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HEART FAILURE NEWS

The month in heart failure! September 2024

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In this column, we provide brief and concise summaries of recent distinctive studies published in the *European Journal of Heart Failure* over September 2024 (*Figure 1*). One study updates the previously published European Society of Cardiology (ESC) quality indicators (QIs) for heart failure (HF), ensuring they align with the latest evidence.[1] Another study examined the impact of canagliflozin on total HF events, focusing on patients with type 2 diabetes (T2D) at high cardiovascular (CV) risk, considering their baseline kidney function.[2] Additionally, a study evaluated the effect of dapagliflozin according to QRS duration across the spectrum of left ventricular ejection fraction (LVEF).[3] Finally, novel data explored the global landscape of glycolytic intermediates and their related synthetic and catabolic enzymes in human HF with preserved ejection fraction (HFpEF) myocardium.[4]

European Society of Cardiology quality indicators update for the care and outcomes of adults with heart failure

In 2022, the ESC, in collaboration with the Heart Failure Association (HFA), established a set of QIs for the management of adults with HF.[5] These QIs have been used to assess adherence to and outcomes associated with HF therapies.[6–8] Additionally, they defined a specific process of care, enabling the interpretation of real-world evidence data.[9,10] With the release of the 2023 ESC focused guideline update for HF,[11] it became necessary to reappraise the existing QIs and develop new ones as needed. The ESC's established methodology for QI development was followed.[12] Five domains of care for the management of HF were identified[1]: (1) structural QIs, (2) patient assessment, (3) initial treatment, (4) therapy optimization, and (5) patient health-related quality of life. In total, 14 'main' and 3 'secondary' QIs were selected across the five domains.

The key new QIs focus on follow-up within 6 weeks after a HF event, the use of sodium–glucose cotransporter 2 inhibitors across the LVEF spectrum, and the administration of intravenous iron in patients with HF and reduced ejection fraction (HFrEF) or mildly reduced ejection fraction (HFmrEF) who have concomitant iron deficiency. This proposed set of QIs is intended to support the integration and assessment of adherence to clinical practice guidelines, allowing institutions to monitor, compare, and improve the quality of care provided to HF patients.

Canagliflozin reduced the total burden of heart failure hospitalizations, with consistent benefits observed across the kidney function spectrum

People with T2D are at high risk of (recurrent) HF hospitalization, especially as kidney function declines.[13–15] Vaduganathan *et al.*[2] examined the effects of canagliflozin from the CANVAS Programme ($n = 10\,142$)[16] and CREDENCE trial ($n = 4401$)[17] on total HF events by baseline kidney function in patients with T2D at high CV risk and/or with chronic kidney disease. In this integrated, participant-level, pooled analysis across three contemporary trials of nearly 15 000 participants with T2D at high CV risk and/or with established chronic kidney disease, canagliflozin significantly reduced the risk of first and total HF events, and the composite of CV death and total HF hospitalizations events (mean event ratio 0.63, 95% confidence interval [CI] 0.54–0.73). For individuals who were hospitalized for HF, treatment with canagliflozin was associated with delayed time to second HF hospitalization by ~4 months. These observed HF benefits were highly consistent across the range of estimated glomerular filtration rate, with larger absolute benefits in participants who had worse kidney function at baseline. These data underscore the HF benefits of canagliflozin in individuals with T2D and support canagliflozin's role not only in preventing initial HF events but also in delaying the time between first and subsequent HF hospitalizations.

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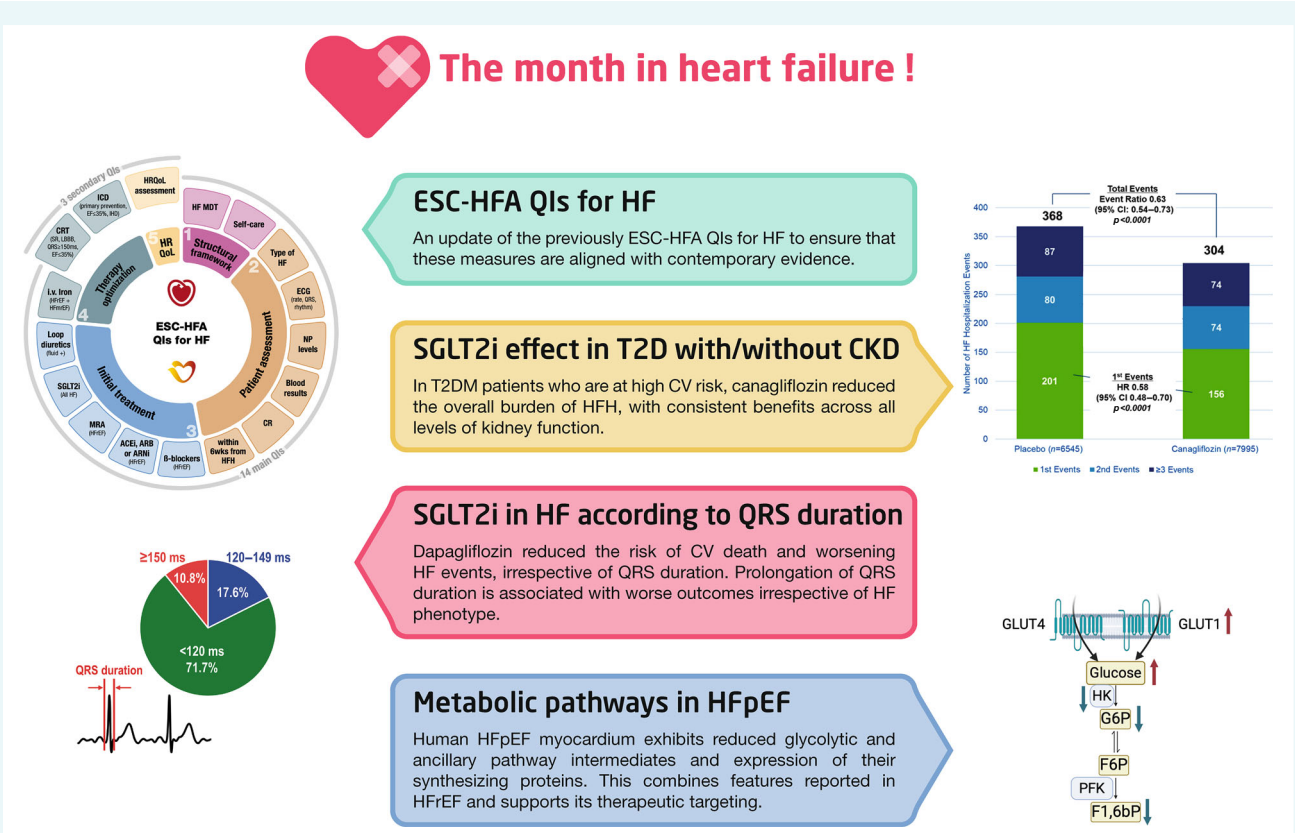

