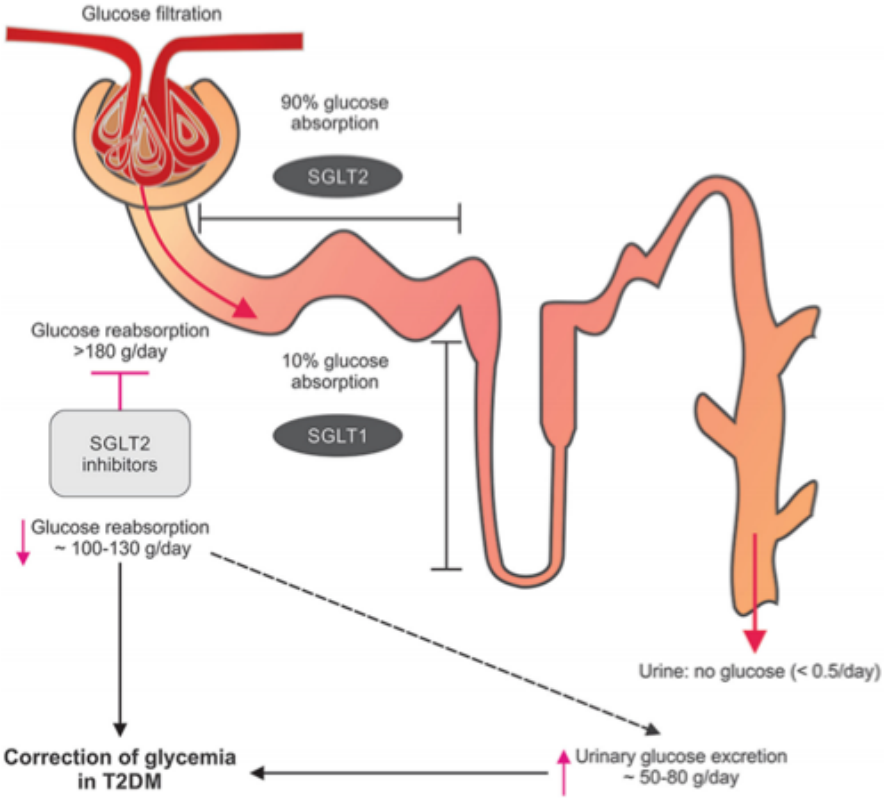
Swedberg K. Lancet. 2010; 376: 875-85

Ivabradine- Practical Tips

Avoid:

- Recent MI
- Pacing more than 40% of the day
- Atrial arrhythmias
- Non-dihydropyridine calcium channel blockers
- Class I antiarrhythmic
- Strong cP450 34A inhibitors

SGLT-2 Inhibition



Kalra S et al. *Adv Ther* 2016;33:1502-1518

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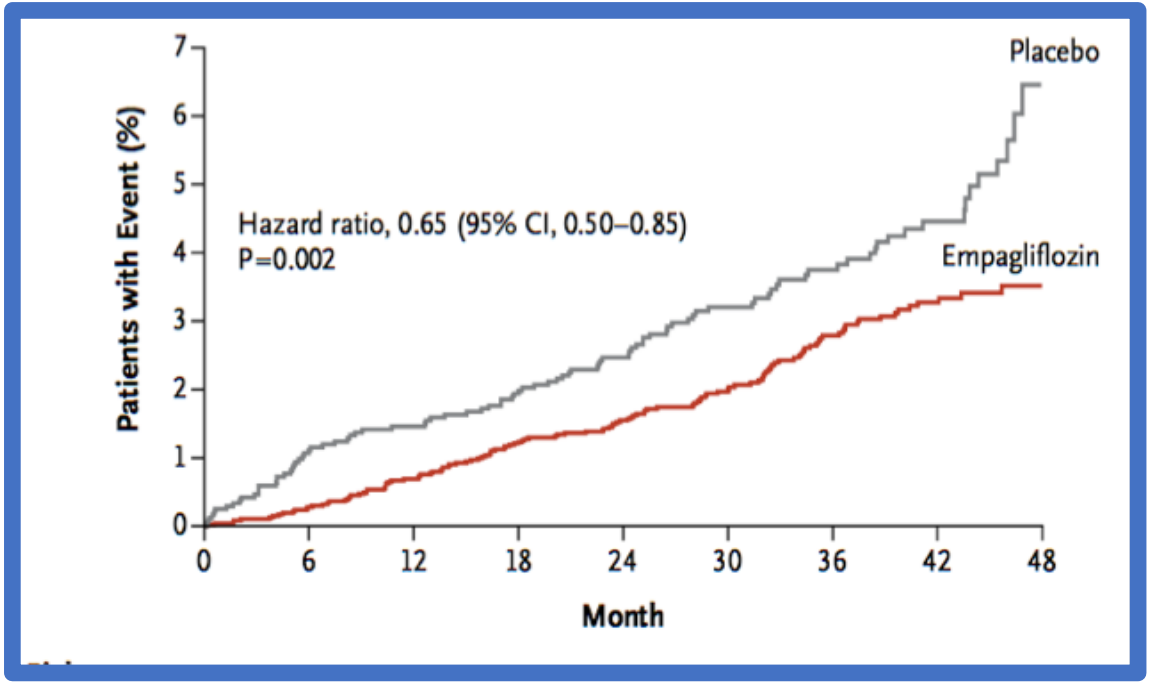
SGLT-2 Inhibitors—Impact on Heart Failure Outcomes

7,020 patients with diabetes at high cardiovascular risk randomized to empagliflozin (10 or 25 mg/day) or placebo for a median of 3.1 years (EMPA-REG OUTCOME Trial)



Heart Failure Hospitalization:

Empagliflozin: n = 126 (2.7%)
Placebo: n = 95 (4.1%)
HR 0.65 (0.55-0.79)

