Empowering European hospital pharmacists in the face of heart failure

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European hospital pharmacists can play a crucial role in the care of heart failure (HF). In this editorial, we highlight that our profession is well suited for the task, and provide evidence that pharmacist support is highly valued in HF management.[1 2]

HF is a high-risk condition with growing prevalence, and is predominantly treated with pharmacotherapy. In the developed world, it currently affects 1–2% of the population, with a notable age dependency.[3] Among individuals aged 70 years and older, the prevalence of HF exceeds 10%. This progressive condition, characterised by a mismatch between the heart's ability to meet the body's demands, causes typical symptoms, such as fatigue and fluid retention, which significantly impair the patient's quality of life. HF leads to considerable morbidity and mortality.[3 4]

Even in so-called 'stable' chronic HF, patients still endure a high residual HF burden. For example, the recent Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) study revealed a staggering 7.9% all-cause mortality at 1 year among ambulatory chronic HF patients who received dapagliflozin. The risks are even greater for those who experienced an acute HF episode, constituting up to 25% of all HF patients. This high-risk group faces a 90-day mortality of up to 15% after hospital discharge, with 30% experiencing readmission during the same period.[3] Healthcare utilisation in HF is greatly affected by the numerous readmissions, making HF one of the leading causes of hospital admissions for older adults.[3] This syndrome accounts for approximately 1–2% of national health expenditures in developed countries.[5]

Given the substantial impact on both patients and healthcare systems, it is imperative to promptly implement guideline-recommended medical therapies in as many eligible HF patients as possible. Guidelines recommend the use of life-saving drugs, including sodium-glucose cotransporter-2 inhibitors, angiotensin receptor neprilysin inhibitors, beta-blockers and mineralocorticoid receptor antagonists. The combination of these four drug classes has been coined as 'the four pillars', 'the fantastic four' or 'the foundational drugs'. These terms are well deserved, owing to the significant complementary reduction in all-cause mortality, as indicated by an HR of 0.39 (95% CI 0.31 to 0.49).[6] This reduction corresponds to a remarkable estimated number-need-to-treat of only four for all-cause mortality at 2 years.

However, guideline implementation remains inadequate, and has been linked to poorer HF outcomes.[7 8] As a result, effective strategies are needed to enhance the adoption of these proven therapies.[9] Considering the high burden of HF as well as the substantial reduction in mortality achievable through evidence-based therapies, there is no time to waste in initiating, titrating and monitoring these life-saving agents.

In response to these challenges, comprehensive care programmes in HF management have gained increased attention in recent years. These programmes entail a holistic approach that surpasses conventional medical treatment and encompasses patient education and multidisciplinary collaboration across the care continuum.[4] In this context, hospital pharmacists have emerged as valuable team members.[2 10] Their expertise in medication management enables them to meet the specific needs of HF patients.[11] Particularly for hospital pharmacists involved in the transitional care of high-risk HF patients, compelling evidence shows a reduction in all-cause hospital readmissions.[10 12]

Consequently, it is incumbent on the hospital pharmacy profession to proactively address the issue of (its role in) HF care. A framework for pharmacist involvement has been established in previous work, along with minimum competencies for appropriate care provision.[13] Unfortunately, HF does not appear to be a routine part of most European hospital pharmacists' clinical duties. In a recent meta-analysis conducted by Parajuli *et al* on the impact of pharmacist involvement on clinical outcomes in HF, only a scant 10% of the data were extracted from Europe-based trials where hospital pharmacists performed the intervention during hospital stay.[10] For instance, in Belgium, almost no hospital pharmacists are actively involved in HF care.

Furthermore, given the constantly evolving cardiovascular pharmacotherapy landscape, we recognise that motivated hospital pharmacists should have access to accredited training in this domain.[11] Currently, available options are limited, one notable example being the Cardiology Pharmacy Specialty Certification offered by the Board of Pharmacy Specialties (https://bpsweb.org/cardiology-pharmacy/).

