What's New in Heart Failure? Highlights and Insights from ESC 2025

Author:	*Han Naung Tun[1,2] 1. Geisel School of Medicine at Dartmouth College, Hanover, New Hampshire, USA 2. Department of Medical Science, Northeastern University, Bouvé College of Clinical and Health Science, Boston, Massachusetts, USA *Correspondence to Han.Naung.Tun@dartmouth.edu

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NEW late breaking trials in heart failure (HF) continue to refine therapy in patients with heart failure with reduced ejection fraction (HFrEF) and post-myocardial infarction (MI). DIGIT-HF,[1] BETAMI-DANBLOCK,[2] REBOOT-CNIC,[3] VICTOR,[4] and DAPA ACT HF-TIMI 68[5] are some studies presenting novel evidence on pharmacological therapy optimisation, including digitoxin, β-blockers, vericiguat, and sodium glucose co-transporter-2 (SGLT2) inhibitors. These studies highlight the strategic use of traditional and innovative therapies, taking patient-specific traits, comorbidities, and time of intervention into account. Interpretation of these studies proves critical for optimisation of benefits and guiding patient-specific HF management.

DIGITOXIN AS ADD-ON THERAPY IN HEART FAILURE WITH REDUCED EJECTION FRACTION: INSIGHTS FROM DIGIT-HF

The DIGIT-HF trial[1] demonstrated that digoxin lowered hospitalisation for HF, but not mortality. As a result of this, a Class 2b recommendation was included in the 2022 USA guidelines for HF for symptomatic patients with HFrEF, despite being on guideline-directed medical therapy. This refers to treatments recommended by major HF guidelines to improve survival, reduce hospitalisations, and relieve symptoms. These typically include angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers or angiotensin receptor-neprilysin inhibitors (ARNI), β-blockers, mineralocorticoid receptor antagonists, SGLT2 inhibitors, and device therapy when indicated. The DIGIT-HF trial randomised digitoxin (0.07 mg/day, dose titrated for serum levels 8–18 ng/mL) versus placebo in 1,212 patients with chronic HF, with a left ventricular EF <40%. Individuals were mainly New York Heart Association (NYHA) Class III, and most had optimal therapy: β-blocker in 93%, mineralocorticoid receptor antagonist in 76%, ARNI in 40%, SGLT2 inhibitor in 20%, and implantable cardioverter defibrillator in 64%.[1]

The all-cause mortality or hospitalisation for HF endpoint was reached at a median follow-up of approximately 40 months in 39.5% of those treated with digitoxin compared to 44.1% in the placebo arm (P=0.03). Individual component effects favoured outcomes but did not reach statistical significance. Gender- or outcome-component inconsistency did not

exist, as opposed to digitoxin.[1] The side-effects were more frequent with digitoxin (4.7% versus 2.8%), primarily ventricular arrhythmias (approximately equal to 3%). Interestingly, it is preferred for use in patients with renal disease because it is not concentrated by enterohepatic clearance.

> **Even 'old drugs' like digitoxin can add meaningful benefit in modern HFrEF care**

Further trial interpretation is limited as the DIGIT-HF trial was stopped early when funds ran out, and it included only 55% of target population. Fewer events than expected and later addition of ARNI and SGLT2 inhibitors may have diluted intergroup contrasts. Event curves diverged early, but became superimposed in long-term follow-up, and this is best explained by fewer late events. This study stated that digitoxin lowered the composite endpoint in advanced HFrEF by a modest amount, thus endorsing future potential adjuvant use in patients not optimally controlled by guideline-directed medical therapy. This trial highlights that even 'old drugs' like digitoxin can add meaningful benefit in modern HFrEF care, and I am excited to see data from the upcoming DECISION trial on digoxin.[6]

β-BLOCKERS AFTER MYOCARDIAL INFARCTION WITHOUT HEART FAILURE: INSIGHTS FROM BETAMI-DANBLOCK AND REBOOT-CNIC

Two large contemporary trials provided new data about the long-debated post-MI β-blocker role in the context of preserved or mildly reduced ejection fraction (EF). The BETAMI-DANBLOCK trial,[2] a collaborative study of Norwegian and Danish centres recruiting 5,574 patients (mean age 63; 21% females), found that β-blocker therapy decreased the composite of death, MI, revascularisation, stroke, HF, or arrhythmias at a median of 3.5 years (14.2% versus 16.3%; HR: 0.85; 95% CI: 0.75–0.98). Benefit was principally due to fewer repeated MIs with a suggestion of a larger effect in subjects with mildly impaired EF (40–49%).[2]

In comparison with the larger REBOOT-CNIC trial[3] of 8,438 patients with acute coronary syndromes (mean age: 61 years; 19% women) which was randomised in Spain and Italy and found no overall benefit in outcomes at a median of 3.7 years (22.5% versus 21.7%; HR: 1.04; 95% CI: 0.89–1.22), subgroup results did suggest the potential for harm in women with normal EF, and highlighted the relevance of sex-adjusted analyses.[3]

Altogether, these trials highlight that standard long-term β-blockade therapy is probably not useful in all patients

with a normal EF post-MI.[2,3] Instead, the suggestion of benefit in those with mildly impaired EF and the troublesome sex differences require more fine-grained therapy tailored at the patient level.

