

# The new face of HFpEF: systemic inflammation

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## Abstract

Systemic inflammation is proposed as background of development and progres of heart failure, especially in heart failure with preserved ejection fraction (HFpEF). High-sensitivity C-reactive protein seems to be an optimal biomarker of systemic inflammation. Knowledge of systemic inflammation is important for new therapeutic fields in HFpEF with potential in inhibition of IL-1 $\beta$ , IL-6 or galectin-3.

Key words: HFpEF, systemic inflammation

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There has been a lot of recent progress in heart failure with preserved ejection fraction (HFpEF), leading to changes in therapeutic approaches. This is due to positive results from two major trials with sodium-glucose cotransporter 2 (SGLT2) inhibitors: EMPEROR-Preserved and DELIVER [1, 2]. These are the first studies dedicated to HF with an EF > 40% that have demonstrated clinical benefits in terms of reducing the risk of cardiovascular death and/or worsening HF (hospitalisation due to HF exacerbation, exacerbation without hospitalisation but requiring increased diuretic doses).

For many years, the distinct pathophysiology of HFpEF compared to heart failure with reduced ejection fraction (HFrEF) has been emphasised. Recent years have focused on understanding the phenomenon of systemic inflammation [3] and its significance in HFpEF. According to current knowledge in cardiology, inflammatory processes play a role in the development and progression of HF, are of particular importance in HFpEF, especially in certain subphenotypes. This was proven in the COACH (Counseling in Heart Failure) and BIOSTAT-CHF (Biology Study to Tailored Treatment in Chronic Heart Failure) studies [4, 5]. This association is likely related to a higher burden of comorbidities in HFpEF, such as diabetes, hypertension, obesity, and chronic kidney disease. The current concept indicates the involvement of systemic inflammation in myocardial remodeling in HFpEF

(Paulus paradigm) with inflammation at the level of small vessels (microvascular inflammation) [6].

A promising biomarker for identifying systemic inflammation is high-sensitivity C-reactive protein (hsCRP). Measurement of CRP levels using a high-sensitivity method allows the detection of low-grade inflammatory processes with CRP levels of 2–10 mg/L. This was the focus of studies in which elevated levels of this biomarker were documented in populations with both acute and stable clinical presentations of HF (Table 1). Interleukin 6 (IL-6), which stimulates CRP production, was found to be associated with atrial fibrillation (OR 1.35; 95% CI: 1.03–1.77;  $p = 0.028$ ), lower glomerular filtration rate, higher N-terminal pro-B-type natriuretic peptide, and worse exercise tolerance among 2329 patients in the BIOSTAT-CHF study [11]. Higher IL-6 levels were also associated with HFpEF (OR 1.63; 95% CI: 1.06–2.5;  $p = 0.027$ ) and had predictive value for mortality (OR 1.22; 95% CI: 1.16–1.29;  $p < 0.001$ ). Each doubling of IL-6 was an independent risk factor for hospitalisation for HF and cardiovascular death and all-cause mortality at 2-year follow-up (HR 1.16; 95% CI: 1.11–1.21;  $p < 0.001$ ). The IL-6 signaling pathway seems to be particularly relevant for HFpEF [11].

Another important factor is the role of epicardial adipose tissue (EAT) as a direct inducer of systemic inflammation [12]. The MESA study [13], which included 6785 individuals

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**Table 1.** Review of selected trials evaluating inflammatory processes in heart failure

Trial name	Population	Inflammatory biomarkers
RELAX [7]	HFpEF	Elevated CRP levels in 57% of the population
TIME-CHF [8]	Elderly patients HFrEF HFpEF	Median hsCRP 6.6 mg/L 8.5 mg/L
ASCEND-HF [9]	AHF	Median hsCRP 12.6 mg/L
COACH [4]	HFrEF HFpEF	33 biomarkers from various pathophysiological pathways (inflammation, oxidative stress, remodeling, cardiac stretch, angiogenesis, atherosclerosis, and kidney function)
CANTOS [10]	Post-heart attack patients	hsCRP
BIOSTAT-CHF [5, 11]	HFrEF HFpEF	IL-6

AHF – acute heart failure; CRP – C-reactive protein; HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction; hsCRP – high-sensitivity C-reactive protein; IL-6 – interleukin 6

without cardiovascular diseases, revealed that the presence of epicardial adipose tissue in cardiac computed tomography was a predictor of HFpEF development (log rank  $p < 0.001$ ) but not HFrEF (log rank  $p = 0.1$ ) in a long-term follow-up ( $> 15$  years).

