

Acute Treatment With Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure

The ATOMIC-AHF Study



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ABSTRACT

BACKGROUND Omecamtiv mecarbil (OM) is a selective cardiac myosin activator that increases myocardial function in healthy volunteers and in patients with chronic heart failure.

OBJECTIVES This study evaluated the pharmacokinetics, pharmacodynamics, tolerability, safety, and efficacy of OM in patients with acute heart failure (AHF).

METHODS Patients admitted for AHF with left ventricular ejection fraction $\leq 40\%$, dyspnea, and elevated plasma concentrations of natriuretic peptides were randomized to receive a double-blind, 48-h intravenous infusion of placebo or OM in 3 sequential, escalating-dose cohorts.

RESULTS In 606 patients, OM did not improve the primary endpoint of dyspnea relief (3 OM dose groups and pooled placebo: placebo, 41%; OM cohort 1, 42%; cohort 2, 47%; cohort 3, 51%; $p = 0.33$) or any of the secondary outcomes studied. In supplemental, pre-specified analyses, OM resulted in greater dyspnea relief at 48 h (placebo, 37% vs. OM, 51%; $p = 0.034$) and through 5 days ($p = 0.038$) in the high-dose cohort. OM exerted plasma concentration-related increases in left ventricular systolic ejection time ($p < 0.0001$) and decreases in end-systolic dimension ($p < 0.05$). The adverse event profile and tolerability of OM were similar to those of placebo, without increases in ventricular or supraventricular tachyarrhythmias. Plasma troponin concentrations were higher in OM-treated patients compared with placebo (median difference at 48 h, 0.004 ng/ml), but with no obvious relationship with OM concentration ($p = 0.95$).

CONCLUSIONS In patients with AHF, 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 [ATOMIC-AHF]; [NCT01300013](https://clinicaltrials.gov/ct2/show/study/NCT01300013)) (J Am Coll Cardiol 2016;67:1444-55) © 2016 by the American College of Cardiology Foundation.

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The morbidity and mortality associated with acute heart failure (AHF) remain substantial with few therapeutic advances in recent decades, a finding suggesting that new AHF therapies represent a major unmet medical need (1). Although AHF is a heterogeneous condition, impaired cardiac contractility is a central pathophysiological feature in at least one-half of these patients and may be a key therapeutic target. However, trials of many inotropic agents have failed to demonstrate either efficacy or safety because of adverse effects such as arrhythmias, hypotension, myocardial ischemia, and increased mortality (2); consequently, recent guidelines limit the use of these agents to patients with cardiogenic shock or evidence of marked end-organ hypoperfusion (3,4).

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Omecamtiv mecarbil (OM) is a selective small molecule activator of cardiac myosin that prolongs myocardial systole (5). In contrast to traditional inotropes, which increase myocardial contraction rate and shorten systole duration, OM increases stroke volume by extending the duration of systole without changing the velocity of myocardial contraction (i.e., no change in pressure with respect to time, $+dp/dt$). In pre-clinical models, OM increased cardiac contractility and stroke volume without apparent effects on myocardial oxygen demand (6) or cardiac myocyte calcium transients (5), which are putative mechanisms of harm for traditional inotropic agents, such as beta-agonists and phosphodiesterase-3 inhibitors. In healthy volunteers (7) and in patients with chronic heart failure (CHF) and systolic dysfunction (8), OM increased stroke volume and cardiac output while decreasing heart rate. In the ATOMIC-AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure; NCT01300013) study, we sought to evaluate pharmacokinetics (PK),

pharmacodynamics (PD), safety, tolerability, and efficacy of intravenous (IV) OM in patients with AHF.

METHODS

ATOMIC-AHF was a prospective, phase II, randomized, double-blind, placebo-controlled, dose-escalation, sequential-cohort trial comparing OM with placebo in patients hospitalized for AHF. Patients were enrolled from 106 centers in Europe, Australia, and North America. Each participating center's Institutional Review Board approved the study, and all participants provided written informed consent. The executive committee was responsible for the trial design, and the national leaders supervised patient recruitment and clinical management of the trial. An independent data monitoring committee regularly reviewed unblinded data prepared by an external biostatistical group. An independent clinical events committee (CEC) (Duke Clinical Research Institute, Durham, North Carolina) adjudicated deaths, rehospitalizations, and major cardiovascular events. We vouch for the completeness and accuracy of the data and the analyses as well as the fidelity of the study to the protocol.

PATIENTS. We enrolled men and women 18 through 85 years of age with a history of CHF and left ventricular (LV) ejection fraction (EF) $\leq 40\%$, 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): BNP ≥ 400 pg/ml or N-terminal (NT)-proBNP $\geq 1,600$ pg/ml; BNP ≥ 600 pg/ml or NT-proBNP $\geq 2,400$ pg/ml with atrial fibrillation. Eligible patients had persistent

ABBREVIATIONS AND ACRONYMS

AHF	= acute heart failure
BNP	= B-type natriuretic peptide
BP	= blood pressure
CEC	= clinical events committee
CHF	= chronic heart failure
cTn	= cardiac troponin
cTnl	= cardiac troponin I
EF	= ejection fraction
ESD	= end-systolic dimension
HF	= heart failure
IV	= intravenous
LV	= left ventricular
OM	= omecamtiv mecarbil
PD	= pharmacodynamics
PK	= pharmacokinetics
SET	= systolic ejection
SVT	= supraventricular tachyarrhythmia
VT	= ventricular tachyarrhythmia

Dr. McMurray's employer, Glasgow University, has been paid by Cytokinetics and Amgen for his time spent working on the clinical trial program with omecamtiv mecarbil. Dr. McMurray has had travel and accommodation costs paid by Cytokinetics and Amgen in relation to advisory board and clinical trial meetings about omecamtiv mecarbil. Dr. Ponikowski has received consultancy and speaker honoraria from Amgen, Bayer, Cardiorentis, Johnson & Johnson, Novartis, and Servier; and has received an institutional research grant from Singulex. Dr. Metra has received consulting fees from Amgen, Bayer, Mast Therapeutics, Novartis, Servier, and Trevena. Dr. Filippatos has received research grants or consulting fees, or both, from Bayer, Novartis, Cardiorentis, Vifor, and the European Union. Dr. Ezekowitz has received research grants or honoraria from Amgen, Novartis, Trevena, and Cardiorentis. Dr. Dickstein has received honoraria and research support from Abbott, Amgen, AstraZeneca, Bayer, Biotronik, Boston Scientific, Johnson & Johnson, Medtronic, Merck, Novartis, Pfizer, Sanofi, Servier, Sorin, and St. Jude Medical; and has received a research grant from the University of Bergen. Dr. Cleland has received research grants from Alere, Amgen, Roche Diagnostics, Novartis, Philips, Servier, and StealthPeptides; has served as a consultant for Amgen, Novartis, Philips, Roche Diagnostics, Merck, Medtronic, Servier, and Zoll; and has received speaker honoraria from Bayer and Novartis. Dr. Kim is a former employee of and shareholder in Amgen; and is current employee of and shareholder in MyoKardia. Drs. Wolff and Malik are employees of and shareholders in Cytokinetics. Drs. Lei, Knusel, and Wasserman are employees of and shareholders in Amgen.