Zinnman B et al. *N Engl J Med* 2015;373:2117-2128

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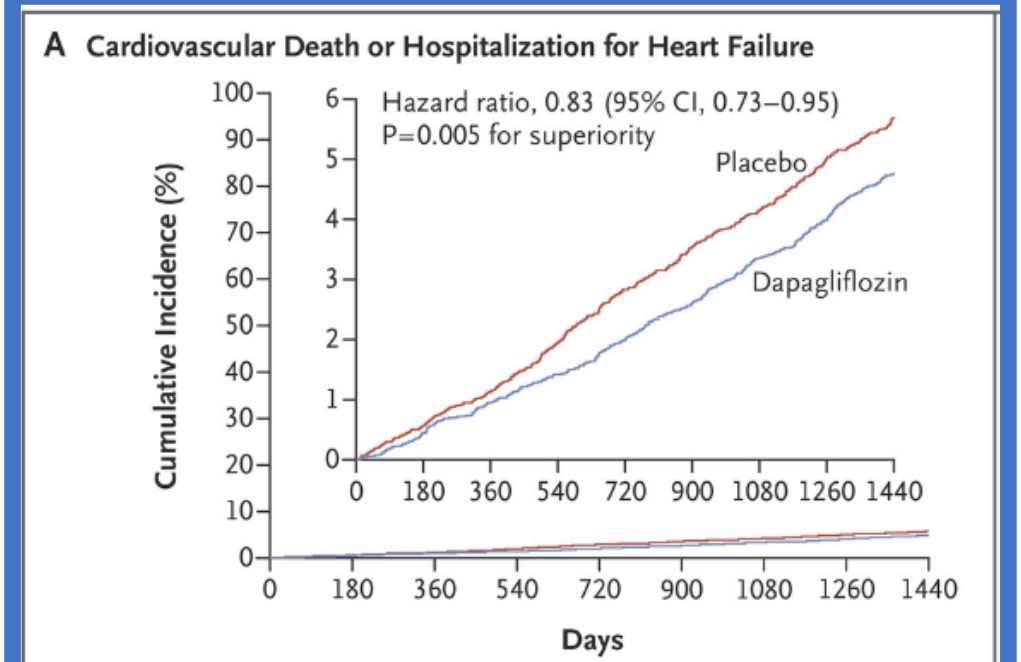
SGLT-2 Inhibitors—Impact on Heart Failure Outcomes

17,160 patients with diabetes at high cardiovascular risk randomized to dapagliflozin (10 mg daily) or placebo for a median of 4.2 years (DECLARE-TIMI 58)



Heart Failure Hospitalization and CV death:

Dapagliflozin: n = 417 (4.9%)
Placebo: n = 496 (5.8%)
HR 0.83 (0.73-0.95)

Zinnman B et al. *N Engl J Med* 2015;373:2117-2128

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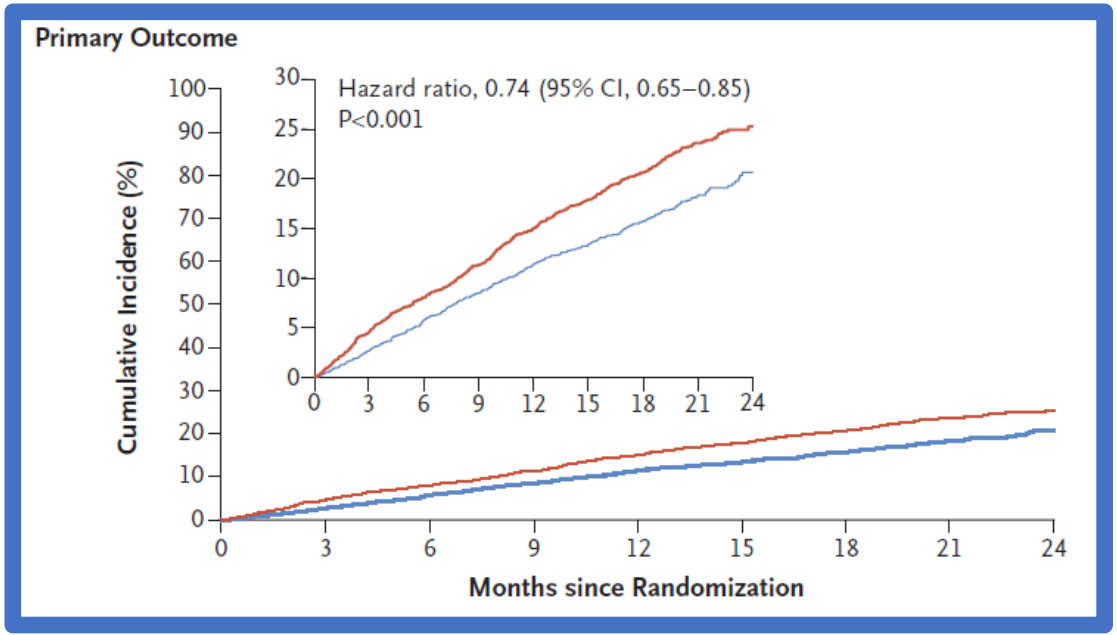
SGLT-2 Inhibitors—HFrEF

4,744 patients with heart failure (NYHA II-IV, EF < 40%) with elevated BNP/HF hospitalization randomized to dapagliflozin (10 mg daily) or placebo for a median of 18.2 months (DAPA HF). ~ 45% with DM.



CV death, HF hospitalization, urgent visit for IV diuresis:

Dapagliflozin: n = 386 (16.3%)
Placebo: n = 502 (21.2%)
HR 0.74 (0.65-0.85)

McMurray JJV et al. N Engl J Med 2019.

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SGLT-2 Inhibitor - Practical Tips

Diuretic adjustment	Blood pressure	Lipids
Fungal infections	UTI’s	DM medications

Advances in pharmacologic therapy for HFpEF

MRA

ANRI?

SGLT-2 Inhibitors?

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2013 Heart Failure Guidelines

Recommendations	COR	LOE
Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines	I	B (27,91)
Diuretics should be used for relief of symptoms due to volume overload.	I	C
Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT	IIa	C
Management of AF according to published clinical practice guidelines for HF*p*EF to improve symptomatic HF	IIa	C
Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HF*p*EF	IIa	C
ARBs might be considered to decrease hospitalizations in HF*p*EF	IIb	B (589)
Nutritional supplementation is not recommended in HF*p*EF	III: No Benefit	C

ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin-receptor blockers; CAD, coronary artery disease; COR, Class of Recommendation; GDMT, guideline-directed medical therapy; HF, heart failure; HF*p*EF, heart failure with preserved ejection fraction; LOE, and Level of Evidence.

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

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2017 Heart Failure Guidelines

Recommendations for Stage C HF*p*EF (Continued)		
COR	**LOE**	**Recommendations**
IIb	**B-R**	**In appropriately selected patients with HF*p*EF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations.[83,166,167]**
See Online Data Supplement C.		
III: No Benefit	**B-R**	**Routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QoL in patients with HF*p*EF is ineffective.[171,172]**
See Online Data Supplement C.		

