# Updates in Heart Failure

**Emma Siegel, PharmD, BCACP**
**Tara Schreck, PharmD, BCACP**
*Clinical Pharmacists*
OhioHealth Advanced Heart and Vascular Clinic

Pharmacy Forward: Advancing Practice for a Healthier Tomorrow!

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OHIO PHARMACISTS ASSOCIATION

# Disclosure Statement

- Speaker(s) have no relevant financial relationship(s) with ineligible companies to disclose.
  *and*
- None of the planners for this activity have relevant financial relationships with ineligible companies to disclose.

# Learning Objectives

At the completion of this activity, the participant will be able to:

1. Recall the pillars of guideline-directed medical therapy (GDMT) in heart failure
2. Review emerging data regarding finerenone, digitoxin, cardiac amyloidosis, and intravenous iron
3. Explain how new data may change clinical practice

# Abbreviations SE1

- GDMT: guideline-directed medical therapy
- HFrEF: heart failure with reduced ejection fraction
- LVEF/EF: left ventricular ejection fraction
- HF: heart failure
- ARNI: angiotensin receptor blocker/neprilysin inhibitor
- ACEi: angiotensin converting enzyme inhibitor
- ARB: angiotensin receptor blocker
- MRA: mineralocorticoid antagonist
- SGLT2i: sodium glucose cotransporter 2 inhibitor
- NYHA: New York Heart Association
- T2DM: Type 2 diabetes
- CKD: chronic kidney disease
- HLD: hyperlipidemia
- HTN: hypertension
- SQ: subcutaneous
- PO: by mouth
- EGFR: estimated glomerular filtration rate
- BMP: basic metabolic panel
- WNL: within normal limits
- BP: blood pressure
- HR: heart rate
- HFpEF: heart failure with preserved ejection fraction
- ECHO: echocardiogram
- cMRI: cardiac magnetic resonance imaging
- GI: gastrointestinal
- LV: left ventricle
- CAD: coronary artery disease
- AF: atrial fibrillation
- OSA: obstructive sleep apnea
- HFmrEF: heart failure with mildly reduced ejection fraction
- RCT: randomized controlled trial
- BB: beta blocker
- RAASi: renin-angiotensin-aldosterone system inhibitor
- NsMRA: non-steroidal mineralocorticoid receptor antagonist
- MR: mineralocorticoid receptor
- KCCQ: Kansas City Cardiomyopathy Questionnaire
- DOE: dyspnea on exertion
- ID: iron deficiency
- QOL: quality of life
- TSAT: transferrin saturation
- FCM: ferric carboxymaltose
- 6MWD: six minute walk distance
- CABG: coronary artery bypass graft
- AVR: aortic valve replacement
- ATTR: transthyretin amyloidosis
- hATTR: hereditary transthyretin amyloidosis
- wATTR: wild-type transthyretin amyloidosis
- AL: light chain amyloidosis
- EKG: electrocardiogram

## Slide 4

**SE1** Add at end once all slides completed

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# HFrEF

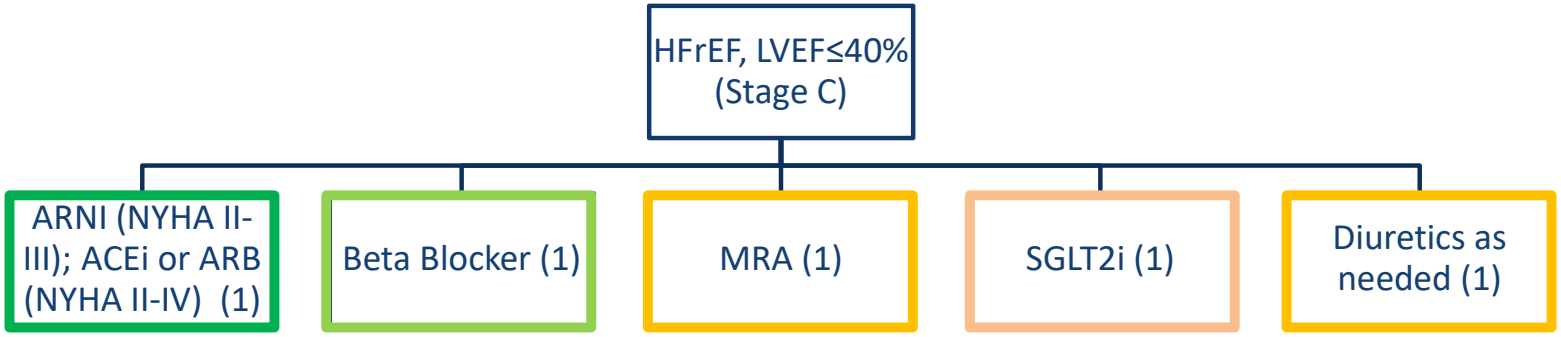
# What is HFrEF?

