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Research Article
Efficacy and Safety of Omecamtiv Mecarbil in Adult Patients with Heart Failure with Reduced Ejection Fraction

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Abstract

Background and Objective: Irregular ventricular contraction is common in patients with heart failure. There is no promising treatment option available that effectively improves myocardial function by acting directly on the myocardium. The present study compares the efficacy and safety of omecamtiv mecarbil versus placebo in Chinese patients with reduced ejection fraction. **Materials and Methods:** Diabetes patients aged >18 years on treatment for heart failure-related symptoms and with ejection fraction of ≤35% (left ventricular) and natriuretic peptide levels of ≥400 pg/mL received oral omecamtiv mecarbil (25/37.5/50 mg, twice daily, the OM group) or placebo (100 patients in each group) for 48 weeks. Hospitalization, the change in KCCQ score, death due to heart failure and adverse events were evaluated and analyzed. **Results:** Patients of the OM group had greater clinical success as compared to placebo (cardiovascular events (death), hospitalization due to heart failure and urgent outpatient visits due to worsening heart failure ($p<0.05$ for all)). Compared to the placebo, the in-patients and the out-patients of the OM group had a significantly greater reduction in KCCQ total symptom from baseline at each subsequent post-treatment visit ($p<0.05$ for all). The most frequent adverse events are tachyarrhythmia, angina, stroke and QT prolongation across both groups. Adverse events leading to treatment discontinuation were also similar across both groups, with a slightly greater numbers who received placebo. **Conclusion:** Oral omecamtiv mecarbil could be a better alternative in the management of heart failure among Chinese patients with low ejective fraction.

Key words: Cardiovascular events, ejection fraction, heart failure, myocardial function, omecamtiv mecarbil, tachyarrhythmia

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Irregular ventricular contraction is common condition in patients with heart failure (HF)[1]. Unattended patients with irregular ventricular contraction cause impairment of the systolic function of the left ventricle, which may lead to HF. Several therapeutic options and treatments are available for management of left ventricle failure[2-5]. At present, too many drugs are used to improve the remodeling of the left ventricle including improving function of left ventricular, thereafter improving ejection fraction volume of heart. Amiodarone is generally used for management of irregular ventricular contraction of heart through extending action potentials of the atrium and ventricles, that increases the duration of the relaxation phase of cardiac muscle[2-4]. In addition, such drugs (e.g., amiodarone) act on sodium and calcium channels of cardiac muscle cells, to prevent influx of these ions which promote ventricular contraction. Moreover, such drugs act on the β-receptor and block its hyperstimulation. Being lipid solubility properties of such drugs, the duration of effect is usually prolonged which makes them suitable for effective management of diseases with less frequency of dosing. Amiodarone alleviates the incidence of irregular ventricular contraction and improves the effective fraction of left ventricles. Though amiodarone is the gold standard drug in the treatment of HF due to irregular heartbeats, nevertheless, it has several side effects after long-term usage[6]. Among the reported side effects, hepatic and renal impairments are the life-threatening adverse events. Therefore, there is a need for effective and safe treatment options in conditions that lead to manage HF.

The HF is characterized by a significantly decreased ejection fraction, that leads to decreased cardiac output and increased pressure in ventricles. So far, there is no promising treatment option available that effectively improves myocardial function by acting directly on the myocardium. Recently, it was reported that the cardiac myosin activators act directly on the cardiac sarcomere to increase the function of the myocardium[7-14]. Cardiac myosin activators (omecamtiv mecarbil) significantly improve the contractility of cardiac muscle by targeting particularly myosin, that thereby increases the generation of several myosin heads that bind to the actin monofilament. In available literature the omecamtiv mecarbil is reported effective in patients with heart failure with the reduced ejection fraction through increase in the systolic ejection time and through improving in the stroke volume of patients with heart failure. In addition, it decreased left ventricular systolic volume and left ventricular diastolic volume[7-15]. It reduces natriuretic peptide levels and heart rate that improvise in reversing cardiac remodeling. In early studies, omecamtiv mecarbil demonstrates a beneficial effect in improving cardiac performance[14-18]. The efficacy and safety of omecamtiv mecarbil among Chinese diabetes patients with reduced ejection fraction have not yet been evaluated.

