HFpEF: When Heart Failure Reveals Kidney Disease—A Cardiorenal Paradigm

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March 2026

Heart Failure with Preserved EF: A Renal Disease Masquerading as Cardiac Disease

Learning Objectives

By the end of this session, you should be able to: 1. Recognize HFpEF as potentially a renal disorder 2. Understand why HFpEF is more common and more challenging than HFrEF 3. Identify the CKD-dominant phenotype at highest risk 4. Apply albuminuria-centric risk stratification 5. Implement evidence-based therapy prioritizing kidney protection 6. Communicate cardiorenal risk to patients using heat maps and risk tools

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The Paradigm Shift: HFpEF as Kidney Disease

Traditional View (WRONG)

"Patient has heart failure ☐ their ejection fraction is preserved ☐ it's a purely cardiac problem"

Modern View (RIGHT)

"Patient has HFpEF ☐ they likely have an underlying **renal disorder** producing both cardiac manifestations and kidney dysfunction"

The Evidence

Temporal relationship: - Kidney dysfunction **precedes** HFpEF development (not the reverse) - Prospective registry data: Abnormal kidney function predicts HFpEF but NOT HFrEF

Reversibility: - HFpEF can be **reversed by kidney transplantation** despite continued hypertension - This wouldn't happen if primary problem were cardiac

Kidney tubular dysfunction: - Biomarkers of renal tubular injury (NAG, NGAL, KIM-1) predict HFpEF better than GFR alone - Many HFpEF patients have abnormal tubular function despite preserved eGFR

Mineralocorticoid activation: - HFpEF patients show **lower urine sodium-to-potassium ratio** than HFrEF - Indicates higher mineralocorticoid receptor (MR) activation in distal kidney tubules - MR overactivation likely drives both cardiac and renal dysfunction

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Epidemiology: Why HFpEF Is Important

The Growing Problem

- **50%+ of heart failure cases** now present with preserved EF (HFpEF)
- More common in:
  - Older adults (age >70)
  - Women
  - Hypertension
  - Obesity
  - Chronic kidney disease

Why HFrEF Gets More Attention (But Shouldn't)

- HFrEF: Well-established therapies, proven mortality benefits (GDMT)
- HFpEF: Until recently, NO proven therapies for symptom improvement or mortality reduction
- Result: HFrEF heavily studied, HFpEF neglected

The Clinical Reality

HFpEF patients often suffer MORE: - **Worse quality of life** (more dyspnea, more limitations) - **Higher hospitalization rates** than HFrEF - **Comparable mortality** to HFrEF (despite preserved EF) - **Older age + comorbidities** = frailty, polypharmacy challenges

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Pathophysiology: How Kidney Disease Becomes HFpEF

The Central Mechanism: Mineralocorticoid Receptor Overactivation

In the kidney: - Hyperglycemia and obesity cause LIGAND-INDEPENDENT MR activation - This occurs even with normal aldosterone levels - Leads to distal nephron sodium retention and potassium loss

Systemic consequence: - Volume expansion ☐ hypertension ☐ concentric LVH - Central venous pressure elevation ☐ "renal tamponade" (pressure backflow reduces GFR)

In the heart: - MR activation in cardiomyocytes causes TGF-β and inflammatory pathway activation - Results in cardiac fibrosis and diastolic dysfunction

The Paulus-Tschöpe Paradigm

Comorbidities (obesity, DM, hypertension, CKD) trigger:

1. **Systemic inflammation** (IL-6, TNF-α, CRP)

2. **Endothelial dysfunction** in coronary microvasculature
3. **Reduced nitric oxide** bioavailability
4. **Impaired cGMP signaling** ☐ titin hypophosphorylation
5. **Cardiomyocyte stiffness** ☐ diastolic dysfunction

All of these mechanisms are **also happening in the kidney**, creating bidirectional organ damage.

Galectin-3: The Molecular Bridge

Galectin-3 is a protein that: - Precedes development of BOTH CKD and HFpEF - Mediates TGF-β signaling in fibrosis - Levels correlate with diastolic dysfunction severity - Reduced by MRA therapy

Clinical correlation: Galectin-3 levels >10.3 ng/mL predict CKD stage 3-4 with 60% sensitivity.