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dyspnea 2 h after receipt of at least 40 mg of IV furosemide (or an equivalent dose of an alternative loop diuretic) and were randomized within 24 h of their initial IV dose of loop diuretic (the initial portion of cohort 1 required randomization within 16 h of presentation, after which the protocol was amended to allow enrollment out to 24 h after first diuretic dose). Patients receiving IV inotropic agents (other than dopamine ≤ 5 $\mu\text{g}/\text{kg}/\text{min}$) were excluded. Other major exclusions were acute coronary syndrome within 30 days, blood pressure (BP) $>160/100$ mm Hg, systolic BP <90 mm Hg, heart rate <60 or >110 beats/min, estimated glomerular filtration rate calculated by the Modification of Diet in Renal Disease equation <20 ml/min/1.73 m² during screening, severe pulmonary disease, and significant stenotic valvular disease.

Subjects were centrally randomized 1:1 to IV OM or matching placebo within each cohort. Randomization through an interactive voice response system was stratified by geographic region (North America and Australia vs. rest of the world) and by planned participation in the PK/PD substudy.

PROCEDURES. ATOMIC-AHF enrolled 3 sequential cohorts (~200 patients per cohort) ([Online Figure 1](#)) targeting mean OM plasma concentrations at 48 h of 115 ng/ml, 230 ng/ml, and 310 ng/ml and using 3 escalating dose regimens ([Online Appendix](#)). As specified by protocol, enrollment was paused between cohorts to allow for a data monitoring committee safety data review; enrollment resumed on the committee's recommendation. Through PK/PD modeling, these doses were designed to attain progressively higher target plasma concentrations, with the low dose anticipated to have minimal cardiac effect, an intermediate dose, and the high dose chosen to maximize the PD response and minimize occurrence of excessive plasma concentrations in most patients ($>99\%$). Patients received OM or placebo infused over 48 h and had to remain hospitalized for at least 24 h after infusion termination ([Online Figure 2](#)). Patients were evaluated in person during hospitalization and on day 30 and by telephone at 6 months for vital status.

OUTCOMES. The primary efficacy endpoint evaluated dyspnea improvement using a patient-reported 7-level Likert scale. A responder was defined as a patient with minimally, moderately, or markedly improved dyspnea by 6 h after the start of infusion and moderately or markedly improved dyspnea at 24 and 48 h, without experiencing worsening heart failure (HF) or death from any cause by 48 h. Worsening HF was defined as worsening symptoms or signs of HF necessitating initiation, reinstatement, or

intensification of IV or mechanical HF treatment. Secondary and exploratory endpoints included other evaluations of symptoms and clinical events ([Online Appendix](#)).

Patients in sinus rhythm could participate in a PK/PD substudy that provided additional PK data through supplementary blood sampling and explored the relationship between OM plasma concentrations and select echocardiographic measurements. Echocardiograms were obtained at baseline, 24 h, and 48 h.

ATOMIC-AHF used standardized, intensive serial monitoring of cardiac troponin (cTn) plasma concentrations in all patients by means of a sensitive cardiac troponin I (cTnI) assay (Siemens ADVIA Centaur TnI-Ultra, Siemens Healthcare GmbH, Erlangen, Germany; 10% coefficient of variation = 0.03 ng/ml, 99th percentile upper reference limit = 0.04 ng/ml) ([9](#)). Samples were obtained at baseline and again at the following times: 4, 15, 24, 48, 72 h; day 5 or day of discharge; and day 30 after study drug initiation.

The CEC adjudicated all rehospitalizations, deaths, and cases of potential myocardial infarction or ischemia. A CEC review for potential myocardial ischemia or infarction could be triggered by either the investigators or the CEC through clinical evidence of an event (e.g., chest pain, electrocardiogram changes) or by pre-specified changes in cTnI (>0.04 ng/ml in patients without previously detectable cTnI or an increase in cTnI >0.03 ng/ml in patients with previously detectable cTnI). Adverse events and serious adverse events were recorded through day 30.

STATISTICAL ANALYSIS. All analyses were performed in patients who received at least 1 dose of investigational product. The planned sample size of 600 patients provided 88% power to detect superiority of 1 of the OM doses over placebo for the primary endpoint of dyspnea response, assuming response rates of 23% and 40% in the placebo and OM groups, respectively ([10,11](#)). See the [Online Appendix](#) for additional details.

RESULTS

From May 2011 to April 2013, 613 patients were enrolled in ATOMIC-AHF from 106 centers in 19 countries, and 606 patients received investigational product ([Online Figure 3](#)). Patients enrolled in this study ([Table 1](#)) had a mean age of 66 ± 11 years and were predominantly white (88%) and male (77%) with multiple comorbidities. Before the index admission, most patients were receiving guideline-recommended pharmacological therapy for chronic symptomatic HF ($>80\%$ New York Heart Association functional class II to III). Investigators attributed the cause of HF to

coronary artery disease in 62% of patients, and mean LVEF was $26 \pm 8\%$. At baseline, most patients also had impaired renal function, elevated troponin, and raised plasma NT-proBNP concentrations. Some heterogeneity among treatment groups was evident despite randomization; for example, more patients assigned to OM had elevated troponins (median pooled placebo, 0.044 ng/ml; pooled OM, 0.054 ng/ml). Additionally, differences in baseline characteristics emerged among the cohorts over time during the 2-year enrollment period, including increasing enrollment from Eastern European sites, decreasing nonwhite representation, fewer patients hospitalized for HF within the 12 months before enrollment, and greater baseline troponin concentrations. A protocol amendment resulted in a longer time from first diuretic dose to randomization in the later cohorts compared with the first cohort.

EFFICACY EVALUATION. The response rates of the primary endpoint of dyspnea relief within 48 h among the placebo groups of the 3 cohorts were not statistically different ($p = 0.316$). Therefore, as specified in the protocol, the pooled placebo group was used for the statistical analysis of the primary endpoint. The global test of dyspnea relief response rate was similar among the 3 individual OM cohorts and did not differ from the pooled placebo group ($p = 0.331$), although the response rate did improve numerically with increasing OM dose (**Central Illustration**, panel A). Thus, the primary endpoint was not achieved.

However, as noted earlier, because of the months-long time delays among cohorts for data monitoring committee reviews, differences in time to randomization, region of enrollment, and baseline characteristics were observed among the cohorts, so a pre-specified supplemental analysis of comparisons between placebo and OM groups within each cohort was performed (**Central Illustration**, panel B). Cohort 3 had a 41% relative improvement in dyspnea relief at 48 h (14% absolute difference: placebo 37%, OM 51%; nominal $p = 0.034$). An exploratory post hoc logistic regression analysis across all cohorts demonstrated greater dyspnea response rates with higher total dose (response rate ratio per 50 mg increase in OM dose: 1.06, 95% confidence interval [CI]: 1.01 to 1.11; $p = 0.025$ adjusting for region, cohort, age, baseline dyspnea numeric rating scale, and duration between presentation and randomization as covariates; $p = 0.035$ unadjusted) or with increased OM exposure integrated as the area under the curve of OM plasma concentrations (response rate ratio per increase of 4,000 h·ng/ml in the area under the curve at 48 h: 1.06; 95% CI: 1.02 to 1.11; $p = 0.007$ adjusted; $p = 0.016$ unadjusted).

