Review Article

# Safety and efficacy of omecamtiv mecarbil for heart failure: A systematic review and meta-analysis

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## ARTICLE INFO

## ABSTRACT

*Aim:* To assess the safety and efficacy of omecamtiv mecarbil compared with placebo in heart failure (HF) patients.
*Methods:* We searched PubMed, Web of Science, Cochrane Library, and SCOPUS until August 15th, 2021. We included all randomized controlled studies comparing omecamtiv mecarbil with placebo in heart failure patients. The meta-analysis was carried out using Rev Man software V5.4.
*Results:* A total of eight studies were included in our systematic review. Pooled analysis showed that omecamtiv mecarbil is not associated with increased incidence of death, any adverse events, hypotension, heart failure, ventricular tachyarrhythmia, dyspnea, dizziness, and serious adverse events. Regarding the efficacy, omecamtiv mecarbil significantly reduced heart rate with some studies demonstrating its significant improvement in left ventricular ejection fraction and systolic function.
*Conclusion:* Omecamtiv mecarbil is a well-tolerated drug in heart failure patients. The limited data regarding the efficacy suggested that it may improve ejection fraction and systolic function.
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## 1. Introduction

Heart failure (HF) is a complex clinical syndrome subsequent to an impairment of ventricular filling or ejection of blood. HF symptoms include dyspnea, fatigue, peripheral edema, and pulmonary edema.[1] HF patients could be classified as having HF with reduced, mildly reduced or preserved ejection fraction.[2]

The total number of HF patients is increasing,[3] so HF is still a serious clinical and public health issue.[3] Not only does heart failure hugely impact the quality of life, functioning, and survival, but also it imposes high costs on the health care system.[4] In the latest decades, various innovations have been used for managing HF patients, either medical, device implantation, or transplantation.[4]

Omecamtiv mecarbil (OM) (formerly known as CK-1827452 or AMG 423) is a selective cardiac myosin activator, which binds to the catalytic domain of myosin5. Cardiac myosin is the cytoskeletal motor protein found in the cardiac muscle cell, which is directly responsible for converting the chemical energy to mechanical force, leading to the heart's contraction. Preclinical research has reported that OM increases the contractility of the heart and does not increase neither the intracellular myocyte calcium concentrations nor the myocardial oxygen consumption.[5–7]

This review aimed at examining the available high-quality randomized evidence regarding the use of omecamtiv mecarbil in clinical heart failure to assess the safety and efficacy of omecamtiv mecarbil in managing HF patients.

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## 2. Methods

This systematic review and meta-analysis was performed and reported according to the Cochrane guidelines and the preferred reporting items (PRISMA) guidelines.[8]

### 2.1. Literature search

A systematic search was done on PubMed, Scopus, Cochrane, and Web of Science, till 15th August 2021, using the following search terms: Cardiac Failure- Heart Decompensation- Decompensation, Heart -Heart Failure, Right-Sided- Heart Failure, Right Sided-Right- Sided Heart Failure- Right Sided Heart Failure-Myocardial Failure- Congestive Heart Failure- Heart Failure, Congestive - AMG-423/CK 1827452/CK-1827452/omecamtiv mecarbil/and cardiac myosin activator.

### 2.2. Eligibility criteria and study selection

We included all randomized controlled trials (RCTs) comparing omecamtiv mecarbil with placebo in heart failure patients with ejection fraction ≤40%. We used Endnote software to exclude the duplicates. We performed title and abstract screening, followed by a full-text screening of suitable studies.

### 2.3. Quality assessment

We used the Cochrane risk of bias tool for assessing the quality of included RCTs (version 1).[9] The assessed domains include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The judgment includes low, high, or unclear risk of bias.

### 2.4. Data extraction

We extracted data related to the following: 1) Summary about the included studies: Site, NCT, inclusion criteria, study interventions, sample, primary outcomes, and results 2) Baseline characteristics of the included patients: study arms, sample, age, sex, BMI, comorbidities, and systolic blood pressure. 3) The study outcomes as stated below. Data were extracted in a preformulated excel sheet.

### 2.5. Study outcomes

The study outcomes included death for any cause, cardiac (heart) failure events, drug related adverse events, any adverse events, hypotension, adverse events leading to discontinuation, ventricular tachyarrhythmia, dyspnea, dizziness, and serious adverse. Also the efficacy outcomes included change in the heart rate and Natriuretic Peptide Tests (BNP, NT-proBNP) after (20–24 weeks). The primary outcomes of the studies that did not report any of the previously stated outcomes were presented qualitatively.

