

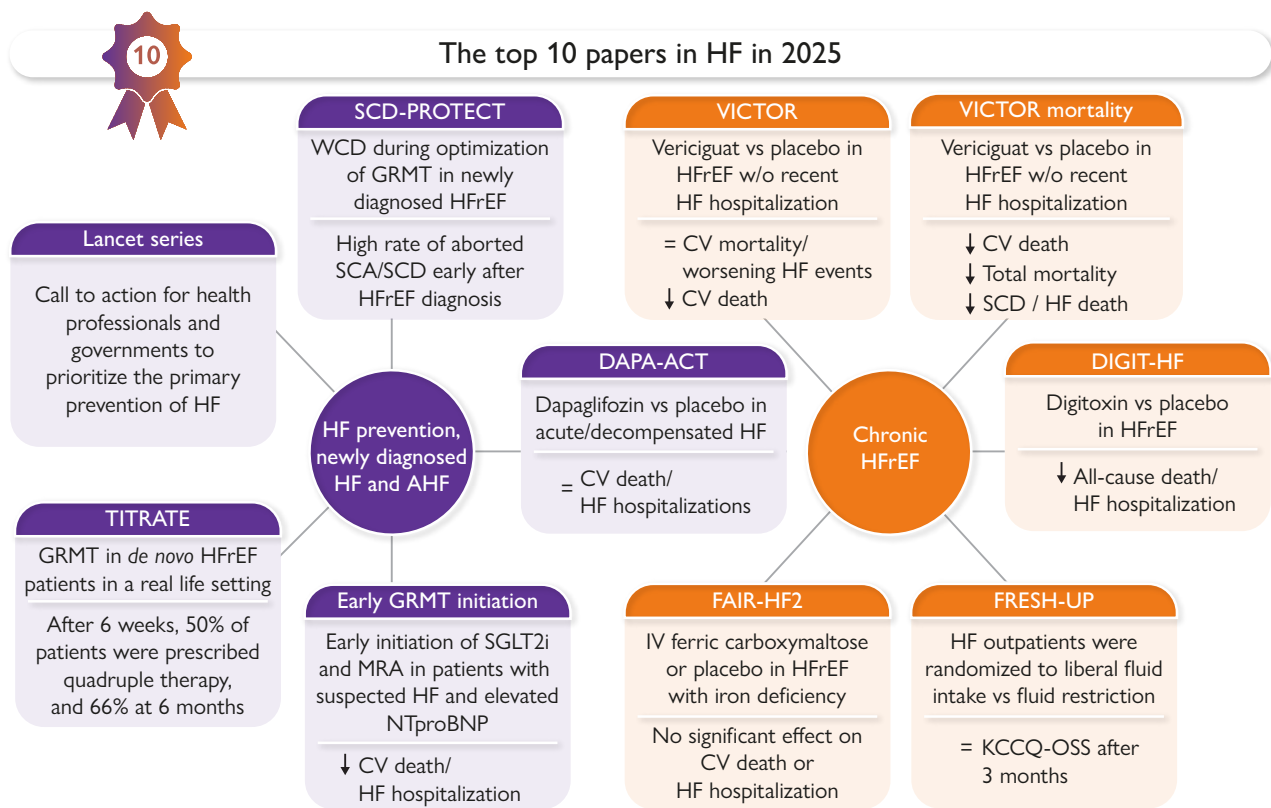
The year in cardiovascular medicine 2025: the top 10 papers in heart failure

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Graphical Abstract



The year in cardiovascular medicine 2025: The top 10 papers in heart failure.
Left: Papers on heart Failure (HF) prevention, newly diagnosed HF and acute HF (AHF).
Right: Studies in chronic HF with reduced ejection fraction (HFrEF).

AHF, acute heart failure; CV, cardiovascular; GRMT, guideline-recommended medical therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; SCA, sudden cardiac arrest; SCD, sudden cardiac death; SGLT2i, sodium-glucose cotransporter-2 inhibitors; WCD, wearable cardioverter defibrillator

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In 2025, several impactful papers influencing the treatment of patients with heart failure (HF) have been published raising hope that prognosis in these patients will further improve.

Of major importance are efforts to prevent HF, and a Lancet series calls to action for health care professionals, health systems, and governments to prioritize the primary prevention of HF.¹ The first of three review articles focuses on HF epidemiology, pathophysiology, and risk factors. The prevention of HF must include screening for HF risk and detection of pre-HF, e.g. using biomarkers. Dedicated clinical workflows across the life course, scalable implementation strategies, and increased public awareness may finally successfully reduce HF burden.