The HFpEF Phenotype Map

Shah Phenomapping Study

Research identified THREE distinct HFpEF phenotypes with vastly different prognoses:

Phenotype 1: Obese/Metabolic - Younger patients - High BMI, diabetes, metabolic syndrome - Better prognosis - Responds well to weight loss strategies

Phenotype 2: Pulmonary Hypertension - Mixed features - Intermediate risk - Responds to targeted PH therapy

Phenotype 3: CKD-DOMINANT ☐ - **Older** (median 75 years) - **Advanced CKD** is defining feature - 43% atrial fibrillation - Pulmonary hypertension, RV dysfunction - **Highest mortality risk: HR 4.2** (4.2x higher HF hospitalization) - **BUT responds BEST to MRA and kidney-protective therapy**

Clinical Pearl

The CKD-dominant phenotype—the highest risk group—is exactly the type of patient your nephrology colleagues see daily. This explains why **nephrologists are essential in HFpEF management**.

Albuminuria: The Dominant Risk Driver

Albuminuria Dominates eGFR

A critical insight: **In early CKD, albuminuria predicts outcomes better than eGFR decline.**

ARIC Study (n=10,975): Incident heart failure risk by albuminuria status | UACR Category | Relative Risk | |—|—| | <5 mg/g (optimal) | Reference | | 5-9 mg/g (intermediate-normal) | 1.54 | | 10-29 mg/g (high-normal) | 1.91 | | 30-299 mg/g (microalbuminuria) | 2.49 | | ≥300 mg/g (macroalbuminuria) | **3.47** |

ARIC: Atherosclerosis Risk in Communities Study - see references for full citation

Clinical translation: A patient with eGFR 85 but UACR 400 mg/g (high albuminuria, normal function) faces: - **Higher HF risk** than patient with eGFR 35 but UACR 15 mg/g (low function, normal albuminuria) - This has profound implications for therapy prioritization

The "Albuminuria Paradox"

In adults with albuminuria and preserved eGFR: - **Absolute risk of CV events » risk of dialysis** - Without intervention, more likely to suffer MI/stroke/HF hosp than to need dialysis - This explains why CV-protective therapy (SGLT2-i, GLP-1 RA) should be prioritized over "kidney-protective" strategies alone

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KDIGO Heat Map: Integrated Cardiorenal Risk

The KDIGO CKD classification (combining eGFR + albuminuria) predicts heart failure risk:

	ALBUMINURIA (UACR mg/g)		
	A1 (<30)	A2 (30–300)	A3 (>300)
G1 ≥90	LOW HF: Ref	MOD–HIGH HF: 2.49x	HIGH HF: 3.47x
G2 60–89	LOW HF: Ref	MOD–HIGH HF: 2.49x	HIGH HF: 3.47x
G3a45–59	MODERATE HF: 1.54x	HIGH HF: 2.80x	V.HIGH HF: 4.10x
G3b30–44	HIGH HF: 1.91x	V.HIGH HF: 3.20x	V.HIGH HF: 4.80x
G4 15–29	V.HIGH (CV Eq) HF: 2.50x	V.HIGH HF: 4.00x	V.HIGH HF: 5.50x
G5 <15	V.HIGH HF: 3.50x	V.HIGH HF: 5.00x	HIGHEST HF: 6.50x

Key Insight: eGFR <30 (G4/G5) is **automatic cardiovascular risk equivalent** regardless of albuminuria status.

Diagnostic Approach to HFpEF

Three-Step Diagnosis

Step 1: Suspect HFpEF - Dyspnea + peripheral edema + preserved EF on echo - Risk factors: age >70, hypertension, obesity, CKD

Step 2: Biomarker Assessment - NT-proBNP or BNP elevation (use higher thresholds in CKD: ≥200-400 pg/mL) - Normal NT-proBNP essentially rules out HFpEF

Step 3: Echocardiographic Confirmation - HFA-PEFF diagnostic algorithm (scores three domains: functional, morphological, biomarker) - Scores ≥5 = HFpEF confirmed - Scores 2-4 = further testing needed (stress echo or invasive)

HFA-PEFF Scoring (Simplified)

Parameter	Points
E/e' ratio ≥9 (elevated diastolic stress)	1
LA volume index ≥34 mL/m² (dilated)	1
LV mass index ≥115 (M) or >95 (F) g/m² (hypertrophy)	1
Tricuspid regurgitation velocity >2.8 m/s	1
NT-proBNP >125 pg/mL or BNP >35 pg/mL	1

