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Part 7: Chronic Heart Failure Continued

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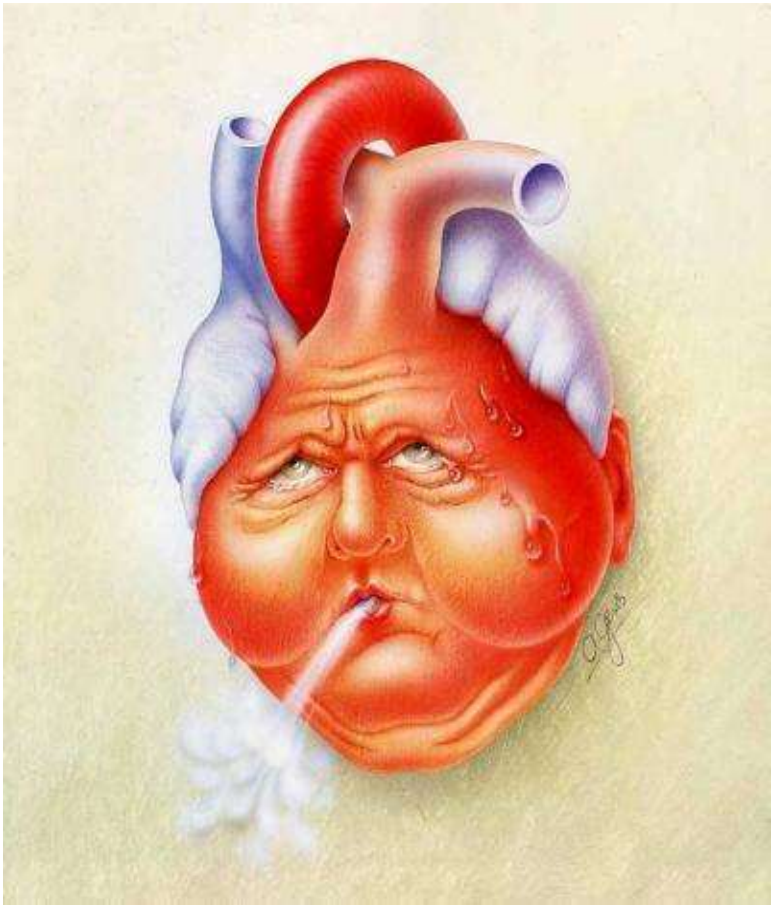
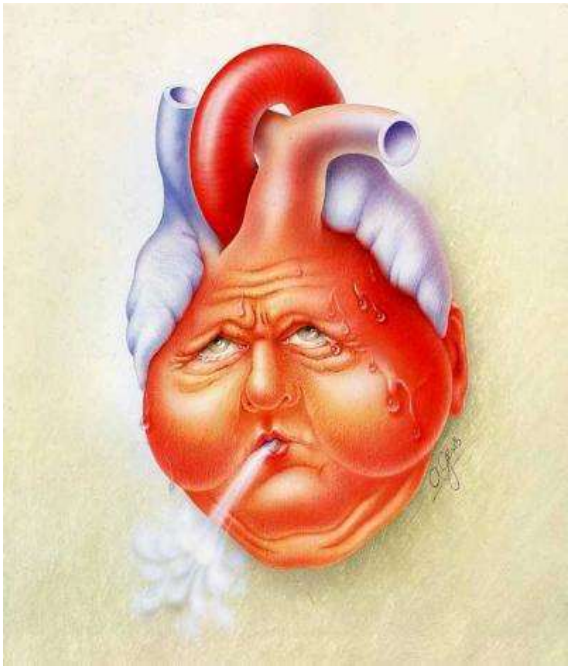
Spring 2021



HF Part 7



- Patient case continued
- Medication therapies for stages in the development and progression of HF
  - Stage C: Ivabradine, digoxin, vericiguat
  - Stage D
- Medication Therapies for HF*p*EF
- Device Therapies for HFrEF (FYI)

HF Case: Part 3

- SB returns to clinic after 3 months for follow up.

- Today she is euvolemic and complains of SOB when trying to exert herself, such as when rushing to catch an elevator.

Which NYHA class is she in today?

HF Case Continued

- Vital Signs: BP 118/68 mmHg, P 60 bpm
- Labs: K+ 4.3 mEq/L, SCr 1.4mg/dL
- Her medications include:
  - Valsartan/sacubitril 49/51 mg BID
  - furosemide 20mg daily
  - carvedilol 12.5mg twice daily
  - aspirin 81mg daily
  - atorvastatin 40mg daily
  - lansoprazole 30mg daily
  - NTG 0.4mg prn (has not needed)

Remember: her EF is 20%

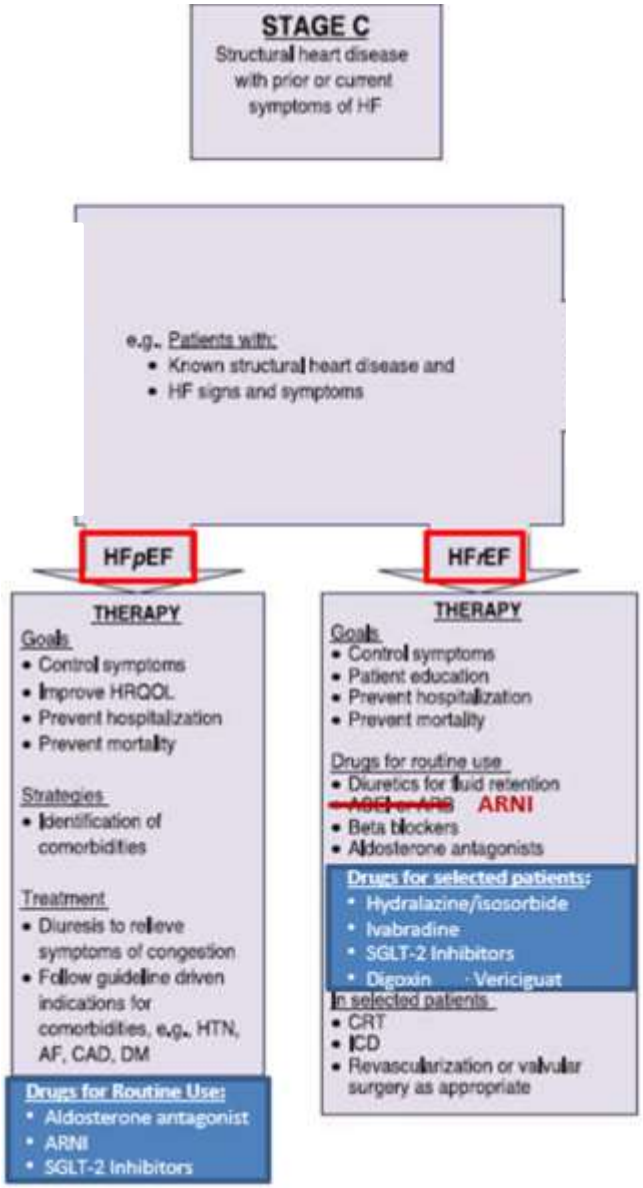
Question #5

- What is the most appropriate choice for her treatment of HF?
  a. **Add spironolactone 25mg daily**
  b. Increase carvedilol to 25mg BID
  c. Increase furosemide to 20mg BID
  d. Increase valsartan/sacubitril 97/103 mg BID
  e. Add hydralazine/isosorbide 37.5/25 mg TID

Why is a SGLT-2 inhibitor an option for this patient AT THIS TIME?