The present study compares the clinical success (cardiovascular (CVS) events (death), hospitalization due to HF and urgent outpatient visits due to worsening HF), clinical benefits (the proportion of patients who died due to CVS events and, the change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) score (total) at each visit for in-and out-patients) and safety of omecamtiv mecarbil versus placebo in Chinese patients with reduced ejection fraction. In addition, sub-group analysis by demography, disease characteristics, HF therapy and vital signs were performed for patients who received omecamtiv mecarbil.

MATERIALS AND METHODS

Study area: From 16 January, 2022 to 1 December, 2022, the study was performed at the Yichang Traditional Chinese Medicine Hospital, Hubei, China, the China Three Gorges University, Hubei, China and the Xiling Hospital, Yichang, Hubei, China.

Ethics approval and consent to participate: Written informed consent was obtained from each enrolled patient. The study received approval from the Institutional Ethics Committee of the Health College of China Three Gorges University vide ICE approval No. ZY2023F077 dated 15 January, 2022. The procedures used in the study were in line with the ethical principles laid down in the Helsinki Declaration and its later amendments[12].

Inclusion criteria: Diabetes patients aged >18 years with HF-related symptoms with left ventricular ejection fraction of <35%. Inpatient or outpatient were eligible if they had natriuretic peptide levels $\geq$400 pg/mL. Each patient was informed about the use of allowed/ disallowed medications at the time of the informed consent process.

Exclusion criteria: Clinically unstable patients and patients with severe hepatic and kidney diseases which may jeopardize were excluded from the study. Patients who had a history of severe liver disease, lung disease and severe heart and thyroid disease were excluded. Patients who were receiving concomitant and contra-indicated medications and undergoing any other form of surgery, were excluded.

Treatments and procedures: Subjects who met the eligibility criteria were randomized to receive (in ratio of 1:1) either oral omecamtiv mecarbil (25/37.5/50 mg, twice daily) or placebo. Each enrolled patient was carefully monitored and followed up for 48 weeks. The dose of omecamtiv mecarbil depended on the plasm concentration of it and was to be adjusted accordingly with the lowest being 25 mg and the highest being 50 mg.

Outcome measure

Assessment of efficacy and safety profiles: The baseline characteristics of each patient were assessed by simple questionnaires and hospital records. The primary outcome of interest was a composite endpoint that comprises CVS events (death) as the first event, hospitalization due to HF and urgent outpatient visits due to worsening HF as the first event. The secondary outcome of interest was the proportion of patients who died due to CVS events and the change in KCCQ score (total) at each visit for in-and out-patients. The KCCQ score was measured at baseline and each subsequent visit for 28-weeks. The KCCQ score ranged from 0 to 100, higher score indicates severe symptoms. In addition, the proportion of patients who were hospitalized due to HF and the proportion of patients who died from any cause were evaluated. Another secondary endpoint was a heart failure event (HFE) associated with study drugs. The HFE was defined as urgent outpatient visits in the emergency ward due to worsening HF symptoms. Moreover, the safety profile of both the study drugs was evaluated. In the safety analysis, change in vital and laboratory events along with overall safety outcomes was evaluated.

Sub-group analysis by demography and disease characteristics was also performed and calculated hazard ratio with 95% confidence interval (CI). Sub-group analysis through use of HF therapy and vital signs was performed.

Statistical analysis: Since this was a pilot study and hence no formal sample size calculation was performed, however, a total of 200 patients (100 patients in each group) were planned to be included to conclude this study. Appropriate statistical tests were used to analyze data (quantitative data) based on type and distribution (normal and non-normal). Normality of data was evaluated using the Kolmogorov and Smirnov method. In the case of non-normal data, the Mann-Whitney test was used to compare the data of two groups. In the case of normal data distribution, a paired t-test was used to compare the data of the two groups. In the case of categorical data, data were analyzed using the Fisher exact test or Chi-square test (χ^2-test) based on the size of the data (if sample size >5 and total sample >40 then χ^2-test). Statistical analysis was performed using GraphPad (version 3.01) Software, San Diego, California, USA. The statistically significant difference was assumed at $p<0.05$.

