ORIGINAL ARTICLE

Effect of Ularitide on Cardiovascular Mortality in Acute Heart Failure

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ABSTRACT

BACKGROUND

In patients with acute heart failure, early intervention with an intravenous vasodilator has been proposed as a therapeutic goal to reduce cardiac-wall stress and, potentially, myocardial injury, thereby favorably affecting patients' long-term prognosis.

METHODS

In this double-blind trial, we randomly assigned 2157 patients with acute heart failure to receive a continuous intravenous infusion of either ularitide at a dose of 15 ng per kilogram of body weight per minute or matching placebo for 48 hours, in addition to accepted therapy. Treatment was initiated a median of 6 hours after the initial clinical evaluation. The coprimary outcomes were death from cardiovascular causes during a median follow-up of 15 months and a hierarchical composite end point that evaluated the initial 48-hour clinical course.

RESULTS

Death from cardiovascular causes occurred in 236 patients in the ularitide group and 225 patients in the placebo group (21.7% vs. 21.0%; hazard ratio, 1.03; 96% confidence interval, 0.85 to 1.25; P=0.75). In the intention-to-treat analysis, there was no significant between-group difference with respect to the hierarchical composite outcome. The ularitide group had greater reductions in systolic blood pressure and in levels of N-terminal pro–brain natriuretic peptide than the placebo group. However, changes in cardiac troponin T levels during the infusion did not differ between the two groups in the 55% of patients with paired data.

CONCLUSIONS

In patients with acute heart failure, ularitide exerted favorable physiological effects (without affecting cardiac troponin levels), but short-term treatment did not affect a clinical composite end point or reduce long-term cardiovascular mortality. (Funded by Cardiorentis; TRUE-AHF ClinicalTrials.gov number, NCT01661634.)

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Acute presentation with new-onset heart failure and rapid worsening of preexisting heart failure are two of the most common causes of hospitalization worldwide.[1] The disorder in each case is characterized by intravascular volume expansion and ventricular distention, which may cause myocardial injury in the absence of coronary artery disease or occlusion.[2-4] Episodes are associated with an accelerated rate of disease progression; each hospitalization for heart failure increases the risk of subsequent admissions as well as the risk of death from cardiovascular causes.[5]

The first few hours after the initial presentation with acute heart failure may represent a period of substantial myocardial vulnerability, which is characterized by rapid increases in cardiac-wall stress.[6] Patients with acute heart failure have elevated levels of N-terminal pro–brain natriuretic peptide (NT-proBNP) and cardiac troponin,[2-4,6] thus mimicking features of an acute coronary syndrome.[7] These observations have led to the hypothesis that very early short-term interventions that attenuate cardiac-wall stress may reduce myocardial injury during a critical period and have favorable long-term effects (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[8-12] Early vasodilator treatment has been proposed as a therapeutic goal in recent guidelines.[13] Short-term interventions have been associated with both favorable and unfavorable longer-term effects on morbidity and mortality.[14-16]

In the Trial of Ularitide Efficacy and Safety in Acute Heart Failure (TRUE-AHF), we examined whether the prompt administration of the natriuretic peptide ularitide in doses sufficient to reduce myocardial-wall stress would reduce the long-term risk of cardiovascular death in patients with acute heart failure.[17] Ularitide, a chemically synthesized analogue of the naturally occurring vasodilator urodilatin, was selected as the study drug because it had been associated with hemodynamic and clinical benefits in two previous randomized clinical trials.[18,19]

METHODS

TRIAL DESIGN AND OVERSIGHT

TRUE-AHF was a randomized, double-blind, parallel-group, placebo-controlled, event-driven trial.[17] The trial protocol and the statistical analysis plan are available at NEJM.org. The ethics committee at each trial center approved the trial, and all the patients provided written informed consent.