Stage C – Has/Had HF Symptoms

- Diuretics
- SGLT-2 inhibitors
- ARNI
- Hydralazine/isosorbide
- Aldosterone Antagonists
- **Ivabradine**
- Digoxin
- Vericiguat
- Device therapy

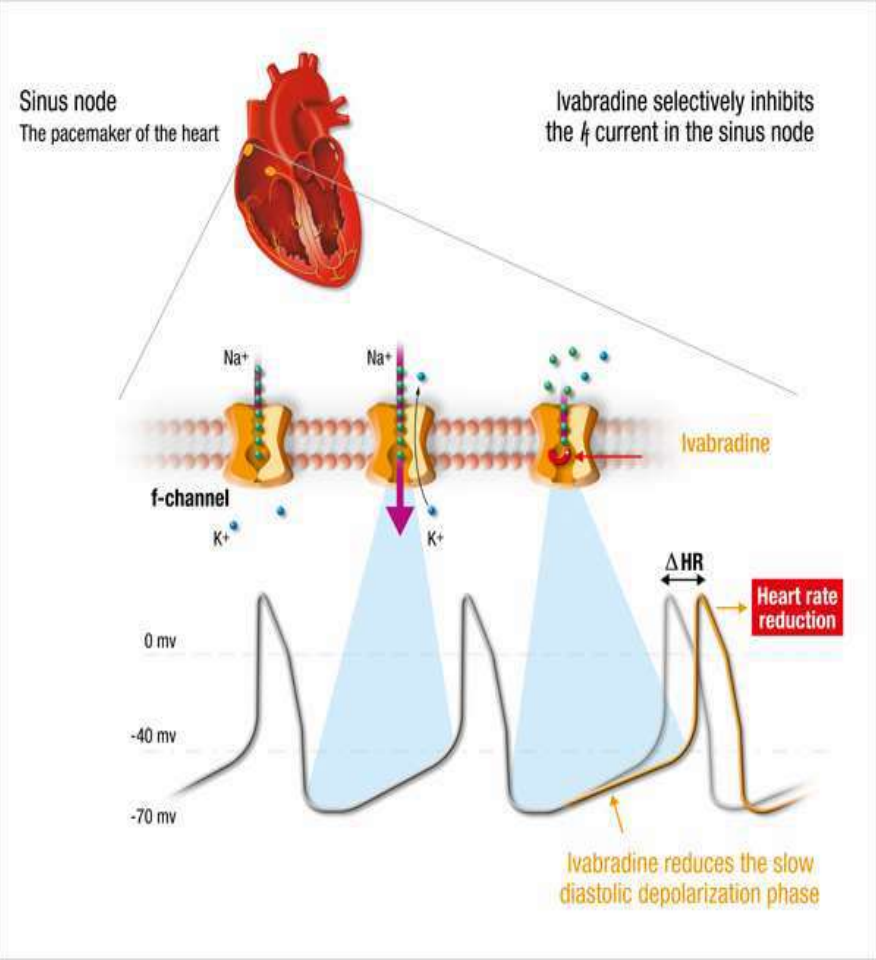


Ivabradine (Corlanor®)

- Blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel in the sinoatrial node which is responsible for the I_f current to decrease HR

- **Indicated in pts with HF*r*EF (EF ≤ 35%) AND**
  - **in NSR w/HR ≥ 70 bpm,**
  - **on max tolerated BB dose,**
  - **NYHA class II or III**

- Benefit: reduce risk of hospitalization for worsening HF; no benefit observed for mortality



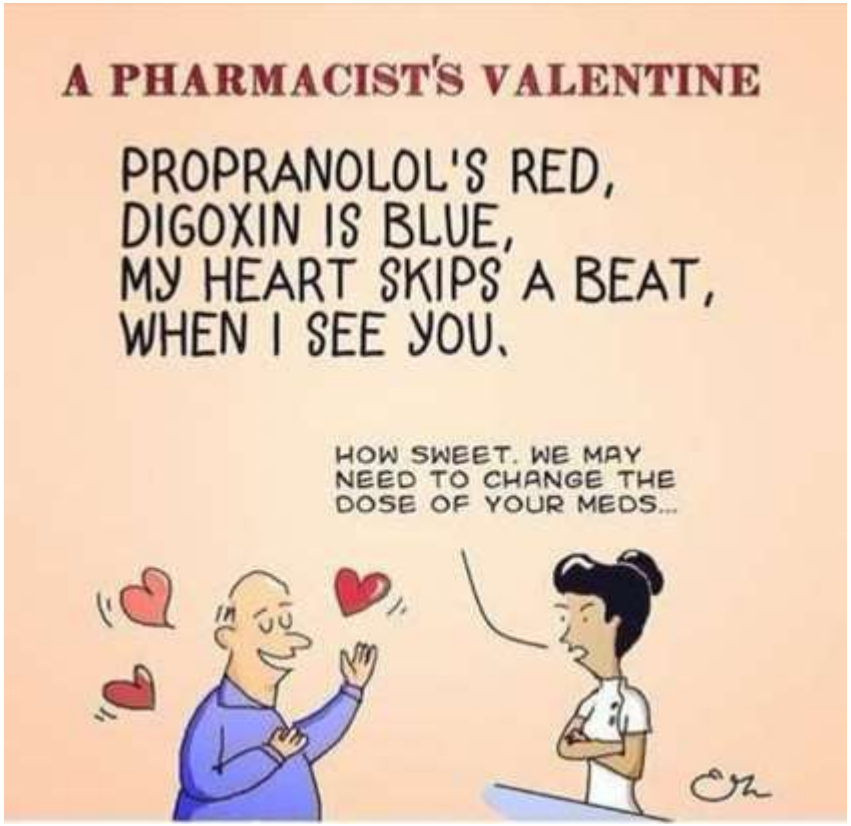
2021 Update of 2017 ACC Expert Consensus Decision Pathway for Optimization of HF Treatment

