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Editorial

Novel Therapies for Heart Failure

February is chosen by both the American Heart Association and British Heart Foundation as the month for heart awareness, and we dedicate this month's editorial to heart failure (HF) — a common and debilitating condition in which unmet medical needs remain globally.

HF is a leading cause of hospitalization in people over 65 years of age, and more than half the patients die within 5 years of diagnosis. Hypertension is a key risk factor for HF and many other heart conditions. Renin–angiotensin–aldosterone system (RAAS)-blockers and beta-blockers are the cornerstone for hypertension and HF treatment, and they are among the most widely prescribed classes of drugs worldwide. RAAS-blockers dilate blood vessels while beta-blockers slow the heart rate, and together they lower blood pressure and decrease oxygen demand from the heart. Landmark trials of RAAS- and beta-blockers have demonstrated these agents to substantially reduce mortality in HF. Despite these existing therapies for HF patients, readmission rates following hospital discharge remain very high. HF prevalence is also on the rise with the aging population, and modern interventional strategies allow more people to survive myocardial infarction but develop HF eventually. As such, there is an urgent need for next-generation HF therapeutics.

Unlike the field of anti-thrombotic research that has achieved considerable success in recent years with the regulatory approval of several new oral anticoagulants and anti-platelet drugs, the research pipeline for HF therapies look sparse with only a few promising candidates making it to the stage of clinical trials. Nevertheless, recent efforts to translate scientific findings into practical tools for HF improvement have started yielding fruit.

Neprilysin is a metalloprotease naturally expressed in a wide variety of tissues and is known since the late 1980s to degrade several vasoactive peptides, the most important substrates being natriuretic peptides (NPs). Overactivity of neprilysin occurs in some HF patients, and the resulting reduction of NP levels may lead to vasoconstriction and hypertension. Neprilysin inhibitors are thus being developed as potential antihypertensive and HF drugs. LCZ696 is an investigational combination drug consisting of valsartan (a RAAS-blocker) and the neprilysin inhibitor sacubitril — and the combination is often referred to as an ARNi (angiotensin receptor-neprilysin inhibitor). Last year, results of the phase 3 clinical trial PARADIGM-HF were published, comparing the efficacy and safety of LCZ696 versus enalapril (a RAAS-blocker) in chronic HF patients. LCZ696 showed a superior benefit compared to enalapril, and the trial is considered a major breakthrough in HF research. LCZ696 is currently under expedited review by both the United States Food and Drug Administration (FDA) and European Medicines Agency, and the outcome is eagerly anticipated.

HF is characterized by a decreased cardiac output from an overloaded heart. Strategies to improve the heart's energy utilization, reduce heart rate and oxygen demand, and increase stroke volume without raising blood pressure are all taken into account when developing novel HF therapies. Omecamtiv mecarbil is an investigational drug that activates myocardial ATPase and strengthens cardiac myosin cross-bridge formation, resulting in improved heart contraction and stroke volume without affecting oxygen consumption, heart rate or blood pressure. COSMIC-HF, the phase 2 clinical trial of oral omecamtiv mecarbil in patients with HF, is currently recruiting patients, and preliminary results are expected to become available later this year.

Stem cells are natural healers to tissue injuries, and the possibility of using stem cells as a therapeutic modality is a focus of active research in regenerative medicine. There have been many clinical trials assessing the use of stem cells in HF treatment, alone or in conjunction with pharmacotherapies, but results to date are not conclusive. More basic insights are needed to elucidate why not all HF patients respond to stem cell therapy and what can be done to enhance the effectiveness of this promising approach to repair a failing heart.

More recently, preliminary data have emerged suggesting microRNAs (miRNAs) as a new potential therapeutic target for HF. High-throughput screening techniques reveal a dysregulated miRNA profile in HF patients and identify microRNA candidates for targeted therapy using antisense oligonucleotides. Encouraging results have been observed in animal models of HF; but it remains to be seen how the findings translate in real patients, as HF is a multifactorial and complex disease. One of the major obstacles in human studies involving anti-miRNAs as therapeutics is how to deliver short fragile oligonucleotides to the sites where their action is needed. The success of therapeutic anti-miRNAs most likely relies on novel effective delivery systems that can work in patients.

Cardiovascular diseases are a leading cause of death worldwide, affecting both men and women of all ages and ethnic backgrounds, and putting a heavy burden on healthcare systems. Cardiovascular diseases are intrinsically intertwined with many other health conditions such as obesity, diabetes, stroke, dyslipidemia, hypertension, and kidney disease. One condition can trigger the development of another which in turns serves as a risk factor for another, and many of these conditions can be asymptomatic in a large proportion of carriers. Enormous research efforts resulting in targeted therapies and interventional devices have significantly improved the prognosis of many cardiovascular diseases, but this leads to a paradox when it comes to HF. Many survivors from heart diseases such as acute coronary syndrome, myocardial infarction and valvular diseases eventually develop HF. HF patients can also suffer from significant comorbidities including renal dysfunction, respiratory disorder, depression, anemia, and diabetes. Unless major breakthroughs in HF therapeutics are achieved soon – both in basic understanding of underlying mechanisms and in clinical testing of new targeted therapies – HF can become a real healthcare burden for the next several decades. Successful managements of cardiovascular conditions rely on an effective interdisciplinary approach to tackle several interlinked diseases simultaneously.

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