

November 2023 at a glance: Focus on cardiogenic shock, post-discharge outcomes and cardiomyopathies

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HFA consensus paper and state-of-the-art reviews

Biomarkers have a key role in the management of heart failure (HF).^{1–5} However, natriuretic peptides have been used mainly to rule out HF whereas threshold to use them to make a diagnosis of HF are needed. Bayes-Genis *et al.*⁶ provided practical algorithms for early diagnosis of HF and ‘heart stress’, i.e. asymptomatic cardiac dysfunction, using N-terminal pro-B-type natriuretic peptide (NT-proBNP) in a consensus paper by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC).

Major advances have occurred in the treatment of cardiomyopathies.^{7,8} Contemporary treatment of dilated, hypertrophic, restrictive and arrhythmogenic cardiomyopathy is summarized and discussed in an extensive review.⁸

Pathophysiology

Buckley *et al.*⁹ investigated the association between neutrophil-related proteins concentrations and adverse cardiac remodelling among patients from the ARIC study. Higher neutrophil activity was associated with a higher likelihood of incident HF and left ventricular (LV) dysfunction.

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome with different phenotypes.^{10–13} Among them, obesity is common and may define a specific one.^{10–12} Chin *et al.*¹⁴ showed that increased epicardial adipose tissue thickness is associated with subclinical cardiac dysfunction in subjects with severe obesity and no known history of cardiovascular (CV) disease, referred to bariatric surgery.

Degenerative aortic valve stenosis (AVS) with preserved ejection fraction (EF) might represent a specific sub-phenotype of HFpEF. In a prospective study, 148 patients with HFpEF, 150 patients with degenerative moderate-to-severe AVS with preserved EF and 66 age- and sex-matched healthy controls underwent functional capacity measurements. Functional capacity was similarly impaired in AVS and HFpEF patients due to both peripheral and central components. Epicardial adipose tissue thickness was inversely correlated with peak oxygen consumption in all subjects, was

greater and directly related to echocardiography-derived disease severity and computed tomography-derived aortic valve calcium burden in patients with AVS and preserved EF.¹⁵

Prognostic variables

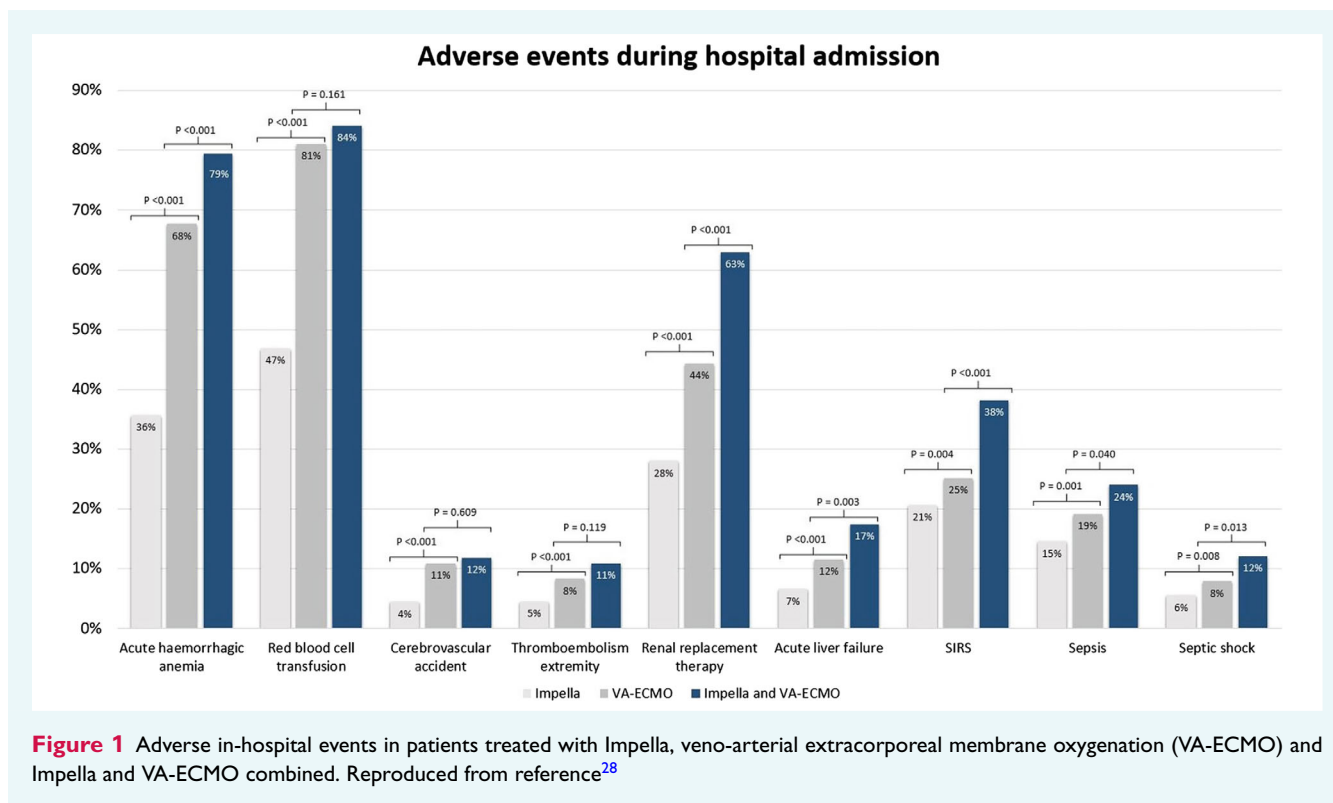
The LIFE-HF model was developed with the aim to provide a prediction of individual (lifetime) risk and treatment benefit in patients with HF and reduced ejection fraction (HFrEF) using data from the PARADIGM-HF and ATMOSPHERE trials ($n = 15\,415$). It was then validated in the SwedeHF registry, ASIAN-HF registry, and DAPA-HF trial ($n = 51\,286$). This model allows a more personalized approach to patients with HFrEF with the calculation of their lifetime duration and of the benefits of treatment.¹⁶

