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Chronic heart failure management: Novelties and perspectives (Part I)

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Abstract
Chronic heart failure (HF) is the important medical and social problem due its high mortality and treatment cost. Despite improvements in outcomes in the last few decades for HF, there still remains a need for novel therapies as many patients incompletely recover with existing therapies and progress to advanced HF. In this review, we will discuss recent advances in the management of HF with a focus on upcoming therapies that hold the greatest promise for clinical use.

Keywords: chromic heart failure, treatment

Introduction
The chronic heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress [1]. HF is the important medical and social problem due its high mortality and treatment cost [2].
Due last guidelines of European Society of Cardiology (2016) HF has 3 main clinical variants: with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF) [1].
The prevalence of HF differs according to definition and region, but has been estimated to be approximately 1% to 2% in developed countries [3]. The prevalence rate tends to increase with age, and it is > 10% among people > 70 years old [4]. The epidemiological and etiological profiles of HFrEF and HFpEF are different. In comparison with HFrEF, patients with HFpEF are older, show female predominance, and often show hypertension and atrial fibrillation (AF) with a lower rate of myocardial infarction (MI) [3].
In the last few decades, pharmacological therapy of HF has evolved from a symptom-relief therapy to the current broad array of disease-modifying therapies. The aim of this manuscript is a review of most top HF trials in few last years.

Material and Methods
The results of modern trials in few last years were reviewed in this paper.

Results and Discussion
Pharmacological treatment of HF has been evolving through increased understanding of its pathophysiology and the development of new drugs. The nowel directions of HF treatment are: novel pharmacological (neprilysin inhibition; effects on myocardial contractile function; metabolic modulators; anti-inflammatory drugs), device (mitral regurgitation; atrial fibrillation; sleep apnoea; atrial septostomy), and biological therapies (gene therapy; cell therapy) [5].
SGLT2 inhibitors. Sodium-glucose co-transporter 2 (SGLT2) inhibitors have demonstrated unprecedented benefits in patients with T2DM, reducing HF. The first completed SGLT2 inhibitor CVOT was the EMPA-REG OUTCOME trial. The study enrolled 7,020 patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD), and were followed up for 3.1 years. The trial demonstrated a significant 14% reduction in the primary composite outcome of CV death, non-fatal myocardial infarction (MI), and non-fatal stroke (HR, 0.86; 95% CI, 0.74-0.99) primarily driven by a 38% reduction in CV death (HR, 0.62; 95% CI, 0.49-0.77). Empagliflozin had a neutral effect on MI or stroke, and thus a CV mortality reduction in the empagliflozin group is thought to be largely due to a reduction in HHF (HR, 0.65; 95% CI,

0.50-0.85) [6].

Two other SGLT2 inhibitors, canagliflozin and dapagliflozin, confirmed the its benefit on HF in the CANVAS PROGRAM and DECLARE-TIMI 58 trial. Canagliflozin reduced the composite of HHF or CV death by 22% (HR, 0.78; 95% CI, 0.67-0.91), and dapagliflozin by 17% (HR, 0.83; 95% CI, 0.73-0.95) [7, 8]. Importantly, these trials included patients with and without established ASCVD. This benefit was observed in a broad population regardless of prior HF, established atherosclerotic cardiovascular diseases (ASCVD), ejection fraction (EF), or kidney function [9].

In DAPA-HF trial with a follow-up median of 18.2 months, the primary outcome occurred in 386 of 2373 patients (16.3%) in the dapagliflozin group and in 502 of 2371 patients (21.2%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001). A first worsening heart failure event occurred in 237 patients (10.0%) in the dapagliflozin group and in 326 patients (13.7%) in the placebo group (hazard ratio, 0.70; 95% CI, 0.59 to 0.83). Death from cardiovascular causes occurred in 227 patients (9.6%) in the dapagliflozin group and in 273 patients (11.5%) in the placebo group (hazard ratio, 0.82; 95% CI, 0.69 to 0.98); 276 patients (11.6%) and 329 patients (13.9%), respectively, died from any cause (hazard ratio, 0.83; 95% CI, 0.71 to 0.97). Findings in patients with diabetes were similar to those in patients without diabetes. The frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia did not differ between treatment groups [9].

An important unanswered question relates to whether the observed benefits of SGLT2 inhibitors is present in patients with HFpEF. In the sub-analysis of the DELARE-TIMI 58 trial, patients with HFpEF (history of HF and EF ≥45%) had a lower rate of HHF compared to those treated with placebo (HR, 0.79; 95% CI, 0.56-1.13). Although not statistically significant, the wide CIs suggest that the data may be underpowered. Indeed, point estimates for those with HFrEF, with HFpEF, and no HF were similar, which may be indicative of the benefits of dapagliflozin being consistent, regardless of HF phenotypes. There are 2 ongoing SGLT2 inhibitor trials designed to investigate the safety and efficacy of SGLT2 inhibitors in HFpEF patients. EMPEROR-PRESEVED randomized 4,126 HFpEF patients to empagliflozin or placebo (NCT03057951), and DELIVER randomized 4,700 patients to dapagliflozin or placebo (NCT01297257); both are expected to be completed in 2020–2021 [10].