RESULTS

Study population and baseline characteristics: A total of 200 patients (100 patients in each group) were randomized and all patients completed the study (Fig. 1). Demographic and baseline characteristics of patients in both treatment groups were comparable (Table 1). In both groups, the majority of patients enrolled were female and belonged to the New York Heart Association (NYHA) III classification. The majority of patients in both groups were using Angiotensin-converting enzyme (ACE) blockers followed by Angiotensin Receptor Blockers (ARBs).

Overall, the patient characteristic was found comparable in both groups. The proportions of patients with diabetes mellitus and atrial fibrillation/flutter were similar in both groups. The median age was also found similar in both groups.

Outcomes measures

Primary outcomes: A summary of primary outcomes was presented in Table 2. Patients treated with OM had greater clinical success as compared to placebo in terms of CVS events (death), hospitalization due to HF and urgent outpatient visits due to worsening of HF. The patients treated with OM had greater clinical benefits and the differences between both the treatments were statistically significant. This demonstrated that the OM had better efficacy in composite endpoints as compared to placebo.

Secondary outcomes: A summary of secondary outcomes was presented in Table 3. Patients treated with OM had numerically greater clinical benefits as compared to placebo for secondary outcomes. The proportion of patients who died due to CVS events was numerically greater in the placebo group as compared to OM-treated group. The proportion of patients who were hospitalized due to HF was numerically greater in the placebo group as compared to OM-treated group. The proportion of patients who died from any cause was numerically greater in the OM-treated group as compared to placebo. The proportion of patients' HF events was numerically greater in the placebo group as compared to OM-treated group. Overall, the patients treated with OM had better clinical outcomes and the differences between both treatments were statistically non-significant. This demonstrated that the OM had numerically better efficacy in composite endpoints as compared to placebo.

