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May 2023 at a glance: focus on pathophysiology, comorbidities and devices

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Win ratio approach

The win ratio is increasingly used as a statistical tool to include multiple variables related both with outcomes as well as symptoms and quality of life and thus gain statistical power from smaller study groups.[1,2] The EMPULSE trial evaluated the clinical benefit of empagliflozin versus placebo in 530 patients with acute heart failure (HF) after initial stabilization using the stratified win ratio approach.[2] Based on the experience from the EMPULSE trial, Pocock *et al.*[3] elucidated how the win ratio method works and what it means, in order to favour its use in future trials. The investigators of the EMPULSE trial were able to integrate deaths, clinical events and patient-reported outcomes into a win ratio strategy, highlighting the most meaningful clinical findings related to patients' benefits.

Natriuretic peptides

Biomarkers are foundation of current management of HF.[4–9] The role of natriuretic peptides to establish the diagnosis of HF is established in international HF guidelines.[10–12] A scientific statement by three HF Societies (Heart Failure Association of the European Society of Cardiology, Heart Failure Society of America and Japanese Heart Failure Society) provides a comprehensive and updated perspective for the use of natriuretic peptides in the prognostic stratification, management and treatment of HF.[13]

Pathophysiology

Giannoni *et al.*[14] reviewed recent evidence regarding chemoreflex physiology and pathophysiology with desensitization of hyperactive chemoreceptors that is emerging as a potential therapeutic option for patients with hypertension and HF.[14]

It has recently been observed that left ventricular ejection fraction (LVEF) may have a U-shaped relationship with mortality with an increase in the risk of death also in patients with a LVEF >65%.[15,16] These patients with supranormal (sn) LVEF (HFsnEF) may have peculiar characteristics compared to those with preserved ejection fraction (HFpEF), with a higher risk of events and a lower response to medical treatment, namely neurohormonal antagonists.[16–20] A recent study included 621 patients with HFpEF, of whom 302 had HFsnEF. Patients with HFsnEF, compared to those with HFpEF and LVEF <65%, had a smaller heart size, increased left ventricular diastolic stiffness, and leftward shift in the end-diastolic pressure–volume relationship.[21] Based on these results, Packer proposed updated categories of HF based on LVEF: (1) LVEF ≤35%; (2) LVEF >35% to <60–65%; and (3) LVEF >60–65%.[22]

Comorbidities

The impact of comorbidities was examined among a total of 15 066 patients from the PARADIGM-HF and ATMOSPHERE trials. The authors found that patients with co-existent peripheral artery disease and stroke were at greatest individual risk whereas chronic kidney disease and hypertension had the highest population attributable fractions for all-cause death.[23]

Body mass index (BMI) and obesity might influence the efficacy of evidence-based treatment. However, the beneficial effects of gliflozins were similar across a wide range of BMI in a recent analysis.[24,25] Cappelletto *et al.*[26] investigated the use of guideline-recommended medical therapy in obese versus non-obese patients with HF and reduced ejection fraction from the Swedish HF Registry. Overall, 16 116 patients were included, of whom 24% were obese. Obesity was independently associated with a higher prescription of each treatment, triple combination therapy, and the achievement of target dose by multivariable logistic regressions. Renin–angiotensin system inhibitors (RASi)/angiotensin receptor–neprilysin inhibitors (ARNi) and beta-blockers were associated with lower mortality, regardless of BMI. Furthermore, lower cardiovascular mortality was observed among obese patients treated with RASi/ARNi compared to non-obese when considering competing risk.

Skeletal muscle abnormalities and cachexia characterize a meaningful proportion of patients with advanced HF.[10,27,28] Experimental models on rats assessed the effects of the small molecule ACM-001 (0.3 or 3 mg/kg/day) in comparison to carvedilol (3 or 30 mg/kg/day), metoprolol (50 or 100 mg/kg/day), nebivolol (1 or 10 mg/kg/day) and tertatolol (0.5 or 5 mg/kg/day) on cardiac mass and function. ACM-001 showed promising results in terms of cardiac function, while different beta-blockers displayed different effects.[29]

The association between HF and hip bone mineral density (BMD) has been investigated among 141 male patients with HF undergoing dual energy X-ray absorptiometry. Patients with lower BMD were older and more sarcopenic, with higher osteoprotegerin and osteocalcin levels versus those with BMD above the median value. Among 47 patients undergoing a re-evaluation of BMD, a significant reduction in BMD was observed at 30 months. Thus, an assessment of bone status might be of help in the prevention of osteoporosis in HF patients.[30]

Amyloidosis

The diagnosis and the management of cardiac amyloidosis improved in the last years.[10,31–34] Transthyretin (ATTR) amyloidosis is a systemic disorder, caused by the deposition of the ATTR protein in different body districts, including heart, nerves, and other organ.[35] Patisiran is an RNA interference therapeutic that blocks the hepatic synthesis of the ATTR protein. The effects of patisiran on left ventricular stroke volume (SV) and mechanics was assessed in the pre-specified cardiac subpopulation of the APOLLO study. SV was determined at baseline and after 9 and 18 months of treatment. Patients treated with patisiran showed a delay in SV impairment compared to those in the placebo group as soon as at 9 months after the initiation of therapy.[36]

Devices

A better characterization of patients that could benefit from preventive implantable cardioverter defibrillator (ICD) implantation is needed.[37,38] The risk of ventricular arrhythmias and sudden death was assessed in an observational retrospective cohort study including 698 patients with non-ischaemic cardiomyopathy classified as New York Heart Association (NYHA) class I and II–III. The primary endpoint of appropriate ICD therapies, sustained ventricular arrhythmias, resuscitated cardiac arrest and sudden death occurred in 8% of patients, without significant differences across NYHA classes. Late gadolinium enhancement (LGE) was the only independent predictor of the primary outcome. Patients with NYHA class I and LGE+ presented a higher risk compared to those with NYHA class II–III and LGE–.[39]

Congestion is a landmark cause of worsening HF. Biomarker testing and novel devices could help in the assessment of congestion.[40,41] A novel device, a passive, inferior vena cava sensor was tested in a chronic ovine model. The inferior vena cava area was accurately remotely measured, providing a higher sensitivity than filling pressures.[42]

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