Score ≥5 = HFpEF diagnosed; 2-4 = pursue stress testing or cardiology referral

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Evidence-Based Therapy for HFpEF

SGLT2 Inhibitors: Class I, Level A (2023 ESC)

EMPEROR-Preserved (Empagliflozin): PubMed | Outcome | Benefit | |———|———| | CV death/HF hosp | 21% reduction | | HF hosp alone | 27% reduction | | Kidney composite | 43% reduction |

DELIVER (Dapagliflozin): PubMed | Outcome | Benefit | |———|———| | CV death/worsening HF | 18% reduction | | Consistent benefit even in LVEF >60% | ☐ |

Clinical Pearl: SGLT2-i is the FIRST class of drug with proven Class I benefit in HFpEF. This is a major advance.

Finerenone: FINEARTS-HF (2024) PubMed

Study Design: 6,001 patients with symptomatic HF, LVEF ≥40%

Results: | Outcome | Benefit | |———|———| | CV death + worsening HF events | **16% reduction** | | Effect consistent across LVEF spectrum | Yes (p-interaction 0.75) | | LVEF >60% (true HFpEF) | **18% reduction** |

Hyperkalemia: More common than with SGLT2-i (14.3% vs 6.9% placebo), but severe hyperkalemia leading to hospitalization rare (0.5% vs 0.2%)

FDA Approval: July 2025 expanded finerenone indication to include HFpEF (LVEF ≥40%)

ARNi (Sacubitril/Valsartan): PARAGON-HF PubMed

Study: Narrowly missed primary endpoint (p=0.059)

But: Strong benefit in subgroups: - Women (27% reduction) - LVEF <57% (22% reduction) - CKD (21% reduction)

Clinical Use: Now FDA-approved across HF spectrum, with Class 2b recommendation for HF-pEF. Most useful in women or those with mildly reduced EF.

Combination Therapy: Synergistic Approach

SGLT2-i + Finerenone: - CONFIDENCE trial: 52% UACR reduction (superior to either alone) - Safe combination with appropriate K+ monitoring - SGLT2-i mitigates finerenone-induced hyperkalemia (8.1% vs 18.7% without SGLT2-i) - Both agents have Class I evidence in HFpEF when used together

SGLT2-i + GLP-1 RA: - Additive CV and kidney benefits - Complementary mechanisms - Both improve HFpEF outcomes

What DOESN'T Work in HFpEF

- **Beta-blockers:** No mortality benefit (may increase HF hosp if EF >60%)
- **ACE-I/ARB monotherapy:** Modest benefit at best
- **Diuretics alone:** Palliative only (reduce symptoms but worsen outcomes if overused)

CKM Framework Integration

CKD Stage ≥4 = Automatic CV Risk Equivalent

Under the Cardiovascular-Kidney-Metabolic (CKM) framework: - eGFR <30 (G4/G5) automatically = CKM Stage 3 (CV risk equivalent) - Warrants intensive prevention identical to secondary prevention in established CVD - Even without symptoms of HF, these patients need cardioprotective therapy

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Patient Communication Strategies

The "Kidney Drives Heart" Message

Accessible explanation: "Your kidneys have been working extra hard for years to filter your blood. When they get tired, they send signals that affect your heart's relaxation. The good news is these are connected problems—treating your kidneys will help your heart, and we have new medications that protect both."

Risk Visualization Using AHA PREVENT Calculator

The PREVENT calculator incorporates eGFR and UACR to provide personalized 10-year and 30-year CV risk estimates. Showing patients their position on this risk spectrum motivates medication adherence.

KDIGO Heat Map for Patient Education

Show patients their position (e.g., "You're in the orange zone"—moderate risk) and explain how therapy aims to shift them toward yellow or green zones.

Clinical Pearls

1. **HFpEF is kidney disease first, heart disease second.** This reframing changes management priorities.
2. **CKD-dominant phenotype has highest risk but responds best to therapy.** Shah phenomapping shows this group (your typical nephrology patient) is at HR 4.2 for hospitalization but shows best response to MRA and SGLT2-i.
3. **Albuminuria dominates early.** In G1-G2 with albuminuria, albuminuria is the primary risk driver—prioritize UACR reduction even with normal eGFR.
4. **SGLT2-i are Class I for HFpEF.** For the first time, we have a proven therapy for HFpEF (unlike years of HFrEF focus).
5. **Finerenone works in HFpEF.** Unlike limited steroidal MRA data, finerenone showed consistent benefit across LVEF spectrum.
6. **Simultaneous therapy initiation is safe.** CONFIDENCE data supports starting SGLT2-i + finerenone together with appropriate monitoring.
7. **Nephrologists' expertise is essential.** Managing volume status, medication dosing in CKD, and cardiorenal interaction makes nephrologists ideal coordinators of HFpEF care.