- Heart failure with **reduced** ejection fraction
- LVEF ≤40% + progressive left ventricular dilatation and adverse cardiac remodeling
  - EF important in classification of patients with HF d/t various patient demographics, comorbidities, prognosis and pharmacotherapy response
- Result from disorders of the pericardium, myocardium, endocardium, heart valves, great vessels or certain metabolic abnormalities
- HF: global pandemic (64 million people worldwide)
  - Increase in prevalence (46%) from 2012 to 2030 --> increase in healthcare costs by 127%
  - HFrEF: 50% of HF population

# HFrEF GDMT

ST2

- Quadruple therapy highly recommended to improve survival
- Rapid initiation – all four classes of medications initiated within 1-4 weeks
- In-hospital start/prior to discharge has been proven to be safe and effective
- Goal optimization – maximally tolerated doses within 3-6 months




**Slide 7**

**ST1** 73% reduction - ACC 2022 guidelines
Schreck, Tara E, 2026-02-09T02:14:17.585

**ST2** 4X4 approach
Schreck, Tara E, 2026-02-09T02:18:05.009

# Emerging Evidence: Digitoxin in HFrEF

# Emerging Evidence: Digitoxin

- Cardiac glycosides can be considered one of the oldest classes of medication in cardiovascular care
- Early studies demonstrated their positive impact on morbidity (ie, exercise capacity, quality of life)
- In 1997, digoxin received FDA approval for use in heart failure
- Digitoxin: related but distinct cardiac glycoside recently studied in the randomized controlled trial, DIGIT (DIGIT-HF)

# Digoxin vs Digitoxin

- **Digoxin**
  - Cardiac glycoside inhibits Na-K-ATPase
  - Excretion: kidney
  - Vd: 6.3L/kg - medium lipid solubility, 20-40% protein bound
  - Bioavailability: 70-85%
  - Half-life: 40h; 5-7 days to reach steady state
  - Dosed 0.125-0.25mg daily
  - Levels (0.5-0.9ng/mL)
- **Digitoxin**
  - Cardiac glycoside inhibits Na-K-ATPase
  - Excretion: liver
  - Vd: 0.6L/kg - highly lipophilic, >90% protein bound
  - Bioavailability: 95-100%
  - Half-life: 7 days; 35 days to reach steady state w/o loading dose
  - Dosed 0.05-0.1mg daily
  - Levels (10.5-23.6nmol/L)

ST2

# Digoxin vs Digitoxin

- **DIG Trial (1997)**
  - Enrolled 6800 patients with LVEF≤45% in NSR
  - Mean age (65), predominantly white men
  - NYHA FC I-II (majority) or III-IV
  - GDMT: ACEi (95%) + diuretics (80%)
  - Beta blocker use was minimal

ST1

- **DIGIT-HF Trial (2025)**
  - Enrolled 1212 patients with NYHA II LVEF≤30% or NYHA III-IV LVEF≤40%
  - Mean age (67), women (23%)
  - NYHA FC II (70%), FC III (29%)
  - GDMT: RAASi, BB, MRA, SGLT2i, cardiac devices

**Slide 11**

**ST1** DIGIT - 11% ARNI; 84% ACEi or ARB
Schreck, Tara E, 2026-02-13T13:39:09.278

**ST1 0** 44% had ICD
Schreck, Tara E, 2026-02-13T13:39:33.466

**ST2** DIGIT-HF - European study (ethnic background poorly described)

Women: 22% DIG + 23% DIGIT-HF
Sex differences should be interpreted cautiously
Schreck, Tara E, 2026-02-13T13:44:58.420

# DIGIT-HF Trial Results

ST1

- Primary composite outcome of death or first heart failure hospitalization: **18% reduction** (HR 0.82, 95% CI 0.69-0.98, p=0.03)
- Number needed to treat to prevent one primary outcome event was 22 patients
- Impact on all-cause mortality: favorable trend, not statistically significant (27.2% digitoxin; 29.5% placebo)
- First hospitalization for worsening heart failure: leaning toward uniform consistent benefit, not statistically significant (28.1% digitoxin; 30.4% placebo)
- DIG trial showed no mortality benefit but did demonstrate significant reduction in HF hospitalization (26.8% vs 34.7%, P<0.001)

**ST1** Primary composite endpoint occurred in 39.5% of digitoxin patients versus 44.1% of placebo patients (12.8 vs 15.7 events per 100 patient-years)

Schreck, Tara E, 2026-02-13T13:52:28.186

# DIGIT-HF Trial Results

- Low serum drug concentration appears to be important in both trials
  - DIG – mortality benefit (0.5-0.9ng/mL); harmful (≥1ng/mL)
  - DIGIT – authors theorized lower concentrations may have been associated with fewer deaths than placebo
- Serous adverse events: 4.7% (digitoxin) vs 2.8% (placebo) with consistency across subgroups
- Key distinctions: drug studied, background/GDMT therapy, pharmacokinetic differences

# Patient Case: Digitoxin

TS is a 75 YOF with a PMH of T2DM, CKD, HLD, HFrEF (EF 30%), and HTN. NYHA III, c/o ankle swelling, occasional cough and dyspnea especially with exertion.