In this editorial, therefore, we aim to motivate and inspire hospital pharmacists to become more involved in HF care. Additionally, our goal is to equip colleagues with insights into novel therapies that can be integrated into their everyday practice. To fulfil these goals, we selected two relevant clinical practice guidelines and five major investigations from the 2023 European Society of Cardiology (ESC) meeting, all of which have been published in peer-reviewed journals. These guidelines were chosen based on their potential to influence clinical practice and patient care, encompassing a range of HF scenarios from acute decompensation to chronic management. The selected ESC guidelines pertain to the 2023 Focused Update on Heart Failure and the Management of Cardiomyopathies.[14 15]

Next, the following HF investigations were selected, in no particular order: Pragmatic Urinary Sodium-based Treatment algoritHm in Acute Heart Failure (PUSH-AHF), Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR kidney), Catheter Ablation for Atrial Fibrillation in patientS With End-sTage Heart Failure and Eligibility for Heart Transplantation (CASTLE-HTX), Ferric Carboxymaltose in Heart Failure with Iron Deficiency (HEART-FID) and Semaglutide in Patients with Heart Failure

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with Preserved Ejection Fraction and Obesity (STEP-HFpEF).[16–20]

GUIDELINES AND TRIAL FINDINGS

The summary of the guidelines can be consulted in the online supplemental materials (new HF guidelines). For the selected studies, we have summarised and tabulated the trial findings to enable hospital pharmacists to comprehend the place as well as the importance of these new data. It is crucial to note that this summary is *not* intended as a critical trial appraisal. Rather, it serves as an invitation for the readers of this journal to explore further trial findings in the HF field. This table can also be found in the Supplementary Materials (online supplemental table 1).

CONCLUSION

Hospital pharmacists can and should play a pivotal role in optimising patient outcomes in HF. As medication experts, their involvement in HF care programmes cannot be overlooked. By fostering a deeper understanding of the evolving HF landscape, we envision that hospital pharmacists will increasingly become invaluable partners in multidisciplinary HF care teams, enhancing the quality of care delivered to HF patients.

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New HF guidelines

Management of HF

The ESC 2023 Focused Update on HF provided targeted recommendations on new pharmacotherapy.[1] In this update, the use of dapaglifozin or empagliflozin was now also expanded to heart failure with mid-range ejection fraction (HFmrEF, EF 41-49%) and to heart failure with preserved ejection fraction (HFpEF, EF≥50%) to reduce the risk of HF hospitalization or cardiovascular (CV) death. As a result, there now is a broad evidence base to consider these gliflozins in all-comer HF patients, regardless of the ejection fraction.[2] At the minimum, both gliflozins reduce HF hospitalizations by about 30% (HR: 0.71; 95% CI: 0.67-0.77). The impact on *all-cause* hospitalizations is dependent on the ejection fraction however, as HF hospitalizations constitute a larger portion in heart failure with reduced ejection fraction (HFrEF, EF≤40%), compared to HFmrEF and HFpEF. Also, an intensive strategy was promoted to initiate and rapidly up-titrate evidence-based treatments before discharge and during frequent and careful follow-up visits in the first weeks after an HF hospitalization to reduce the risk of HF rehospitalization or death. Informed by the recent STRONG-HF data, there is nothing to be gained from postponing trial-proven therapies in HF.[3] Conversely, it is crucial to identify patients before discharge and to implement a strategy to both initiate and uptitrate GDMT in as many patients as possible, as rapidly as possible. Particularly with regard to the latter, hospital pharmacists can play a major role, leveraging electronic health records to identify un(der)treated HF patients, working on multidisciplinary inpatient guidelines, and implementing GDMT uptake strategies before and after discharge.

Intravenous (IV) iron supplementation was recommended in symptomatic patients with HFrEF and HFmrEF, who also had documented iron deficiency, to alleviate HF symptoms and improve the quality of life. With less certainty, IV iron supplementation should be considered in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to reduce the risk of an HF hospitalization.

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Prevention of HF

In patients with both type 2 diabetes and chronic kidney disease *but without HF*, the use of the same two SGLT2 inhibitors was also recommended to reduce the risk of a first HF hospitalization or CV death, based on DAPA-CKD and EMPA-KIDNEY.[4, 5] In the same patient cohort, the use of finerenone was recommended as well, to reduce the risk of a first HF hospitalization.[6]

Cardiomyopathies

At ESC 2023, the Guidelines for the management of cardiomyopathies were presented as well.[7] Herein, all data were assembled with regard to the diagnosis and treatment of several cardiomyopathy entities, among which transthyretin cardiac amyloidosis and hypertrophic cardiomyopathy. At the very least, this guideline is relevant to hospital pharmacists given that recent trials have now identified effective treatments for these conditions, the transthyretin stabilizer tafamidis and the cardiac myosin ATPase inhibitor mavacamten respectively. In the ATTR-ACT study (n=414), use of tafamidis versus placebo led to more wins, leading to a win ratio of 1.695 (95% CI:1.255 - 2.289), which coincided with a substantial reduction of mortality (HR: 0.70; 95% CI: 0.51 - 0.96).[8] For mavacamten, we have data from two pivotal trials which showed that it improved functioning and symptom burden to such a degree that 58.9% fewer patients (95% CI: 44.0-73.9%, p<0.001) underwent septal reduction therapy, a therapeutic option in hypertrophic cardiomyopathy reserved for those with intractable symtoms.[9, 10] Importantly, given that CYP219 plays a major role in mavacamten's exposure, patients should be genotyped as per the package insert, to avoid overexposure in poor metabolizers.