### 2.6. Data synthesis

We used the Review Manager software (V5.4) for performing the analysis. Data were pooled as risk ratio and 95% CI under the fixed-effects model. Data were considered significant if p < 0.05. We measured the heterogeneity using the I-square test and Chi–Square test. Significant heterogeneity was considered if Chi–Square P < 0.1. When heterogeneity was found, we used the random-effect model.

## 3. Results

### 3.1. Literature search

There were 575 results through the first search. After removing the duplicates, there were 412 results. Finally, eight studies were included in the systematic review [10–17]; four of them entered the analysis. Fig. 1 shows the PRISMA flow diagram.

### 3.2. Characteristics of the included studies & patients

All studies were RCTs. The main site was the USA, and some studies were multinational. The mean age ranged from 59.3 to 66 years, while BMI was between 26.3 and 29.1. The males were more than females. Detailed summary and baseline characteristics are shown in (Table 1) and (Table 2), respectively.

### 3.3. Quality assessment

Overall, the included studies showed high quality. Five of them had low bias risk for all domains. The only high risk of bias was for the other bias domain in Greenberg et al trial. Detailed risk of bias assessment domains are presented in Fig. 2.

### 3.4. Outcomes

i. Efficacy outcomes
  1. Heart rate, beats/min

Two studies entered the analysis with a total of 8656 participants, omecamtiv mecarbil reduce heart rate more than placebo (MD = −1.65, 95% CI [−2.17, 1.12], p < 0.00009). The results were homogenous (p = 0.56; $I^2$ = 0%) (Fig. 3A).

2. NT-proBNP, pg/ml

Two studies entered the analysis with a total of 8659 participants, omecamtiv mecarbil reduce NT-proBNP more than placebo
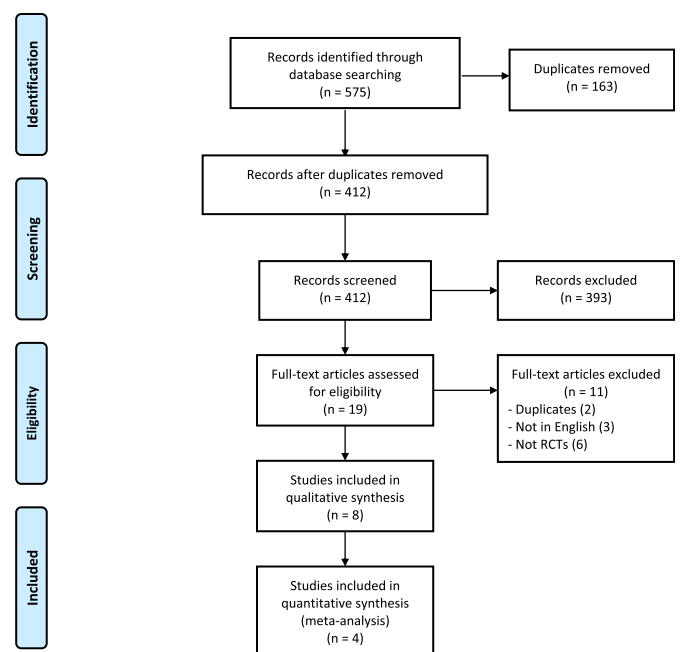


