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EVOLUTION OF CHRONIC HEART FAILURE OVER THE PAST TWO DECADES: A COMPARATIVE LITERATURE REVIEW OF TREATMENT AND CLINICAL CHARACTERISTICS

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Introduction

Chronic heart failure (CHF) continues to be a major global health problem, accounting for substantial morbidity, mortality, and healthcare costs. Although considerable progress has been achieved in the prevention and treatment of cardiovascular diseases, the burden of CHF continues to rise. This trend is primarily driven by population aging, the growing prevalence of cardiovascular risk factors, and increased survival following acute cardiac events. Over the last two decades, significant developments have occurred in the understanding of heart failure, including changes in its epidemiology, clinical manifestations, diagnostic criteria, and therapeutic management.CHF is a multifactorial clinical syndrome that develops as a consequence of structural and functional abnormalities of the myocardium, leading to impaired ventricular filling and/or reduced cardiac output. As a result, the heart is unable to maintain sufficient circulation to meet the body's metabolic requirements.

Keywords: chronic heart failure; epidemiological trends; clinical phenotypes; pharmacological therapy; therapeutic advances; guideline-directed management

Over the past twenty years, the worldwide prevalence of CHF has increased steadily. Epidemiological studies estimate that approximately 1–2% of adults in developed countries are affected by heart failure, whereas the prevalence exceeds 10% among individuals over 70 years of age. Demographic aging and improved survival after myocardial infarction and other cardiovascular diseases have substantially contributed to this increase. At the same time, the growing incidence of obesity, diabetes mellitus, hypertension, chronic kidney disease, and metabolic syndrome has further accelerated the development of heart failure across different populations.The etiological spectrum of CHF has also undergone important changes. While ischemic heart disease and uncontrolled hypertension were previously considered the predominant underlying causes, recent evidence indicates an increasing contribution of metabolic disorders, atrial fibrillation, chronic kidney disease, and age-associated cardiovascular remodeling. Consequently, patients with CHF are now more likely to present with multiple chronic comorbidities and receive numerous concomitant medications, making disease management increasingly challenging. These evolving clinical characteristics have emphasized the importance of individualized treatment approaches, multidisciplinary care, and comprehensive long-term management aimed at improving survival and quality of life. For a long time, HF therapy was limited to relieving congestion with diuretics and improving the cardiac output, reducing the afterload, and increasing contractility with vasodilators and inotropes, respectively. Subsequently, triple neurohormonal blockade and then quadruple therapy have become the standard of care (SoC). To date, several different pathways are successfully targeted with novel drugs [1,2]. Thus, HF

specialists went from an era in which disease-modifying therapies were lacking to a new era, where they needed to tailor pharmacologic treatment according to patients' phenotype. However, now physicians struggle to reach target doses and choose the proper sequence in which to introduce all recommended therapies. Indeed, when novel drugs reach phase III randomized controlled trials (RCTs), they are usually compared to a placebo on top of the SoC. Since plenty of therapies have proved effective, and head-to-head comparisons are unlikely, their respective efficacy is uncertain. In this regard, Pagnesi et al. conducted an NMA including 12 RCTs. Most of them compared Sodium Glucose Transporter 2 inhibitors (SGLT2is) to placebo, whereas two RCTs evaluated Vericiguat, and two studies randomized patients to omecamtiv mecarbil in the experimental group. SGLT2is were found to be superior to Vericiguat and omecamtiv mecarbil on the primary endpoint (a composite of cardiovascular death and HF-related hospitalizations). However, authors correctly identified differences in baseline characteristics (background use of angiotensin receptor neprylisin (ARNI), percentage of New York Heart Association (NYHA) III/IV class patients, N-Terminal Pro-B-Type Natriuretic Peptide (proBNP-NT) levels) as relevant limitations. Despite the triumphs of translational research, HF mortality is still high, comparable to many cancers. In this context, dedicated devices have become crucial to improving clinical outcomes. Besides implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT), several new devices targeting structural abnormalities or modulating autonomic, electrophysiological, and respiratory systems are under investigation. An extensive review of valvular devices is provided by Cammalleri. As for autonomic modulation, growing evidence supports fluid redistribution as a critical process in the worsening of HF. Indeed, many patients do not experiment with fluid retention and weight gain before decompensation. Preclinical investigations demonstrated that the adrenergic system heavily supplies splanchnic circulation and, when stimulated, shifts a large amount of blood to the thoracic compartment. On the one hand, in healthy subjects, this is an essential mechanism to support increases in cardiac output.