Ivabradine (Corlanor®) for HF*r*EF

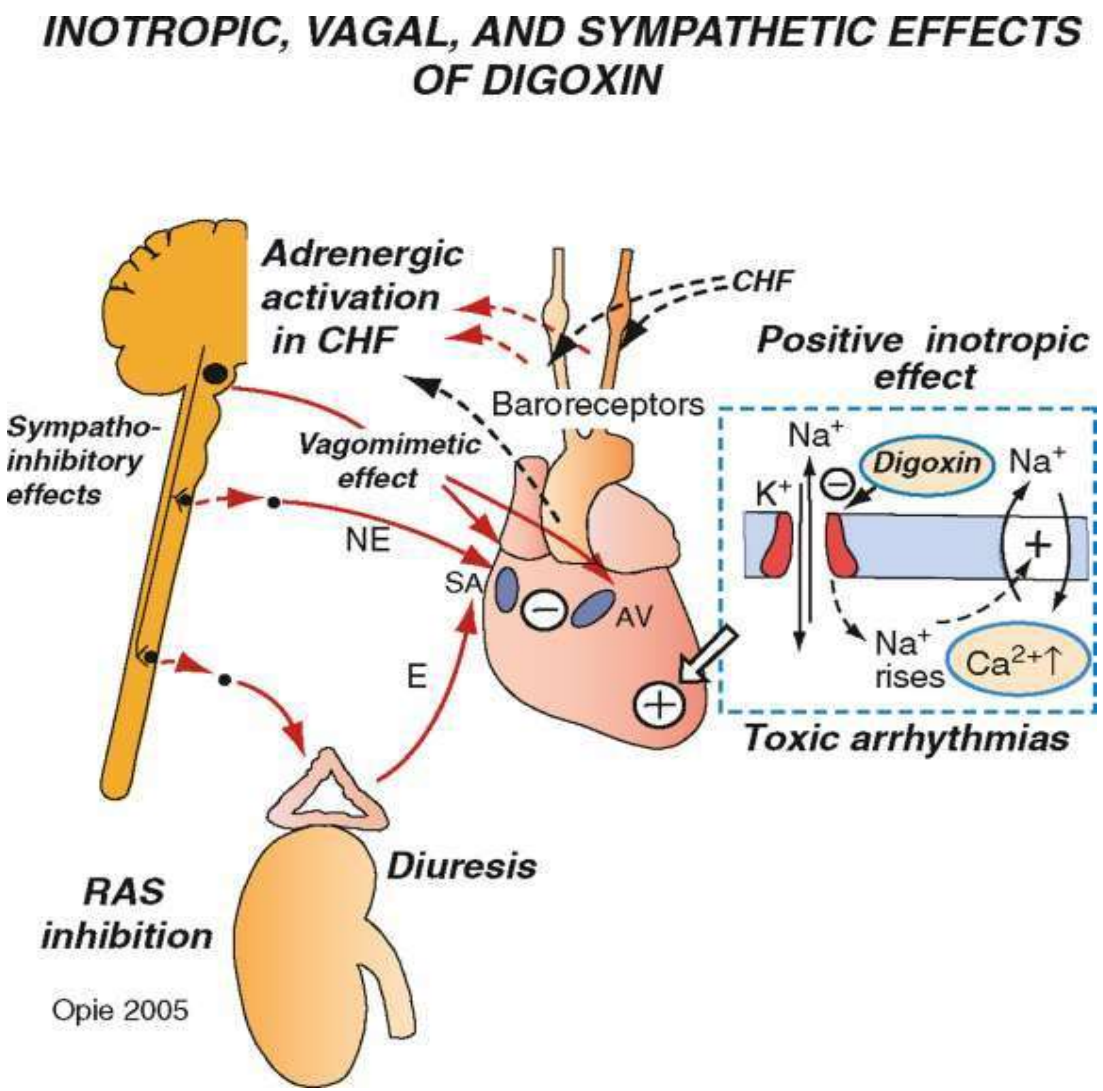
- Dosing: 2.5mg BID (≥ 75yrs) or 5mg BID (< 75 yrs)
  - After 2-4 weeks:
    - increase dose by 2.5mg BID if HR > 60 bpm until max dose 7.5mg BID reached;
    - maintain dose if HR 50-60 bpm;
    - decrease dose by 2.5mg BID or D/C if on 2.5mg BID for HR < 50 bpm or symptoms of bradycardia
- Side Effects: bradycardia, heart block, HTN, Afib, visual side effects (phosphene)
- Doesn't replace BB but added to BB therapy once target doses reached and HR remain > 70 bpm
- Take with meals to enhance absorption
- Avoid taking with strong CYP 3A4 inhibitors!

Stage C – Has/Had HF Symptoms

- Diuretics
- SGLT-2 inhibitors
- ARNI
- Hydralazine/isosorbide
- Aldosterone Antagonists
- Ivabradine
- **Digoxin**
- Vericiguat
- Device therapy



Cardiac Glycoside



HF MOA:

1. (+) inotrope that increases contractility

2. (-) chronotrope: Decrease sympathetic outflow to decrease HR (SA node) and inhibit AV node to slow vent rate and prevent arrhythmias

3. Slowing HR allows for increased vent filling

4. Inhibit SNS to inhibit renin production in kidney

Adapted from Drugs for the Heart, 7th Edition. Figures 6-9.

Digoxin Therapy for HF*r*EF

- Consider adding to maximized standard therapy in patients who remain symptomatic to decrease hospitalizations *(Class IIa)*
  - Digoxin improves NYHA functional class, hemodynamics, and morbidity (not mortality)
  - Ideal in patients with HF and Afib
- Dosing based on CrCl:
  - CrCl < 20mL/min or < 40kg: 0.125 mg QD
  - CrCl > 20mL/min or > 40kg: 0.25 mg QD (max dose in HF)

Digoxin Key Points

- Pharmacokinetics
  - High Vd (half of drug is bound to skeletal muscle receptors)
  - Long T1/2 (1.5 days)
  - Intestinal flora convert dig to inactive products
  - Major route of elimination via kidneys
- Drug interactions
  - Too many to list in a short space!
  - Caution with diuretics
    - Low K or Mg levels sensitize heart to dig toxicity

Digoxin Key Points Continued

- Digoxin levels are not used for monitoring efficacy in patients with HF*r*EF
  - Normal range for Afib 1-2 ng/mL
  - For HF target 0.5-0.9 ng/mL, especially in elderly patients, those with renal dysfunction, and low body mass
  - **Indications for obtaining levels: suspected toxicity, questionable adherence, drug-drug or drug-disease interactions**
  - Level should be drawn 6-24 hours after dosing to allow for complete distribution