The executive committee, together with the sponsor (Cardiorentis), developed and amended the protocol and oversaw the recruitment of patients and the analysis of data; the committee provided an independent interpretation of the results.[17] A clinical-events committee classified deaths and adjudicated nonfatal events, and a medical review committee examined case summaries for unidentified instances of in-hospital heart-failure events in a blinded manner. An independent data and safety monitoring committee reviewed the safety of the patients and the results of interim analyses. Data were analyzed according to a predefined statistical analysis plan, and an independent statistician verified and replicated the analyses. The first author, who had unrestricted access to the data, prepared the drafts of the manuscript, which were then reviewed and edited by all the authors, independent of the sponsor. The authors assume responsibility for the accuracy and completeness of the analyses; the last author attests to the fidelity of the trial to the protocol.

PATIENTS

Men and women between the ages of 18 and 85 years were eligible to enroll in the trial if they met all the following criteria: an unplanned emergency department visit or hospitalization for acute heart failure, dyspnea at rest that had worsened during the previous week, evidence of heart failure on chest radiography, a blood BNP level of more than 500 pg per milliliter or an NT-proBNP level of more than 2000 pg per milliliter, and the possibility of initiating the study drug within 12 hours after the initial clinical evaluation. Patients who continued to have dyspnea at rest for at least 2 hours after the intravenous administration of at least 40 mg of furosemide (or the equivalent) and who had a systolic blood pressure between 116 mm Hg and 180 mm Hg were eligible for randomization. (A full list of the exclusion criteria is provided in the Supplementary Appendix.)

PROCEDURES

Patients underwent randomization in a 1:1 ratio in a double-blind manner to receive a continuous intravenous infusion of either ularitide at a dose of 15 ng per kilogram of body weight per minute

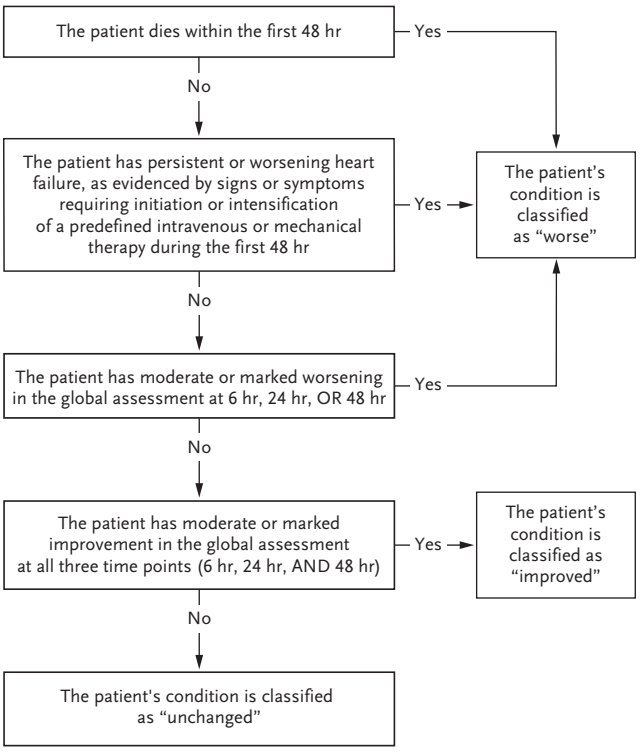


Figure 1. Hierarchical Clinical Composite End Point.

Each patient's clinical course over the first 48 hours of the trial was classified as "worse," "improved," or "unchanged." A patient's condition was classified as worse if he or she died during the first 48 hours, had persistent or worsening heart failure (as determined by the clinical-events committee in a blinded manner), or had moderate or marked worsening on a global assessment at any of the three time points of assessment (6, 24, or 48 hours). A patient's condition was classified as improved if he or she had moderate or marked improvement on a global assessment at all three time points and did not meet any of the criteria for worse condition. A patient's condition was classified as unchanged if the criteria for worse and improved were not met. Details regarding the investigator determination of worsening heart failure and the patient global assessment are provided in the Supplementary Appendix. Adapted with permission from Packer et al.[17]

or matching placebo for 48 hours. This dose had produced meaningful decreases in cardiac filling pressures in previous trials.[18,19] The rate of infusion of the study drug was reduced or discontinued if symptomatic hypotension developed or if there was a decrease in the systolic blood pressure to a value of less than 100 mm Hg or a decrease of more than 40 mm Hg from baseline.