**Fig. 1.** PRISMA diagram.

**Table 1**
Summary of the included studies.

| Results | Primary outcomes | Study interventions and sample | Inclusion criteria | NCT | Site | Study ID |
|---|---|---|---|---|---|---|
| Omecamtiv mecarbil improved cardiac function in patients with heart failure caused by left ventricular dysfunction and could be the first in class of a new therapeutic agent. | Safety and tolerability of omecamtiv mecarbil | Study consisted of 5 cohorts, Patients in each cohort took either Omecamtiv (experimental group) or Placebo (control group) Cohort 1, N = 8 Cohort 2, N = 9 Cohort 3, N = 10 Cohort 4, N = 8 Cohort 5, N = 10 | Heart failure, Patients had to be in sinus rhythm, on stable therapy for heart failure | NCT624442 | UK, Russia, USA, Georgia | **Cleland et al 2011** |
| Regarding Felker et al 2020, HRQL improved in patients with HFrEF assigned to omecamtiv mecarbil (OM-PK group) relative to placebo. Regarding Teerlink et al 2016–2, Omecamtiv mecarbil dosing guided by pharmacokinetics achieved plasma concentrations associated with improved cardiac function and decreased ventricular diameter. | Heart failure symptoms in Felker et al 2020. and safety outcomes in Teerlink et al 2016-2 | Control group (placebo), N = 149 Experimental group 1 (Omecamtiv), N = 149 Experimental group 2 (Pharmacokinetically guided dose titration OM-PK), N = 149 | LVEF ≤40%, and elevated natriuretic peptides ≥200 pg/mL (≥1200 pg/mL if the patient was in atrial fibrillation). | NCT1786512 | USA | **Felker et al 2020& Teerlink et al 2016–2** |
| Doses of omecamtiv mecarbil producing plasma concentrations previously shown to increase systolic function were well tolerated during exercise in these study patients with ischemic cardiomyopathy and angina. There was no indication that treatment increased the likelihood of myocardial ischemia in this high-risk population. | Safety outcomes | Control group (placebo), N = 29 Experimental group 1 (Omecamtiv), N = 31 Experimental group 2 (Omecamtiv), N = 34 | Adults >18 years of age with documented ischemic cardiomyopathy and angina | NCT682565 | Georgia, Russia | **Greenberg et al 2015** |
| improving cardiac systolic function with 20 weeks of OM treatment | LV global longitudinal (GLS) and global circumferential strain (GCS). | Control group (Placebo), N = 149 Experimental group 1 (Omecamtiv fixed dose), N = 150 Experimental group 2 (Omecamtiv titrated), N = 149 | ProBNP ≥200 pg/mL (≥1200 pg/mL if atrial fibrillation), LV ejection fraction ≤40%, and were treated with stable, optimum therapy. | NCT1786512 | UK, USA, Denmark, Japan | **Sorensen et al 2020** |
| Patients who received omecamtiv mecarbil had a lower incidence heart-failure event or death from cardiovascular causes than those who received placebo. | First heart-failure event or death from cardiovascular causes. | Control group (Placebo), N = 4112 Experimental group (Omecamtiv), N = 4120 | Age between 18 and 85 years, left ventricular ejection fraction of 35% or less. The patients were currently hospitalized for heart failure (inpatients) or had either made an urgent visit to the emergency department or been hospitalized for heart failure within 1 year be-fore screening (outpatients). | NCT2929329 | USA | **Teerlink et al 2020** |
| In heart failure patients with reduced EF, omecamtiv mecarbil produced greater therapeutic benefit as baseline EF decreased. These findings are consistent with the drug's mechanism of selectively improving systolic function and presents an important opportunity to improve the outcomes in a group of patients at greatest risk. | First heart-failure event or death from cardiovascular causes. | Subgroup analysis for Teerlink et al 2020 according to ejection fraction. | Age between 18 and 85 years, left ventricular ejection fraction of 35% or less. The patients were currently hospitalized for heart failure (inpatients) or had either made an urgent visit to the emergency department or been hospitalized for heart failure within 1 year be-fore screening (outpatients). | NCT2929329 | USA | **Teerlink et al 2021** |
| intravenous OM did not meet the primary endpoint of dyspnea improvement, but it was generally well tolerated, it increased systolic ejection time, and it may have improved dyspnea in the high-dose group. (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure) | Efficacy (Dyspnea relief), safety | Control group (Placebo), N = 303 Experimental group (Omecamtiv), N = 303 | History of CHF and ejection fraction (EF) < 40%, who were admitted for AHF and had dyspnea at rest or with minimal exertion and had increased plasma concentrations of B-type natriuretic peptides (BNPs), persistent dyspnea 2 h after receipt of at least 40 mg of IV furosemide (or an equivalent dose of an alternative loop diuretic) | NCT1300013 | Europe, Australia, and USA. | **Teerlink et al 2016–1** |

Abbreviations: LVEF; left ventricular ejection fraction, BNp N-Brain natriuretic peptide, CHF, Congestive heart failure, ACH; Acute heart failure, OM; omecamtiv mecarbil.