Digoxin Key Points Continued

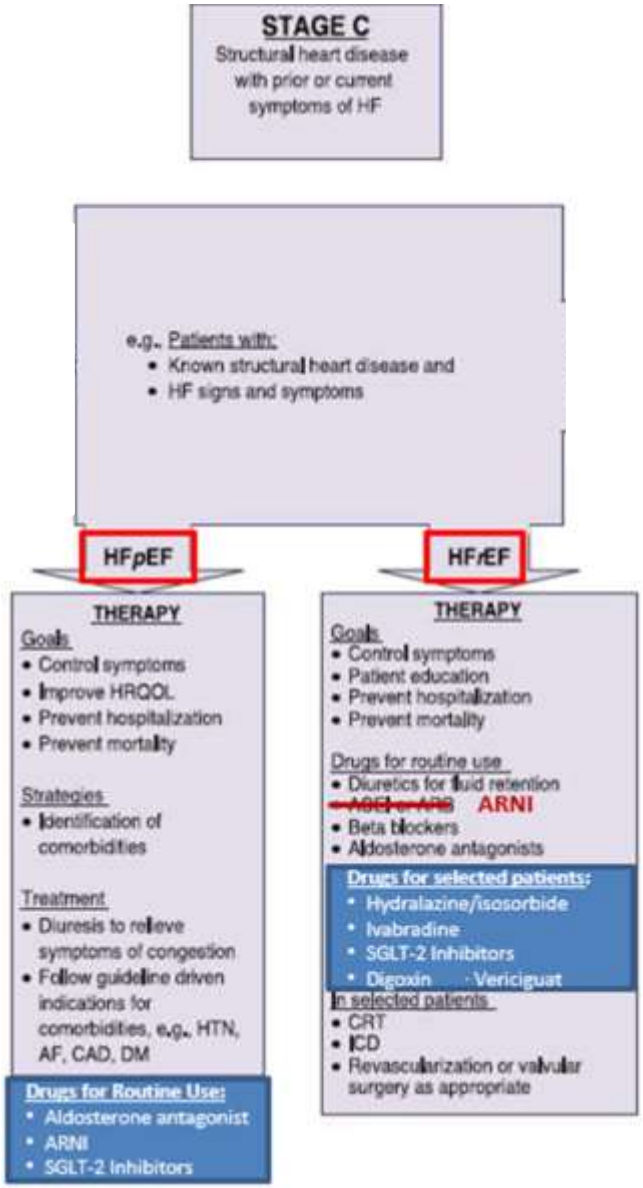
- Non-cardiac side effects:
  - GI: anorexia, N/V, diarrhea
  - CNS: fatigue, weakness, confusion, insomnia
  - Visual: hazy, blurry, difficulty reading, red-green misperception or halos around lights
- Cardiac side effects:
  - SA/AV node depression
  - AV-block, atrial/vent. arrhythmias
  - **Predisposition: low K or Mg levels, high Ca levels,** metabolic alkalosis

Digoxin Key Points Continued

- Monitoring parameters:
  - Digoxin level
  - Electrolytes
  - HR and rhythm
  - Renal function
  - S/Sx of toxicity
  - S/Sx of HF
    - **Discontinue therapy if no improvement noted!**

Stage C – Has/Had HF Symptoms

- Diuretics
- SGLT-2 inhibitors
- ARNI
- Hydralazine/isosorbide
- Aldosterone Antagonists
- Ivabradine
- Digoxin
- **Vericiguat**
- Device therapy



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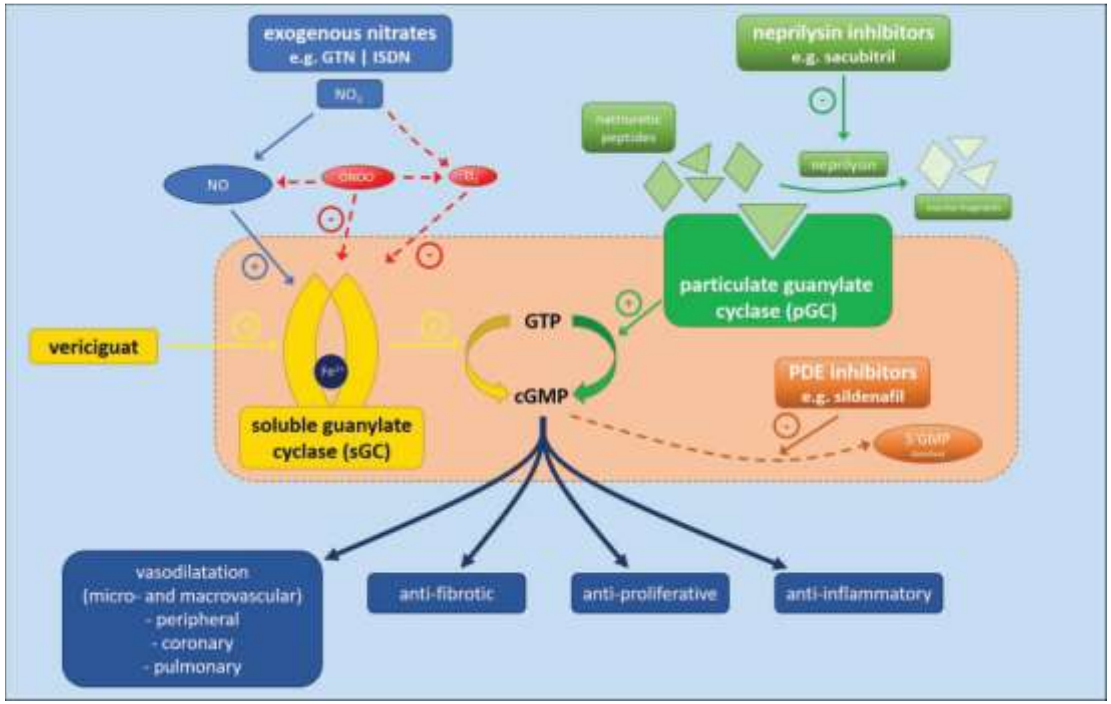
Vericiguat (Verquvo®)

Pharmacologic category: soluble guanylate cyclase (sGC) stimulator

Mechanism of action: enhances cGMP production by stimulating sGC independent of NO. Increased cGMP levels lead to smooth muscle relaxation and vasodilation.



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Vericiguat (Verquvo®)

Indication: Adults w/symptomatic HF despite target doses of GDMT and EF < 45% to decrease risk of CV death and hospitalization.

Dosing: 2.5 mg daily with food. Titrate after ~2 weeks to 5 mg daily; after ~2 weeks, titrate to target dose 10mg daily as tolerated based on BP and clinical symptoms.