Practice Questions

Question 1: A 72-year-old woman with hypertension, obesity (BMI 34), eGFR 42, UACR 180 mg/g presents with dyspnea on exertion. Echocardiography shows preserved EF (58%), E/e' ratio 14, LA volume index 38 mL/m². NT-proBNP is 350 pg/mL. Diagnose and outline initial therapy.

Answer: HFpEF (HFA-PEFF score: E/e' 1 point, LA volume 1 point, NT-proBNP 1 point, likely other morphologic features = ≥5 points). Risk stratification: KDIGO heat map shows G3b/A2 = very high risk. Initial therapy: (1) Optimize BP control <130/80 mmHg; (2) Start SGLT2 inhibitor (dapagliflozin 10 mg) immediately—Class I evidence in HFpEF; (3) If tolerating at 4 weeks, add finerenone 10 mg (eGFR 42, UACR 180, check K+ at 4 weeks); (4) Consider adding GLP-1 RA for weight loss if T2DM; (5) Restrict sodium, optimize diuretic therapy for symptom control.

Question 2: Compare HFrEF and HFpEF in terms of: (a) patient demographics, (b) prognosis, (c) evidence-based therapies.

Answer: - **(a) Demographics:** HFpEF older (median 75 vs 60), more women, more obesity/DM - **(b) Prognosis:** Similar 5-year mortality (~70%) despite preserved EF; HFpEF paradoxically sicker with worse quality of life - **(c) Therapies:** HFrEF has many proven (ARNI, SGLT2-i, MRA, BB), but HFpEF only recently gained Class I evidence (SGLT2-i via EMPEROR-Preserved/DELIVER, finerenone via FINEARTS-HF)

Question 3: A patient with HFpEF, CKD stage 3b, hypertension, obesity, and T2DM asks why you're starting so many medications. How do you explain the four-pillar approach?

Answer: "You have four systems damaged from your diabetes, kidney disease, and high blood pressure: (1) Your kidneys aren't filtering normally, (2) Your heart can't relax properly, (3) Your blood vessels are inflamed, (4) Your whole system is retaining salt. We're using medications that attack each of these problems from different angles—SGLT2 inhibitor protects your kidneys and helps your heart relax, finerenone reduces inflammation and salt retention, ACE inhibitor helps blood vessel function, and controlling your blood sugar and weight addresses the root causes. Together these give you the best chance of avoiding symptoms and hospitalization."

Key Takeaways

☐ **HFpEF is primarily a renal disorder** producing secondary cardiac manifestations

☐ **CKD-dominant phenotype** at highest risk but responds best to kidney-protective therapy

☐ **Albuminuria dominates early.** Reduce UACR aggressively even with normal eGFR

☐ **SGLT2 inhibitors are Class I** for HFpEF (first proven therapy for this population)

☐ **Finerenone provides additional benefit** across full LVEF spectrum in HFpEF

☐ **Combination therapy is safe and superior** (SGLT2-i + finerenone synergistic)

☐ **Nephrologists should lead care** given central role of kidney pathophysiology

☐ **eGFR <30 is CV risk equivalent** requiring intensive cardioprotective prevention

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See Also

Related Student Handouts

- Cardiorenal Syndrome Overview
- GDMT Four Pillars
- SGLT2 Inhibitors in Detail
- GLP-1 Receptor Agonists
- CKD Complications

Clinical Content (01-Clinical-Medicine/Nephrology & Cardiology)

- Cardio-Renal Ecosystem Hub
- CKD Hub - Full Clinical Reference
- Heart Failure Clinical Reference
- Hypertension Management

Atomic Notes (ZK)

- Cardiorenal Syndrome as Bidirectional Dysfunction

Butler-COM Resources

- Butler COM - Nephrology Deep Dive
- Butler COM - Heart Failure GDMT Deep Dive

Related Topics

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