Current medications:

- Insulin glargine 30 units SQ daily
- Entresto 49-51mg PO twice daily
- Empagliflozin 10 mg PO daily
- Spironolactone 12.5mg daily
- Bumetanide 2mg PO twice daily
- Metoprolol XL 200 mg daily

**Would you feel comfortable using digitoxin in this patient?**

Relevant Labs: K+ 4.6 mEQ/L; eGFR 40mL/min/1.73m$^2$; remainder of BMP WNL

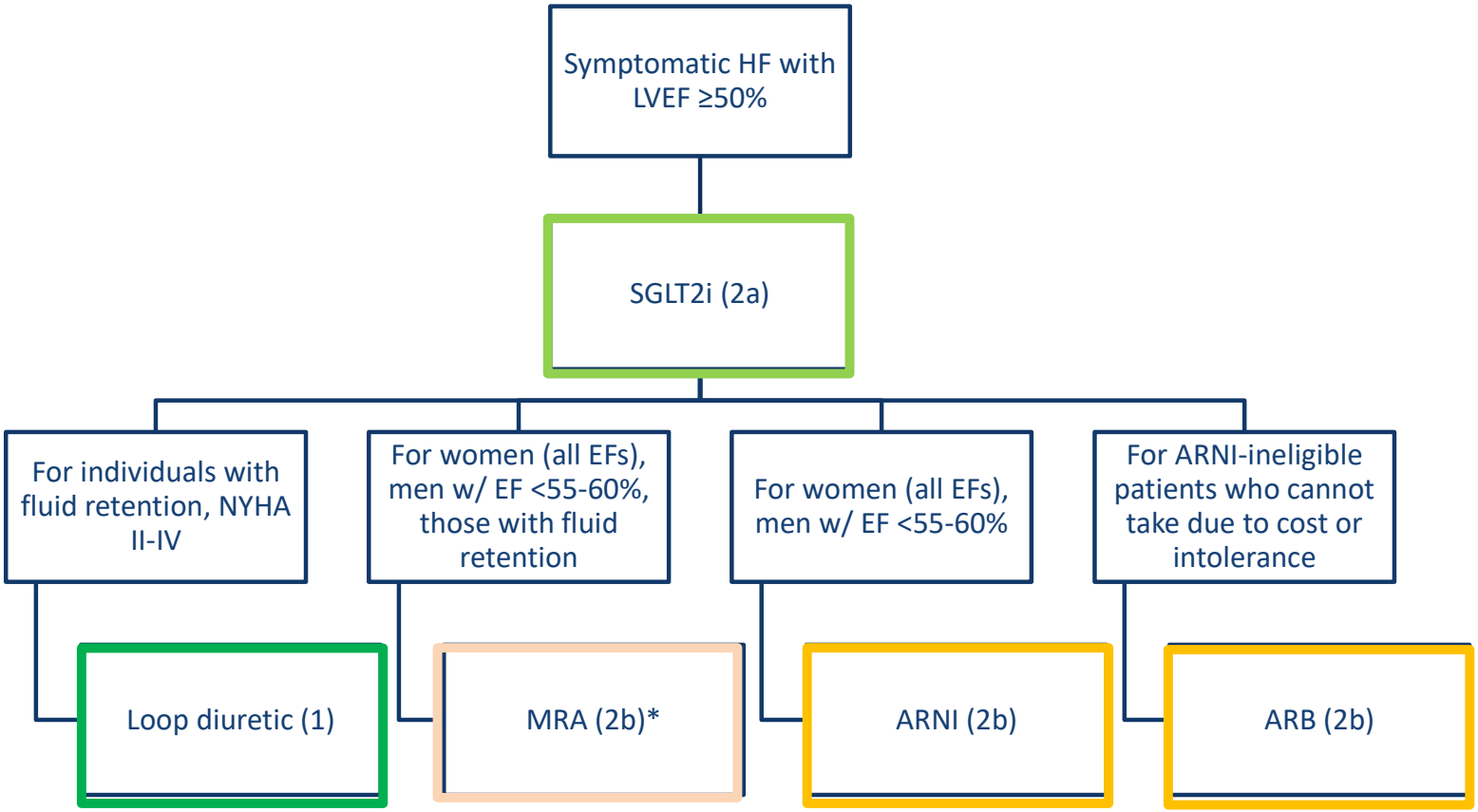
Vitals: BP (100/72); HR (85)

# HFpEF/HFmrEF

# What is HFpEF?

- Heart failure with **preserved** ejection fraction
  - ~~"Diastolic heart failure"~~
- LVEF ≥50% + evidence of spontaneous or provokable increased LV filling pressures
- Contributing comorbidities: HTN, DM, obesity, CAD, CKD, atrial fibrillation, cardiac amyloidosis
- 50% of HF population
  - 1/10 patients by age 45
  - One-year mortality of 20-29%
  - 30d all-cause readmission rate of 21%

# HFpEF GDMT


Symptomatic HF with LVEF ≥50%
SGLT2i (2a)
For individuals with fluid retention, NYHA II-IV
For women (all EFs), men w/ EF <55-60%, those with fluid retention
For women (all EFs), men w/ EF <55-60%
For ARNI-ineligible patients who cannot take due to cost or intolerance
Loop diuretic (1)
MRA (2b)*
ARNI (2b)
ARB (2b)