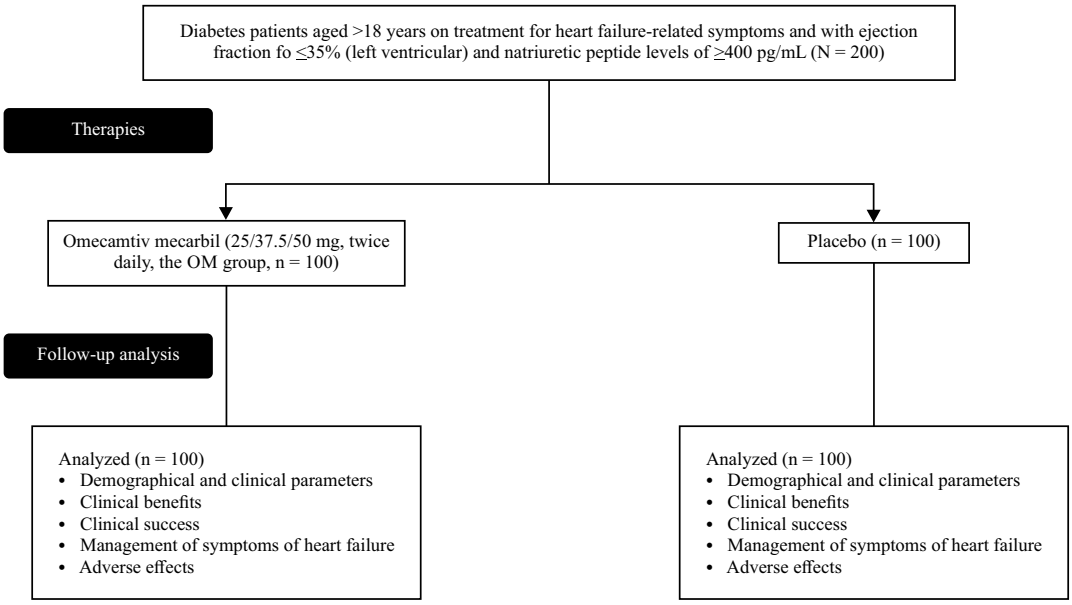

Fig. 1: Flow diagram

Table 1: Baseline characteristics of patients

Characteristics	OM (n = 100)	Placebo (n = 100)	p-value
Median age (years)	54	57	>0.05
Female sex (%)	58	55	>0.05
Clinical conditions (%)			
Atrial fibrillation/flutter	28	26.7	>0.05
Diabetes mellitus	34	33.4	
Ischemic HF	59	56	
LV EF	30	28.8	
NYHA classification (%)			
II	57	56	>0.05
III	41	39	
IV	4	5	
KCCQ (median score, total)			
Out-patients	73.0 (4.8)	74.0 (6.5)	>0.05
In-patients	51.2 (7.3)	50.3 (4.4)	>0.05
SBP (mmHg)	123.3 (17.5)	121.6 (11.2)	>0.05
Heart rate	75.3 (8.4)	73.5 (7.8)	>0.05
Natriuretic peptide levels	1765 (213)	1690 (287)	>0.05
Cardiac troponin	24 (2.4)	23 (3.1)	>0.05
HF treatments (%)			
ACE blocker	87	83	>0.05
ARBs	65	61	
B- receptor blocker	23	21	
CR therapy	43	48	
Defibrillator	21	22	
SGLT2 blocker	34	38	
Mineralocorticoid-receptor blocker	28	24	

Categorial variables presented as frequencies of frequencies with percentages in parenthesis, HF: Heart failure, ACE blocker: Angiotensin-converting enzyme and ARBs: Angiotensin Receptor Blockers

A summary change in KCCQ total symptom inpatients was presented in Table 4. Compared to placebo, the in patients treated with OM had a significantly greater reduction in KCCQ total symptom from baseline at each subsequent post-treatment visit. The patients who received a placebo had greater KCCQ total symptom scores as compared to the patients treated with OM. Overall, the trend of reduction in KCCQ score was noted in both the groups when compared to

baseline. However, improvement in disease symptoms was significantly higher in patients treated with OM when compared to placebo. Looking at the trend, the reduction in KCCQ score among both the treatment groups was gradual at each visit. Overall, this demonstrated that the OM had better efficacy in managing the symptoms of HF among inpatients when compared to placebo.

A summary change in KCCQ total symptom out-patients was presented in Table 5. Compared to placebo, the out-patients treated with OM had a significantly greater reduction in KCCQ total symptom from baseline at each subsequent post-treatment visit. The patients who received a placebo had greater KCCQ total symptom scores as compared to the patients treated with OM. Overall, the trend of reduction in KCCQ score was noted in both the groups when compared to baseline. However, improvement in disease symptoms was significantly higher in patients treated with OM when compared to placebo. Looking at the trend, the reduction in KCCQ score among both the treatment groups was gradual at each visit. Overall, this demonstrated that the OM had better efficacy in managing the symptoms of HF among inpatients and out-patients when compared to placebo.

Sub-group analysis of patients treated with OM: Compared to placebo, the patients treated with OM had significantly greater clinical benefits irrespective of demography and disease characteristics evaluated in this sub-group analysis. A summary of sub-group analysis by demography and disease characteristics was presented in Table 6. In the OM group, the patients aged <65 years had significantly greater clinical benefits as compared to patients aged >65 years. In the OM group, the female patients had significantly greater clinical benefits as compared to male patients. Similarly, in the OM group, the overweight patients had significantly greater clinical benefits as compared to obese patients. In the OM group, the non-diabetes patients (pre-diabetic patients or small increase in blood sugar level) had significantly greater clinical benefits as compared to diabetes patients. In the OM group, the patients with NYHA class III or IV had significantly greater clinical benefits as compared to patients with NYHA class II.

