INTRODUCTION

Irregular ventricular contractions are common in heart failure patients [Ahmad *et al*., 2019], potentially leading to a decline in left ventricular systolic function and subsequent heart failure. Various therapeutic options exist for managing left ventricular failure [Psotka *et al*., 2019; Malik *et al*., 2011; Psotka *et al*., 2017; Gwo-ping *et al*., 2006]. Currently, drugs are commonly used to enhance left ventricular remodeling and improve left ventricular function, ultimately leading to improved ejection fraction volume.

One such drug is Amiodarone, often used to manage irregular ventricular contractions. Amiodarone extends action potentials in the atrium and ventricles, thereby prolonging the relaxation phase of cardiac muscle [Psotka *et al*., 2019; Malik *et al*., 2011; Psotka *et al*., 2017; Gwo-ping *et al*., 2006; Takashi Komatsu *et al*., 2005]. It also acts on sodium (Na+) and calcium (Ca2+) channels, preventing the influx of these ions that promote ventricular contractions. Furthermore, it affects beta receptors, blocking excessive stimulation. The lipid-soluble nature of these drugs provides prolonged effects, making them suitable for less frequent dosing. Amiodarone effectively reduces irregular ventricular contractions and enhances left ventricular fraction, although its long-term use is associated with side effects, particularly hepatic and renal impairments [Yan He *et al*., 2020; Melanie *et al*., 2002].

In response to the need for safer and effective treatments for heart failure, cardiac myosin activators have emerged as a promising option. These activators, including Omecamtiv mecarbil, directly target the cardiac sarcomere, enhancing myocardial function by increasing the number of myosin heads binding to actin monofilaments [Planelles *et al*., 2017; Teerlink *et al*., 2016; Hicks *et al*., 2018]. Omecamtiv mecarbil has demonstrated efficacy in reducing ejection fraction, increasing systolic ejection time, and improving stroke volume. It also reduces left ventricular systolic and diastolic volumes [Teerlink *et al*., 2016; Hicks *et al*., 2018;9-20], lowers natriuretic peptide levels, and heart rate, aiding in cardiac remodeling reversal. Early studies have shown its benefits in enhancing cardiac performance (Wessler BS *et al*., 2019; Vaduganathan *et al*., 2018; Butler *et al*., 2020; Tahhan *et al*., 2018; McMurray *et al*., 2019; Packer *et al*., 2020). Notably, the efficacy and safety of Omecamtiv mecarbil have not been evaluated among Chinese diabetes patients with reduced ejection fraction. Therefore, this study aims to compare the efficacy and safety of Omecamtiv mecarbil with a placebo in Chinese patients with reduced ejection fraction.

MATERIALS AND METHODS

Patients and ethics

We enrolled Chinese diabetes patients aged over 18 years with heart failure-related symptoms and a left ventricular ejection fraction of 35% or lower. Inclusion criteria covered both inpatients and outpatients, with natriuretic peptide levels of 400 pg per milliliter. Exclusion criteria encompassed clinical instability and severe hepatic or kidney diseases. Patients with a history of severe liver disease, lung disease, significant heart or thyroid disease were excluded, as were those with other medical conditions likely to affect study outcomes, those taking contraindicated or interfering medications and those undergoing other surgical procedures. Each patient received detailed information about permissible and prohibited medications during the informed consent process. Written informed consent was obtained from all patients. The study was approved by the institutional ethics committee of the Health College of China Three Gorges University (IRB approval number IRB-2023/349-83/Ref-234) and adhered to ethical principles outlined in the Helsinki Declaration and its subsequent amendments.

Treatments and procedures

Eligible subjects were randomly allocated in a 1:1 ratio to receive either oral omecamtiv mecarbil, administered at varying doses (25/37.5/50mg) twice daily, or a placebo. Patients were randomized using a simple randomization technique. The precise omecamtiv mecarbil dosage for each patient depended on their plasma concentration and was adjusted within the range of 25mg to 50mg. All enrolled patients underwent rigorous monitoring and were followed for 48 weeks to evaluate treatment safety and efficacy.

Assessment of efficacy and safety profiles

Baseline patient characteristics were assessed. The primary outcome focused on a composite endpoint, comprising cardiovascular (CVS) events (death) as the first event, initial hospitalization due to heart failure (HF), and the need for an urgent outpatient visit due to deteriorating HF as the first event. Secondary outcomes included the proportion of patients experiencing CVS event-related deaths, changes in Kansas City Cardiomyopathy Questionnaire (KCCQ) total scores for both in-patients and out-patients at each visit. KCCQ scores, ranging from 0 to 100, reflect symptom severity, with higher scores indicating worse symptoms.

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