There were no statistically significant differences for any of the secondary endpoints when OM treatment cohorts were compared with the pooled placebo (**Table 2**). However, analysis of the dyspnea numeric rating scale area under the curve through day 5 noted increased dyspnea improvement in cohort 3 OM-treated patients compared with its matching placebo group (nominal $p = 0.038$), a finding supporting potential symptom improvement in the highest-dose cohort. The incidence of death or worsening HF through day 7 was driven primarily by worsening HF events, with numerically fewer events in patients assigned to OM within each cohort.

The exploratory endpoints of global rank score, total IV loop diuretic use, CHF medication at discharge, and health resource use were similar between the OM and placebo groups. Supraventricular tachyarrhythmia (SVT) requiring treatment from baseline to discharge occurred in 12 placebo-treated subjects and 3 OM-treated subjects, whereas ventricular tachyarrhythmia (VT) requiring treatment occurred in 2 patients treated with placebo and 4 OM-treated patients. Renal impairment (defined as creatinine increase ≥ 0.3 mg/dl or $\geq 25\%$ from baseline at day 5 or discharge) occurred in 52 (17.2%) patients who received placebo compared with 36 (11.9%) OM-treated subjects. Within each cohort, numerically fewer patients assigned to OM developed renal impairment than did those assigned to placebo, although this difference did not attain statistical significance (**Online Figure 4**).

PHARMACOKINETICS AND PHARMACODYNAMICS.

The 3 dosing regimens targeted OM mean plasma concentrations at 48 h (C_{48}) of 115, 230, and 310 ng/ml. The actual measured C_{48} for the respective cohorts were mean 148 ± 49 ng/ml, 311 ± 115 ng/ml, and 425 ± 173 ng/ml. There was a concentration-dependent reduction in heart rate ($p < 0.0001$) and an increase in BP ($p = 0.0017$) from baseline with OM relative to placebo (**Table 3**). The echocardiographic substudy enrolled 89 of the planned 240 subjects and showed that OM caused plasma concentration-dependent increases in LV systolic ejection time (SET) ($p < 0.0001$) (**Figure 1**). The mean placebo-corrected increase in SET was 23, 34, and 53 ms for OM concentration ranges of 88 to 200 ng/ml, 201 to 300 ng/ml, and >300 ng/ml, respectively ($p < 0.005$ for the difference from placebo for all ranges). There was also a significant concentration-related decrease in left ventricular end-systolic dimension (LVESD) ($p < 0.05$).

SAFETY AND TOLERABILITY. Of the 606 patients who received infusions, 92% (281 of 303) of patients

TABLE 1 Baseline Characteristics

	Pooled		Cohort 1		Cohort 2		Cohort 3	
	Placebo (n = 303)	OM (n = 303)	Placebo (n = 103)	OM (n = 103)	Placebo (n = 99)	OM (n = 99)	Placebo (n = 101)	OM (n = 101)
Demographics								
Age, yrs	66 ± 11	66 ± 11	65 ± 13	65 ± 12	66 ± 10	66 ± 10	66 ± 10	68 ± 11
Male	230 (75.9)	236 (77.9)	81 (78.6)	78 (75.7)	69 (69.7)	81 (81.8)	80 (79.2)	77 (76.2)
Race								
White	270 (89.1)	260 (85.8)	87 (84.5)	87 (84.5)	91 (91.9)	82 (82.8)	92 (91.1)	91 (90.1)
Nonwhite	33 (10.9)	43 (14.2)	16 (15.5)	16 (15.5)	8 (8.1)	17 (17.2)	9 (8.9)	10 (9.9)
Region								
Eastern Europe	160 (52.8)*	164 (54.1)	41 (39.8)	46 (44.7)	59 (59.6)	55 (55.6)	60 (59.4)	63 (62.4)
Western Europe	62 (20.5)*	58 (19.1)	24 (23.3)	19 (18.5)	15 (15.2)	19 (19.2)	23 (22.8)	20 (19.8)
United States/Canada/Australia	81 (26.7)*	81 (26.7)	38 (36.9)	38 (36.9)	25 (25.3)	25 (25.3)	18 (17.8)	18 (17.8)
Heart failure history								
Ischemic heart disease	189 (62.4)	189 (62.4)	66 (64.1)	64 (62.1)	56 (56.6)	58 (58.6)	67 (66.3)	67 (66.3)
Years from HF diagnosis	5.7 ± 5.5	5.9 ± 5.4	6.3 ± 6.3	6.3 ± 6.2	5.1 ± 4.8	5.6 ± 5.0	5.5 ± 5.3	5.8 ± 5.0
NYHA functional class before decompensation								
I	9 (3.0)	6 (2.0)	5 (4.9)	4 (3.9)	4 (4.0)	2 (2.0)	0 (0.0)	0 (0.0)
II	97 (32.2)	89 (29.4)	28 (27.2)	27 (26.2)	27 (27.3)	26 (26.3)	42 (42.4)	36 (35.6)
III	153 (50.8)	151 (49.8)	52 (50.5)	53 (51.5)	54 (54.5)	52 (52.5)	47 (47.5)	46 (45.5)
IV	42 (14.0)	57 (18.8)	18 (17.5)	19 (18.4)	14 (14.1)	19 (19.2)	10 (10.1)	19 (18.8)
Hospitalized for AHF in past 12 months	157 (52)*	169 (56)	65 (63)	64 (62)	53 (54)	59 (60)	39 (39)	46 (46)
Most recent LVEF, %	26 ± 8	26 ± 8	26 ± 7	26 ± 8	26 ± 8	25 ± 7	28 ± 8	28 ± 7
Selected comorbidities								
Previous MI	146 (48.5)	161 (53.1)	58 (57.4)	55 (53.4)	41 (41.4)	48 (48.5)	47 (46.5)	58 (57.4)
Persistent AF or flutter	100 (33.0)	98 (32.3)	27 (26.2)	30 (29.1)	41 (41.4)	32 (32.3)	32 (31.7)	36 (35.6)
Paroxysmal AF or flutter	62 (20.5)*	70 (23.1)	29 (28.2)	20 (19.4)	18 (18.2)	26 (26.3)	15 (14.9)	24 (23.8)
Diabetes mellitus	136 (44.9)	133 (43.9)	43 (41.7)	50 (48.5)	47 (47.5)	41 (41.4)	46 (45.5)	42 (41.6)
Hypertension	244 (80.5)	249 (82.2)	80 (77.7)	86 (83.5)	81 (81.8)	80 (80.8)	83 (82.2)	83 (82.2)
Dyslipidemia	175 (57.8)	170 (56.1)	63 (61.2)	61 (59.2)	59 (59.6)	58 (58.6)	53 (52.5)	51 (50.5)
Previous transient ischemic attack	19 (6.3)	12 (4.0)	4 (3.9)	3 (2.9)	8 (8.1)	6 (6.1)	7 (6.9)	3 (3.0)
Prior stroke	35 (11.6)	39 (12.9)	11 (10.7)	11 (10.7)	14 (14.1)	15 (15.2)	10 (9.9)	13 (12.9)
Peripheral artery disease	47 (15.5)	40 (13.2)	18 (17.5)	18 (17.5)	16 (16.2)	10 (10.1)	13 (12.9)	12 (11.9)
Chronic obstructive pulmonary disease	68 (22.4)	76 (25.1)	24 (23.3)	28 (27.2)	22 (22.2)	21 (21.2)	22 (21.8)	27 (26.7)
Selected baseline outpatient medications								
Diuretics	270 (89.1)*	270 (89.1)	95 (92.2)	90 (87.4)	94 (94.9)	91 (91.9)	81 (80.2)	89 (88.1)
ACE inhibitors/angiotensin receptor blockers	237 (78.2)	239 (78.9)	84 (81.6)	81 (78.6)	74 (74.7)	73 (73.7)	79 (78.2)	85 (84.2)
Beta-blocker	261 (86.1)*	270 (89.1)	94 (91.3)	93 (90.3)	88 (88.9)	86 (86.9)	79 (78.2)	91 (90.1)
Digoxin	70 (23.1)	86 (28.4)	20 (19.4)	33 (32.0)	28 (28.3)	29 (29.3)	22 (21.8)	24 (23.8)
Mineralocorticoid receptor antagonist	168 (55.5)	173 (57.1)	56 (54.4)	56 (54.4)	58 (58.6)	58 (58.6)	54 (53.5)	59 (58.4)
Ivabradine	8 (2.6)	14 (4.6)	3 (2.9)	4 (3.9)	3 (3.0)	4 (4.0)	2 (2.0)	6 (5.9)
Statins	168 (55.5)	159 (52.5)	58 (56.3)	53 (51.5)	50 (50.5)	51 (51.5)	60 (59.4)	55 (54.5)