Patients with HF and improved ejection fraction (HFimEF) may represent a specific subgroup of patients.^{12,17} Among 7948 patients enrolled in the Metabolic Exercise Cardiac Kidney Indexes (MECKI) score database, 1504 had HFimEF and were compared to patients with persistently reduced EF ($n = 6017$). HFimEF patients presented a less severe condition and lower mortality rates compared to the others at an unadjusted analysis but not after multivariable adjustment.¹⁸

Hypotension and bradycardia are among the safety indicators to be considered during the rapid up-titration of guideline-directed medical therapy.¹⁹ Using data from the QUALIFY (QUality of Adherence to guideline recommendations for LIfe-saving treatment in heart failure surveY) international registry ($n = 7317$ patients), Abdin *et al.*²⁰ investigated the relationship between resting heart rate (HR) and systolic blood pressure (SBP) and outcome in patients with HFrEF. Compared to the reference group, higher HR and lower SBP were associated with the highest risk of the combined primary endpoint of CV death and HF hospitalization.

Acute heart failure and post-discharge management

The early post-discharge phase is associated with an increased risk of death and rehospitalizations in the patients hospitalized



due to worsening HF.^{21,22} The impact of non-cardiac comorbidities were investigated in 1078 patients recently admitted for HF in the STRONG-HF trial. Eight comorbidities were considered, and patients were stratified according to their number. The presence of multiple comorbidities neither limited the rapid up-titration of HF therapies, nor attenuated the benefit of high-intensity care on the primary endpoint.²³

Patients with an advanced HF might benefit from intermittent inotropic therapy.²⁴ LeoDOR was a prospective multicentre, double-blind, placebo-controlled trial investigating the safety and efficacy of two regimens of intermittent levosimendan infusions in patients with advanced HF recently hospitalized for acute decompensation. The trial was stopped earlier for slow recruitment during the COVID-19 pandemic. Treatment with levosimendan did not improve the primary endpoint, which was a composite of death, urgent need of mechanical circulatory support, new episodes of decompensation and change in NT-proBNP plasma concentrations.²⁵ Further studies are needed regarding inotropic treatment of acute HF.²⁶