- SBP ≥ 100 mmHg: consider dose up-titration if not on target dose; maintain dose if at target.
- SBP 90-99 mmHg: maintain current dose
- SBP < 90 mmHg: decrease dose (if current dose 5 or 10mg) or interrupt therapy (if current dose 2.5 mg or pt has symptomatic hypotension)

Vericiguat (Verquvo®) Continued

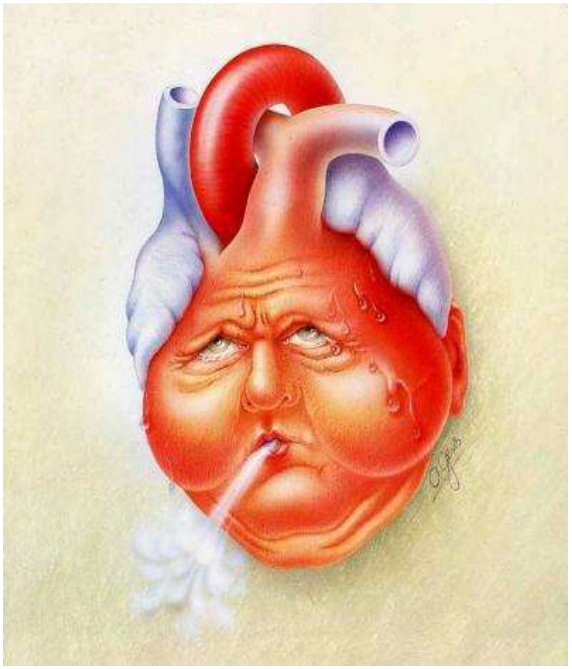
Contraindications:

- Pregnancy!
  - Females of reproductive potential: Exclude pregnancy before the start of treatment
  - To prevent pregnancy, females of reproductive potential must use effective forms of contraception during treatment and for one month after stopping treatment.

Side Effects: hypotension (16%), anemia (10%), GI (dyspepsia, nausea)

Drug interactions: long-acting nitrates, PDE-5 inhibitors (hypotension)

HF Part 7



- HF*p*EF
  - Pathophysiology
  - Management of Comorbidities
  - Drug therapies

Differences in HF

HFrEF

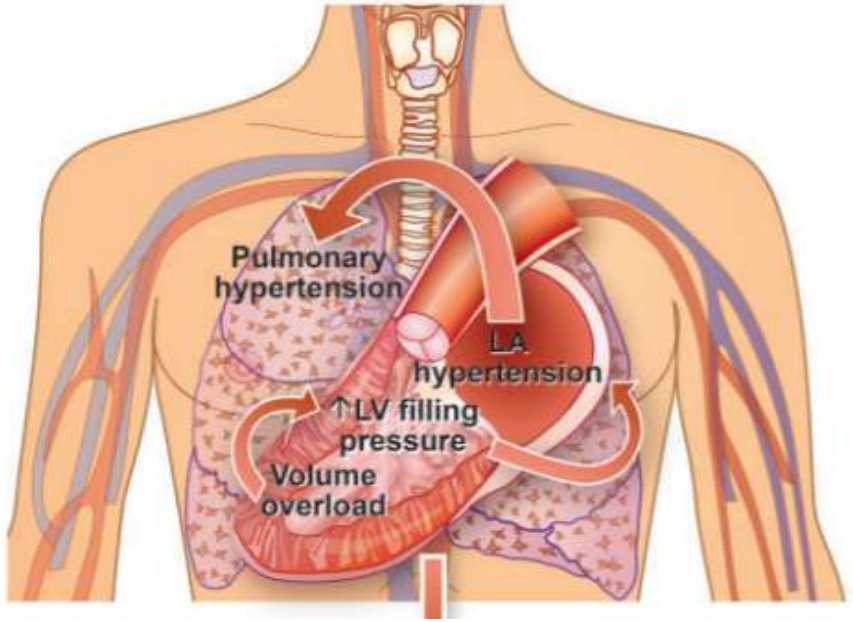
- ~ 50% of all pts with HF
- Decreasing prevalence
- Improving survival rate
- RF: CHD, HTN, valvular heart disease (aortic or pulmonic), toxins (alcohol, chemotherapy, cocaine), viral infections (HIV), peripartum, pulmonary hypertension

HFpEF

- ~50% of all pts with HF
- Increasing prevalence due to increasing age and rate of obesity
- Highest risk: elderly, women
- Other RF: HTN, DM, A fib, CHD, renal insufficiency, valvular heart disease (mitral or tricuspid)
- No improvement in survival rate
- Have more co-morbidities; non-cardiac causes of death more common

HF*p*EF Pathophysiology

- Abnormality of diastolic distensibility, filling, or relaxation of left ventricle
  - Preserved EF
  - Increased myocardial mass
  - Impaired relaxation and ↑ ventricular stiffening



- Congestion develops from:
  - Plasma volume expansion
  - Increased LV end diastolic pressure (preload)
  - Left atrial remodeling and HTN
  - Pulmonary venous congestion

HF*p*EF Pathophysiology Continued

- *Similar morbidity to HFrEF*
- *Similar symptoms to HFrEF*
- *Similar factors precipitate HF symptoms*
- Mechanism of HFpEF different from HFrEF!

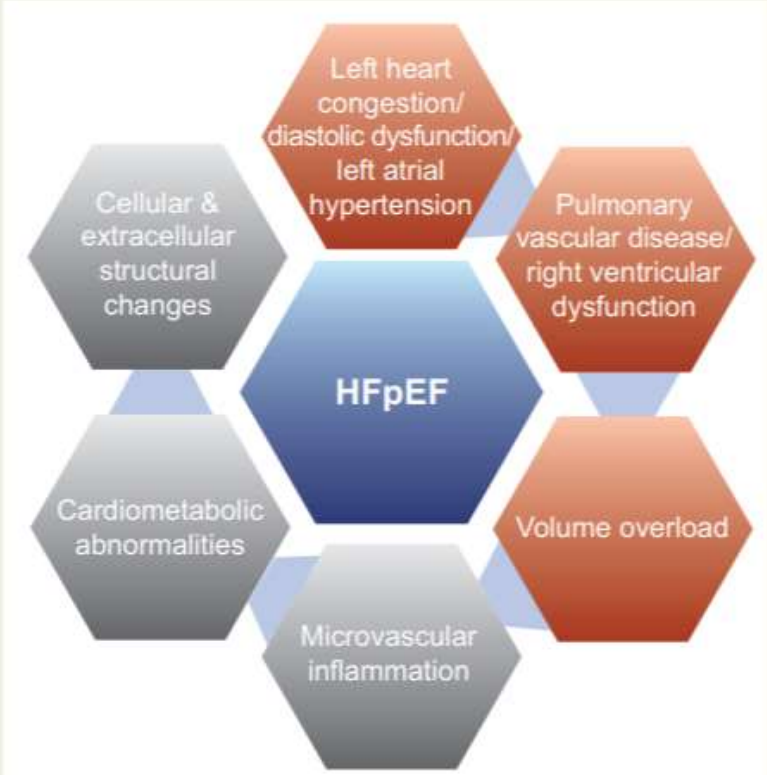


Figure 2 Mechanisms in heart failure with preserved ejection fraction. Six mechanisms are outlined in this review—three haemodynamic (orange) and three cellular/molecular (grey). Data for cardiometabolic abnormalities are largely from other animal models and heart failure with reduced ejection fraction, but hypothesized to be applicable to heart failure with preserved ejection fraction.