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assigned to placebo and 93% (282 of 303) assigned to OM completed 48 h; the mean duration of infusion was similar across all groups. There were 191 (63%) patients reporting any adverse event in the placebo group compared with 177 (58%) in the OM group (Table 4). Rates for serious adverse events were similar in patients assigned to placebo (n = 70; 23%) and OM (n = 66; 22%).

All-cause rehospitalizations (placebo: n = 47, 15.5%; OM: n = 39, 12.9%) and rehospitalizations for HF (placebo: n = 19, 6.3%; OM: n = 22, 7.3%) within 30 days were similar between pooled OM and

placebo. There were 10 deaths (3.3%) within 30 days in patients assigned to placebo versus 8 (2.6%) in patients assigned to OM; all causes of death were cardiovascular (Table 4). By 6 months, 39 deaths (12.9%) had occurred among patients assigned to placebo and 38 (12.5%) among those assigned to OM.

Adverse event rates for SVT, VT, and myocardial ischemia were similar in patients assigned to placebo or OM (Table 4). Investigators reported SVT adverse events in 20 (6.6%) patients in the pooled placebo compared with 11 (3.6%) in the OM

TABLE 1 Continued

	Pooled		Cohort 1		Cohort 2		Cohort 3	
	Placebo (n = 303)	OM (n = 303)	Placebo (n = 103)	OM (n = 103)	Placebo (n = 99)	OM (n = 99)	Placebo (n = 101)	OM (n = 101)
Characteristics on presentation								
Body mass index, kg/m ²	29.1 ± 5.9	29.1 ± 5.9	28.4 ± 5.1	30.1 ± 6.6	29.5 ± 6.8	28.5 ± 5.8	29.4 ± 5.8	28.7 ± 5.1
Systolic BP, mm Hg	119 ± 18*	117 ± 17	115 ± 18	118 ± 18	119 ± 19	116 ± 17	123 ± 17	117 ± 15
Diastolic BP, mm Hg	72 ± 11	71 ± 11	71 ± 10	71 ± 10	71 ± 12	72 ± 12	73 ± 12	70 ± 10
Pulse rate, beats/min	78 ± 13	78 ± 13	79 ± 13	78 ± 13	78 ± 12	79 ± 13	79 ± 13	78 ± 14
Respiratory rate, breaths/min	21 ± 5	22 ± 4	22 ± 5	22 ± 4	22 ± 4	22 ± 4	21 ± 4	22 ± 4
O ₂ saturation	95 ± 4	95 ± 3	96 ± 3	96 ± 3	94 ± 5	95 ± 3	95 ± 4	95 ± 3
Dyspnea NRS (range 0-10)†	5.8 ± 2.2	6.2 ± 1.9	5.9 ± 2.2	6.1 ± 1.9	5.7 ± 2.2	6.3 ± 1.9	5.8 ± 2.1	6.3 ± 2.0
Troponin I, URL 0.04 ng/ml	0.044* (0.023- 0.080)	0.054 (0.026- 0.095)	0.032 (0.017- 0.070)	0.060 (0.0712- 0.606)	0.051 (0.028- 0.079)	0.044 (0.030- 0.084)	0.047 (0.029- 0.085)	0.056 (0.026- 0.092)
NT-proBNP, pg/ml	9,026 (4,704- 16,208)	9,153 (4,432- 16,247)	8,450 (4,127- 16,890)	7,674 (3,721- 14,867)	10,856 (5,648- 17,009)	10,488 (5,610- 16,026)	8,721 (4,055- 14,174)	10,416 (4,763- 17,135)
eGFR, ml/min/1.73 m ²	53 ± 18*	52 ± 18	53 ± 19	52 ± 18	49 ± 17	53 ± 19	56 ± 17	50 ± 18
Time from presentation to randomization	15.3 ± 8.2*	14.3 ± 8.8	13.7 ± 7.8	11.8 ± 7.6	16.3 ± 8.2	15.8 ± 9.7	15.9 ± 8.3	15.2 ± 8.7
Time from first diuretic dose to randomization	12.6 ± 7.3*	12.0 ± 7.5	10.9 ± 7.1	10.3 ± 7.3	13.4 ± 7.4	13.1 ± 7.7	13.6 ± 7.3	12.6 ± 7.3

Values are mean ± SD, n (%), or median (interquartile range). *Denotes significant differences (p < 0.05) between individual placebo cohorts. †Smaller value indicates better dyspnea condition.
ACE = angiotensin-converting enzyme; AF = atrial fibrillation; AHF = acute heart failure; BP = blood pressure; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; Nonwhite = includes American-Indian or Alaska Native, Asian, Black or African-American, Native Hawaiian or Pacific Islander, Mixed Race or Other; NRS = numerical rating scale; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; OM = omecamtiv mecarbil; URL = upper reference limit.

group, predominantly resulting from atrial fibrillation or flutter, whereas reports of VTs were similar. The CEC confirmed 3 (1.0%) post-randomization myocardial infarctions in the placebo group compared with 7 (2.3%) in the OM-treated cohorts (Online Table 1).