Investigators used a patient global assessment to inquire about changes in symptoms of heart failure at 6, 24, and 48 hours after the initiation of the study infusion (see the Supplementary Appendix). Levels of NT-proBNP and high-sensitivity troponin T were assessed before the start of the infusion and after 48 hours. At 48 hours, the study-drug infusion was stopped.

For the first 120 hours, patients were monitored for persistent or worsening heart failure. The investigators described the features of these in-hospital heart-failure events and the interventions that were used to treat them. (The definitions that were used to identify and adjudicate these episodes are provided in the Supplementary Appendix.[15,17]) In addition, patients were allowed to receive any oral or intravenous medications for heart failure that were deemed to be clinically appropriate. Patients were followed for the occurrence of rehospitalization for 6 months and for the occurrence of death for the entire duration of the trial.

PRIMARY AND SECONDARY OUTCOMES

The trial had two primary outcomes: cardiovascular death over the entire duration of the trial and the clinical course of patients during the first 48 hours, as assessed by a hierarchical clinical composite end point (Fig. 1, with additional details provided in the Supplementary Appendix).[15,20] When the trial was initiated, it focused only on the short-term clinical course of patients, and the clinical composite was the sole primary end point.[17] However, after the Relaxin for the Treatment of Acute Heart Failure (RELAX-AHF) trial reported a potential mortality reduction,[14] we added cardiovascular mortality as a coprimary end point after approximately 40 patients had been enrolled and then redesigned the trial to extend follow-up to achieve a predetermined number of events. We divided the alpha level across the two primary end points, with 0.04 assigned to cardiovascular mortality and 0.01 to the hierarchical clinical composite end point.

The secondary end points of the trial are summarized in the Supplementary Appendix. These end points, which were to be tested hierarchically, included the length of stay in the hospital and in the intensive care unit during the index episode, the number of episodes of in-hospital heart-failure events through the first 120 hours, the proportion of patients with an in-hospital heart-failure event through the first 120 hours, rehospitalization for heart failure within 30 days after the initial hospital discharge, the time until completion of intravenous treatment for heart failure, and death or rehospitalization for a cardiovascular cause during the first 180 days.

STATISTICAL ANALYSIS

The sample size was based on the primary efficacy analysis of cardiovascular mortality, which was tested at a two-sided significance level of 0.04. We expected to recruit 2152 patients over a 2-year period with a follow-up of at least 1 year to observe 652 deaths from cardiovascular causes, a trial design that provided a power of 90% to detect a relative reduction of 22% in the risk of cardiovascular death. These assumptions were based on a 6-month rate of cardiovascular death of 8.6% in the ularitide group and 11.0% in the placebo group. We evaluated time-to-event data with Kaplan–Meier estimates and used Cox proportional-hazards models to calculate hazard ratios, 96% confidence intervals, and two-sided P values for the risk of cardiovascular death, using age, sex, baseline systolic blood pressure (<140 mm Hg vs. ≥140 mm Hg), time from the first clinical evaluation until the initiation of the study-drug infusion (≤6 hours vs. >6 hours), and region as prespecified covariates.

We performed the primary efficacy analysis for the hierarchical clinical composite end point at a two-sided significance level of 0.01. We used the Cochran–Mantel–Haenszel test to compare the differences in the distribution of ranks, with the time from the first physician evaluation until the initiation of the study-drug infusion and baseline systolic blood pressure as stratification variables. All P values that were calculated for analyses other than the primary end points are nominal (see the Supplementary Appendix).

We included data from all the patients who had undergone randomization in the analyses of the primary and secondary outcomes, according to the intention-to-treat principle, and used multiple imputation to account for missing data. The trial design incorporated an option to increase the total enrollment on the basis of the results of a midpoint interim analysis; this option was not exercised. A second interim analysis that was performed for futility after all the enrolled patients had been followed for at least 6 months led to termination of the trial because no benefit was seen with respect to cardiovascular mortality.

