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Commentary

Omecamtiv mecarbil for heart failure: Unpacking the latest systematic review and meta-analysis

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Abbreviations: FDA: U.S. Food and Drug Administration; HFrEF: Heart Failure with Reduced Left Ventricular Ejection Fraction; OM: Omecamtiv Mecarbil

Commentary

In February 2023, a systematic review and meta-analysis of six randomized controlled trials (RCTs) with a total of 9,596 patients assessed the effectiveness and safety of omecamtiv mecarbil (OM) versus placebo in patients with heart failure with reduced left ventricular ejection fraction (HFrEF) [1]. HFrEF is a significant health problem associated with high morbidity and mortality worldwide. OM is a novel drug that targets cardiac myosin, a cytoskeletal motor protein responsible for converting chemical energy to mechanical force.

The analysis found that while the use of OM was associated with a reduced risk of stroke compared to placebo, no significant differences in other clinical outcomes were observed, such as all-cause death, hospital readmissions, myocardial infarction, or cardiovascular death. However, OM was associated with an increased rate of dizziness and hypotension, although the safety profile of OM was otherwise similar to that of placebo.

Several studies have shown positive results regarding the use of OM in symptom improvement among major RCTs. However, the benefits of OM in symptom improvement were inconsistent. For instance, the GALACTIC-HF trial showed a positive result for its primary endpoint, a composite of cardiovascular death or heart failure (HF) events, but not for individual outcomes [2]. Similarly, while the COSMIC-HF trial showed significant improvement in symptoms, the GALACTIC-HF and ATOMIC-AHF trials did not find significant changes in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ TSS) or dyspnea relief [2,4]. These findings are consistent with contemporary recommended medical therapies for HFrEF, which improve mortality and cardiovascular outcomes without improving exercise capacity.

The analysis found that patients using OM had a lower risk of stroke, but this conclusion was based on only two RCTs (GALACTIC-HF and METEORIC-HF trials) [2,5]. However, the use of OM did not reduce the risk of supraventricular tachyarrhythmias/atrial fibrillation and flutter, individually or when combined as a composite outcome. A subgroup analysis of the GALACTIC-HF trial investigated the impact of baseline atrial fibrillation and flutter at baseline in the setting of OM use [6]. Patients with baseline atrial fibrillation and receiving digoxin showed a reduced clinical improvement with OM use. Conversely, patients without baseline atrial fibrillation and those

taking digoxin without underlying atrial fibrillation showed a more significant clinical improvement with OM use.

It is important to note the limitations of this meta-analysis, including the lack of subgroup analyses in individual trials on baseline characteristics and demographics, a lack of differentiating inpatient versus outpatient analyses, and heterogeneous baseline of HFrEF severity.

In December 2022, the U.S. Food and Drug Administration (FDA) rejected the approval of OM for the treatment of HFrEF. Although the GALACTIC-HF trial demonstrated a significant reduction in the composite endpoint of cardiovascular death or heart failure events with OM compared to placebo, the FDA requested the need for an additional clinical trial to establish substantial evidence of effectiveness. Future research should identify patient subgroups that may benefit from OM treatment and explore whether combining OM with other heart failure therapies could lead to improved outcomes. Moreover, long-term safety and efficacy data on OM are necessary, as the current RCTs had a limited follow-up period. Additionally, the potential of OM for treating heart failure with preserved ejection fraction should be investigated, as the current study only included patients with HFrEF. Future trials should prioritize adequately addressing the concerns brought up by the FDA approval for the treatment of HFrEF. Additionally, efforts should be made to ensure that the trial populations accurately represent the patient populations that OM would be used to treat, including underrepresented minority groups and those with comorbidities.

Heart failure is a significant public health problem, and the search for effective therapies is ongoing. Although the FDA's decision not to approve OM for the treatment of HFrEF may be disappointing, it is crucial to continue exploring novel treatments to address this unmet medical need. The limited therapeutic options available to patients with heart failure highlight the urgent need for more effective treatments. OM represents a promising approach to target the underlying pathophysiology of heart failure, and further research is necessary to clarify its role in the management of this condition. The potential benefit of OM, particularly for patients with refractory heart failure, justifies further exploration of its safety and efficacy, including long-term follow-up data. Overall, it is essential to continue to pursue new therapies to improve the outcomes of patients with heart failure, a condition that affects millions of people worldwide.

Conflict of Interest

The author has no conflict of interest.

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Disclosures

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