Cardiac troponin I (cTnI) was intensively monitored throughout the study with 4,750 samples centrally analyzed at a blinded core laboratory. The median baseline cTnI in the pooled OM groups was 0.054 ng/ml (interquartile range [IQR]: 0.026 to 0.095 ng/ml) compared with 0.044 ng/ml (IQR: 0.023 to 0.080 ng/ml) in the pooled placebo group. The median change from baseline to end of study drug infusion (48 h) was 0.000 ng/ml (IQR: -0.017 to 0.012 ng/ml) for the pooled OM group and -0.004 ng/ml (IQR: -0.017 to 0.001 ng/ml) for the pooled placebo group. Within cohort 3, the change from baseline troponin in the high-dose OM group versus the cohort 3 placebo was 0.001 ng/ml (IQR: -0.011 to 0.021 ng/ml) and -0.005 ng/ml (IQR: -0.015 to 0.001 ng/ml), respectively. OM exposure (maximum concentration [Figure 2] or C_{48h} [Online Figures 5A and 5B]) did not predict the maximum change from baseline in cTnI. In similar analyses made on the basis of the 89 patients in the PK/PD substudy, neither the maximal change in SET nor the maximal change in LVEF predicted the maximum change from baseline in cTnI (Online Figures 6 and 7).

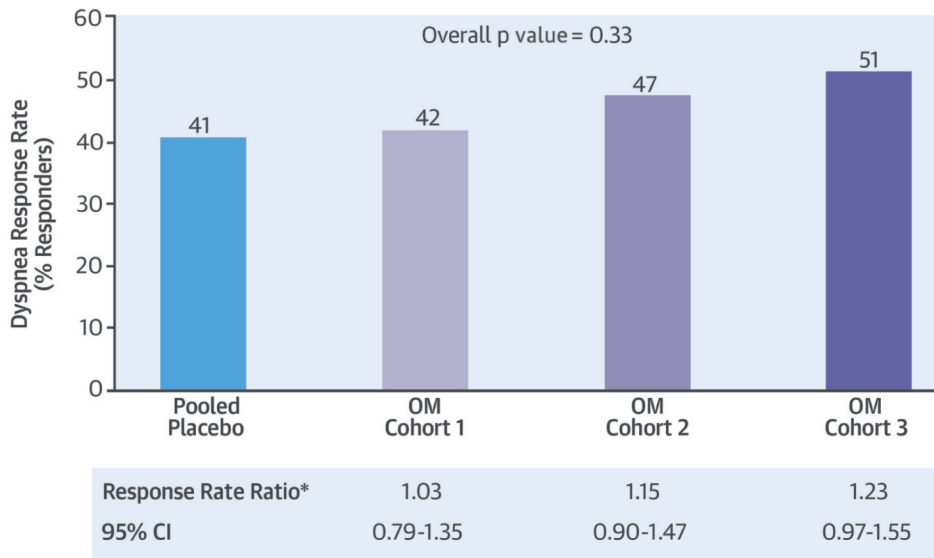
DISCUSSION

In ATOMIC-AHF, a phase II dose-finding study, OM did not improve the primary endpoint of dyspnea or any pre-specified secondary outcome when compared with placebo. However, there was a suggestion of greater dyspnea relief in the high-dose OM cohort compared with its concurrent placebo group, as assessed by both Likert and numeric rating scales. OM appeared generally well tolerated, with approximately dose-proportional PK properties associated with prolonged ventricular systole and decreased LVEF. Although OM-treated patients had a small numeric excess of episodes of myocardial ischemia, this difference was not temporally related to study drug exposure. The small increases in plasma troponin in patients assigned to OM had no apparent relationship with OM plasma concentrations. There was no increase in symptomatic hypotension or arrhythmias in the OM-treated patients.

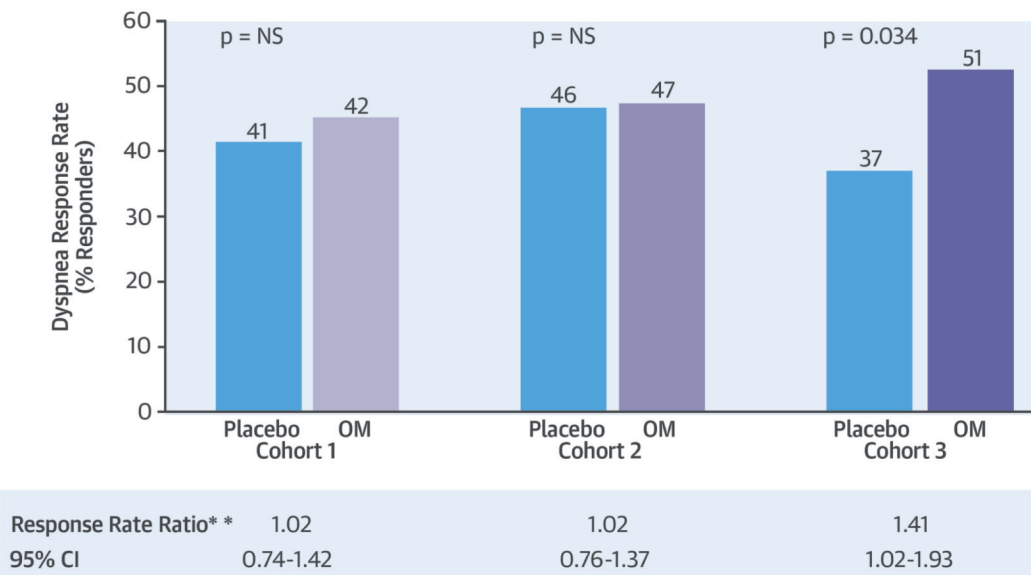
OM improves cardiac performance through a novel mechanism of selectively activating cardiac myosin (5). The PD signature of this mechanism of action, prolongation of myocardial systole, has been demonstrated in healthy volunteers (7) and in patients with CHF (8). This same signature was evident in patients with AHF in ATOMIC-AHF, and the relationship between the OM plasma concentrations and prolongation of the SET in ATOMIC-AHF

CENTRAL ILLUSTRATION ATOMIC-HF: Effect of OM on Dyspnea in Acute Heart Failure

A. Comparison with Pooled Placebo



B. Comparison with Paired Placebo Groups



Teerlink, J.R. et al. J Am Coll Cardiol. 2016; 67(12):1444-55.

Although omecamtiv mecarbil (OM) did not improve the primary endpoint of dyspnea relief when comparing the 3 OM dose groups with pooled placebo (A), OM did improve dyspnea response in the patients receiving the highest dose when compared with the paired placebo groups (B). Columns represent the percentage of patients with dyspnea relief at 48 h. *Ratio of response rate to pooled placebo. **Ratio of response rate to placebo within each cohort. ATOMIC-HF = Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure; CI = confidence interval.