Stage C – Manage Comorbidities and Symptoms

- Manage contributing factors and comorbidities:
  - Obesity
  - HTN (ACEI/ARB and BB)
  - AFib (BB or Non DHP CCB; anticoagulation)
  - CHD (BB or CCB)
  - DM
  - CKD
  - Pulm HTN (PDE-5 Inh)
  - OSA
  - COPD

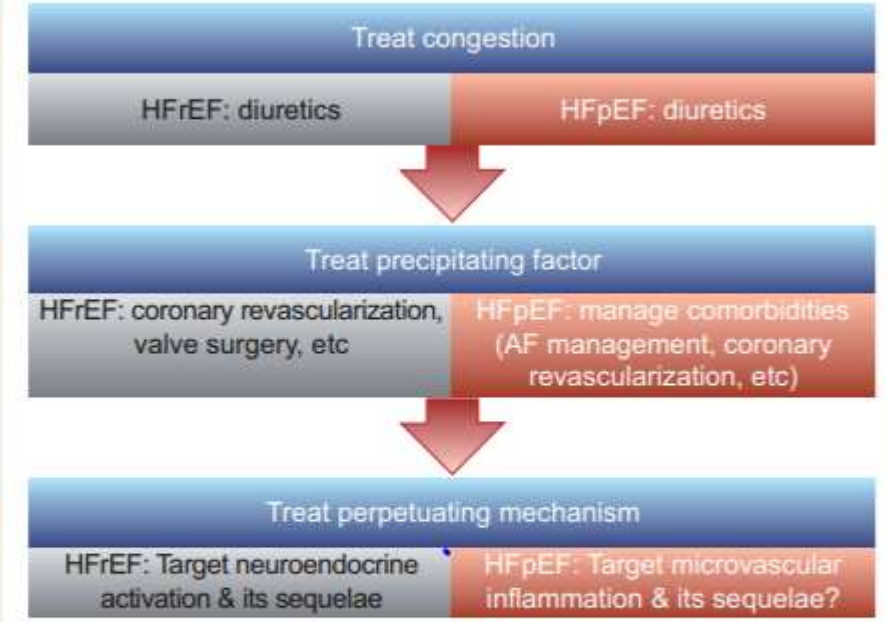


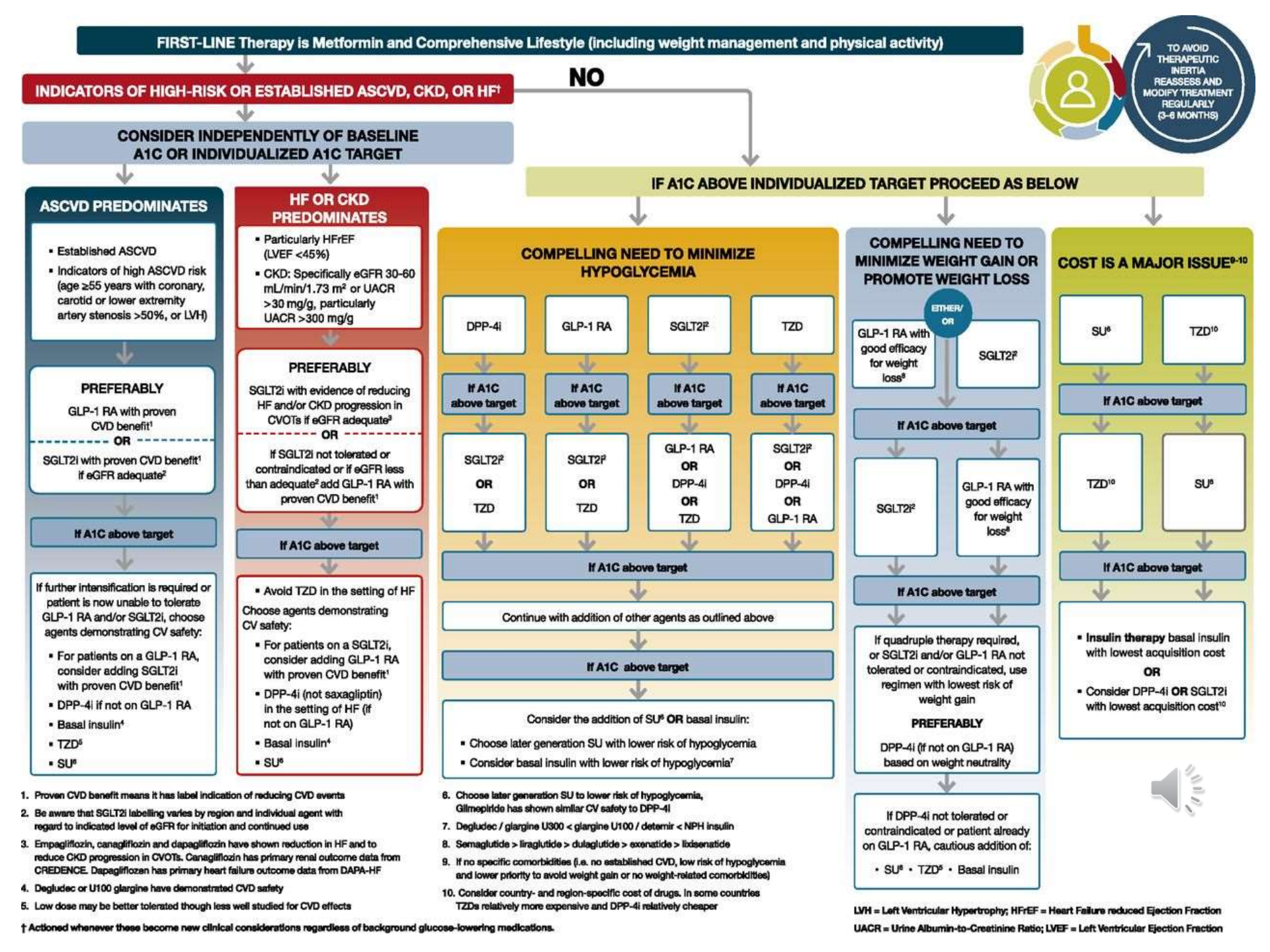
Figure 1 Principles of managing heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. AF, atrial fibrillation.