Yancy CW et al. *J Am Coll Cardiol* 2017;70:776-803

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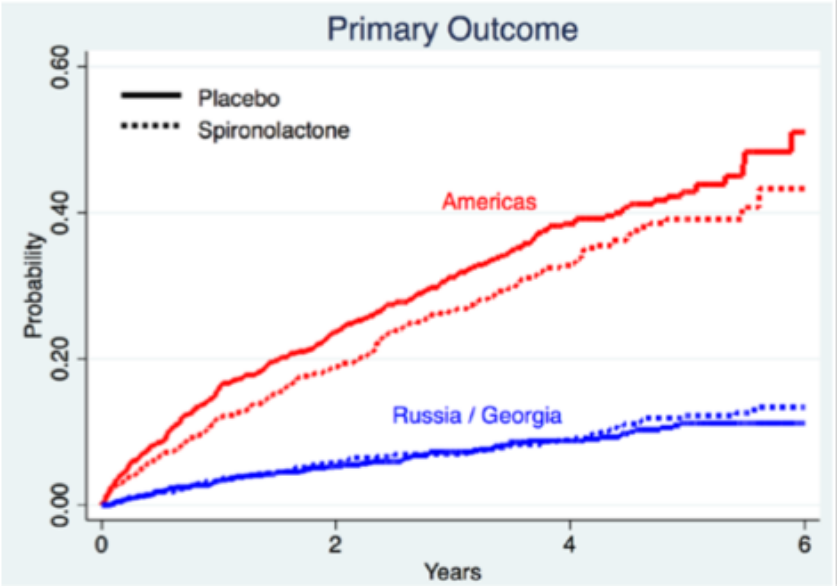
Mineralocorticoid Receptor Antagonist (MRA)

Regional analysis of 1,767 patients from the Americas (as compared to 1678 from Russia and Georgia) enrolled in the TOPCAT trial which randomized patients with symptomatic heart failure with a LVEF ≥45% to spironolactone or placebo for a mean of 3.3 years



CV death, aborted cardiac arrest or HF hospitalization:
Americas

Spironolactone: n = 242 (27.3%)
Placebo: n = 280 (31.8%)
HR 0.82 (0.69-0.98)

Pfeffer MA et al. Circulation 2015;131:34-42

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Aldosterone Receptor Antagonists

Caution vs avoid:
Cr > 2 in men
Cr > 2.5 in women

Frequent KCL monitoring:
More than HFrEF?

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

Sacubitril-Valsartan in HFpEF

Paramount Trial

- Sacubitril-Valsartan vs Valsartan
- Sacubitril-Valsartan resulted in a greater reduction in NT-proBNP at 12 weeks

Paragon Trial

- Sacubitril-Valsartan vs Valsartan
- Randomized with Run-in Period
- Composite endpoint of CV death and total HF hospitalizations
- Primary end point not met
- Women? Mid-range EF?

Solomon SD et al. *Lancet* 2012;380:1387-1395
Solomon SD et al. *JACC Heart Fail* 2017;5:471-482
Solomon SD et al. NEJM. 2019; 381: 1609-1620.

SGLT2 Inhibitors and HFpEF

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Ongoing SGLT-2 Inhibitor HFpEF Studies

TABLE 4 Ongoing Trials of SGLT-2 Inhibitors in Patients With HFpEF and DM

Trial	Therapy	Population	Primary Outcome	Expected Enrollment
EMPEROR-PRESERVED (NCT03057951)	Empagliflozin	EF >40%, ± type 2 DM, Elevated NT-proBNP	Time to CV death or hospitalization for HF from baseline to 38 months	4,126
EMBRACE-HF (NCT03030222)	Empagliflozin	EF >40% or <40% Type 2 DM PA diastolic pressure ≥12 mm hg	Change in PA diastolic pressure from baseline to 8 to 12 weeks	60
ERADICATE-HF (NCT03416270)	Ertugliflozin	EF >20% (HFpEF and HFrEF) and DM Elevated BNP	Proximal tubule sodium reabsorption at 1 and 12 weeks	36
PRESERVED-HF (NCT03030235)	Dapagliflozin	EF ≥45% Type 2 DM Elevated NP	Change from baseline in NT-proBNP at 6 and 12 weeks	320

BNP = brain natriuretic peptide; EMBRACE-HF = Empagliflozin Impact on Hemodynamics in Patients With Heart Failure; EMPEROR-PRESERVED = Empagliflozin Outcome Trial in Patients With Chronic Heart Failure with Preserved Ejection Fraction; ERADICATE-HF = Ertugliflozin in Diabetes With Preserved or Reduced Ejection Fraction Mechanistic Evaluation in Heart Failure; HF = heart failure; PA = pulmonary artery; PRESERVED-HF = Dapagliflozin in PRESERVED Ejection Fraction Heart Failure; SGLT-2 = sodium glucose cotransporter-2; other abbreviations as in Table 1.

McHugh K et al. J Am Coll Cardiol 2019;73:602-611

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Implantable Hemodynamic Monitoring in Heart Failure