# Other HFpEF Recommendations

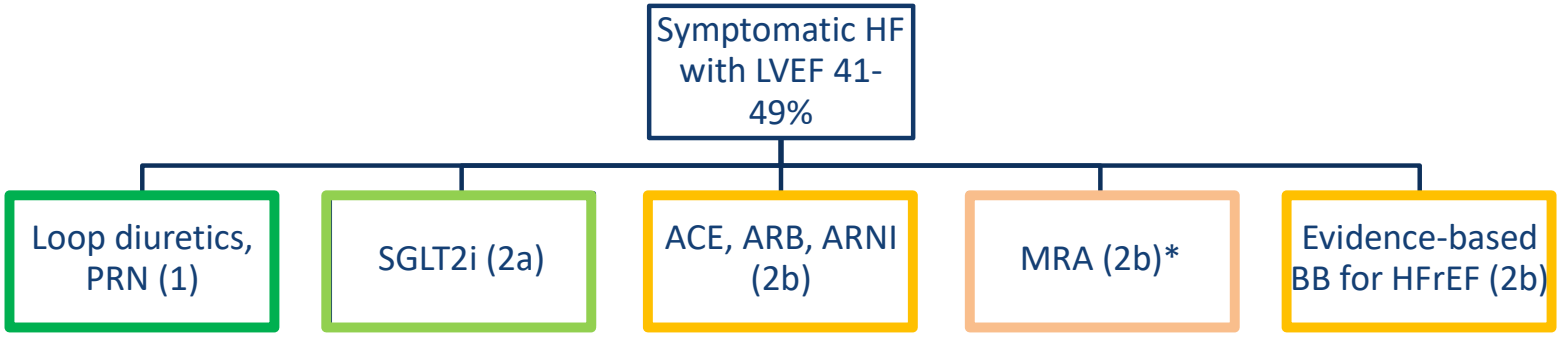
- Treat HTN (1)
- Manage AF (2a)
- Other comorbidity management remains important:
  - CAD
  - OSA
  - Obesity...*incretin mimetic therapies?*
  - T2DM
  - CKD

# What is HFmrEF?

- LVEF between 41-49%
- Usually in a dynamic trajectory to improvement from HFrEF or to deterioration to HFrEF

# HFmrEF GDMT

- No prospective RCTs for HFmrEF
  - Several HFpEF / HFrEF studies included EFs between 41-49%: data obtained via post hoc and subset analyses
- Patients with EF on lower end of spectrum tend to respond better to HFrEF GDMT




# Emerging Evidence: Finerenone in HFrEF/HFmrEF

# Emerging Evidence: Finerenone

- **Finerenone**: non-steroidal mineralocorticoid receptor antagonist (nsMRA)
- **MOA**: antagonizes effects of aldosterone by **selectively** blocking mineralocorticoid receptor-mediated sodium reabsorption and overactivation in both epithelial and non-epithelial tissues
- **Benefits in HF**: reduces myocardial and vascular fibrosis and inflammation / volume retention

# Finerenone Characteristics

| Characteristic | Spironolactone | Eplerenone | Finerenone |
|---|---|---|---|
| MR Class/Structure | Steroidal, non-selective | Steroidal, selective | Non-steroidal |
| Metabolites | Multiple, active | No active | No active |
| Half-life | 13-16h | 3-6h | 2-3h |
| Tissue distribution | Kidney >> heart | Kidney > heart | Heart = kidneys |
| Receptor selectivity | + | ++ | +++ |
| Potency of antagonism of MR | +++ | + | +++ |

# Finerenone: Data in HFpEF

**FINEARTS-HF:** finerenone vs placebo (n = 6001)

- Patient population: EF ≥40%, age ≥40, symptomatic HF
- Primary outcome: composite of total worsening HF events and death from CV causes (RR 0.84, p = 0.007)
  - Driven by reduction in worsening HF events
- Relevant secondary outcomes:
  - Improvement in KCCQ (+1.6; p < 0.001); however, no associated with improvement in NYHA functional class
  - No statistically significant increased risk of worsening kidney function with nsMRA
  - Similar rates of serious adverse events, but higher rates of hyperkalemia and Scr increase

**TOPCAT:** spironolactone vs placebo – controversial trial that did NOT meet statistical significance for primary endpoint in similar patient population

# Finerenone: Additional Data

- **FIDELIO-DKD**: finerenone vs placebo in patients with CKD + T2DM
  - Lower risk of CKD progression and CV events
  - Incidence of hyperkalemia-related discontinuation = 2.3%
- **FIGARO-DKD**: finerenone vs placebo in patients with CKD + T2DM
  - Improved CV outcomes (composite of death from CV causes, nonfatal MI/stroke, or HFH)
  - Incidence of hyperkalemia-related discontinuation = 1.2%
- **ARTS and ARTS-HF**: finerenone led to less (spironolactone) or similar (eplerenone) rates of hyperkalemia
- Ongoing trials: role in HFrEF unclear
  - REDEFINE-HF: EF ≥40% and recent heart failure hospitalization
  - CONFIRMATION-HF: any EF and recent heart failure hospitalization (w/ SGLT2i)
  - FINALITY-HF: EF <40% and ineligible or intolerant of sMRA