The primary endpoint was a composite of cardiovascular death or HF hospitalisation, which occurred in **18.0%** of the vericiguat group versus **19.1%** in the placebo group

INSIGHTS FROM THE VICTOR TRIAL AND POOL ANALYSES OF VICTORIA AND VICTOR

Vericiguat, an oral soluble guanylate cyclase stimulator, restores impaired nitric oxide signalling, a hallmark of HFrEF. While the VICTORIA trial established its benefit in patients with recent worsening HF, the VICTOR trial explored its role in a broader ambulatory population without recent HF hospitalisation.[4]

This Phase III, double-blind, placebo-controlled study enrolled 6,105 adults with HFrEF (left ventricular EF ≤40%, NYHA Class II–IV) across 616 centres in 42 countries.[4] Patients were on optimised guideline-directed medical therapy and had no recent HF decompensation. Participants were randomised 1:1 to vericiguat (target dose 10 mg) or placebo, with a median follow-up of 18.5 months. The primary endpoint was a composite of cardiovascular death or HF hospitalisation, which occurred in 18.0% of the vericiguat group versus 19.1% in the placebo group (HR: 0.93; 95% CI: 0.83–1.04; P=0.22). While HF hospitalisation was not significantly reduced (11.4% versus 11.9%; HR: 0.95), cardiovascular death was lower with vericiguat (9.6% versus 11.3%; HR: 0.83), translating into a reduction in all-cause mortality (12.3% versus 14.4%; HR: 0.84). Benefits were consistent across prespecified subgroups, and serious adverse events were similar between groups. Additional pooled analyses of VICTORIA and VICTOR, as well as prespecified mortality outcomes, were presented at the ESC Congress 2025.[7]

EARLY SODIUM-GLUCOSE CO-TRANSPORTER-2 INHIBITOR THERAPY IN HOSPITALISED HEART FAILURE: DAPA ACT HF-TIMI 68 INSIGHTS

Hospitalisation for HF continues to be a significant cardiovascular burden with high short- and long-term morbidity and mortality. Although disease-modifying therapies are the norm in chronic HF, the issue of safely initiating therapy during hospitalisation has been underexamined, with particular reference to the SGLT2 inhibitors. DAPA ACT HF-TIMI 68[5] attempted to fill the void with a trial of whether early in-hospital initiation of dapagliflozin would decrease cardiovascular death or worsening HF in individuals hospitalised for HF.

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This double-blind, placebo-controlled study enrolled 2,401 patients across 210 sites in the USA, Canada, and Europe. Participants were randomised within a median of 3.6 days after admission to either dapagliflozin 10 mg daily or placebo. Over the first 2 months, the primary endpoint occurred in 10.9% of patients treated with dapagliflozin versus 12.7% with placebo (HR: 0.86; 95% CI: 0.68–1.08; P=0.20). Cardiovascular death and worsening HF individually also trended favourably, and all-cause mortality was numerically lower with dapagliflozin (3.0% versus 4.5%; HR: 0.66).[5] Safety signals were reassuring, with only modest differences in hypotension and renal events.[5] From a clinical viewpoint, the results support a proactive approach: why delay therapies that could significantly decrease early risk until the time of hospital discharge? Hospitalisation could very well turn out to be the best opportunity to fine-tune HF care.

SUMMARY AND TAKEAWAYS

Digitoxin reduces hospitalisations modestly in advanced HFrEF, and may be added to standard therapy. New trials in post-MI care and in HF provide valuable lessons in patient prognoses. Long-term β-blockade in preserved EF patients post-MI is not helpful in all cases, but patients with a mildly depressed EF may benefit, with sex-related responses. Vericiguat reduces cardiovascular death modestly and is well tolerated, and early start of SGLT2 inhibitors, like dapagliflozin, in HF hospitalisation is safe and reduces early risk, highlighting proactive therapy. These studies illustrate the need for proper selection of therapy, early therapy, and use of established and novel agents to maximise benefit of therapies for HF.

References

1. Bavendiek U et al.; DIGIT-HF Study Group. Digitoxin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2025;DOI:10.1056/NEJMoa2415471.
2. Munkhaugen J et al.; BETAMI–DANBLOCK Investigators. Beta-blockers after myocardial infarction in patients without heart failure. N Engl J Med. 2025;DOI:10.1056/NEJMoa2505985.
3. Ibanez B et al.; REBOOT-CNIC Investigators. Beta-blockers after myocardial infarction without reduced ejection fraction. N Engl J Med. 2025;DOI:10.1056/NEJMoa2504735.
4. Butler J et al. Vericiguat and mortality in heart failure and reduced ejection fraction: the VICTOR trial. Eur Heart J. 2025;DOI:10.1093/eurheartj/ehaf655.
5. Berg DD et al.; DAPA ACT HF-TIMI 68 Trial Committees and Investigators. Dapagliflozin in patients hospitalized for heart failure: primary results of the DAPA ACT HF-TIMI 68 randomized clinical trial and meta-analysis of sodium-glucose cotransporter-2 inhibitors in patients hospitalized for heart failure. Circulation. 2025;DOI:10.1161/CIRCULATIONAHA.125.076575.
6. van Veldhuisen DJ et al. Efficacy and safety of low-dose digoxin in patients with heart failure. Rationale and design of the DECISION trial. Eur J Heart Fail. 2024;26(10):2223-30.
7. Rossello X et al. β blockers after myocardial infarction with mildly reduced ejection fraction: an individual patient data meta-analysis of randomized controlled trials. Lancet. 2025;DOI:10.1016/S0140-6736(25)01592-2.