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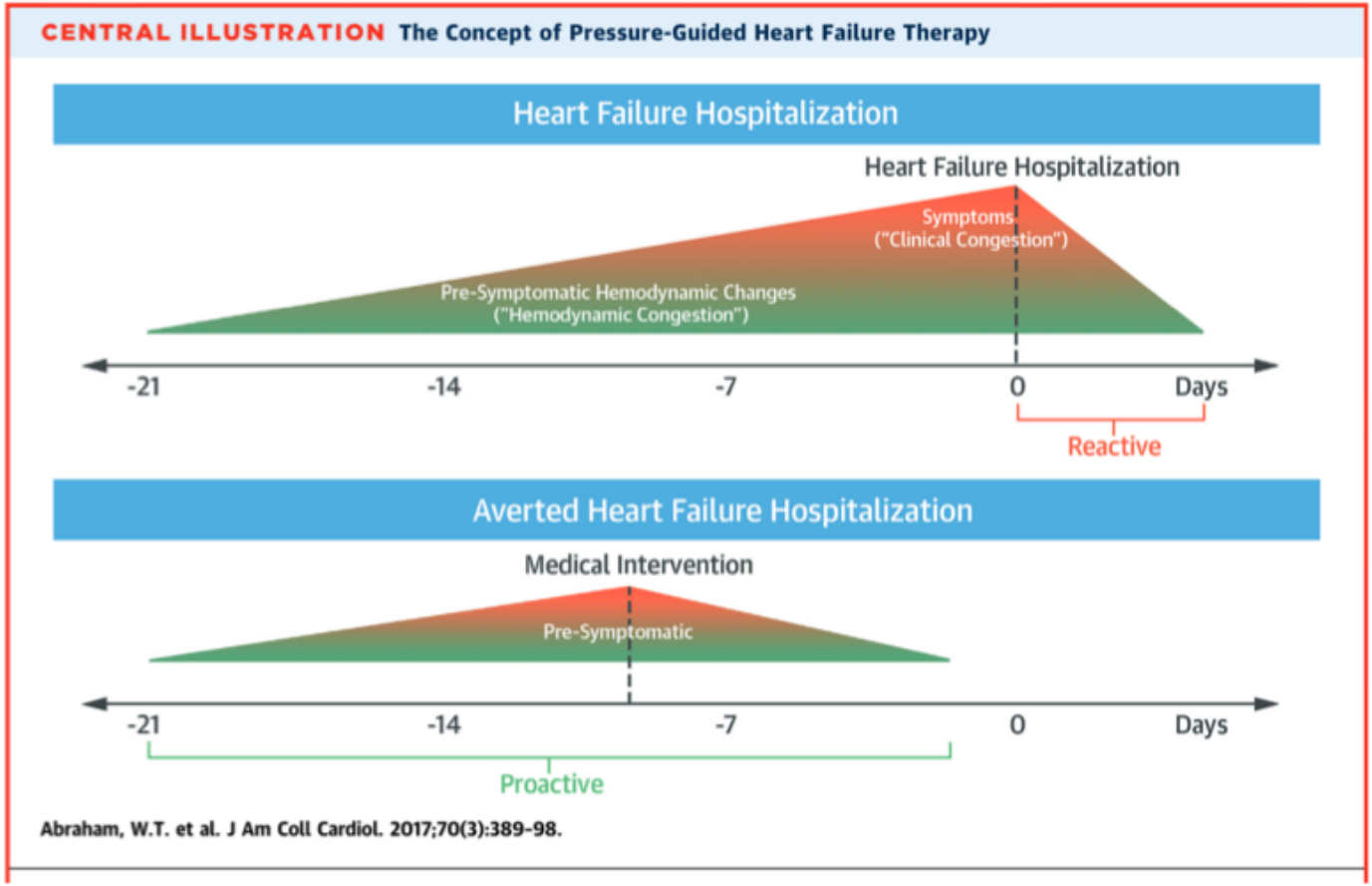
Pressure Guided Heart Failure Therapy



Abraham, W.T. et al. J Am Coll Cardiol. 2017;70(3):389-98.

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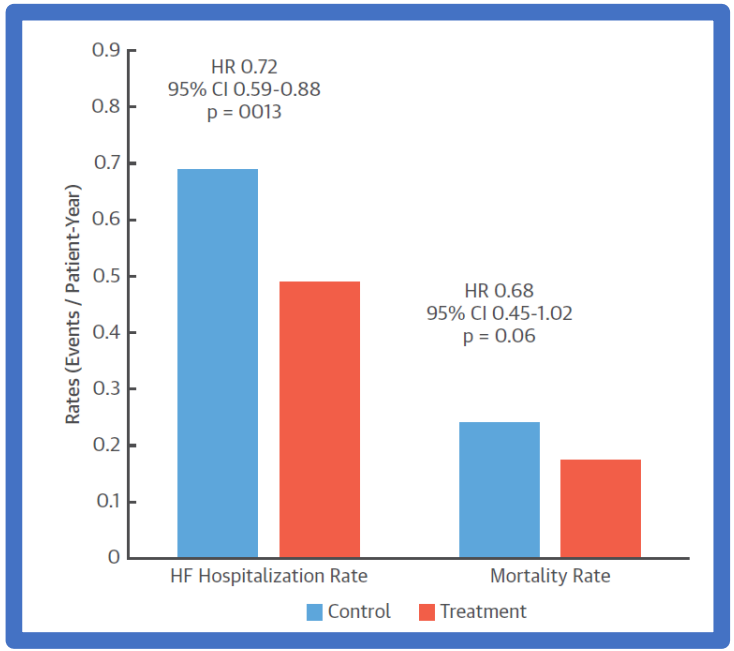
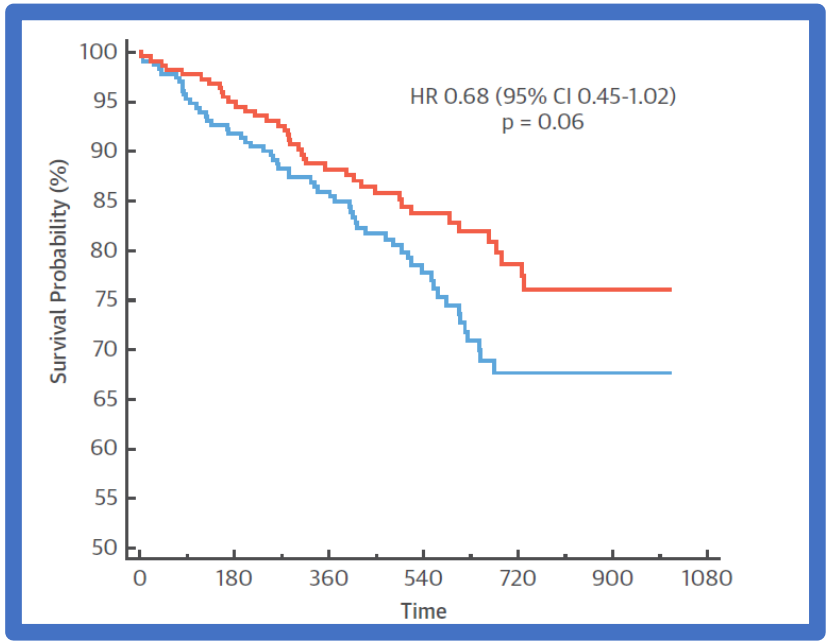
Implantable Hemodynamic Monitoring for HFrEF

Subgroup of 456 patients with a LV EF ≤40% enrolled in the CHAMPION trial which randomized patients with chronic heart failure (regardless of EF) and hospitalization to wireless implantable hemodynamic monitoring or control.