# MRAs in HFpEF/HFmrEF: Guideline Updates

| Heart Failure Type | ESC (2021) | ACC/AHA/HFSA (2022) | JCS/JHFS (2025) |
|---|---|---|---|
| Preserved EF | No recommendation | 2b | 2a nsMRA<br>2b sMRA |

| Heart Failure Type | ESC (2021) | ACC/AHA/HFSA (2022) | JCS/JHFS (2025) |
|---|---|---|---|
| Mildly Reduced EF | 2b | 2b | 2a nsMRA<br>2b sMRA |

# Dosing, Side Effects, and Monitoring

- Dosing:
  - Do NOT initiate if eGFR <25 mL/min/1.73m$^2$ or if serum potassium >5 mEq/L
  - Initial dose determined by eGFR (10 or 20 mg daily)
  - Maintenance dose determined by eGFR and K+ (10, 20, or 40 mg daily)
- No known off-target ADE (gynecomastia, menstrual irregularities, etc)
- Monitoring: renal function, K+, volume status
  - If serum potassium cannot be maintained <5.5 mEq/L, consider discontinuation
  - If serum creatinine increases >30%, consider dose reduction or discontinuation

# Patient Case: HFpEF

EC is a 79 YOF with a PMH of T2DM, CKD, obesity, HFpEF (EF 55%), atrial fibrillation, and nicotine use. NYHA III, c/o DOE, orthopnea.

Current medications:

- Insulin glargine 25 units QHS
- Tirzepatide 15 mg SQ weekly
- Empagliflozin 10 mg daily
- Torsemide 100 mg BID
- Metoprolol XL 50 mg daily

**Would you feel comfortable using finerenone in this patient?**

Relevant Labs: K+ 4.6 mEQ/L; eGFR 46 mL/min/1.73m$^2$; remainder of BMP WNL

# Hot Topic: Iron Deficiency in Heart Failure

# Iron Deficiency in HF

- Iron deficiency (ID) occurs in 40-70% of patients with HF (+/- anemia)
  - Several theories: dietary deficiencies, impaired iron absorption due to gut edema, increased blood loss in setting of AC/AP
  - Chronic inflammation: upregulation of hepcidin – limits GI absorption and release of iron stores
- Effects of ID:
  - Reduced exercise capacity/worse QOL
  - HF hospitalizations
  - Increased cardiovascular and all-cause mortality
- Diagnosis: DIFFERS from other conditions (inflammation)
  - Ferritin <100 ng/mL, **OR** ferritin 100-299 ng/mL + TSAT >20%

# ID in HF: Clinical Trials

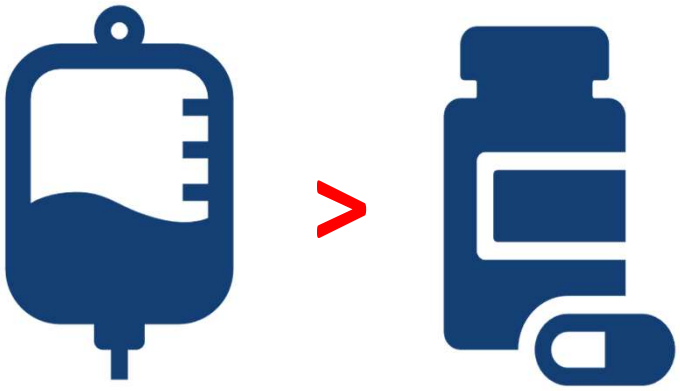
**LOTS** of clinical trials:

1. **FAIR-HF** (2009): ferric carboxymaltose (FCM) vs placebo in HFrEF
   - Improved sx/functional class
2. **CONFIRM-HF** (2015): FCM vs placebo in HFrEF
   - Improved 6MWD, reduced rate of HF hospitalizations
3. **AFFIRM-AHF** (2020): FCM vs placebo in acute HF (EF <50%)
   - Reduction in HFH, BUT no mortality benefit
4. **IRONOUT-HF** (2017): PO iron vs placebo in HFrEF
   - No benefit

# ID in HF: Clinical Trials

**BOTTOM LINE**:

- IV > oral (efficacy, tolerability)
- Better evidence in HFrEF > HFpEF
- Most evidence w/ FCM
- Mostly shown to improve QOL/exercise capacity
- *Some* data on decreased HFH
- Limited data on mortality