2017 Focused Update of the 2013 ACCF/AHA Guideline for Management of HF; Lam et al. Eur Heart Journal 2018;39:2780-2792.

Stage C: HFpEF Therapies

- Diuretics to manage volume overload
- SGLT-2 inhibitors to improve glycemic control in patients with DM and decrease risk for CV related death
  - EMPEROR Preserved (empagliflozin) results soon!
  - DELIVER (dapagliflozin) results late 2021
- Metformin for BS control unless contraindicated (severe renal or hepatic impairment)

2017 Focused Update of the 2013 ACCF/AHA Guideline for Management of HF; Kjeldsen et al. Hypertension 2020;75:23-32; Lam et al. Eur Heart Journal 2018;39:2780-2792. 2016 ESC Guideline for Acute and Chronic HF



1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozen has primary heart failure outcome data from DAPA-HF
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU to lower risk of hypoglycemia, Gilmepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

Stage C: HFpEF

- ARNI to reduce risk of CV related death and hospitalization due to HF
  - CHARM (candesartan) showed decrease hospitalization
- ARNI, ARB, or ACEI and BB for BP control in HTN
  - BB may be less effective
- Add AA to combo therapy for further BP lowering
- AA to decrease hospitalizations
  - EF > 45% with elevated BNP (or NT-proBNP) or HF hospitalization within 1 year and no contraindication for use (CrCl > 30 ml/min, Scr < 2.5 mg/dL, K+ < 5 mEq/L)

2017 Focused Update of the 2013 ACCF/AHA Guideline for Management of HF; Kjeldsen et al. Hypertension 2020;75:23-32; Lam et al. Eur Heart Journal 2018;39:2780-2792; 2016 ESC Guideline for Acute and Chronic HF

STAGE D
Refractory HF

Stage D –Advanced HF

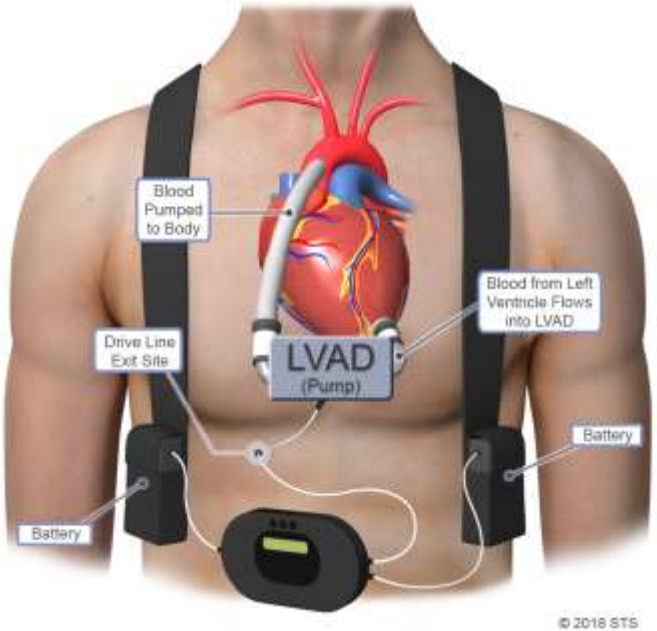
e.g., Patients with:
- Marked HF symptoms at rest
- Recurrent hospitalizations despite GDMT

THERAPY

Goals
- Control symptoms
- Improve HRQOL
- Reduce hospital readmissions
- Establish patient's end-of-life goals

Options
- Advanced care measures
- Heart transplant
- Chronic inotropes
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation

- Refractory HF:
  - Symptoms at rest
  - Recurrent hospitalizations despite max GDMT
- Therapies:
  - Ventricular assist devices
  - Heart transplant
  - Chronic inotropes
  - Palliation



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Congratulations!
You made it!

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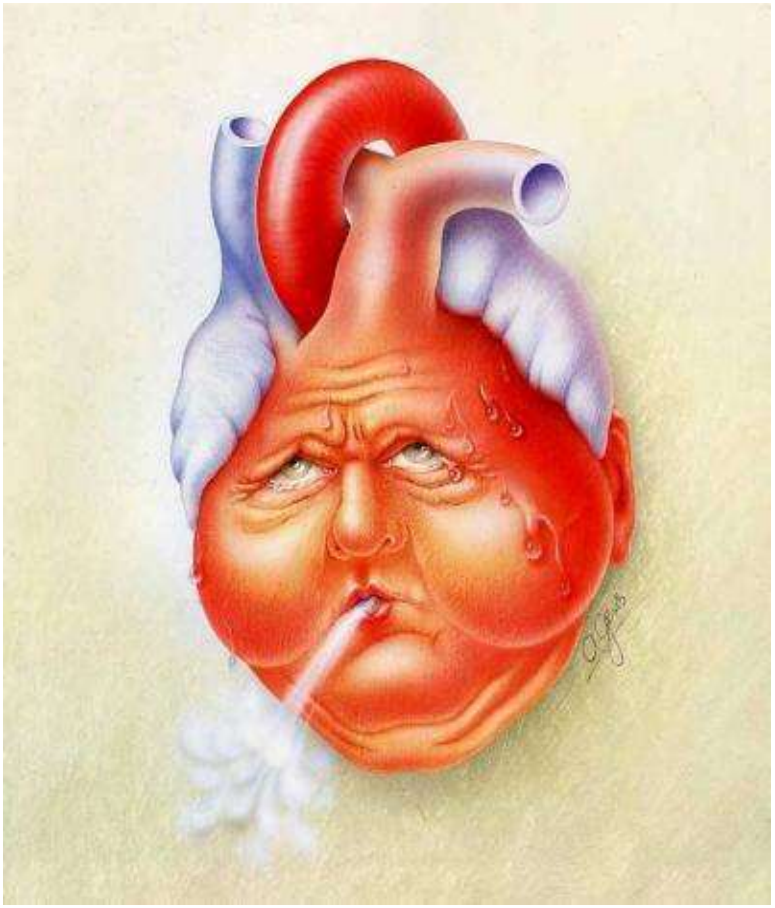
FYI: Device Therapy for HFrEF