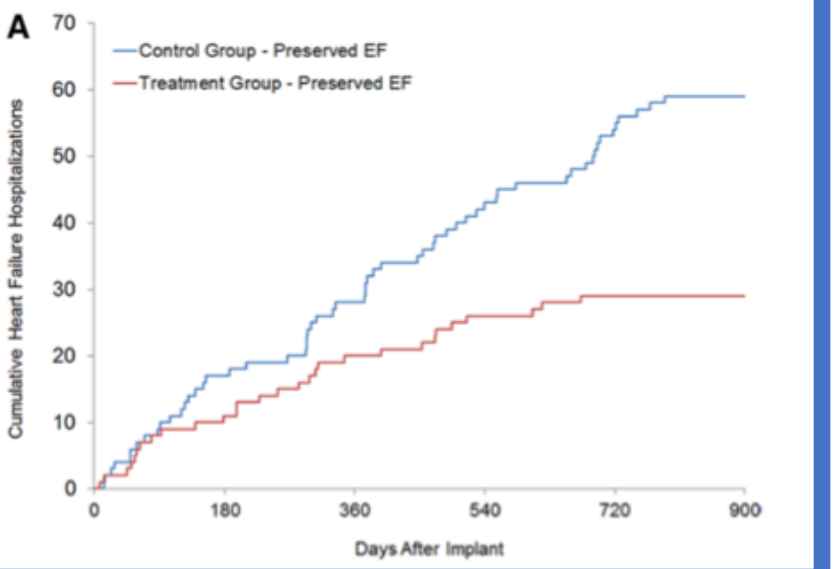




Givertz et al. JACC. 2017;15: 1875-1886

Implantable Hemodynamic Monitoring for HFpEF

Subgroup of 119 patients with a LV EF ≥40% enrolled in the CHAMPION trial which randomized patients with chronic heart failure (regardless of EF) and hospitalization to wireless implantable hemodynamic monitoring or control.



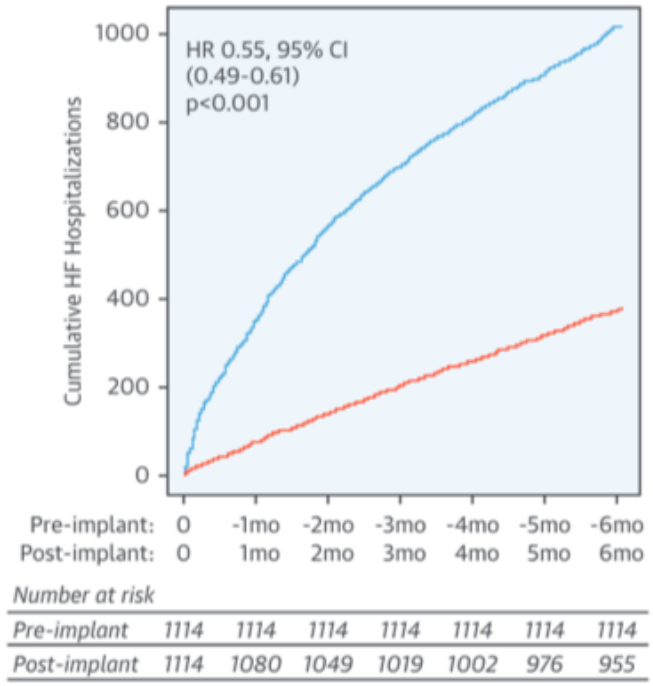
HF Hospitalization at 6 months:
Monitoring: 12.9%
Control: 22.8%
HR: 0.54 (0.38-0.70)

HF Hospitalization, study duration:
Monitoring: 29.9%
Control: 38.6%
HR: 0.50 (0.35-0.70)

Adamson PB et al. *Circ Heart Fail* 2014;7:935-944

Real World Experience

A



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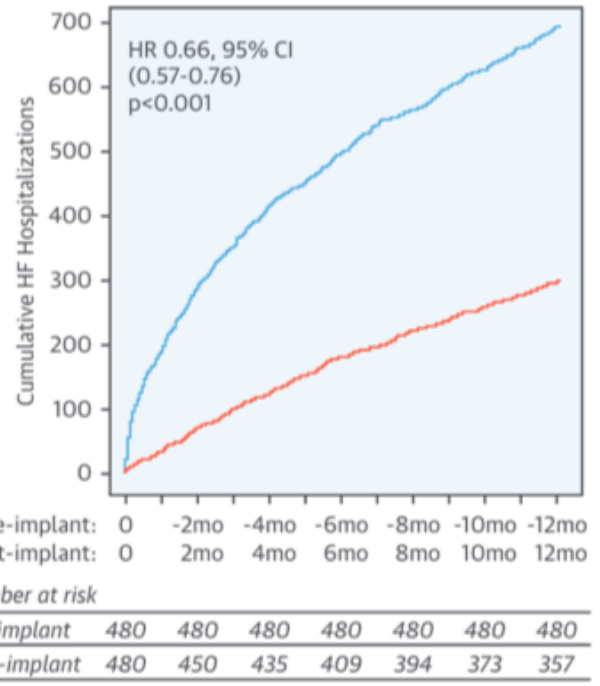

Pre-implant HFH Post-implant HFH

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Desai AS. JACC. 2017; 69: 2657-2365

Implantable Hemodynamic Monitoring- Considerations

HFpEF > HFrEF	Rural Location	Hospitalized
Hard Exam	Co-Morbidities	HF partner

Percutaneous Mitral Valve Therapy in Functional Mitral Regurgitation

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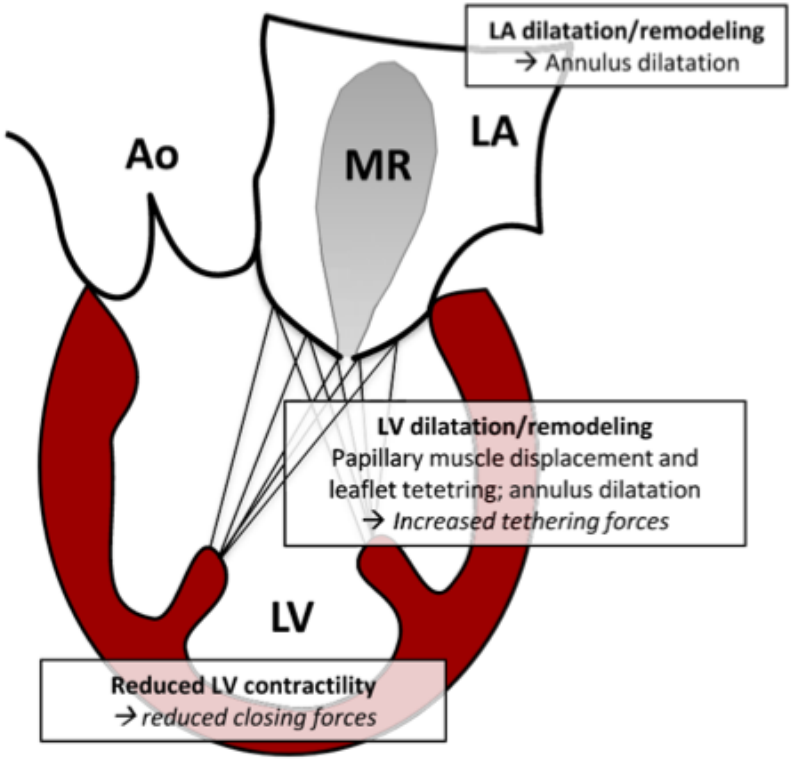
Functional Mitral Regurgitation in Heart Failure