On the other hand, its dysregulation in HF may contribute to a further increase in filling pressure and exercise intolerance. These concepts lead investigators to assess different approaches towards a common target: the greater splanchnic nerve (GSN) [4]. In this Special Issue, we present a pre-specified retrospective analysis of a single-arm, two-center, open-label prospective study evaluating permanent surgical ablation of the right GSN via thoracoscopic surgery in hemodynamic-adjudicated HF with preserved ejection fraction (HFpEF) patients (Surgical Resection of the Greater Splanchnic Nerve in Subjects Having Heart Failure With Preserved Ejection Fraction, NCT03715543). In this study, Gajewski et al. (Contribution 6) demonstrated that hemodynamic effects are appreciable 24 h after the procedure. As with ICD and CRT, cardiac contractility modulation (CCM) therapy is provided by leads positioned in the right ventricle. Recently, the interplay between cardiac implantable electronic devices (CIEDs) and tricuspid regurgitation (TR) has been reviewed and recognized as a distinct clinical entity that increased the risk of death [3,5]. Herein, a unique prospective study aimed to assess TR after CCM implantation was published by Masarone et al. Nearly half of the cohort had moderate TR, whereas patients with severe regurgitation were excluded. Conversely, the use of DOACs was linked to significantly fewer bleedings (both overall and gastrointestinal). Advances in immunosuppression regimens have improved outcomes and reduced rejection rates. However, recipients are exposed to a high infection risk. Thus, antimicrobial prophylaxis is a milestone in their comprehensive management. Pneumocystis Jiroveci is an increasingly diagnosed opportunistic pathogen, especially within the first six months post HTx. Trimethoprim-sulfamethoxazole (TMP-SMX) is the first choice. Allergic or intolerant patients are usually switched to Dapsone. This latter option, however, has a

less favorable safety profile than TMP-SMX. Indeed, documented glucose-6-phosphate dehydrogenase (G6PD) deficiencies may trigger hemolytic anemia. In this Special Issue, Lor et al. present a retrospective study of HTx patients who received prophylaxis with Dapsone after normal G6PD activity was documented.

Interestingly, 22% of patients developed significant anemia, and nearly 10% required hospitalization or blood transfusion. On the other hand, Dapsone withdrawal resulted in the rapid recovery of baseline hemoglobin levels. Therefore, periodic laboratory monitoring with a blood count is advisable. Besides long-term management, the main issue remains donor shortage. Hence, it is crucial to broaden the pool of potential donors to decrease the death rates among patients on the waiting list. AB0 compatibility is an essential prerequisite to HTx. Indeed, ABH antigens are expressed both on red blood cells and endothelial cells. Thus, ABO antibodies are responsible for hyperacute rejection. Historically, zero patients had longer wait times, since recipients with high titers of antibodies received no organs. AB0-independent approaches were successfully implemented in kidney and liver transplantation to overcome this barrier, leading to higher transplantation rates and reduced wait times without significant safety drawbacks. Limited data, however, exist for this approach in HTx. Cao et al. compared the outcomes between match and mismatch groups of patients with blood type A. The mismatch group was further divided based on donor and recipient subtypes. Due to reduced antigen expression, this has potentially critical implications, since non-A1 donors may have reduced immunogenicity, allowing for safe HTx. Although the investigators did not analyze each mismatch subgroup distinctly (i.e., non-A1 donors and A1 recipients; 44% vs. non-A1 recipients and A1 donors; 56%), the fact that significant differences in outcomes between match and mismatch groups were lacking makes it unlikely that worse outcomes among non-A1 recipients will be found.

Continued research, early prevention, optimized treatment strategies, and multidisciplinary care models are essential for further reducing the burden of chronic heart failure and improving the quality of life of affected individuals.

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