TABLE 2 Secondary Endpoints

Secondary Endpoint	Pooled Placebo (n = 303)	Cohort 1		Cohort 2		Cohort 3	
		Placebo (n = 103)	OM (n = 103)	Placebo (n = 99)	OM (n = 99)	Placebo (n = 101)	OM (n = 101)
Dyspnea numerical response AUC through day 5*	3.5 (3.3-3.8)	3.6 (3.1-4.0)	3.5 (3.1-3.9)	3.2 (2.8-3.6)	3.6 (3.2-4.0)	3.8 (3.4-4.3)	3.7 (3.3-4.0); p = 0.038†
Patient global assessment response	127 (41.9)	35 (34.0)	44 (42.7)	50 (50.5)	48 (48.5)	42 (41.6)	51 (50.5)
Death or worsening HF within 7 days	52 (17.2)	25 (24.3)	13 (12.6); p = 0.027†	15 (15.2)	9 (9.1)	12 (11.9)	9 (8.9)
Length of initial hospital stay; median days (95% CI)	9 (8 to 9)	9 (8 to 10)	8 (7 to 9)	8 (7 to 9)	7 (7 to 8)	9 (9 to 11)	9 (8 to 10)
Days alive out of hospital through 30 days; median (95% CI)	22 (21 to 23)	22 (21 to 23)	22 (21 to 23)	23 (22 to 24)	23 (23 to 24)	21 (20 to 23)	22 (21 to 23)
NT-proBNP change from baseline (pg/ml) at 48 h; median (95% CI)	-1,805 (-2,271 to -1,370)	-1,602 (-2,099 to -797)	-2,076 (-2,746 to -1,292)	-1,987 (-3,373 to -1,695)	-2,161 (-4,273 to -1,336)	-1788 (-2,805 to -890)	-1742 (-2,517 to -1,017)

Values are mean (95% CI) or n (%) unless otherwise indicated. *Smaller value indicates better dyspnea condition. Analysis of covariance model least square means (SE) for the 6 cohort/treatment arm, when compared within the same cohort, are 3.6 (0.2), 3.4 (0.2), 3.4 (0.2), 3.4 (0.2), 4.1 (0.2), 3.6 (0.2). †Nominal p value compared with matching placebo from same cohort; all others nonsignificant.
AUC = area under the curve; CI = confidence interval; other abbreviations as in Table 1.

was nearly identical to that seen in the previous 2 studies. These findings demonstrated that this mechanism of action is operative in AHF and provides evidence that this effect translated into a physiological benefit with a significant reduction in LVESD, a finding consistent with an improvement in cardiac performance and related to improved long-term survival (12). Although SET is inversely related to heart rate, it has also been long recognized that patients with reduced cardiac output or EF have decreased SETs (13), and thus OM may be viewed as effectively normalizing ejection time.

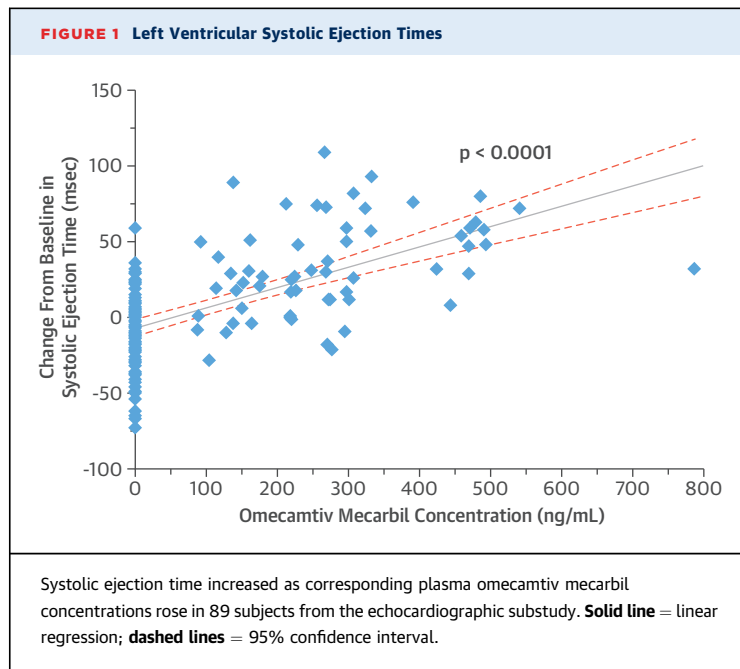
The most common presenting symptom in patients with AHF, dyspnea at rest or with minimal exertion, remains a clinically meaningful endpoint (14). OM

increased cardiac output and reduced LV filling pressures in animal models (5,6), and it improved cardiac function in humans (7,8), thereby providing a mechanism for dyspnea relief in patients. Previous trials suggested that selection of symptomatic patients and objective signs of congestion early in their hospital course provide the best opportunity to demonstrate a clinical benefit on dyspnea (15,16). In ATOMIC-AHF, dyspnea relief was evaluated by a responder variable requiring early and sustained improvement in dyspnea compared with standard therapy without evidence of clinical worsening within the first 48 h. In an attempt to increase the power of this phase II study for a symptom endpoint, the primary analysis pre-specified comparisons

TABLE 3 Placebo-Corrected Change From Baseline in Selected Pharmacodynamic Variables

Placebo-Corrected Change From Baseline in:	OM Plasma Concentration*			PK Slope†	PK Slope p Value
	≥88 to 200 ng/ml	>200 to 300 ng/ml	>300 to 787 ng/ml		
Heart rate, beats/min	0.1 (-1.4 to 1.1)	-2.0‡ (-3.6 to -0.4)	-2.3§ (-3.9 to -0.6)	-0.006	<0.0001
Systolic BP, mm Hg	0.3 (-1.1 to 1.7)	0.6 (-1.2 to 2.4)	2.4§ (0.6 to 4.2)	0.005	0.0017
Systolic ejection time, ms	23.4§ (7.4 to 39.4)	33.6 (19.8 to 47.4)	53.2 (38.0 to 68.3)	0.113	<0.0001
LV end-systolic dimension, cm	-0.01 (-0.4 to 0.4)	-0.03 (-0.4 to 0.3)	-0.23 (-0.61 to 0.14)	-0.001	0.047
LV end-diastolic dimension, cm	-0.04 (-0.4 to 0.3)	0.05 (-0.2 to 0.3)	-0.07 (-0.4 to 0.2)	-0.0004	0.25
LV fractional shortening, %	-1.2 (-5.0 to 2.6)	0.5 (-2.5 to 3.4)	1.3 (-2.1 to 4.7)	0.004	0.26
LV stroke volume, mL¶	5.5 (-2.7 to 13.8)	4.8 (-2.7 to 12.2)	6.3 (-1.7 to 14.3)	0.014	0.10

Values are mean placebo-corrected change from baseline (95% confidence interval). *Number of echocardiographic observations within concentration ranges = 14 to 23. †Positive slope indicates increase in variable with respect to increasing OM plasma concentrations. ‡p < 0.05. §p < 0.01. ||p < 0.0001. ¶LV stroke volume on the basis of LV outflow tract velocity time integral.
LV = left ventricular; PK = pharmacokinetics; other abbreviations as in Table 1.



among the pooled placebo group and the individual OM dose cohorts. This endpoint was not met, perhaps reflecting a failure of OM to improve dyspnea. However, major differences in the characteristics and

behavior of the placebo group among the cohorts undermined the validity of the pooled placebo group as the comparator. The placebo response rate was much higher than predicted (41% actual vs. 23% predicted), thus reducing the power of the trial to observe a beneficial treatment effect. In addition, patients were randomized, on average, 15 h after presentation, a significantly longer period of time than in a recent clinical trial (16), thereby potentially limiting the ability to discern a treatment effect. When the effect of high-dose OM was compared with the matching placebo, a 14% absolute (41% relative) treatment effect emerged at 48 h, which was additionally supported by analyses suggesting a relationship between OM dose, as well as plasma concentrations, and dyspnea improvement. Patients treated with OM in high-dose cohort 3 also had improved dyspnea relief as measured by the numerical rating scale over 5 days.