RESULTS

PATIENTS

From August 2012 through May 2014, we enrolled 2157 patients at 156 centers in 23 countries. A total of 1088 patients were assigned to receive ularitide and 1069 to receive placebo (Fig. S2 in the Supplementary Appendix). The characteristics of the two groups were similar at baseline (Table 1, and Table S1 in the Supplementary Appendix).

STUDY-DRUG ADMINISTRATION AND FOLLOW-UP

We administered the study drug to 1072 patients in the ularitide group and 1056 in the placebo group at a median of 6.1 hours (interquartile range, 4.6 to 8.4) after the initial clinical evaluation. (Reasons for nontreatment are provided in Fig. S2 in the Supplementary Appendix.) Ularitide was discontinued in 194 patients (18.1%) and placebo in 78 patients (7.4%); the dose was reduced (but not discontinued) in 106 patients (9.9%) in the ularitide group and in 55 (5.2%) in the placebo group (P<0.001 for both comparisons) (Table S2 in the Supplementary Appendix). The primary reason for both discontinuation and dose reduction was hypotension. One patient in the placebo group was lost to follow-up for cardiovascular mortality. The median duration of follow-up was 15 months, with no significant difference between the groups; follow-up ended in January 2016.

PRIMARY AND SECONDARY OUTCOMES

The coprimary outcome of death from cardiovascular causes occurred in 236 patients in the ularitide group and 225 patients in the placebo group (21.7% vs. 21.0%; hazard ratio, 1.03; 96% confidence interval [CI], 0.85 to 1.25; P=0.75) (Table 2 and Fig. 2). The lack of a significant difference between the two groups was seen consistently across prespecified subgroups (except for a nominally significant interaction for geographical region), as well as in subgroups that were defined according to baseline levels of NT-proBNP and cardiac troponin (Fig. S3 in the Supplementary Appendix). The distribution of responses for the clinical composite (the second coprimary outcome) did not differ significantly between the groups (Table 2, and Table S3 in the Supplementary Appendix). In a post hoc analysis that excluded the patients who had been identified before the database lock as having been ineligible for the trial, a benefit of ularitide was shown with respect to the hierarchical clinical composite outcome (P=0.03) but not with respect to cardiovascular mortality (Table S4 in the Supplementary Appendix).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Ularitide (N=1088)	Placebo (N=1069)
Age — yr	68.7±11.4	68.3±11.3
Group — no. (%)		
<65 yr	362 (33.3)	387 (36.2)
≥65 yr	726 (66.7)	682 (63.8)
Male sex — no. (%)	714 (65.6)	706 (66.0)
Nonblack race — no. (%)†	989 (90.9)	973 (91.0)
Body-mass index‡	29.3±6.3	29.2±6.7
Left ventricular ejection fraction — no./total no. (%)		
<40%	445/690 (64.5)	449/681 (65.9)
≥40%	245/690 (35.5)	232/681 (34.1)
Region — no. (%)		
North America	159 (14.6)	152 (14.2)
Latin America	171 (15.7)	160 (15.0)
Western Europe	212 (19.5)	208 (19.5)
Eastern Europe	546 (50.2)	549 (51.4)
Interval between clinical evaluation and initiation of treatment — no. (%)		
≤6 hr	533 (49.0)	528 (49.4)
>6 hr	555 (51.0)	541 (50.6)
Clinical history — no. (%)		
Coronary artery disease	556 (51.1)	549 (51.4)
Diabetes	414 (38.1)	429 (40.1)
Previous episode of heart failure	825 (75.8)	806 (75.4)
NYHA class within past month — no./total no. (%)		
I	40/816 (4.9)	46/830 (5.5)
II	265/816 (32.5)	269/830 (32.4)
III	396/816 (48.5)	398/830 (48.0)
IV	115/816 (14.1)	117/830 (14.1)
Blood pressure — mm Hg		
Systolic	134.2±17.8	135.1±17.9
Diastolic	79.0±13.1	79.4±13.5
Heart rate — beats/min	85.4±18.8	85.6±19.1
Laboratory values		
Median N-terminal proBNP (IQR) — pg/ml	7156 (4230–13,238)	7121 (3974–12,599)
Median cardiac troponin T (IQR) — pg/ml	34 (22–54)	33 (21–54)
Hemoglobin — g/dl	13.1±1.78	13.2±1.89
Serum creatinine — mg/dl	1.24±0.37	1.23±0.35
Treatment at randomization — no. (%)		
Intravenous nitrates	101 (9.3)	110 (10.3)
Intravenous dobutamine	4 (0.4)	6 (0.6)