Lavall D. ESC HF. 2018; 5: 552-561

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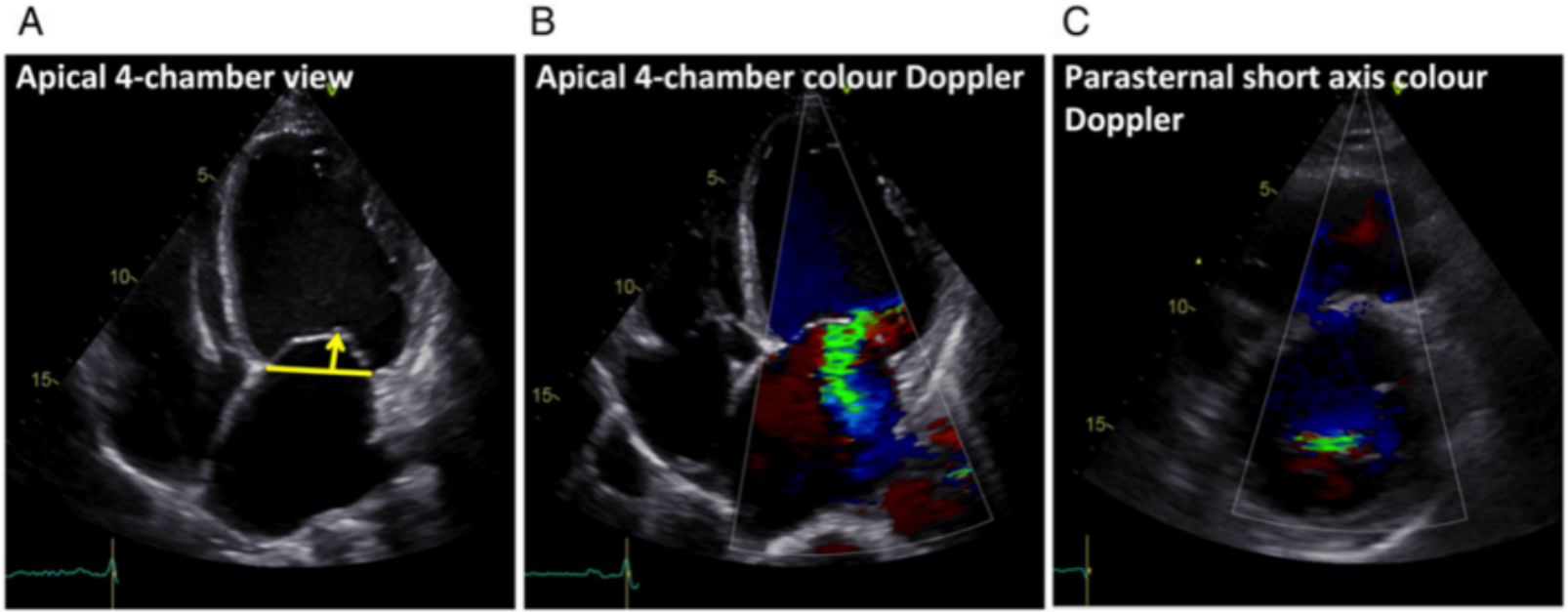
Functional Mitral Regurgitation in HFrEF