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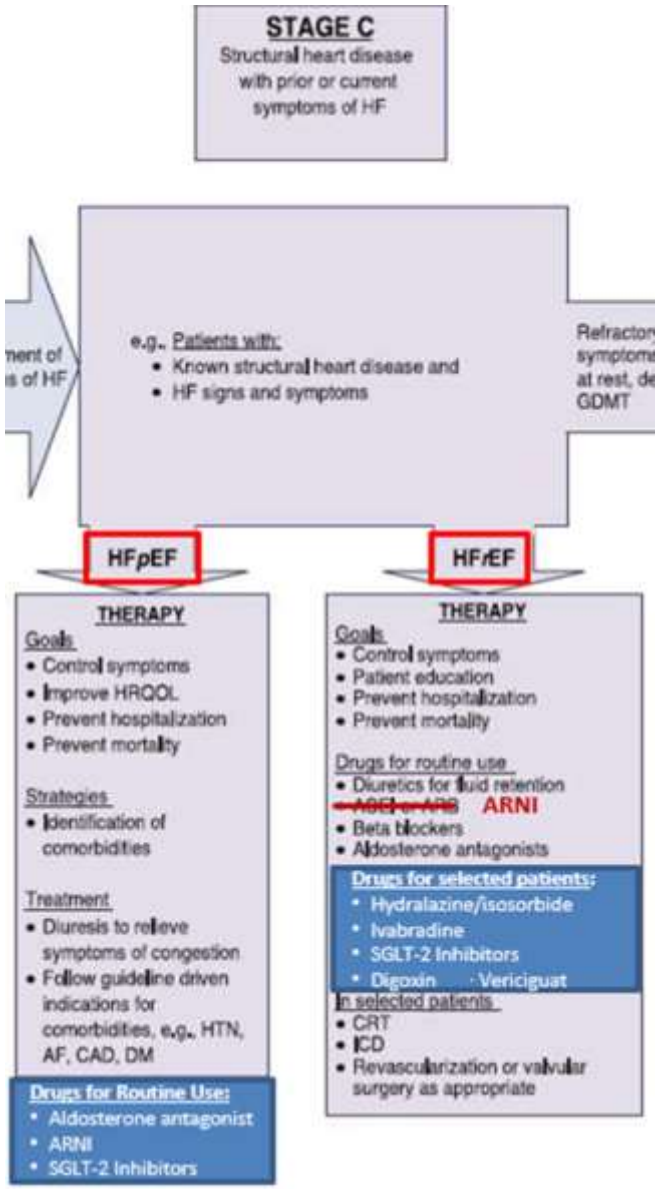
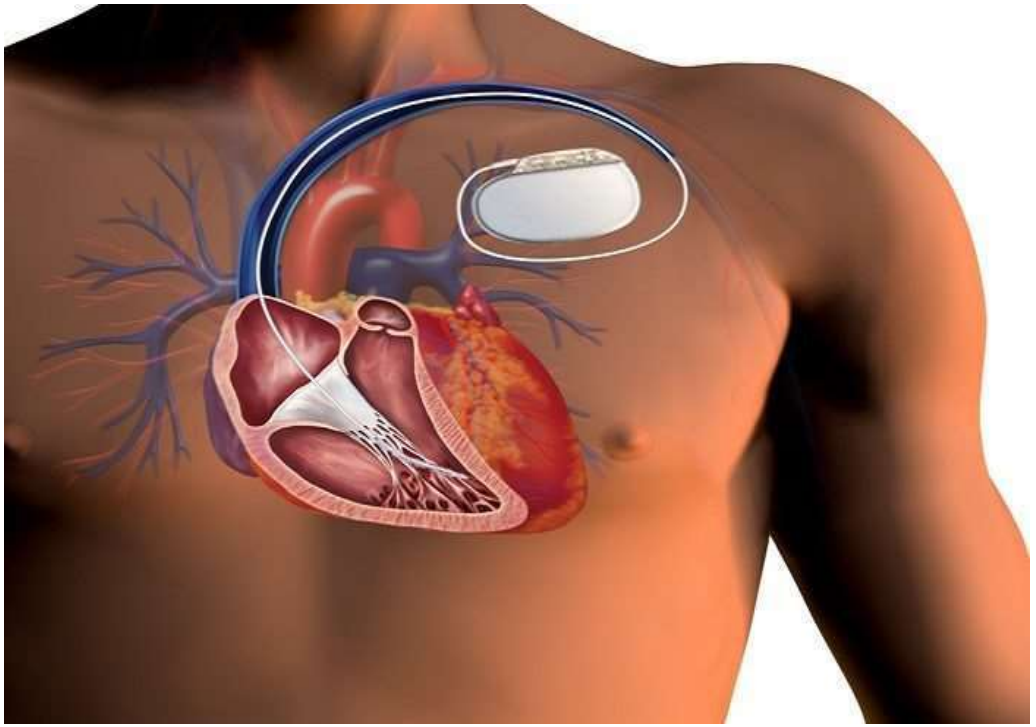
Stage C - Has HF*r*EF

- Diuretics
- SGLT-2 inhibitors
- ARNI
- Hydralazine/isosorbide
- Aldosterone Antagonists
- Ivabradine
- Digoxin
- Vericiguat
- **Device therapy- FYI**



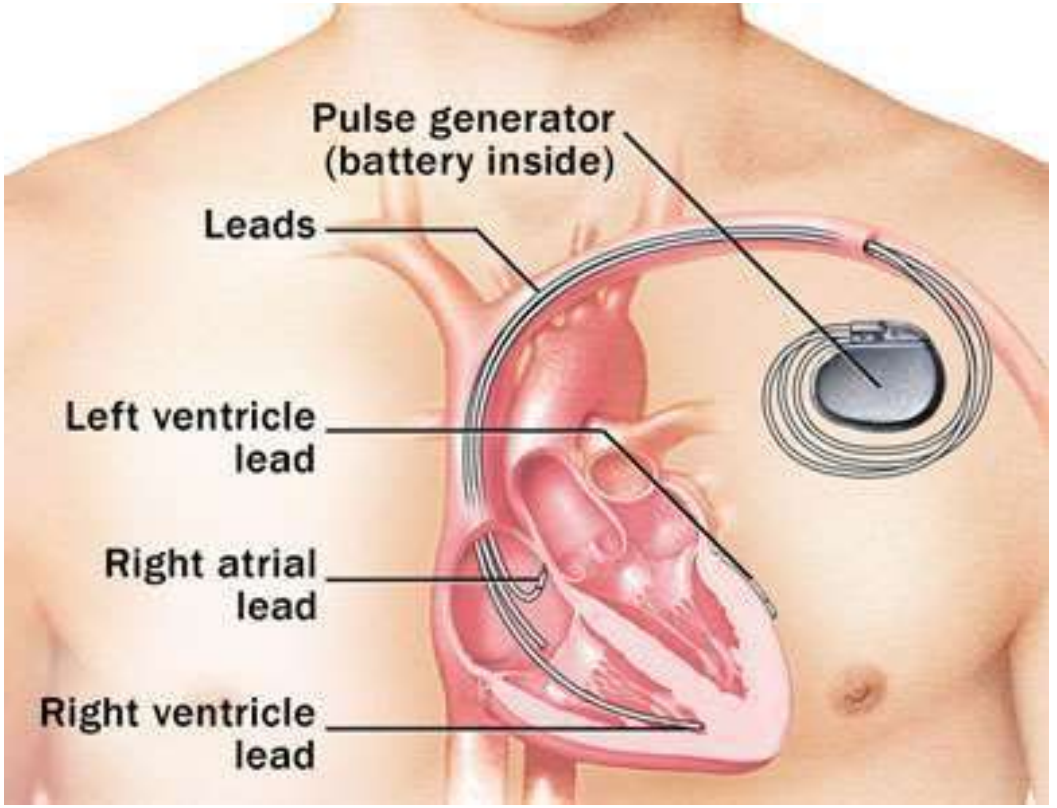
Device Therapy

- Implantable cardioverter defibrillators
  - Reduce mortality in cardiac arrest survivors, and are superior in HF compared to antiarrhythmic drugs



Device Therapy

- Cardiac resynchronization therapy (CRT)



Device Therapy: Indications

- Ischemic or non-ischemic cardiomyopathy
  - If ischemic, must wait > 40 days after AMI
- EF < 35%
- NYHA functional class II-III despite optimal medical therapy
- Reasonable expectation of survival with good functional status for > 1 year