* Plus–minus values are means ±SD. There were no significant differences between the groups. The number of patients with available data is provided in Table S1 in the Supplementary Appendix. To convert the values for creatinine to micromoles per liter, multiply by 88.4. BNP denotes brain natriuretic peptide, IQR interquartile range, and NYHA New York Heart Association.
† Race was reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Table 2. Primary and Secondary Outcome Measures and Biomarkers of Drug Response.

Measure	Ularitide (N=1088)	Placebo (N=1069)	P Value
Primary outcomes			
Cardiovascular death	236 (21.7)	225 (21.0)	0.75
Hierarchical clinical composite outcome ≤48 hr after randomization — no./total no. (%)			0.82
Improved	508/1045 (48.6)	490/1032 (47.5)	
Unchanged	468/1045 (44.8)	456/1032 (44.2)	
Worse	69/1045 (6.6)	86/1032 (8.3)	
Secondary outcomes*			
Median length of hospital stay during first 30 days (IQR) — hr	160.8 (96.0 to 228.9)	148.2 (94.0 to 216.8)	0.16
Median length of stay in intensive care unit during first 120 hr (IQR) — hr	68.0 (49.3 to 93.6)	69.8 (50.3 to 94.3)	0.24
No. of episodes of in-hospital worsening of heart failure during first 120 hr	115	126	0.63
In-hospital worsening of heart failure during first 120 hr — no. (%)	90 (8.3)	94 (8.8)	0.70
Rehospitalization for heart failure ≤30 days after index hospital discharge — no./total no. (%)	75/1055 (7.1)	74/1053 (7.0)	1.00
Median duration of intravenous therapy for heart failure during index admission (IQR) — hr	70.5 (42.7 to 115.4)	68.9 (44.6 to 115.5)	0.53
Mean (±SD) change in serum creatinine from baseline to 72 hr — mg/dl	0.15±0.38	0.09±0.33	0.002
All-cause mortality or hospitalization for a cardiovascular cause at 6 mo — no. (%)	443 (40.7)	398 (37.2)	0.10
Biomarkers of drug response			
Decrease in N-terminal proBNP from baseline to 48 hr			
No. of patients evaluated	967	956	
Median (IQR) — pg/ml	−3816 (−7166 to −1614)	−2595 (−5611 to −574)	<0.001
Ratio of cardiac troponin T at 48 hr vs. baseline			
No. of patients evaluated	603	579	
Median (IQR)	1.01 (0.86 to 1.19)	1.00 (0.88 to 1.15)	0.70

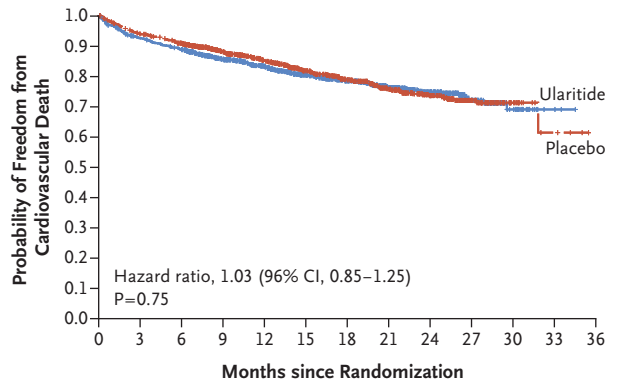
* The analyses of secondary outcome measures are exploratory, because the protocol specified the performance of hierarchical testing of the secondary outcomes only if the result for at least one of the coprimary outcomes was significant.