In the FAIR-HF2 trial, 1105 patients with HF and reduced ejection fraction [HFrEF, left ventricular ejection fraction (LVEF) < 45%, 33% women] and iron deficiency were randomized to i.v. ferric carboxymaltose or placebo.² Several primary endpoints were investigated: i.v. iron vs placebo reduced cardiovascular (CV) death or first HF hospitalization [hazard ratio (HR), .79; 95% confidence interval (CI), .63–.99; $P = .04$], total HF hospitalizations (rate ratio, .80; 95% CI, .60–1.06; $P = .12$), and CV death or first HF hospitalization in patients with a transferrin saturation < 20% (HR, .79; 95% CI, .61–1.02; $P = .07$), while adverse events were comparable among ferric carboxymaltose and placebo groups. Due to a complex statistical analysis plan, these results did not fulfil the criteria for a significant effect, but add to the totality of evidence that ferric carboxymaltose in patients with HF and iron deficiency reduces HF hospitalizations.

In the VICTOR trial, 6105 HFrEF patients without a HF hospitalization during the last 6 months were randomly assigned to the soluble guanylate cyclase stimulator vericiguat (target dose 10 mg) or placebo.³ The primary composite endpoint CV death or HF hospitalization was not significantly reduced (HR, .93; 95% CI, .83–1.04; $P = .22$). Heart failure hospitalizations were not lowered by vericiguat (HR, .95; 95% CI, .82–1.10); however, CV death was reduced (HR, .83; 95% CI, .71–.97; no P value was given with the primary endpoint neutral). Serious adverse events were similar among the vericiguat (23.5%) and placebo (24.6%) groups with symptomatic hypotension being the most prevalent adverse event (11.3% in the vericiguat group vs 9.2% in the placebo group).

A detailed mortality analysis of VICTOR was simultaneously published as VICTOR was powered to independently assess CV death.⁴ Death from any cause was reduced by vericiguat vs placebo (HR, .84; 95% CI, .74–.97; $P = .015$). Also sudden cardiac death (1.6 vs 2.2 events per 100 patient-years; HR, 0.75; 95% CI, .56–.99; $P = .042$) and HF-related deaths (1.7 vs 2.4 events per 100 patient-years; HR, .71; 95% CI, .54–.94; $P = .016$) were lower with vericiguat vs placebo.

The publicly funded DIGIT-HF trial sought to provide new data on the efficacy of digitalis glycosides almost 30 years after the DIG trial. DIGIT-HF randomized 1212 patients with HFrEF, with LVEF ≤ 40% (and a New York Heart Association (NYHA) functional Class III or IV or LVEF ≤ 30% and NYHA Class II) to digitoxin (at a starting dose of .07 mg once daily) or placebo, on top of guideline-recommended medical therapy (GRMT).⁵ The primary outcome (composite of death from any cause or first HF hospitalization) was significantly reduced (39.5%) in the digitoxin group vs placebo group (44.1%; HR, .82; 95% CI, .69–.98; $P = .03$). Mortality tended to be lower in the digitoxin group (HR, .86; 95% CI, .69–1.07), and adverse events were not different among digitoxin and placebo. These data indicate that digitalis glycosides have the potential to reduce hard endpoints in HFrEF, even when GRMT is well installed. The data further show that potential adverse effects of digitalis inferred from non-randomized analyses are not substantiated in randomized studies.

The German SCD-PROTECT study evaluated the risk of sudden cardiac arrest in 19 598 patients with newly diagnosed ischaemic and non-ischaemic HFrEF who received a wearable cardioverter-defibrillator (WCD).⁶ Left ventricular ejection fraction at study start was $27.5 \pm 9.4\%$. The incidence rate of the first appropriate treatment by WCD was 6.10 (95% CI, 5.31–7.00) events per 100 patient-years in patients with non-ischaemic cardiomyopathy and 8.64 (95% CI, 7.41–10.05) events per 100 patient-years in patients with myocardial infarction/coronary artery disease. Improvement in LVEF to >35% was observed in 52% patients over a mean of 66 ± 44 days. Inappropriate shocks occurred in 0.5% of patients. Thus, SCD-PROTECT highlights a substantial risk of sudden cardiac arrest due to ventricular arrhythmias during the early phase of GRMT optimization in patients with newly diagnosed HFrEF, regardless of ischaemic or non-ischaemic origin.