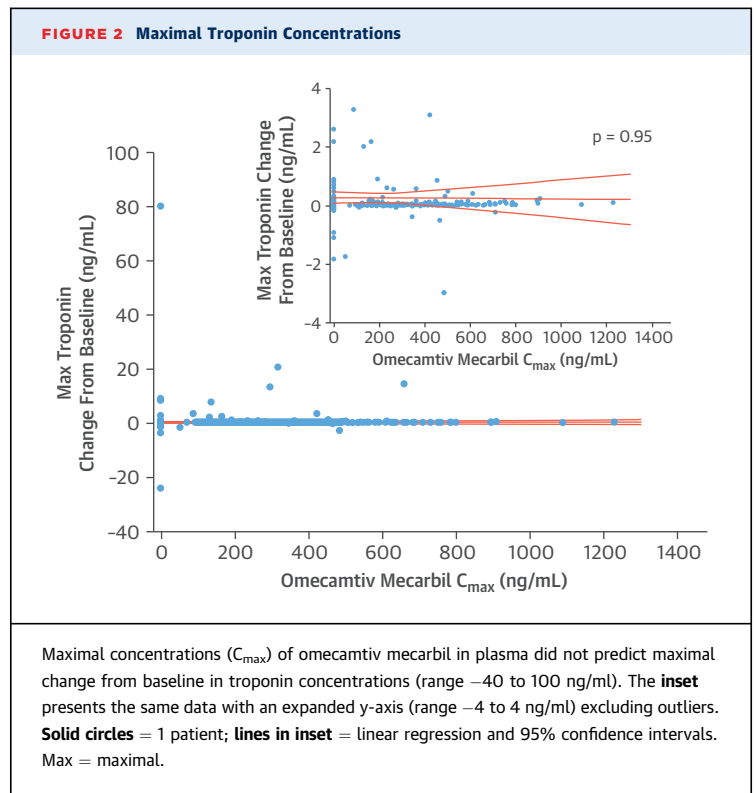
Increased troponins in patients admitted for AHF (17) have been related to increased long-term mortality rates in some studies (18-20), but not others (21). Previous clinical studies demonstrated that the dose-limiting toxicity of OM is provocation of myocardial ischemia; thus, ATOMIC-AHF used intensive sampling of cardiac troponin in all patients,

TABLE 4 Adverse Events					
Patient Incidence	Pooled Placebo (n = 303)	Pooled OM (n = 303)	Cohort 1 OM (n = 103)	Cohort 2 OM (n = 99)	Cohort 3 OM (n = 101)
All AEs	191 (63.0)	177 (58.4)	73 (70.9)	49 (49.5)	55 (54.5)
3 most common AEs					
Cardiac failure*	53 (17.5)	46 (15.2)	17 (16.5)	14 (14.1)	15 (14.9)
Hypokalemia	18 (5.9)	20 (6.6)	7 (6.8)	7 (7.1)	6 (5.9)
Hypotension	14 (4.6)	24 (7.9)	14 (13.6)	5 (5.1)	5 (5.0)
All serious AEs	70 (23.1)	66 (21.8)	24 (23.3)	24 (24.2)	18 (17.8)
3 most common serious AEs					
Cardiac failure*	29 (9.6)	26 (8.6)	8 (7.8)	11 (11.1)	7 (6.9)
Acute renal failure	4 (1.3)	6 (2.0)	2 (1.9)	2 (2.0)	2 (2.0)
Hypotension	0 (0.0)	3 (1.0)	3 (2.9)	0 (0.0)	0 (0.0)
Deaths through 30 days					
HF	10 (3.3)	8 (2.6)	1 (1.0)	4 (4.0)	3 (3.0)
Sudden cardiac death	9 (3.0)	4 (1.3)	0 (0.0)	2 (2.0)	2 (2.0)
MI	1 (0.3)	2 (0.6)	1 (1.0)	1 (1.0)	0 (0.0)
Other cardiovascular	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (1.0)
AEs leading to discontinuation of investigational product	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.0)
Number of subjects reporting AEs of ischemic heart disease, MI, increased troponins	15 (5.0)	15 (5.0)	7 (6.8)	4 (4.0)	4 (4.0)
Number of subjects reporting AEs of SVTs or VTs	5 (1.7)	9 (3.0)	2 (1.9)	2 (2.0)	5 (5.0)
SVTs	34 (11.2)	26 (8.6)	13 (12.6)	5 (5.1)	8 (7.9)
AF or atrial flutter	20 (6.6)	11 (3.6)	6 (5.8)	0 (0.0)	5 (5.0)
VTs	16 (5.3)	7 (2.3)	3 (2.9)	0 (0.0)	4 (4.0)
	18 (5.9)	16 (5.2)	8 (7.8)	5 (5.1)	3 (3.0)

Values are n (%). *Cardiac failure includes both "Cardiac failure" and "Cardiac failure congestive" preferred terms.
AE = adverse event; SVT = supraventricular tachyarrhythmia; VT = ventricular tachyarrhythmia; other abbreviations as in Table 1.

with additional sampling when there was any clinical suspicion of ischemia. Consistent with other AHF studies (19,21), baseline troponin was greater than the 99th percentile upper reference limit in more than one-half the enrolled patients. An analysis of the troponin change from baseline over time revealed a slightly higher troponin concentration in patients assigned to OM versus placebo at 48 h. In pooled data, no relationship between OM exposure (either maximum concentration or C_{48h}) and the maximal troponin increase from baseline was apparent. Additionally, analysis for the echocardiographic substudy revealed no relationship between maximal change in either SET or LVESD and the maximal change in troponin. The absence of a discernible association of OM exposure, its PD effect on SET, or one of its main physiological effects (LVESD) with the small magnitude of the troponin change made it difficult to draw definitive conclusions about the clinical significance of these troponin findings. Whereas most studies have demonstrated that OM inhibits non-actin-dependent cardiac myosin adenosine triphosphatase (5,22) and does not increase myocardial oxygen consumption (6), a recent study in anesthetized animals suggested OM-related increased myocardial oxygen consumption (23). Although methodological limitations undermined this study (24), these data, combined with the small numeric increase in the incidence of myocardial infarction, support the need to continue assessing whether OM contributes to myocardial injury.

Currently available inotropes have demonstrated proarrhythmic effects linked to increased mortality. Dobutamine, dopamine, milrinone, and levosimendan all have well-recognized adverse effects of tachycardia that can limit their clinical utility. In the OPTIME-HF (Organized Program to Initiate Life-saving Treatment in Hospitalized Patients With Heart Failure) trial, patients treated with milrinone had a >2-fold risk of developing VT or atrial fibrillation and a 3-fold risk of developing new atrial fibrillation or atrial flutter during the index hospitalization (25). In REVIVE II (Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy), levosimendan treatment increased heart rate by 2 to 8 beats/min, remaining statistically significant for at least 5 days, and was associated with a 50% increase in VT and a 4-fold increase in ventricular extrasystoles and atrial fibrillation compared with placebo (26). These proarrhythmic effects are inextricably linked to these agents' mechanisms of action, which increase contractility through increased intracellular cyclic adenosine monophosphate and calcium. As a cardiac myosin activator, OM does not increase these



intracellular signals and effectors (5), and it had no evidence of increased arrhythmogenicity in previous clinical studies (7,8). In ATOMIC-AHF, OM decreased heart rate versus placebo and did not increase risk of SVT or VT. OM improved left atrial function and reduced volumes in healthy volunteers; such an effect could reduce the propensity to atrial arrhythmias (7).