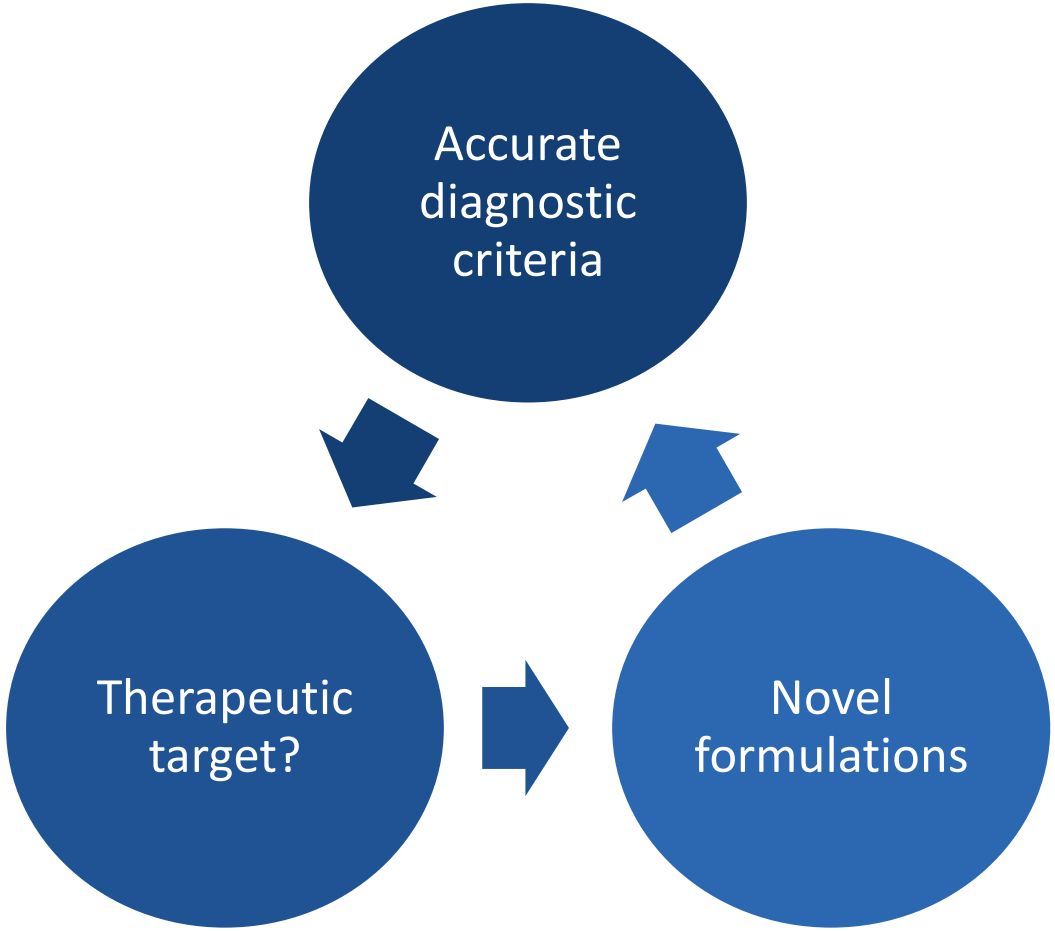


**Caution**: excess iron can endothelial cell damage, infection, and hypophosphatemia

# Intravenous Iron: Guideline Recommendations

| Association | Recommendation | Class/LOE |
|---|---|---|
| ESC (2021; updated 2023) | IV iron supplementation is recommended in symptomatic patients with **HFrEF and HFmrEF** and ID to **alleviate HF symptoms and improve QOL**. | IA |
| | IV iron supplementation with **FCM** or ferric derisomaltose should be considered in symptomatic patients with HFrEF and HFmrEF and iron deficiency to **reduce the risk of HF hospitalization**. | 2A/A |
| AHA/ACC/HFSA (2022) | In patients with **HFrEF** and ID with or without anemia, **IV iron** replacement is reasonable to improve functional status and QOL. | 2A/B-R |

# Areas of Additional Research



# FCM Dosing in HF

**Table 1:Recommended Dosage in Patients with Iron Deficiency with Heart Failure**

| | Weight less than 70 kg | | | Weight 70 kg or more | | |
|---|---|---|---|---|---|---|
| | Hb (g/dL) | | | Hb (g/dL) | | |
| | < 10 | 10 to 14 | > 14 to < 15 | < 10 | 10 to 14 | > 14 to < 15 |
| Day 1 | 1,000 mg | 1,000 mg | 500 mg | 1,000 mg | 1,000 mg | 500 mg |
| Week 6 | 500 mg | No dose | No dose | 1,000 mg | 500 mg | No dose |

Administer a maintenance dose of 500 mg at 12, 24 and 36 weeks if serum ferritin <100 ng/mL or serum ferritin 100-300 ng/mL with transferrin saturation <20%. There are no data available to guide dosing beyond 36 weeks or with Hb ≥15 g/dL.