**Table 2**
Baseline characteristics of the enrolled patients in the included studies.

| Smoking (%) | Dyslipidemia (%) | PCI (%) | CABG (%) | SBP (M±SD) | Comorbidities | | | BMI (M±SD) | Sex, Male (%), Female (%) | Age, (M±SD) | Sample | Study arms | Study ID |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Other (%) | Hypertension (%) | Diabetes mellitus (%) | | | | | | |
| NR | NR | 18 (40%) | 12 (27%) | 119.7 ± 18.4 | IHD = 29 (64%) NIHD = 16 (35.5%) | 22 (49%) | 10 (22%) | 26.3 ± 4.6 | 39(86.7), 6(13.3) | 59.3 ± 13.8 | 45 | Omecamtiv mecarbil Placebo | Cleland et al 2011* |
| NR | NR | NR | NR | 121.4 ± 17.1 | IHD = 56 (51.2%) NIHD = 30 (34.88%) | 56 (65%) | 44 (51%) | NR | 74(86%), 12(14%) | 63.5 ± 9.9 | 86 | (None, very mild or mild symptoms) Omecamtiv mecarbil | Felker et al 2020 |
| NR | NR | NR | NR | 119.7 ± 15 | IHD = 47 (85%) NIHD = 34 (42%) | 59 (73%) | 33 (41%) | NR | 65(80.2%), 16(19.8%) | 64 ± 9.8 | 81 | (None, very mild or mild symptoms) Placebo | |
| NR | NR | NR | NR | 120 ± 15.3 | IHD = 41 (64%) NIHD = 23 (36) | 39 (61%) | 26 (41%) | NR | 53(82.8%), 11(17.2%) | 61.8 ± 10.6 | 64 | (Moderate, severe, or very severe symptoms) Omecamtiv mecarbil | |
| NR | NR | NR | NR | 118.9 ± 14.1 | IHD = 42 (65%) NIHD = 25 (35%) | 51 (76%) | 28 (42%) | NR | 54(80.6%), 13(19.4%) | 63.2 ± 9.8 | 67 | (Moderate, severe, or very severe symptoms) Placebo | |
| 14 (21.5%) | NR | NR | NR | 120 ± 10 | IHD = 51 (78.5%) | NR | NR | 26.6 ± 3.8 | 52(80%), 13(20%) | 63.84 ± 9.1 | 65 | Omecamtiv mecarbil | Greenberg et al 2015 |
| 6 (20.7) | NR | NR | NR | 121.1 ± 12.04 | IHD = 21 (72%) | NR | NR | 26.5 ± 3.4 | 23(79.3), 6(20.7%) | 62.3 ± 9.8 | 29 | Placebo | |
| NR | NR | NR | NR | NR | AF = 28 (19%) | NR | NR | NR | 127(84.7%), 23(15.3%) | 63 ± 10 | 150 | Omecamtiv mecarbil | Sorensen et al 2020 |
| NR | NR | NR | NR | NR | AF = 33 (22%) | NR | NR | NR | 119(79.9%), 30(20.1%) | 64 ± 10 | 149 | Placebo | |
| NR | NR | NR | NR | 116.3 ± 15.4 | IHD = 2193 (53.3%) AF = 1146 (27.8%) | NR | 1652 (40%) | NR | 3245(78.8%), 875(21.2%) | 64.5 ± 11.3 | 4120 | Omecamtiv mecarbil | Teerlink et al 2020 |
| NR | NR | NR | NR | 116.6 ± 15.3 | IHD = 2222 (54%) AF = 1099 (26.7%) | NR | 1657 (40%) | NR | 3238(78.8%), 874(21.2%) | 64.5 ± 11.4 | 4112 | Placebo | |
| NR | NR | NR | NR | 116.3 ± 15.4 | IHD = 2193 (53.3%) AF = 1146 (27.8%) | NR | 1652 (40%) | NR | 3245(78.8%), 875(21.2%) | 64.5 ± 11.3 | 4120 | Omecamtiv mecarbil | Teerlink et al 2021 |
| NR | NR | NR | NR | 116.6 ± 15.3 | IHD = 2222 (54%) AF = 1099 (26.7%) | NR | 1657 (40%) | NR | 3238(78.8%), 874(21.2%) | 64.5 ± 11.4 | 4112 | Placebo | |
| 170 (56.1%) | NR | NR | NR | 117 ± 17 | IHD = 189 (62.4%) AF = 168 (55.4%) | 249 (82%) | 244 (81%) | 29.1 ± 5.9 | 230(75.9%), 73(24.1%) | 66 ± 11 | 303 | Omecamtiv mecarbil | Teerlink et al 2016-1 |
| 175 (57.8%) | NR | NR | NR | 119 ± 18 | IHD = 189 (62.3%) AF = 162 (53.5%) | 133 (44%) | 136 (45%) | 29.1 ± 5.9 | 236(77.9%), 67(22.1) | 66 ± 11 | 303 | Placebo | |
| NR | 95 (63%) | 61 (41%) | 47 (31%) | 121 ± 16 | IHD = 97 (65%) | 94 (63%) | 70 (47%) | 29.5 ± 6.1 | 127(84.7%), 23(15.3%) | 63 ± 10 | 150 | Omecamtiv mecarbil (fixed dose) | Teerlink et al 2016-2 |
| NR | 99 (66%) | 63 (42%) | 40 (27%) | 119 ± 16 | IHD = 101 (68%) | 109 (73%) | 55 (37%) | 28.5 ± 5.6 | 125(83.9%), 24(16.1%) | 63 ± 12 | 149 | Omecamtiv mecarbil (titration) | |
| NR | 111 (74%) | 62 (42%) | 28 (19%) | 119 ± 14 | IHD = 89 (60%) | 101 (68%) | 61 (41%) | 29.7 ± 5.7 | 119(80%), 30(20%) | 64 ± 10 | 149 | Placebo | |