The mechanisms of action of SGLT2 inhibitors in reducing HF are not full understood. These medications block the SGLT2 transporter in the proximal renal tubule, thereby increasing urinary excretion of glucose and sodium that results in calorie loss, reduction in body weight and blood pressure, and improves ventricular preload condition [11]. Some additional proposed mechanisms include improvement in arterial stiffness, plasma uric acid levels, inflammatory epicardial adipose tissue, renally mediated attenuation of renin-angiotensin-aldosterone system stimulation and sympathetic nervous system activity, anti-fibrotic effects by suppressing collagen synthesis, and red blood cell mass expansion augmenting oxygen delivery capacity to tissue [10, 11].

Neprilysin inhibition. Neprilysin is a neutral endopeptidase that non-specifically breaks down vasoactive substances including natriuretic peptides, adrenomedullin, bradykinin, and other vasodilators [12]. The PARADIGM-HF trial tested the combination of a neprilysin inhibitor and angiotensin receptor blocker (ARB) (sacubitril/valsartan), with an incremental 20% reduction in cardiovascular mortality, 16% reduction in all-cause mortality, and 21% reduction in HF hospitalization with better quality of life when sacubitril/valsartan replaced enalapril [13].

A recent randomized trial in acute HF (PIONEER-HF), tested the approach of initiating sacubitril/valsartan in hospital during an episode of acute decompensated HF. This trial concluded, that among patients with HFrEF who were hospitalized for acute decompensated heart failure, the initiation of sacubitril-valsartan therapy led to a greater reduction in the NT-proBNP concentration than enalapril therapy. The time-averaged reduction in the NT-proBNP concentration was significantly greater in the sacubitril-valsartan group than in the enalapril group; the ratio of the geometric mean of values obtained at weeks 4 and 8 to the baseline value was 0.53 in the sacubitril-valsartan group as compared with 0.75 in the enalapril group (percent change, -46.7% vs. -25.3%; ratio of change with sacubitril-valsartan vs. enalapril, 0.71; 95% confidence interval [CI], 0.63 to 0.81; P<0.001). The greater reduction in the NT-proBNP concentration with sacubitril-valsartan than with enalapril was evident as early as week 1 (ratio of change, 0.76; 95% CI, 0.69 to 0.85). The rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly between the two groups [14].

The effect of angiotensin receptor-neprilysin inhibition in patients with heart failure with preserved ejection fraction was evaluated in PARAGON-HF trial. Sacubitril-valsartan did not result in a significantly lower rate of total hospitalizations for heart failure and death from cardiovascular causes among patients with heart failure and an ejection fraction of 45% or higher. The study showed a 13% relative reduction in the primary composite endpoint of cardiovascular death and total (first and recurrent) heart failure hospitalizations, but narrowly missed statistical significance [15]. A pre-specified subgroup analysis of PARAGON-HF assessed gender differences in heart failure hospitalization and cardiovascular death, compared to valsartan, among patients with HFpEF (n=4,796; 2,479 women and 2,317 men). In women, sacubitril/valsartan reduced the risk of total heart failure hospitalization, with a 33% relative rate reduction (95% CI: 15-47), and an absolute reduction of 4 events per 100 person-years. In men, there was a 7% relative rate increase in the sacubitril/valsartan group versus the valsartan group, with an absolute increase of 0.9 events per 100 person-years. Sacubitril/valsartan was associated with a gradient of risk reduction ranging from patients hospitalized within 30 days of screening (rate ratio, 0.73; 95% CI: 0.53-0.99) to patients never hospitalized (rate ratio, 1.00; 95% CI: 0.80-1.24) [16].

Anti-inflammatory medicines. Various cytokines have been shown to play important roles in determining cardiac function under pathophysiological conditions. Several cytokines, including tumor necrosis factor α, transforming growth factor β, and interleukins (ILs), such as IL-1, IL-4, IL-6, IL-8, and IL-18, are involved in the development of various inflammatory cardiac pathologies. There have been many clinical trials to improve cardiac pathology by blocking these cytokines, but most have failed to demonstrate clinical efficacy [17].

Anti-inflammatory therapy using canakinumab, a monoclonal antibody targeting IL-1β, led to a significantly lower rate of

recurrent cardiovascular events in patients with previous MI compared to placebo. In Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) trial therapy with canakinumab, an interleukin-1β inhibitor, is related to a dose-dependent reduction in HHF and the composite of HHF or heart failure-related mortality in a population of patients with prior myocardial infarction and elevations in high-sensitivity C-reactive protein [18]. IL-1 blockade with anakinra has also been explored in small HFrEF trials with improvements in quality of life, ventricular vascular coupling, C-reactive protein, and peak exercise capacity at 12 weeks [19].

The novel drugs more specifically targeting inflammatory pathways active in HF are needed.

Glucagon like peptide (GLP-1) analogues. GLP-1 analogues such as liraglutide target the incretin pathway and have shown potential to improve myocardial metabolism, and exert cardioprotective effects. Liraglutide reduced cardiovascular and all-cause mortality in high-risk diabetics (independent of HF status) in the LEADER trial raising interest for potential study in HF. A total of 9340 patients underwent randomization in this trial. The median follow-up was 3.8 years. The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, 0.85; 95% CI, 0.74 to 0.97; P=0.02). The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group [20].

However, when tested specifically in HFrEF (with or without diabetes) in the FIGHT trial, there was no benefit over 6 months of treatment. There was in fact a signal of harm with an accompanying increase in heart rate and trend towards more HF hospitalizations which was also seen in the LIVE trial [21, 22].

Conclusions

Therapy of chronic heart failure has advanced remarkably in the last few decades, and recent breakthroughs suggest that the future holds even more promise. A number of new pharmacological pathways, device therapies and biologicals are undergoing advanced stages of investigation with potential for clinical utility in the near future.

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