# Patient Case: IV iron

PS is a 68 YOM weighing 73.4 kg with a PMH of CABG (2009), AVR (2015), nicotine use, and HFrEF (EF 39%). C/o worsening SOB and DOE with limited activity. PS's physician decides to draw iron levels and a CBC:

Relevant results:

- Iron: 64 mcg/dL
- TIBC 340 mcg/dL
- Iron saturation: 19%
- Ferritin: 29 ng/mL
- Hgb 9.9 g/dL; HCT 31.2%

**Is PS a good candidate for IV iron?**

**Which iron product/dose would you recommend?**

# Hot Topic: Cardiac Amyloidosis

# Cardiac Amyloidosis

- Underdiagnosed, particularly in HFpEF population
- Progressive disease associated with poor prognosis if left untreated
- Characterized by build-up of abnormal deposits of amyloid fibrils
  - Misfolded proteins --> buildup in organ(s), tissues --> organ failure
- TTR (transthyretin)
  - Protein produced in the liver
  - Transports thyroxine and vitamin A throughout the body
  - Supports memory, neuroprotection, cognitive function

# General Disease Review

| | |
|---|---|
| Two Types of Amyloid that affect the Heart | Light chain amyloidosis (AL)<br>Transthyretin amyloidosis (ATTR) |
| Two Subtypes of Transthyretin Amyloid Cardiomyopathy (ATTR-CM) | Hereditary or Variant (hATTR)<br>Wild-type (wATTR) |

# Non-Cardiac Red Flags

- Orthostatic hypotension
- Neuropathy (peripheral, autonomic)
- Nephrotic syndrome
- Bilateral carpel tunnel sydrome
- Lumbar spinal stenosis
- Biceps tendon rupture
- Ocular/vitreous rupture
- GI – chronic diarrhea alternating with constipation

# Cardiac Red Flags

- HFpEF
- AFib/embolic stroke
- Hypertrophic cardiomyopathy
- Low-flow, low gradient aortic stenosis
- Pacemaker/heart block
- Angina with normal cors
- EKG findings
- Intolerance to standard heart failure medications (ie, RAASi, BB)

# Workup Process

## Imaging

EKG

with strain

cMRI

## AL

Immunofixation labs

Bone marrow biopsy, fat pad aspirate, or organ biopsy

## ATTR

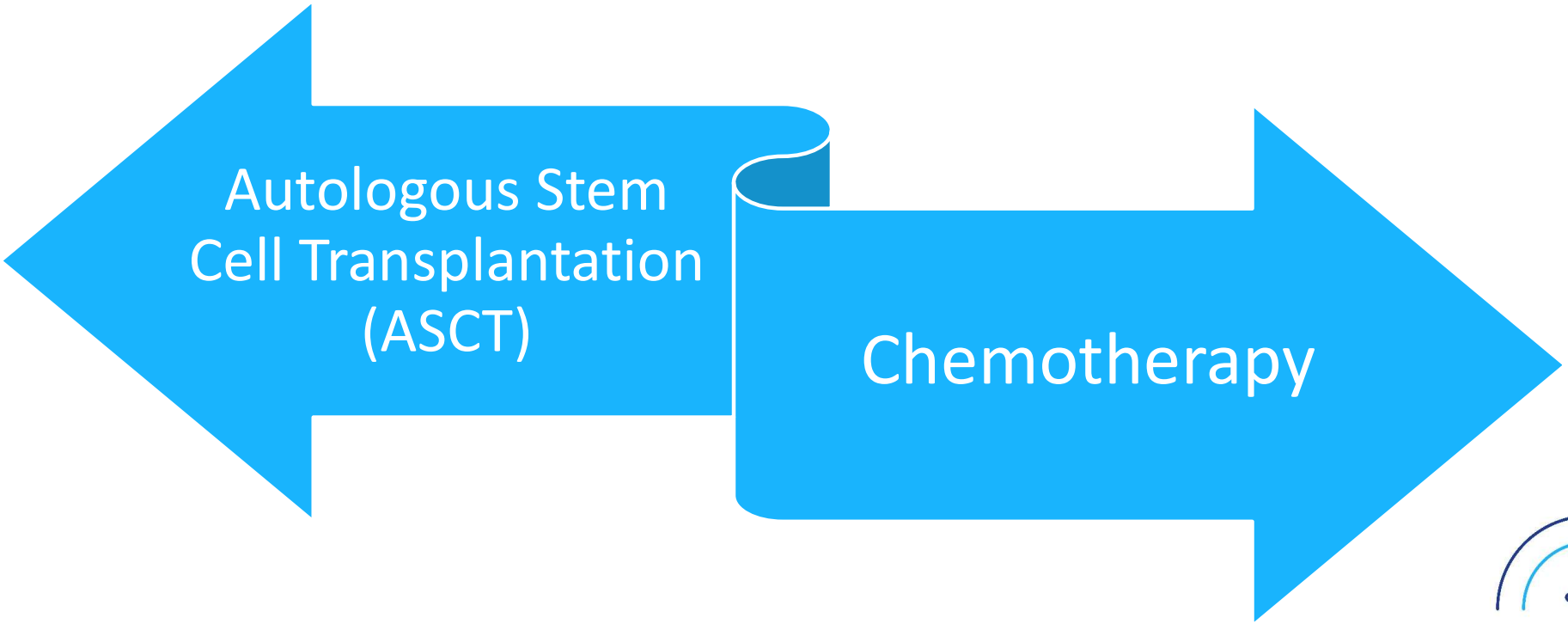
Techetium pyrophosphate (PYP) scan

- Grade 2/3

Genetic testing

- Wild-type ATTR (wATTR)
- Variant ATTR (vATTR)