Abbreviations: BMI; Body mass index, IHD; Ischemic heart disease, NIHD; Non ischemic heart disease, SBP; Systolic blood pressure, NR; not reported, CABG; Coronary artery bypass surgery, and PCI; percutaneous coronary intervention.

(MD = −164.5, 95% CI [−209.8, −11.17], p < 0.00001), but the results were heterogenous (p = 0.02; $I^2$ = 81%), and the results became insignificant after using random effect model as following (MD = 457.69, 95% CI [−1163.99, 248.62], p = 0.2) (Fig. 3B).

ii. Safety outcomes
1. Drug Related Adverse Events
   - Any adverse events

Three studies entered the analysis accounting for 1145 participants, and there were non-significant differences between the omecamtiv mecarbil group and placebo group (RR = 0.97, 95% CI [0.88, 1.08], p = 0.61). The results were homogenous (p = 0.49; $I^2$ = 0%) (Fig. 4A).

- Hypotension

Two studies entered the analysis accounting for 700 participants, and there were non-significant differences between the omecamtiv mecarbil group and placebo group (RR = 0.57, 95% CI [0.03, 9.52], p = 0.70), but the results were heterogeneous (p = 0.06; $I^2$ = 72%) (Fig. 4B).

- Adverse events leading to discontinuation

Three studies entered the analysis (N = 1164 participants), and there were non-significant differences between the omecamtiv mecarbil group and placebo group (RR = 1.0, 95% CI [0.62, 1.6], p = 0.98). The results were homogenous (p = 0.58; $I^2$ = 0%) (Fig. 4C).

2. Death for any cause

Three studies entered the analysis accounting for 9283 participants, and there were non-significant differences between the omecamtiv mecarbil group and placebo group (RR = 1.00, 95% CI [0.93, 1.08], p = 0.96). The results were homogenous (p = 0.89; $I^2$ = 0%) (Fig. 5A).

3. Cardiac (heart) failure events (not include sudden cardiac death.)

Three studies entered the analysis with a total of 9284 participants, and there were non-significant differences between the omecamtiv mecarbil group and placebo group (RR = 0.94, 95% CI [0.88, 1.01], p = 0.09). The results were homogenous (p = 0.79; $I^2$ = 0%) (Fig. 5B).

4. Ventricular tachyarrhythmia

Three studies entered the analysis with a total of 9283 participants, and there were non-significant differences between the omecamtiv mecarbil group and placebo group (RR = 0.95, 95% CI [0.82, 1.11], p = 0.51). The results were homogenous (p = 0.90; $I^2$ = 0%) (Fig. 5C).