Figure 1 Key messages from latest heart failure studies. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor–neprilysin inhibitor; CI, confidence interval; CKD, chronic kidney disease; CR, cardiac rehabilitation; CRT, cardiac resynchronization therapy; CV, cardiovascular; ECG, electrocardiogram; EF, ejection fraction; ESC-HFA, Heart Failure Association of the European Society of Cardiology; HF, heart failure; HFH, heart failure hospitalization; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; HRQoL, health-related quality of life; ICD, implantable cardioverter-defibrillator; IHD, ischaemic heart disease; LBBB, left bundle branch block; MDT, multidisciplinary team; MRA, mineralocorticoid receptor antagonist; NP, natriuretic peptide; QI, quality indicator; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SR, sinus rhythm; T2D, type 2 diabetes.

Dapagliflozin reduced the risk of cardiovascular death and worsening heart failure events, regardless of QRS duration and heart failure phenotype

Intraventricular conduction delay, with prolongation of QRS duration, occurs in up to 30% of HF patients.[18] Prolonged QRS duration is a known predictor of poor outcomes in HFrEF patients.[19] This led to the question as to whether any new treatment can improve outcomes in patients with longer QRS duration.[20–22]

A pooled analysis of the DAPA-HF[23] and DELIVER[24] trials was performed. Overall, 4008 patients had HFrEF, and 5816 had HFmrEF/HFpEF. QRS duration was <120 ms in 71.7%, 120–149 ms in 17.6%, and ≥150 ms in 10.8%. The rate of the primary composite outcome of CV death or worsening HF was 9.2 (95% CI 8.7–9.7), 14.3 (13.0–15.7), and 15.9 (14.1–17.9) per 100 patient-years in the <120, 120–149, and ≥150 ms groups, respectively. Dapagliflozin, compared with placebo, reduced the risk of the primary outcome consistently across the QRS duration subgroups (hazard ratio [HR] [95% CI] 0.75 [0.67–0.85], 0.79 [0.65–0.96], and 0.89 [0.70–1.13] in the <120, 120–149, and ≥150 ms groups, respectively; p for interaction = 0.28). The effect of dapagliflozin on the primary outcome was consistent across the QRS duration regardless of HF phenotype that is, HFrEF or HFmrEF/HFpEF.[3]

Heart failure with preserved ejection fraction myocardium exhibits reduced glycolytic and ancillary pathway intermediates and expression of their synthesizing proteins

In HFpEF, obesity and diabetes mellitus (DM) are prevalent comorbidities, prompting investigations into potential myocardial

metabolic defects.[25–27] Despite this interest, the specific profile of a key metabolic pathway—including glycolytic intermediates, their regulatory enzymes, and associated pathways—remains inadequately defined. To address this gap, Koleini *et al.*[4] conducted an analysis of the glycolytic landscape in HFpEF myocardium using endomyocardial biopsies from 37 HFpEF patients and 21 non-failing controls. These biopsies were evaluated using both non-targeted and targeted metabolomics, along with immunoblotting, to assess metabolites and the protein expression of enzymes involved in glycolysis and related pathways. The study revealed elevated glucose levels and increased GLUT1 expression in HFpEF patients. However, key glycolytic intermediates—glucose-6-phosphate, fructose-1,6-bisphosphate (F1,6bP), and 3-phosphoglycerate—were significantly reduced by 78%, 91%, and 73%, respectively, compared to controls. Notably, these metabolic differences could not be explained by variations in body mass index, DM history, sex, or age between the control and HFpEF groups. Furthermore, pronounced obesity was linked to even greater reductions in F1,6bP and phosphoenolpyruvate. Many of these features more closely resemble those seen in HFrEF rather than DM, suggesting that neither obesity nor DM were the primary drivers of these disparities. Together with previous findings, these results underscore the metabolic inflexibility in HFpEF and reinforce the need to target it therapeutically.[28,29]

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