Lavall D. ESC HF. 2018; 5: 552-561

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Mitral Clip

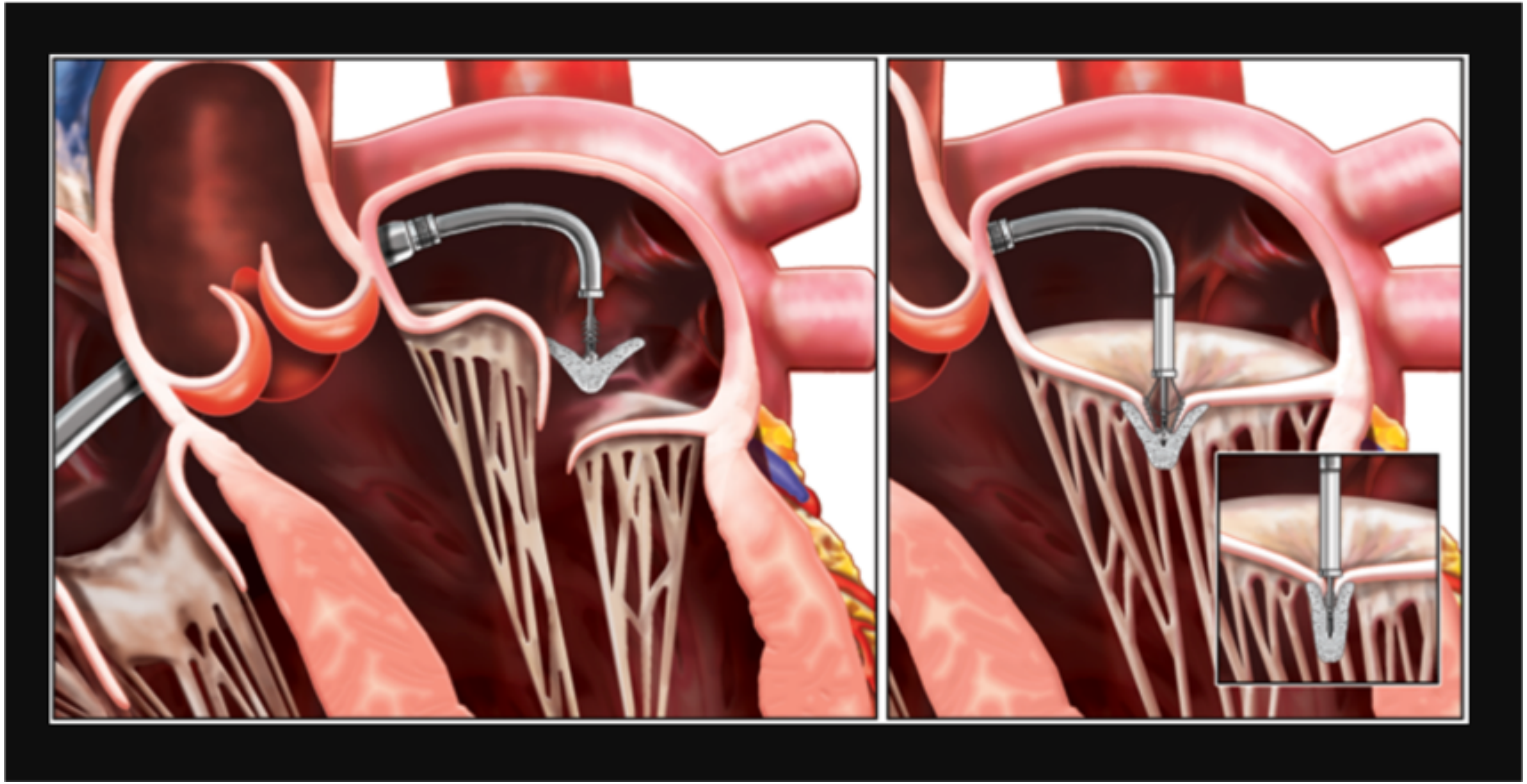

Photo from ACC.org

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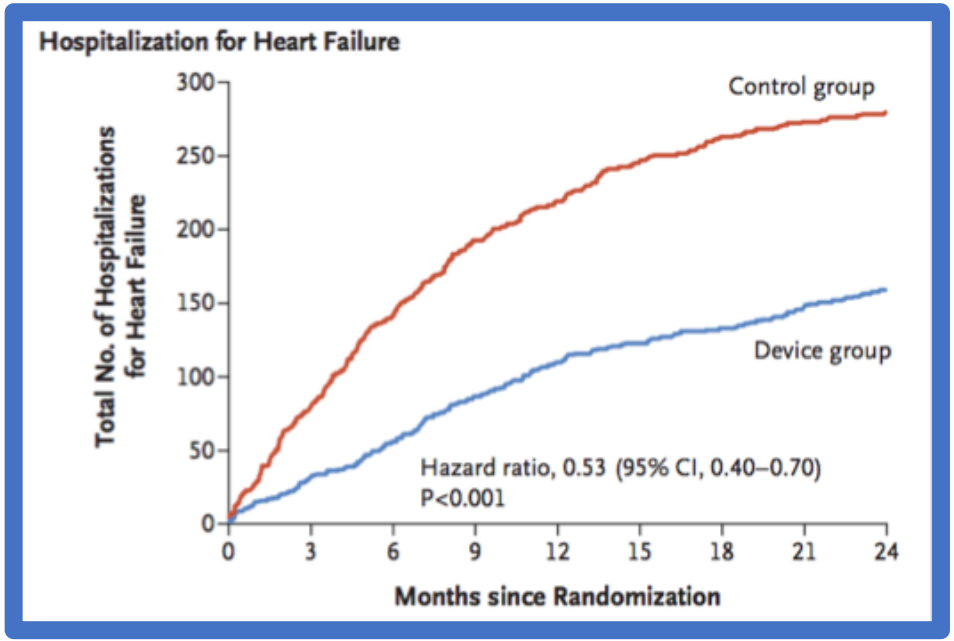
COAPT

614 patients with heart failure and severe secondary mitral regurgitation who remained symptomatic after use of maximal doses of GDMT randomized to transcatheter mitral valve repair and medical therapy or medical therapy alone.



Heart Failure Hospitalization within 24 months:

Mitral clip: 35.8%
Control: 67.9%
HR 0.53 (0.0.40-0.70)

Stone et al. *N Engl J Med* 2018;379:2307-2318

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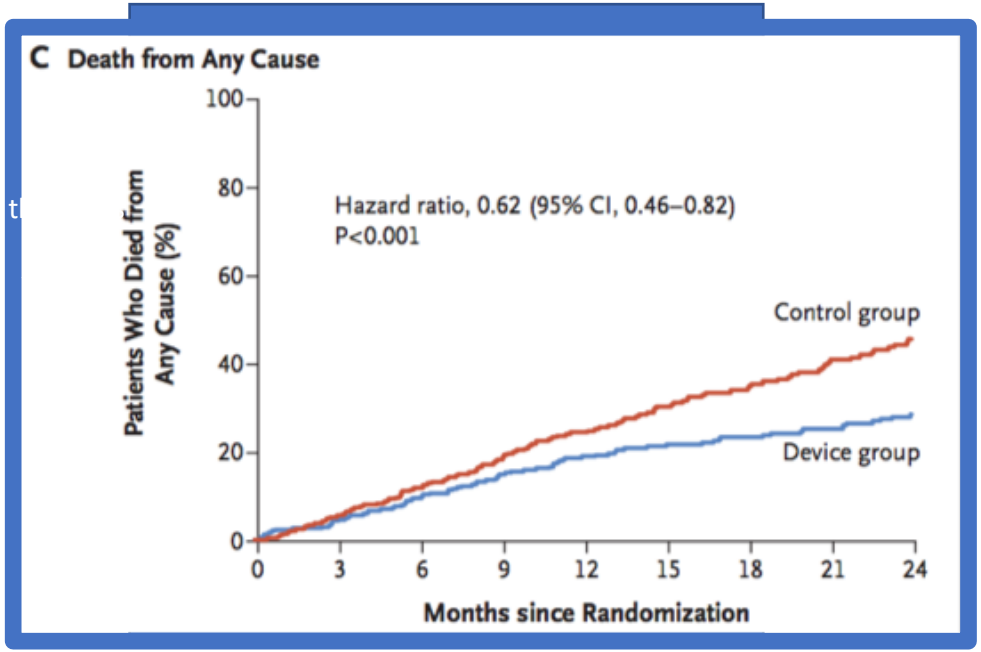
Percutaneous Mitral Valve Therapy in Functional Mitral Regurgitation- Considerations

COAPT patients were on maximally tolerated GDMT; HF consultation (MITRA-HF negative trial)