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Supplementary Table 1: A short summary on five selected heart failure trials presented at the 2023 meeting of the European Society of Cardiology

Study	Setting and design	Patients	N	Follow-up	Comparison	Outcomes	Main Results	Relevance for pharmacists
PUSH-AHF[1]	Single-center, open-label, randomized controlled trial	Acute HF patients requiring IV loop diuretics	310	6 months	Natriuresis--guided vs. standard diuretic therapy	Effect on natriuresis and clinical outcome	Natriuresis-guided approach increased natriuresis (409 vs. 345 mmol, p = 0.0061) No significant difference in all-cause mortality or HF rehospitalization rates Safety and feasibility demonstrated	Pragmatic trial in a generalizable acute HF patient population. A soft endpoint was chosen. The validation of a previous consensus-derived proposal, is important as there is only very limited guidance on how to use loop diuretics in the acute phase.[2]
ADVOR kidney[3]	Prespecified analysis within the ADVOR trial	Acute HF patients requiring IV loop diuretics	519	3 months	Acetazolamide + IV loop diuretics vs. IV loop diuretics	According to baseline renal function: the acetazolamide effects on decongestion, diuresis, natriuresis estimated glomerular filtration rate and clinical outcome	Acetazolamide retains diuretic efficacy across a broad range of renal function Increase in worsening renal function with acetazolamide (40.5% vs. 18.9%, p < 0.001), but without impact on creatinine levels or heart failure outcomes	Acetazolamide remains effective. It does not improve hard clinical outcomes per se however. The analysis does show the association between 'dry at discharge' and better HF outcomes. The main takeaway is that IV acetazolamide was associated with a

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								shorter hospital stay, and less congestion at discharge.
CASTLE-HTX[4]	Single-center, open-label, randomized controlled trial	Patients with symptomatic AF and end-stage HF	194	18 months	Catheter ablation vs. usual care	Composite of death left ventricular assist device, urgent heart transplant	Reduction of primary outcome in favor of ablation (8% vs. 30%,p<0.001) Reduced deaths (6% vs. 20%)	Arrhythmia burden is an important determinant of prognosis in patients with AF and HF. It is unclear to what extent trial findings can be translated to clinical practice due to certain limitations (single-center, unblinded, very large, and very fast risk reductions based on a few events).
HEART-FID[5]	Double-blind, randomized, placebo-controlled trial	Ambulatory HFrEF patients with iron deficiency	3065	12 months	IV iron (ferric carboxymaltose) vs. placebo	Hierarchical composite of death, HF hospitalizations, 6-minute walk distance	No significant difference in the composite primary endpoint IV iron vs. placebo: Mortality: 8.6% vs. 10.3%, p-value not specified HF hospitalizations: 297 vs. 332, p-value not specified	After previous trials, it is not completely certain what IV iron holds for HF patients in terms of reducing morbidity, particularly on the current GDMT background. At a minimum, IV iron improves functionality, and QoL and likely reduces HF

							Modest effect on 6-minute walking distance (p=0.02) The use of IV iron wassafe	readmissions in AHF patients.[6]
STEP-HFpEF[7]	Double-blind, randomized, placebo-controlled trial	HfpEF patients with obesity	529	57 weeks	Semaglutide vs. placebo	Change from baseline in the KCCQ-CSS score and body weight	KCCQ-CSS score change higher in the semaglutide group: (16.6 vs 8.7, p < 0.001) Greater weight loss in semaglutide group (-13.3% vs. -2.6%, p<0.001) Improved 6-minute walk distance and NT-proBNP reduction	Some might argue whether this was an obesity study or a 'real' HFpEF investigation. Patients lost weight and felt better. The trial was not designed for HF outcomes but importantly did highlight the safety of intentional weight loss in HF (hence, refuting the so-called obesity paradox in HF).

Abbreviations: HF: heart failure; IV: intravenous; AF: atrial fibrillation; HFrEF: heart failure with reduced ejection fraction; GDMT: guideline-directed medical therapy: AHF: acute heart failure; HFpEF: heart failure with preserved ejection fraction; KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score; NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

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