Table 2: Results of the primary endpoint within treatment period

	OM (n = 100)		Placebo (n = 100)			
Parameter	Values	Events	Values	Events	Hazard ratio (95% CI)	p-value
Composite outcome	36.6	23.8	38.7	26.6	0.90 (0.76-0.89)	0.041
CVS events (death) as 1st even (%)	7.9	NA	8.4	NA		
hospitalization due to HF as 1st event (%)	27	NA	26.8	NA		
Needs urgent outpatient visit due to worsening HF as 1st event (%)	1.9	NA	2.6	NA		

HR values with p-values are derived from a hierarchical testing strategy

Table 3: Secondary endpoints result within treatment period

	OM (n = 100)		Placebo (n = 100)			
Parameter	Values	Events	Values	Events	Hazard ratio (95% CI)	p-value
Proportion of patients who died due to CVS events (%)	18.9	11.2	18.7	11.2	0.98 (0.86 to 1.01)	>0.05
Proportion of patients who were hospitalized due to HF	26.8	17.6	29.3	18.8	0.91 (0.82 to 1.01)	>0.05
Proportion of patients who died from any cause (%)	26.4	14.9	26.3	13.8	0.98 (0.92 to 1.1)	>0.05
Proportion of patients' heart-failure events (%)	29.6	19.3	30.4	19.8	0.98 (0.82 to 0.98)	>0.05

HR values with p-values are derived from a hierarchical testing strategy

Table 4: Change in KCCQ total symptom inpatients

Visit	OM (n = 100)	Placebo (n = 100)	p-value
Week 12	22.3 (0.9)	39.6 (1.7)	<0.05
Week 16	18.4 (1.8)	36.6 (1.9)	<0.05
Week 24	17.9 (2.1)	34.3 (1.2)	<0.05
Week 28	15.6 (1.5)	32.3 (1.7)	<0.05

p-values are based on the Mann-Whitney U test

Table 5: Change in KCCQ total symptom outpatients

Visit	OM (n = 100)	Placebo (n = 100)	p-value
Week 12	32.4 (2.9)	42.2 (2.7)	<0.05
Week 16	29.3 (1.7)	39.3 (1.9)	<0.05
Week 24	28.2 (1.5)	38.6 (2.2)	<0.05
Week 28	27.7 (1.8)	37.7 (2.5)	<0.05

p-values are based on the Mann-Whitney U test

Table 6: Sub-group analysis by demography and disease characteristics for patients who received omecamtiv mecarbil

Visit	Hazard ratio (95% CI)
Age (<65 years)	0.87 (0.73-1.22)
Age (≥65 years)	0.91 (0.82-1.34)
Female	0.83 (0.78-1.12)
Male	0.86 (0.81-1.32)
Overweight	0.78 (0.66-1.32)
Obese	0.86 (0.76-1.12)
Non-diabetes vs diabetes	0.82 (0.75-0.92)
Ischemic HF	0.81 (0.79-0.98)
Myocardial infarction history	0.93 (0.69-0.82)
NYHA class II	0.97 (0.76-1.22)
NYHA class III or IV	0.86 (0.78-1.12)
Atrial fibrillation/flutter	0.81 (0.79-0.98)
LVEF	0.93 (0.69-0.82)

Table 7: Sub-group analysis by heart failure therapy for patients who received omecamtiv mecarbil

Visit	Hazard ratio (95% CI)
ACE blocker use	0.86 (0.76-1.12)
ARB blocker use	0.82 (0.75-0.92)
MRA blocker use	0.81 (0.79-0.98)
ARN blocker use	0.93 (0.69-0.82)
CRT blocker use	0.97 (0.76-1.22)
ICD blocker use	0.86 (0.78-1.12)

Table 8: Sub-group analysis by vital signs and other clinical characteristics for patients who received omecamtiv mecarbil