5. Dyspnea

Two studies entered the analysis with a total of 539 participants, and there were non-significant differences between the omecamtiv mecarbil group and placebo group (RR = 1.56, 95% CI [0.73, 3.3], p = 0.25). The results were homogenous (p = 0.80; $I^2$ = 0%) (Fig. 5D).

6. Dizziness

Two studies entered the analysis with a total of 539 participants, and there were non-significant differences between the omecamtiv mecarbil group and placebo group (RR = 1.5, 95% CI [0.63, 3.57], p = 0.36). The results were homogenous (p = 0.95; $I^2$ = 0%) (Fig. 5E).

7. Serious adverse events

Two studies entered the analysis with a total of 1051 participants, and there were non-significant differences between the omecamtiv mecarbil group and placebo group (RR = 1.01, 95% CI [0.8, 1.28], p = 0.9). The results were homogenous (p = 0.44; $I^2$ = 0%) (Fig. 5F).

3.5. Qualitative evidence

Biering-Sørensen et al[13] (N = 448) reported that the systolic cardiac function was improved with the treatment of omecamtiv mecarbil for 20 weeks with improved left ventricular myocardial deformation, through the assessment of the global longitudinal (GLS) and the global circumferential strain (GCS). Felker et al[10] (N = 448) concluded that omecamtiv mecarbil showed a statistically significant improvement in the Total Symptom Score (TSS) in
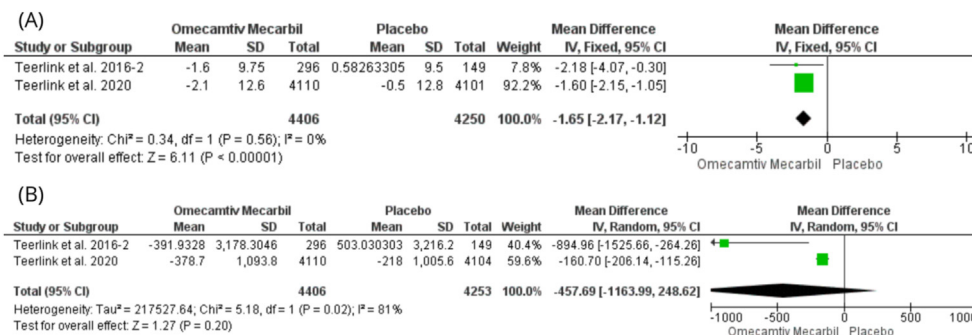


Fig. 2. Risk of bias summary.

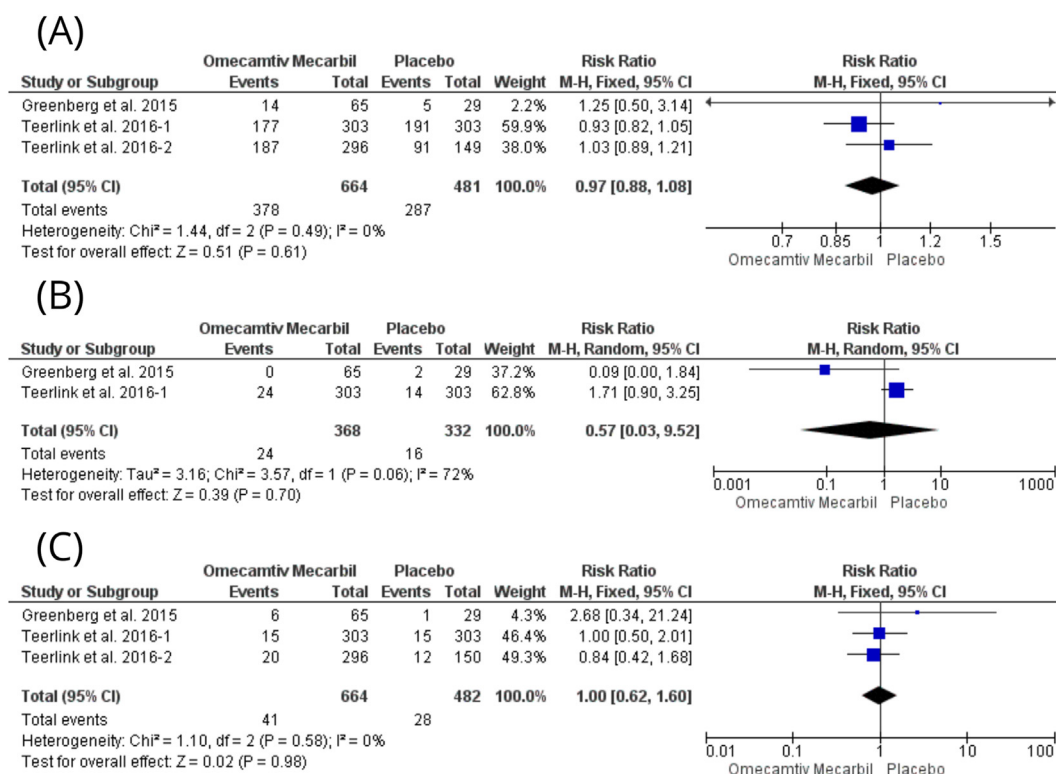**Fig. 3.** (A) Heart rate, beats/min (B) NT-proBNP, pg/ml.



