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Sex and Gender Differences in Heart Failure with Preserved Ejection Fraction: From Pathophysiology to Modern Therapeutic Guidelines

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Introduction: Heart failure with preserved ejection fraction (HFpEF) represents a critical global public health challenge, with recent epidemiological data confirming that women constitute over 55–60% of the HFpEF population and face a significantly higher lifetime risk than men. With the release of the landmark 2026 European Society of Cardiology Guidelines for the Management of Heart Failure[1], which simplify the classification to a binary framework (left ventricular ejection fraction ≥50% for HFpEF), understanding biological sex-specific trajectories has become paramount for clinical optimization. *Aim*: To systematically evaluate sex- and gender-specific discrepancies in pathophysiology, diagnostic criteria, and therapeutic responses in patients with HFpEF, integrated with the latest 2026 clinical mandates.

Methods: A targeted analysis was conducted on the latest heart failure registries, the newly established ESC 2026 framework, and recent sex-stratified pooled meta-analyses investigating modern medical therapies, including sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, and angiotensin receptor neprilysin inhibitors (ARNIs)[2].

Results: Recent evidence from the 2025-2026 literature highlights highly distinct clinical and structural phenotypes:

1. *Pathophysiology & Diagnostics*: In women, HFpEF is driven by microvascular inflammation, concentric left ventricular remodeling, and visceral adiposity. The 2026 ESC Guidelines mandate sex-specific echocardiographic calibration, defining left ventricular hypertrophy with lower thresholds for women (left ventricular mass index ≥95 g/m²) than men (≥115 g/m²) to prevent systemic underdiagnosis. Furthermore, concomitant obesity—prevalent in females—is recognized to falsely suppress diagnostic N-terminal pro-brain natriuretic peptide levels.
2. *Clinical Phenotype & Prognosis*: Women are older at presentation, report substantially lower quality-of-life scores, and suffer from higher non-cardiovascular rehospitalization rates compared to men, despite demonstrating better age-adjusted survival.
3. *Therapeutic Efficacy:* SGLT2 inhibitors remain the Class I foundation for both sexes. However, recent consensus data emphasize that women derive therapeutic benefit from sacubitril/valsartan up to much higher LVEF ceilings (≤65%) than men. Additionally, the widespread implementation of GLP-1 receptor agonists in 2025/2026 has revolutionized the treatment of the obesity-HFpEF phenotype, showing profound efficacy in reducing functional impairment, a benefit overwhelmingly realized by female patients.

Conclusion: Sex disparities in HFpEF reflect deeply separate biological pathways. The 2026 ESC Guidelines represent a major step forward by institutionalizing sex-calibrated diagnostic cut-offs. The seamless transition into daily clinical practice requires precise phenotypic profiling (incorporating SGLT2i, gender-targeted ARNI application, and GLP-1 receptor agonists) to fully realize the promise of precision cardiovascular medicine.

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LITERATURE

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