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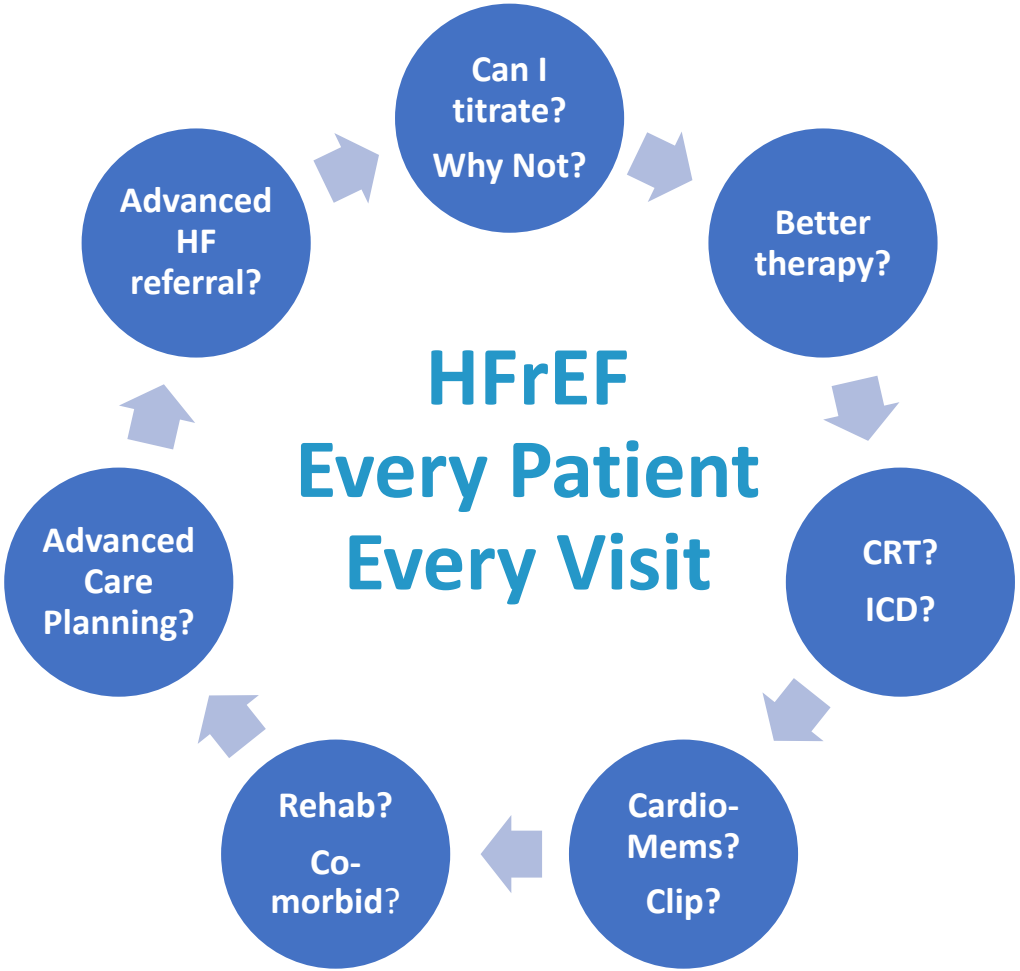
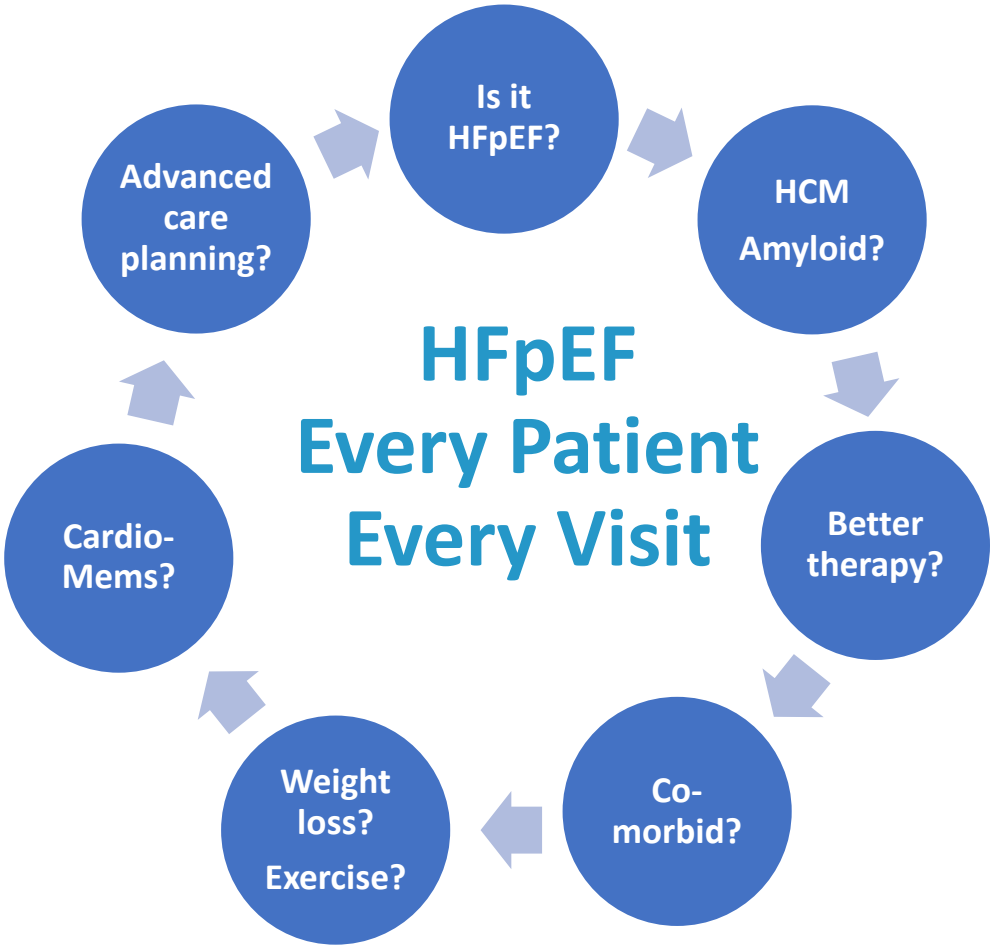

HFrEF
Every Patient
Every Visit
Can I titrate? Why Not?
Better therapy?
CRT? ICD?
Cardio-Mems? Clip?
Rehab? Co-morbid?
Advanced Care Planning?
Advanced HF referral?


HFpEF
Every Patient
Every Visit
Is it HFpEF?
HCM Amyloid?
Better therapy?
Co-morbid?
Weight loss?
Exercise?
Cardio-Mems?
Advanced care planning?

Key Takeaways

ARNI's and SGLT-2 inhibitors are changing treatment paradigms for HF.

An implantable hemodynamic monitor is a helpful tool for preventing symptoms and HF hospitalizations in some patients with HF.

Transcatheter mitral valve therapies may be appropriate for some patients with functional mitral regurgitation and refractory symptoms.

Despite recent advances, heart failure remains a challenging disease with poor prognosis.

Thank you