Worsening HF during initial hospitalization has emerged as a clinically important event with both short- and long-term prognostic implications (19,27-29). In ATOMIC-AHF, too few events occurred to evaluate this endpoint meaningfully, although there were numerically fewer worsening HF events among patients who received OM than in patients who received placebo within each cohort. Both milrinone (25) and levosimendan (26) have been associated with increases in mortality; in the current study, 180-day all-cause mortality was 12.9% in the placebo and 12.5% in the OM group. More data are required to assess differences in mortality.

STUDY LIMITATIONS. ATOMIC-AHF was a phase II, dose-finding study that was underpowered to assess the potential impact of OM on clinical outcomes. In addition, the serial enrollment of the cohorts separated by months resulted in differences in the patient populations and placebo response rates among the

cohorts, thereby confounding the comparisons of the pooled placebo cohort with the individual OM cohorts.

CONCLUSIONS

In patients with AHF, IV OM did not meet the primary endpoint of dyspnea improvement, but it was generally well tolerated, it increased SET, and it may have improved dyspnea in the high-dose group. ATOMIC-AHF provides the basis for additional investigation of IV OM in patients with decompensated HF, as well as the development of oral OM for the treatment of patients with CHF, as has been recently explored in the COSMIC-HF study (NCT01786512).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Available interventions that increase myocardial contractile function in patients with HF and reduced LVEF have safety liabilities including increased oxygen requirements, hypotension, heart rate acceleration, arrhythmias, and increased mortality. Treatment with the selective cardiac myosin activator OM increased SET and at high dose seemed to improve dyspnea without the foregoing adverse effects in patients with AHF, but there were small increases in serum troponin levels.

TRANSLATIONAL OUTLOOK: Further studies are needed to evaluate the safety and efficacy of an oral preparation of OM in a larger group of patients with HF and reduced EF.

REFERENCES

- Felker GM, Pang PS, Adams KF, et al. Clinical trials of pharmacological therapies in acute heart failure syndromes: lessons learned and directions forward. *Circ Heart Fail* 2010;3:314-25.
- Hasenfuss G, Teerlink JR. Cardiac inotropes: current agents and future directions. *Eur Heart J* 2011;32:1838-45.
- McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur Heart J* 2012;33:1787-847.
- Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62:e147-239.
- Malik FI, Hartman JJ, Elias KA, et al. Cardiac myosin activation: a potential therapeutic approach for systolic heart failure. *Science* 2011;331:1439-43.
- Shen YT, Malik FI, Zhao X, et al. Improvement of cardiac function by a cardiac myosin activator in conscious dogs with systolic heart failure. *Circ Heart Fail* 2010;3:522-7.
- Teerlink JR, Clarke CP, Saikali KG, et al. Dose-dependent augmentation of cardiac systolic function with the selective cardiac myosin activator, omeamtiv mecarbil: a first-in-man study. *Lancet* 2011;378:667-75.
- Cleland JG, Teerlink JR, Senior R, et al. The effects of the cardiac myosin activator, omeamtiv mecarbil, on cardiac function in systolic heart failure: a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial. *Lancet* 2011;378:676-83.
- Newby LK, Jesse RL, Babb JD, et al. ACCF 2012 expert consensus document on practical clinical considerations in the interpretation of troponin elevations: a report of the American College of Cardiology Foundation task force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2012;60:2427-63.
- Teerlink JR, Metra M, Felker GM, et al. Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multicentre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study. *Lancet* 2009;373:1429-39.
- Hsu J. Multiple Comparisons: Theory and Methods. London, United Kingdom: Chapman & Hall, 1996.
- Kramer DG, Trikalinos TA, Kent DM, et al. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. *J Am Coll Cardiol* 2010;56:392-406.
- Weisler AM, Harris WS, Schoenfeld CD. Systolic time intervals in heart failure in man. *Circulation* 1968;37:149-59.
- West RL, Hernandez AF, O'Connor CM, et al. A review of dyspnea in acute heart failure syndromes. *Am Heart J* 2010;160:209-14.
- O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* 2011;365:32-43.
- Teerlink JR, Cotter G, Davison BA, et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. *Lancet* 2013;381:29-39.
- Januzzi JL Jr., Filippatos G, Nieminen M, Gheorghide M. Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: Heart Failure Section. *Eur Heart J* 2012;33:2265-71.
- Metra M, Bettari L, Pagani F, et al. Troponin T levels in patients with acute heart failure: clinical and prognostic significance of their detection and release during hospitalisation. *Clin Res Cardiol* 2012;101:663-72.
- Metra M, Cotter G, Davison BA, et al. Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program: correlation with outcomes. *J Am Coll Cardiol* 2013;61:196-206.
- O'Connor CM, Fiuzat M, Lombardi C, et al. Impact of serial troponin release on outcomes in patients with acute heart failure: analysis from the PROTECT pilot study. *Circ Heart Fail* 2011;4:724-32.
- Felker GM, Hasselblad V, Tang WH, et al. Troponin I in acute decompensated heart failure: insights from the ASCEND-HF study. *Eur J Heart Fail* 2012;14:1257-64.
- Liu Y, White HD, Belknap B, et al. Omeamtiv mecarbil modulates the kinetic and motile properties of porcine beta-cardiac myosin. *Biochemistry* 2015;54:1963-75.
- Bakkehaug JP, Kildal AB, Engstad ET, et al. Myosin activator omeamtiv mecarbil increases myocardial oxygen consumption and impairs cardiac efficiency mediated by resting myosin ATPase activity. *Circ Heart Fail* 2015;8:766-75.
- Teerlink JR, Malik FI, Kass DA. Letter by Teerlink et al Regarding article, "Myosin Activator Omeamtiv Mecarbil Increases Myocardial Oxygen Consumption and Impairs Cardiac Efficiency Mediated by Resting Myosin ATPase Activity." *Circ Heart Fail* 2015;8:1141.
- Cuffe MS, Califf RM, Adams KF Jr., et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA* 2002;287:1541-7.
- Packer M, Colucci WS, Fisher L, et al. Effect of levosimendan on the short-term clinical course of

patients with acutely decompensated heart failure. *J Am Coll Cardiol HF* 2013;1:103-11.

27. Cotter G, Metra M, Weatherley BD, *et al.* Physician-determined worsening heart failure: a novel definition for early worsening heart failure in patients hospitalized for acute heart failure—association with signs and symptoms, hospitalization duration, and 60-day outcomes. *Cardiology* 2010;115:29-36.

28. Kelly JP, Mentz RJ, Hasselblad V, *et al.* Worsening heart failure during hospitalization for acute heart failure: insights from the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF). *Am Heart J* 2015;170:298-305.

29. Butler J, Gheorghiade M, Kelkar A, *et al.* In-hospital worsening heart failure. *Eur J Heart Fail* 2015;17:1104-13.

KEY WORDS arrhythmia, cardiac myosin activator, dyspnea, inotrope

APPENDIX For an expanded discussion of study methods, including additional figures and a table, please see the online version of this article.