It is established that sodium-glucose cotransporter-2 inhibitors (SGLT2i) reduce the risk of CV death or HF worsening in outpatients with HF.⁷ The DAPA ACT TIMI-68 study assessed the efficacy and safety of in-hospital initiation of dapagliflozin (10 mg daily) in patients hospitalized for HF. In total, 2401 patients (median age 69, 34% women, 72% had LVEF ≤ 40%) were randomized, and the primary outcome occurred in 133 patients (10.9%) in the dapagliflozin group and 150 (12.7%) in the placebo group (HR, .86; 95% CI, .68–1.08; $P = .20$). The use of dapagliflozin was safe. In a meta-analysis of patients hospitalized for HF (including DAPA ACT TIMI-68), SGLT2i reduced the early risk of CV death or worsening HF (HR, .71; 95% CI, .54–.93; $P = .012$) and of all-cause death (HR, .57; 95% CI, .41–.80; $P = .001$). So, this trial added valuable data and helped to validate the efficacy and safety of in-hospital initiation of SGLT2i.

In a large cohort study, the potential effect of early initiation of GRMT, which started at the point of detection of elevated natriuretic peptide levels in community-based patients with suspected HF, was investigated.⁸ The authors show that many of these patients were admitted to hospital or died prior to a diagnostic echocardiography. Two in five patients with suspected HF and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels of ≥400 pg/mL had a pre-existing non-HF-related indication (Type 2 diabetes, chronic kidney disease, or resistant hypertension) for a SGLT2i and/or mineralocorticoid receptor antagonist (MRA). If both a SGLT2i and MRA were initiated at the measurement of an elevated NT-proBNP, for every 1000 patients treated, 84 would avoid either a HF hospitalization or death at 12 months (number needed to treat of 12; 95% CI, 11–14).

Sequencing and rapid up-titration of GRMT remains a challenge despite guidelines recommending this. TITRATE-HF prospectively included 1508 *de novo* HFrEF patients in a real-life setting (70 years, 31% women, median LVEF, 30%).⁹ After 6 weeks post-HFrEF diagnosis, 50% of patients were prescribed quadruple therapy, and at 6 months, 66% of the patients, but only 1.3% achieved target doses for all four drug classes. While side effects accounted for 20%–37% of cases where target doses were not reached, a large proportion was attributed to physicians accepting suboptimal doses. Most titrations occurred in the first 60 days after diagnosis, fading afterwards. So, rapid initiation of GRMT for HFrEF is feasible in real-world clinical practice. Nonetheless, these results highlight the urgency for a proactive approach and ongoing dose titration of pharmacological therapy beyond the initial first months to fully optimize treatment.

Although fluid restriction still frequently is recommended to patients with HF, no solid data underpin this recommendation. FRESH-UP was a multicentre open-label trial, in which 504 HF outpatients (67% male) were randomized to advice for liberal fluid intake vs advice for fluid restriction (1500 mL per day of fluid).¹⁰ The primary outcome of

the trial, health status after 3 months assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ)-OSS, was 74.0 in the liberal fluid intake group vs 72.2 in the fluid restriction group (difference, 2.17; 95% CI, $-.06$ – 4.39 ; $P = .06$). Thirst distress was higher in the fluid restriction group, and no differences were observed for safety events between the two groups. The findings question the benefit of fluid restriction in chronic HF.

Declarations

Disclosure of Interest

J.B. received honoraria for lectures/consulting from Novartis, Abbott, Bayer, Pfizer, Boehringer Ingelheim, AstraZeneca, Cardior, CVRx, BMS, Amgen, Edwards, Roche, and Zoll, not related to this article, and research support for the department from Zoll, CVRx, Abiomed, Norgine, and Roche, all not related to this article. The institution of Dr. De Boer has received research grants and/or fees from Alnylam, AstraZeneca, Abbott, Bristol-Myers Squibb, NovoNordisk; Dr. de Boer has had speaker engagements with and/or received fees from and/or served on an advisory board for Abbott, AstraZeneca, Bristol Myers Squibb, Menarini Benelux BV, NovoNordisk, Roche, and Zoll. S.Z. has served on advisory boards or speaker engagements with AskBio, Abbott, Alnylam, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, CSL Vifor, Cytokinetics, Edwards, Eli Lilly, GSK, Medtronic, Merck, Novartis, Novo-Nordisk, Pfizer, Viartis and serves on a clinical trial committee for studies sponsored by AstraZeneca, Boehringer Ingelheim, Cytokinetics, Merck, Pfizer, Salubris Bio. Non industry: CCS, CHFS, Charite, CPD Network, CSN, EOCl, Liv, Medscape, Medudy, Radcliffe, Reach MD, Sciarc, Translational Medicine Academy, Voxmedia.

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