Cardiogenic shock

Cardiogenic shock is still burdened by a very high risk of mortality.²⁷ A large European observational study investigated the use of Impella and venoarterial extracorporeal membrane oxygenation (VA-ECMO) in acute myocardial infarction-related cardiogenic shock (AMICS) in 2020–2021. Impella and/or VA-ECMO were used in 20% of AMICS cases. Impella was more frequently used in older patients, while VA-ECMO use was more common among

patients who suffered from an out-of-hospital cardiac arrest. Patients treated with Impella, compared to those on VA-ECMO, had a slightly lower in-hospital mortality (61% vs. 67%, $p = 0.001$) and less adverse events including acute haemorrhagic anaemia (36% vs. 68%), cerebrovascular accidents (4% vs. 11%), peripheral thromboembolisms (5% vs. 8%), systemic inflammatory response syndrome (21% vs. 25%), acute kidney injury (44% vs. 53%), and acute liver failure (7% vs. 12%) (Figure 1). The average index in-hospital costs for patients supported with Impella, VA-ECMO and Impella + VA-ECMO were of €36 655.18, €43 322.53 and €66 150.86, respectively, rising to €93 060.85, €130 703.27, and €218 061.87, respectively, in the survivors.²⁸

The optimal timing of LV unloading during VA-ECMO for cardiac arrest or shock remains unknown. Between December 2018 and August 2022, 60 patients at two centres in Korea were randomized in a 1:1 ratio to receive early ($n = 30$) or conventional ($n = 30$) LV unloading strategies. LV unloading was performed using a percutaneous transeptal left atrial cannulation via the femoral vein incorporated into the ECMO venous circuit. The early strategy did not improve the VA-ECMO weaning rate, despite the more rapid improvement in pulmonary congestion.²⁹

Cardiomyopathies

Hammersley *et al.*³⁰ described phenotypes, clinical outcomes and rates of disease progression in patients assessed by late gadolinium enhancement CV magnetic resonance at an early-stage of non-ischaemic cardiomyopathy. Patients were classified into different subgroups: isolated LV dilatation, non-dilated LV

cardiomyopathy, or early dilated cardiomyopathy. Myocardial fibrosis was present in 65 of the 256 patients (26%). There was no difference in its prevalence between subgroups. Non-sustained ventricular tachycardia (hazard ratio [HR] 5.1, 95% confidence interval [CI] 2.36–11.00, $p < 0.001$), myocardial fibrosis (HR 3.77, 95% CI 1.73–8.20, $p < 0.001$) and diabetes mellitus (HR 5.12, 95% CI 1.73–15.18, $p = 0.003$) were associated with major adverse CV events in a multivariable model.

The prevalence of transthyretin amyloid cardiomyopathy (ATTR-CM) is rapidly growing.^{31–33} Tafamidis is now recommended for the treatment of patients with ATTR-CM and New York Heart Association (NYHA) class I or II symptoms to reduce symptoms, CV hospitalization and mortality.^{4,7,34} Elliott *et al.*³⁵ assessed long-term all-cause mortality in patients with NYHA class III symptoms enrolled in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) long-term extension (LTE) study (31.3% of the patients receiving tafamidis and 35.6% of those on placebo). The risk of all-cause mortality was reduced with continuous tafamidis treatment compared with delayed tafamidis treatment (placebo then tafamidis) over a median follow-up of approximately 5 years, emphasizing the importance of early treatment.

Comorbidities

Screening for and treatment of iron deficiency (ID) with intravenous ferric supplementation is recommended in patients with HF.^{4,36–38} Three different definitions of ID are available: (i) serum ferritin concentration of < 100 ng/ml, or $100–299$ ng/ml with transferrin saturation $< 20\%$ (guideline definition), (ii) serum iron concentration ≤ 13 $\mu\text{mol/L}$, or (iii) transferrin saturation $< 20\%$. Papadopoulou *et al.*³⁹ evaluated these definitions of ID in 801 consecutive patients referred for heart transplantation at a single UK centre between January 2010 and May 2022. The prevalence of ID varied from 39% to 55% according to the definition. ID, defined by either serum iron or transferrin saturation, was associated with an increased rate of adverse clinical outcomes.

Chronic obstructive pulmonary disease (COPD) worsens the prognosis in patients with HF and mildly reduced ejection fraction or HFpEF. A pre-specified analysis of the DELIVER trial investigated the association between baseline COPD and the safety and efficacy of dapagliflozin. Dapagliflozin was consistently beneficial, regardless of baseline concomitant COPD.⁴⁰

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