**Fig. 4.** (A) Any adverse events (B) Hypotension (C) Adverse events lead to discontinuation.

the pharmacokinetically-guided dose titration group compared with placebo. Moreover, the point-estimates of the Kansas City Cardiomyopathy Questionnaire (KCCQ) effect had a similar or greater magnitude compared to those found in other effective drugs for heart failure. Also, Cleland et al[14] (N = 45) demonstrated that omecamtiv mecarbil improved cardiac function in heart failure patients. Teerlink et al[16] stated that in HF patients with reduced ejection fraction, omecamtiv mecarbil showed better therapeutic benefit as baseline ejection fraction decreased, supporting the selective improvement of the systolic function and offering an opportunity for outcomes' improvement of patients at most significant risk.

## 4. Discussion

This study shows that omecamtiv mecarbil is safe as there were no statistically significant differences between omecamtiv mecarbil and placebo in any of death for any cause, any adverse events,

adverse events leading to discontinuation, and hypotension. Also, most of the included studies proved the drug's efficacy as it may be used to improve ejection fraction and systolic function. Based on our search, we believe that our study is the first meta-analysis to focus on omecamtiv mecarbil's safety and efficacy in HF patients. These results are in line with those of previous studies and confirm the tolerability of omecamtiv mecarbil.

In preclinical models, OM increased heart function in Sprague Dawley rats and beagle dogs in a dose-dependent manner, as determined by echocardiography.[5] OM has shown a dose-dependent increase in systolic ejection time (SET), fractional shortening, stroke volume, and LVEF.[14,18]