Because the tests for the two coprimary outcomes were not significant, and given the hierarchical testing plan, all secondary end-point analyses were exploratory. There was no benefit of ularitide for any of the clinical secondary outcome measures (Table 2).

BIOMARKERS OF DRUG RESPONSE

The mean decrease in systolic blood pressure in the ularitide group was greater by 6.8 mm Hg at 6 hours and by 3.9 mm Hg at 48 hours than in the placebo group (P<0.001 for both comparisons); these between-group differences dissipated over a period of 72 to 120 hours (Fig. S4 in the Supplementary Appendix). Among the 1923 patients (89%) for whom data were available, the magnitude of the decrease in levels of NT-proBNP at 48 hours was 47% greater in the ularitide group than in the placebo group (P<0.001). Cardiac troponin T measurements were obtained at baseline and at 48 hours in 1182 patients (55%); there was no significant between-group difference in the change in the cardiac troponin T level between baseline and 48 hours (P=0.70) (Table 2).

During the first 48 hours, there were 55 adjudicated episodes of in-hospital heart-failure events in 46 patients in the ularitide group, as compared with 87 episodes in 75 patients in the placebo group. A post hoc comparison showed that this difference was nominally significant (P=0.005)



No. at Risk

Ularitide	1088	988	942	789	669	546	456	356	234	106	26	2	0
Placebo	1069	987	934	786	668	547	444	338	219	104	19	5	0

Figure 2. Kaplan–Meier Estimates of the Probability of Freedom from Death from Cardiovascular Causes.

Death from cardiovascular causes occurred in 236 patients in the ularitide group and in 225 patients in the placebo group. Tick marks indicate censoring of data.

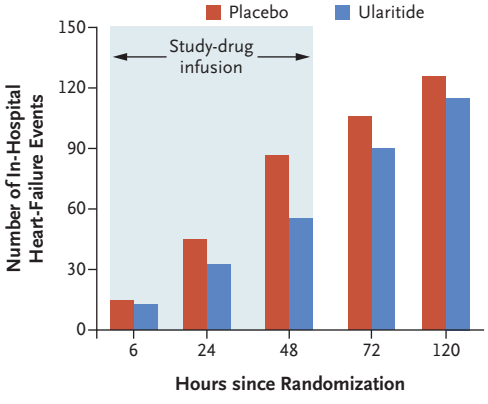


Figure 3. In-Hospital Heart-Failure Events.

Investigators recorded each episode of persistent or worsening heart failure as an event requiring a specific intervention during the interval from the initiation of the study-drug infusion to 120 hours. A patient could have more than 1 heart-failure event during the study interval. (Details regarding the definition of persistent or worsening heart failure are provided in the Supplementary Appendix.) The cumulative total number of in-hospital heart-failure events during the 120-hour period was 115 in the ularitide group and 126 in the placebo group, a difference that was not significant (P=0.63). However, in a post hoc analysis, the cumulative total number of in-hospital heart-failure events during the first 48 hours (i.e., during the study-drug infusion) was 55 in the ularitide group and 75 in the placebo group, a difference that was nominally significant (P=0.005).

(Fig. 3). (The timing and treatment of these events are summarized in Tables S5 and S6 in the Supplementary Appendix.) The between-group difference in in-hospital heart-failure events dissipated after the cessation of study-drug treatment.

SAFETY

Patients in the ularitide group were more likely than those in the placebo group to have hypotension and to discontinue treatment because of it (Table S7 in the Supplementary Appendix). At 48 hours, the ularitide group had significantly higher hematocrit values (P<0.001) and serum creatinine levels (P=0.005) and lower hepatic aminotransferase values (P<0.001) than did those in the placebo group (Table S8 in the Supplementary Appendix). The increase in the serum creatinine level persisted at 72 hours but not after 30 days.