# AL Treatment Path



# ATTR-CM Treatment Paradigm

## Liver

- Suppression of amylogenic TTR
- TTR Silencing

## TTR Tetramer

- Misfolded state
- TTR Stablization

## Amyloid Fibril

- Diastolic dysfunction
- Fibril degradation

# FDA Approved Rx

| Drug | MOA | Indication | Route | Dose | ADE |
|---|---|---|---|---|---|
| Tafamidis | TTR Stabilizer | ATTRw, ATTRv | Oral | 61mg Once Daily | Diarrhea |
| Acoramidis | TTR Stabilizer | ATTRw, ATTRv | Oral | 712mg Twice Daily | Diarrhea, abdominal pain |
| Vutrisiran | TTR Silencer | ATTR-CM ATTR-PN | SubQ | 25mg Every 3 Months | Pain in extremity, arthralgia, dyspena, low vitamin A levels |

# Non-FDA Approved Rx for ATTR-CM

| Drug | MOA | Indication | Route | Dose | ADE |
|---|---|---|---|---|---|
| Patisiran | siRNA | Polyneuropathy of hATTR (ATTR-PN) | IV | 0.3mg/kg <100kg; 30mg set dose ≥100kg | Infusion-related reactions (IRR), URI, dyspepsia, low vitamin A levels<br>- Premedication required |
| Inotersen | ASO | Polyneuropathy of hATTR (ATTR-PN) | SubQ | 284mg Once Weekly | Thrombocytopenia (BBW), glomerulonephritis (BBW), stroke, cervicocephalic arterial dissection, inflammatory and immune effects, liver dysfunction, low vitamin A levels |
| Eplontersen | ASO | Polyneuropathy of hATTR (ATTR-PN) | SubQ | 45mg Once Monthly | Nausea, low vitamin A levels, thrombocytopenia (mild) |

# Additional Therapy
## Non-FDA approved + Limited Evidence!

| | |
|---|---|
| Fibril Disrupter | • Doxycycline + TUDCA (tauroursodeoxycholic acid) |
| Stabilizer | • Diflunisal |
| Alternative therapies | • Green tea extract (EGCG)<br>• Curcumin |

EGCG = epigallocatechin gallate

# Treatment Selection: ATTR-CM

- Initial Rx: tafamidis, acoramidis, or vutrisiran
  - Patient preference
  - Payor
  - Access/affordability
- Dual therapy (ATTR silencer + ATTR stabilizer) - insufficient data
- Change in therapy with disease progression – insufficient data

# ATTR-CM Future Treatment

Single dose therapy repairs specific point of target DNA through utilization of guide RNA

**TTR Silencer – CRISPR Cas9**

Designed to target and remove ATTR deposits

**Fibril Degradation - Monoclonal Antibody (mAbs)**

**Seeding Inhibitors**

Emerging treatment that inhibit amyloid aggregation by blocking amyloid seeds

# Multidisciplinary Care

- Complex, systemic disease with multi-organ involvement
- Challenging condition to diagnose and treat
- Symptoms can be nonspecific
- Disease progression can lead to multiple complications and poor prognosis
- Multidisciplinary care is vital for delivery of effective treatment
  - Timely accurate diagnosis
  - Appropriate Rx for underlying disease and complications
  - Close monitoring including medication tolerance and disease response
  - Supportive therapy
  - Navigation of barriers – access to care, cost

# Future Direction

| | | |
|---|---|---|
| Initial therapy | Combination therapy | Heart failure management |
| Disease progression assessment | Disease prevention | Access to care |

# Patient Case: Cardiac Amyloidosis

BD is a 88 YOM a PMH of HFpEF, (EF: 67%), AFib, HTN, HLD, T2DM, CVA and neuropathy. He is a newly referred patient to the advanced heart failure clinic for cardiac amyloidosis work-up.

**Is BD a good candidate for tafamidis 61mg PO Qday?**

Relevant results:

- Immunofixation labs: unremarkable
- Immunoglobulin labs: unremarkable
- PYP scan: Grade 3 (highly suggestive of cardiac amyloidosis)
- Genetic testing: no indication for genetic predisposition; wATTR-CM

**What is another treatment option?**

# Assessment Question #1

Which of the following is a Class 1 recommendation in HFrEF and a Class 2A recommendation in HFpEF?

A. Metoprolol XL
B. Sacubitril/Valsartan
C. Empagliflozin
D. Finerenone

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**C. Empagliflozin**
D. Finerenone

# Assessment Question #2

Which of the following is a common side effect of finerenone?

A. Gynecomastia
B. Hyperkalemia
C. Weight gain
D. Hypotension

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# Assessment Question #3

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A. TTR stabilization
B. Anticoagulation
C. Fibril degradation
D. TTR silencing

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# References SE1


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## Slide 59

**SE1** Organize once all slides done

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# Need More Information?

Emma Siegel, PharmD, BCACP
*Emma.siegel2@ohiohealth.com*

Tara Schreck, PharmD, BCACP
*Tara.schreck@ohiohealth.com*

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