On the other hand, a recent study reported some quantitative and qualitative diversity of omecamtiv mecarbil effects on the contractility and calcium-transient in healthy and failing rat myocardium. The drug has not provided a positive inotropic effect in rats' myocardium, indicating that omecamtiv mecarbil effectiveness on the contractile strength might differ among the species
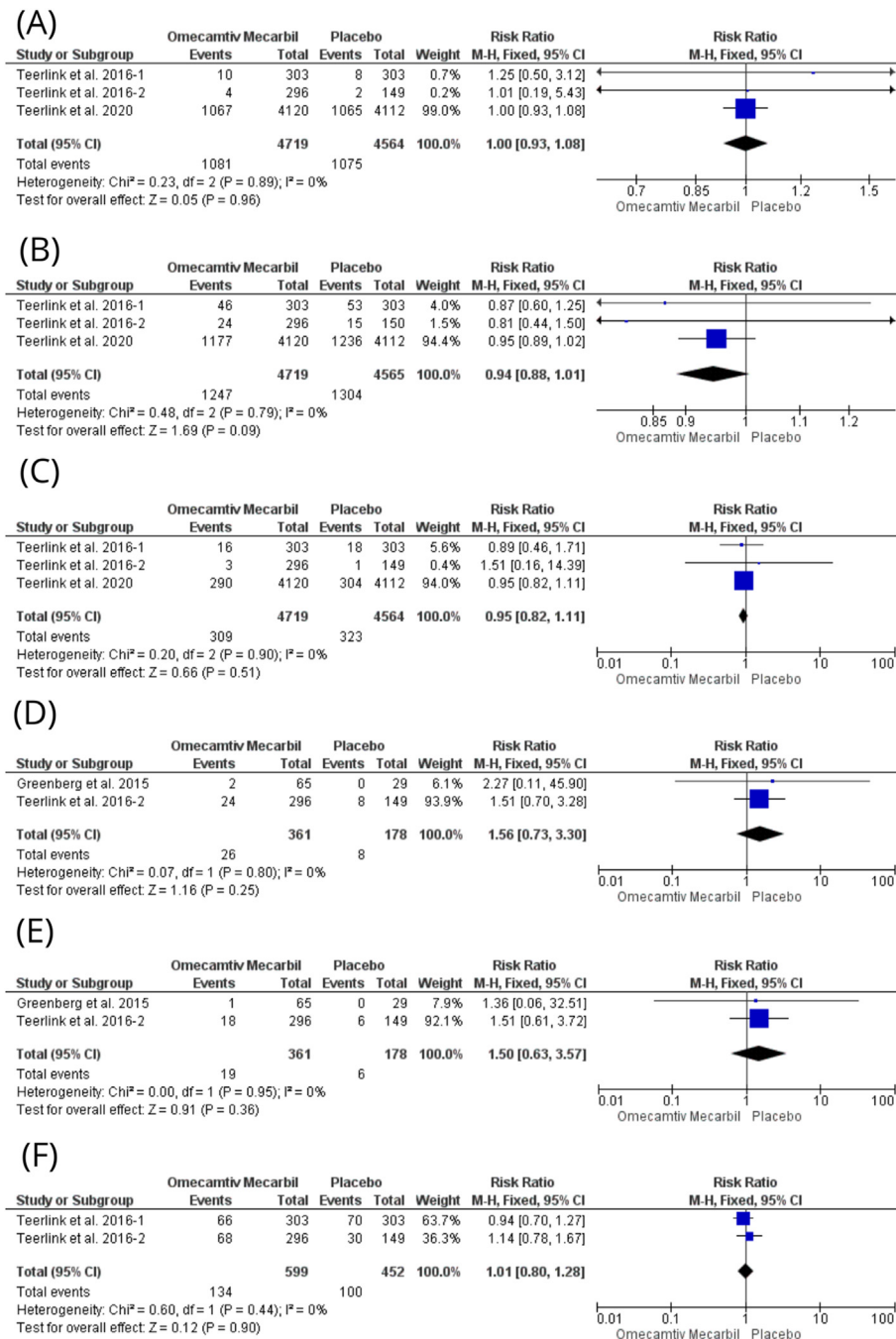
**Fig. 5.** (A) Death for any cause (B) Cardiac (heart) failure events (C) Ventricular tachyarrhythmia (D) Dyspnea (E) Dizziness (F) Serious adverse events.

and require future research. Therefore, the $Ca^{2+}$ content levels in cardiac cells might be necessary for omecamtiv mecarbil effectiveness.[19]

Renal impairment is reported to be very prevalent in chronic HF patients.[20,21] A recent non-randomized study supported OM for treating HF patients, whether or not they have renal impairment, and that the drug's pharmacokinetics showed a non-meaningful affection by the renal function or hemodialysis.[21] Similar to our findings, they reported that OM was well-tolerated.[21] Trivedi et al also stated that OM was well tolerated, in their studied healthy subjects. Moreover, OM administration with meals showed an increase in the rate of OM absorption.[22]

This study mainly focused on the safety of omecamtiv mecarbil in HF patients. More research targeting the efficacy is recommended, and further safety assessment is encouraged. We recommend future RCTs with larger sample sizes to evaluate the safety and efficacy of the drug, as well as targeting the optimum dose and duration for the drug usage. We also recommend the assessment of the drug for the different classifications of heart failure individually.

There are strength points that support the evidence of our meta-analysis. First, we only included RCTs in our study to prevent bias with other research designs. The included studies had a low risk of bias in most domains. Also, our pooled meta-analysis has included 8838 participants with some of the outcomes, which increased the validity of our study. On the other hand, we faced some limitations.

The pooled analysis only included two studies, and most of the outcomes had only 700 included participants. Also, we did not consider different doses of the drug in our analyses. Also, there are a variety of follow-up periods. Moreover, there were variations in the criteria of included heart failure patients in the included studies.

## 5. Conclusion

In this study, Omecamtiv mecarbil was generally a well-tolerated drug in heart failure patients. Limited data regarding the efficacy suggested that it may be used to improve ejection fraction and systolic function. However, future research and assessment are still recommended, bearing in mind the doses, follow-up periods compared with other medications.

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