Visit	Hazard ratio (95% CI)
Heart rate (high)	0.86 (0.76-1.12)
Heart rate (low)	0.82 (0.75-0.92)
Systolic BP (high)	0.81 (0.79-0.98)
Systolic BP (low)	0.93 (0.69-0.82)
eGFR (high)	0.86 (0.78-1.12)
eGFR (low)	0.78 (0.66-1.32)
NT-proBNP (low)	0.86 (0.76-1.12)
NT-proBNP (high)	0.82 (0.75-0.92)

Table 9: Summary of adverse events during treatment period and follow-up

Event	OM (n = 100)	Placebo (n = 100)
Adverse event leading to treatment discontinuation (%)	10	12
SAEs (%)	54	59
Common adverse effects of interest (%)		
Tachyarrhythmia	7.5	8.9
QT prolongation	8.9	10.3
Ventricular arrhythmia	2.7	8.3
Myocardial infraction	3.4	8.2
Unstable angina leading to hospitalization	6.4	9.4
Revascularization of coronary artery needed	3.2	8.5
Stroke	6.5	9.3

Values are expressed as percentage of patients

A summary of sub-group analysis by HF therapy was presented in Table 7. Compared to the placebo, the patients treated with OM had significantly greater clinical benefits irrespective of the HF therapy received. In the OM group, the patients who used ARBs and mineralocorticoid receptor antagonists (MRA blockers) had significantly greater clinical benefits as compared to patients who received other HF therapy. In the OM group, the patients who had angiotensin receptor/neprilysin (ARN) blockers had significantly greater clinical benefits as compared to patients who had CRT blockers.

A summary of sub-group analysis by vital signs and other clinical characteristics was presented in Table 8. Compared to placebo, the patients treated with OM had significantly greater clinical benefits irrespective of vital signs and other clinical characteristics. In the OM group, the patients who had irregular heart rates had significantly greater clinical benefits.

Adverse events: The most common adverse events that occurred in either group were presented in Table 9. Both the study drugs were comparable in terms of reporting adverse events, with the most frequent adverse events being tachyarrhythmia, angina, stroke and QT prolongation during 28 weeks. Adverse events leading to treatment discontinuation were also similar across both groups, with a slightly greater number of patients' placebo.

DISCUSSION

In China, there is no head-to-head study comparing the efficacy and safety of omecamtiv mecarbil versus placebo in Chinese diabetes patients with reduced ejection fraction. To the best of our understanding/knowledge, this is the first clinical study carried out to evaluate the efficacy and safety profiles of omecamtiv mecarbil versus placebo in Chinese diabetes patients with reduced ejection fraction. The findings of the current study are consistent with those reported in previous studies[7-15] in which omecamtiv mecarbil was found effective in reducing ejection fraction through increasing systolic ejection time and improving the stroke volume. Moreover, omecamtiv mecarbil decreased left ventricular systolic and diastolic volumes[16]. Further, it reduces natriuretic peptide levels and heart rate which helps in reversing cardiac remodeling[17,18]. In early studies, omecamtiv mecarbil demonstrated a beneficial effect in improving cardiac performance. Earlier, there was no promising treatment option available that effectively improves myocardial function by acting directly on the myocardium. Recently, it was reported that the cardiac myosin activators act directly on the cardiac sarcomere to increase the function of the myocardium. Omecamtiv mecarbil significantly improves the contractility of cardiac muscle cells by targeting particularly myosin, which thereby increases the generation of several myosin heads that bind to the actin monofilament. In the present study, the patients treated with OM had greater clinical success as compared to placebo in terms of CVS events (death), hospitalization due to HF and urgent outpatient visits due to worsening HF. The patients treated with OM had greater clinical benefits and the differences between both the treatments were statistically significant. This demonstrated that the OM had better efficacy in composite endpoints as compared to placebo.