DISCUSSION

In the TRUE-AHF trial, ularitide exerted its expected short-term hemodynamic effects.[21] The drug produced systemic vasodilation (as evidenced by decreases in systolic blood pressure), which was accompanied by decreases in NT-proBNP levels (reflecting a reduction in cardiac-wall stress). Both the hematocrit and serum creatinine levels increased during the infusion, pointing to hemoconcentration[22-24] and (together with a decrease in liver enzymes indicative of less hepatic congestion[9]) to aggressive decongestion; these effects were paralleled by a decrease in the rate of in-hospital heart-failure events during the infusion. Such early worsening events have been linked to increases in both cardiac filling pressures and cardiac troponin levels,[25-28] which suggests that these events may reflect undertreated ventricular distention and acute cardiac injury at the time of initial admission. A reduction in cardiac-wall stress that is achieved rapidly after clinical presentation might be expected to reduce myocardial necrosis, preserve ventricular function, maintain clinical stability, and reduce the long-term risk of cardiovascular death.[9-12]

However, even though the time from clinical evaluation to pharmacologic intervention was shorter than in previous studies,[14-16,29-32] and despite evidence of meaningful cardiac decongestion, the long-term risk of cardiovascular death was not reduced among patients who received ularitide. This lack of benefit raises doubt about

the theories that early ventricular distention causes myocardial necrosis and adversely affects the natural history of heart failure after hospitalization and that rapid reversal of short-term ventricular distention preserves myocardial viability.[9,11,12,16,17,31] For all the patients who underwent randomization, a clinical composite end point was also not affected by treatment.

Our findings differ from those of the RELAX-AHF trial, in which treatment with the vasodilator serelaxin (at a median of 7 hours after clinical evaluation) led to decreases in NT-proBNP levels and in rates of in-hospital worsening of heart failure, reductions that were followed by decreases in cardiovascular mortality.[9,14] However, in the RELAX-AHF trial, the reported survival benefits may have been due to chance, since investigators did not adjudicate in-hospital heart-failure events, the trial was not designed to reliably evaluate the risk of cardiovascular death, and the reduced risk of death was least apparent among patients who received very early therapy.[33] The patients who received serelaxin had a small (<10%) transient decrease in cardiac troponin levels, a finding that was not observed in TRUE-AHF or in trials of other vasodilators.[27,34] The importance of this finding is questionable, since serelaxin did not reduce mortality in the recently completed RELAX-AHF-2 trial.[35]

Hypotension was an expected side effect of ularitide. In other large-scale trials involving patients with acute heart failure, hypotension that was reported before the initiation of the infusion or during the infusion was associated with unfavorable effects on morbidity and mortality,[15,36] which suggests that hypotension may limit the benefits of any reduction in cardiac-wall stress. However, our patients had higher systolic blood pressures than did the patients with acute heart failure who were enrolled in most earlier trials,[15,29-32] so they should have had better tolerance for vasodilator therapy. In the RELAX-AHF trial, serelaxin was associated with hypotensive effects similar to those reported in our trial.[37]

The results of our trial should be interpreted with caution. Our study design allowed patients to receive the study drug very early after the initial clinical evaluation (median, 6 hours). Possibly, even earlier intervention (e.g., 1 to 3 hours after evaluation) might have shown more favorable results, although the subgroup of patients with the earliest intervention did not have a more favorable response in our trial or in an earlier study.[34] Cardiac troponin T was remeasured at only one point in time and in only about half the patients; our findings might have been different if we had sampled this value more extensively. However, cardiovascular mortality was not reduced by ularitide, so any drug-related effect on myocardial injury that we might have missed was transient and unlikely to have been clinically relevant.

In conclusion, we evaluated the effect of early administration of the vasodilator ularitide in patients with acute heart failure. Ularitide reduced cardiac-wall stress more markedly than placebo, as indicated by more rapid reduction in NT-proBNP levels. However, in an intention-to-treat analysis, the drug did not reduce myocardial injury (as indicated by cardiac troponin T levels), did not affect a clinical composite end point, and did not influence disease progression, as shown by the lack of effect on cardiovascular mortality.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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