Understanding the phenomenon of systemic inflammation is crucial for identifying new treatment options, such as inhibition of IL-1 $\beta$ , IL-6, or galectin-3. According to the studies conducted so far for IL-1 $\beta$  blockade, there was a significant 38% reduction in the risk of hospitalisation for HF and death from any cause for those patients who responded to therapy with canakinumab (documented reduction in hsCRP levels  $< 2$  mg/L) compared to the placebo group (CANTOS trial) [10]. Currently, there is an ongoing study using the IL-6 inhibitor, ziltivekimab – a monoclonal antibody against IL-6 – in the HFpEF population [14].

However, it is still an open question what effect weight loss has on the inhibition of HF progression and the severity of systemic inflammation. This year will be the completion of two studies on semaglutide in the HFpEF population – the STEP-HFpEF and STEP-DM trials [15], which may answer this question. The STEP programme is the first to evaluate the effect of once-weekly semaglutide at a dose of 2.4 mg on symptoms, physical capacity, and functional improvement in obese HFpEF patients. A total of 1146 patients with obesity and HFpEF were randomised in the STEP-HFpEF programme [15].

In conclusion, SGLT2 inhibitors have revolutionised the approach to HF across the spectrum. Thanks to landmark

trials like EMPEROR-Preserved and DELIVER, we now have therapy dedicated to patients with HF and an EF  $> 40\%$  [1, 2, 16]. The published Heart Failure Association European Society of Cardiology (HFA ESC) position statement jointly with the European Heart Rhythm Association and the European Society of Hypertension on profiling patients with HFpEF to tailor therapy with a central position of SGLT2 inhibitors and diuretics in case of congestion (Figure 1), was one of the most important reports of this year's HFA ESC Congress [17]. Nonetheless, the search for HFpEF therapies – particularly considering systemic inflammation as a therapeutic target – continues.

## Article information

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ML – 100%.

### Conflict of interest

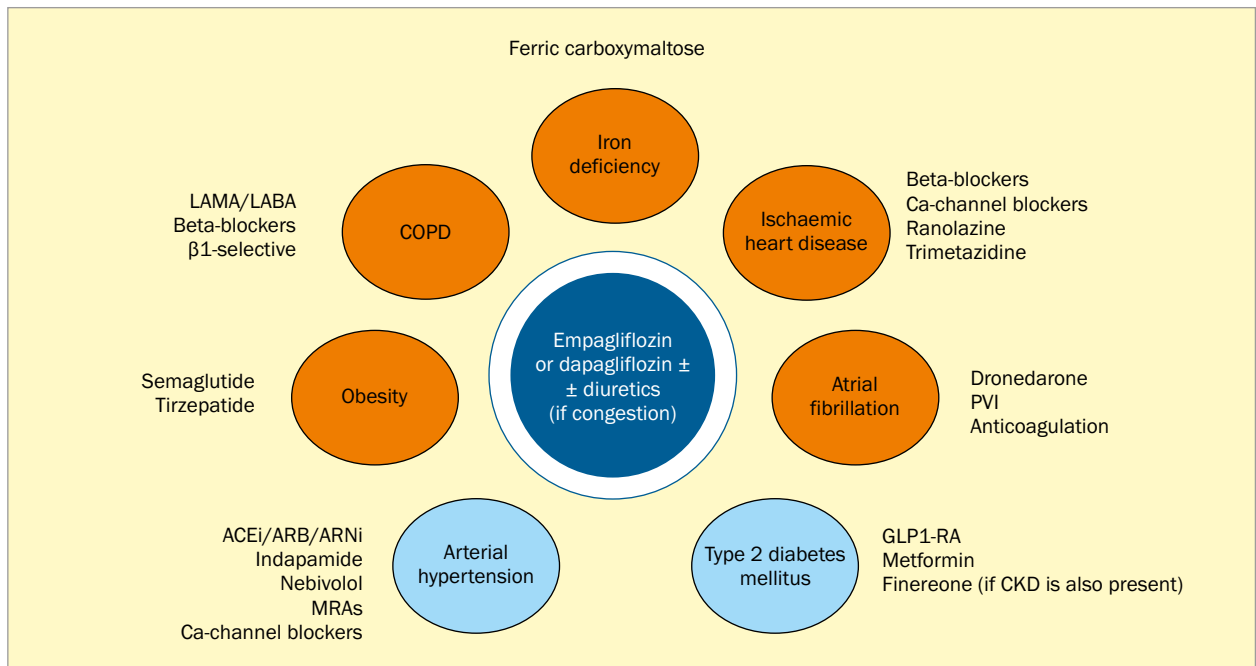
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**Figure 1.** Profiling heart failure with preserved ejection fraction patients for personalized treatment [16]; ACEi – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blocker; ARNi – angiotensin receptor neprilysin inhibitor; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; GLP1-RA – glucagon-like peptide 1 receptor agonists; LABA – long-acting  $\beta$ -agonist; LAMA – long-acting muscarinic receptor antagonist; MRA – mineralcorticoid receptor antagonist; PVI – pulmonary vein isolation

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