Patients treated with OM had numerically greater clinical benefits as compared to placebo for secondary outcomes. The proportion of patients who died due to CVS events was numerically greater in the OM-treated group as compared to placebo. The proportion of patients who were hospitalized due to HF was numerically greater in the placebo group as compared to OM-treated. The proportion of patients who died from any cause was numerically greater in the placebo group as compared to OM-treated. The proportion of patients' HF events was numerically greater in the placebo group as compared to OM-treated. Overall, the patients treated with OM had better clinical outcomes and the differences between both treatments were statistically non-significant. This demonstrated that the OM had numerically better efficacy in composite endpoints as compared to placebo.

Compared to the placebo, the patients treated with OM had a significantly greater reduction in KCCQ total symptoms from baseline at each subsequent post-treatment visit during 28 weeks. The patients who received a placebo had greater KCCQ total symptom scores as compared to the patients treated with OM. Overall, the trend of reduction in KCCQ score was noted in both the groups when compared to baseline. However, improvement in disease symptoms was significantly higher in patients treated with OM when compared to placebo. Looking at the trend, the reduction in KCCQ score among both the treatment groups was gradual at each visit. Overall, this demonstrates that the OM had better efficacy in managing the symptoms of HF among inpatients when compared to placebo.

Compared to placebo, the patients treated with OM had significantly greater clinical benefits irrespective of demography and disease characteristics evaluated in this sub-group analysis. In the OM group, the patients aged <65 years had significantly greater clinical benefits as compared to patients aged >65 years. In the OM group, the female patients had significantly greater clinical benefits as compared to male patients. Similarly, in the OM group, the overweight patients had significantly greater clinical benefits as compared to obese patients. In the OM group, the non-diabetes patients had significantly greater clinical benefits as compared to diabetes patients. In the OM group, the patients with NYHA class III or IV had significantly greater clinical benefits as compared to patients with NYHA class II. Compared to the placebo, the patients treated with OM had significantly greater clinical benefits irrespective of the HF therapy received. In the OM group, the patients who used ARBs and MRA blockers had significantly greater clinical benefits as compared to patients who received other HF therapy. In the OM group, the patients who had ARN blockers had significantly greater clinical benefits as compared to patients who had CRT blockers. Compared to placebo, the patients treated with OM had significantly greater clinical benefits irrespective of vital signs and other clinical characteristics. In the OM group, the patients who had irregular heart rates had significantly greater clinical benefits.

Both the study drugs were comparable in terms of reporting adverse events, with the most frequent adverse events being tachyarrhythmia, angina, stroke and QT prolongation.

Overall, for the primary composite endpoint, OM showed slow significantly greater clinical benefits in Chinese patients with HF symptoms. Omecamtiv mecarbil have no superior secondary endpoints. However, omecamtiv mecarbil has positive effects in numerically more patients than those did using placebo in Chinese diabetes patients with HF. The possible reason for no superior secondary endpoints might be due to the low sample size. Hence, the present study emphasis to perform of a larger randomized multicentric study to confirm the findings.

There are some limitations of the study, for example, the results of the current study may not be generalized to all the Chinese population due to the low sample size used. Therefore, a study with a large sample size is required to perform to validate the results.

CONCLUSION

Oral omecamtiv mecarbil have greater clinical benefits, clinical success (cardiovascular events (death), hospitalization due to heart failure and urgent outpatient visits due to worsening heart failure) and better management of symptoms of heart failure. This study has demonstrated that oral omecamtiv mecarbil could be a better alternative in the management of heart failure among Chinese patients with low ejective fraction. The present study encourages to conduct of a larger randomized multicentric study to confirm the findings of the present study.

SIGNIFICANCE STATEMENT

A preliminary study has demonstrated that oral omecamtiv mecarbil for 48 weeks have greater clinical benefits, clinical success, manageable adverse effects and could be a better alternative in the management of heart failure (clear symptoms and natriuretic peptide levels of $\geq$400 pg/mL) among Chinese adult patients with low ejective fraction (left ventricular ejection fraction of $\leq$35%). The findings will help physicians to uncover critical areas of the management of heart failure with low ejective fraction that many clinicians have not evaluated. The present study encourages to conduct of a larger randomized multicentric study to confirm the findings.

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