ORIGINAL ARTICLE

Effects of Serelaxin in Patients with Acute Heart Failure

M. Metra, J.R. Teerlink, G. Cotter, B.A. Davison, G.M. Felker, G. Filippatos, B.H. Greenberg, P.S. Pang, P. Ponikowski, A.A. Voors, K.F. Adams, S.D. Anker, A. Arias-Mendoza, P. Avendaño, F. Bacal, M. Böhm, G. Bortman, J.G.F. Cleland, A. Cohen-Solal, M.G. Crespo-Leiro, M. Dorobantu, L.E. Echeverría, R. Ferrari, S. Goland, E. Goncalvesová, A. Goudev, L. Køber, J. Lema-Osores, P.D. Levy, K. McDonald, P. Manga, B. Merkely, C. Mueller, B. Pieske, J. Silva-Cardoso, J. Špinar, I. Squire, J. Stępińska, W. Van Mieghem, D. von Lewinski, G. Wikström, M.B. Yilmaz, N. Hagner, T. Holbro, T.A. Hua,* S.V. Sabarwal, T. Severin, P. Szecsödy, and C. Gimpelewicz, for the RELAX-AHF-2 Committees Investigators†

ABSTRACT

BACKGROUND

Serelaxin is a recombinant form of human relaxin-2, a vasodilator hormone that contributes to cardiovascular and renal adaptations during pregnancy. Previous studies have suggested that treatment with serelaxin may result in relief of symptoms and in better outcomes in patients with acute heart failure.

METHODS

In this multicenter, double-blind, placebo-controlled, event-driven trial, we enrolled patients who were hospitalized for acute heart failure and had dyspnea, vascular congestion on chest radiography, increased plasma concentrations of natriuretic peptides, mild-to-moderate renal insufficiency, and a systolic blood pressure of at least 125 mm Hg, and we randomly assigned them within 16 hours after presentation to receive either a 48-hour intravenous infusion of serelaxin (30 μg per kilogram of body weight per day) or placebo, in addition to standard care. The two primary end points were death from cardiovascular causes at 180 days and worsening heart failure at 5 days.

RESULTS

A total of 6545 patients were included in the intention-to-treat analysis. At day 180, death from cardiovascular causes had occurred in 285 of the 3274 patients (8.7%) in the serelaxin group and in 290 of the 3271 patients (8.9%) in the placebo group (hazard ratio, 0.98; 95% confidence interval [CI], 0.83 to 1.15; P=0.77). At day 5, worsening heart failure had occurred in 227 patients (6.9%) in the serelaxin group and in 252 (7.7%) in the placebo group (hazard ratio, 0.89; 95% CI, 0.75 to 1.07; P=0.19). There were no significant differences between the groups in the incidence of death from any cause at 180 days, the incidence of death from cardiovascular causes or rehospitalization for heart failure or renal failure at 180 days, or the length of the index hospital stay. The incidence of adverse events was similar in the two groups.

CONCLUSIONS

In this trial involving patients who were hospitalized for acute heart failure, an infusion of serelaxin did not result in a lower incidence of death from cardiovascular causes at 180 days or worsening heart failure at 5 days than placebo. (Funded by Novartis Pharma; RELAX-AHF-2 ClinicalTrials.gov number, NCT01870778.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Teerlink at the Section of Cardiology (111C), San Francisco Veterans Affairs Medical Center, 4150 Clement St., San Francisco, CA 94121, or at john.teerlink@ucsf.edu.

*Deceased.

†A complete list of the committee members and investigators in the RELAX-AHF-2 trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Metra and Teerlink contributed equally to this article.

N Engl J Med 2019;381:716-26.
DOI: 10.1056/NEJMoa1801291
Copyright © 2019 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org by IAIN SQUIRE on August 27, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

Acute heart failure remains a leading cause of hospitalization. Among hospitalized patients with acute heart failure, 10 to 15% have worsening heart failure during the hospitalization,[1-6] and 10 to 15% die within 60 to 90 days after discharge[7]; these numbers are dramatically higher than those among patients with stable chronic heart failure.[8-11] The risk of death among hospitalized patients remains 5 to 10 times as great, even months after the initial episode, as the risk among patients who had not been hospitalized, which suggests that congestion and end-organ damage caused by decompensation may accelerate the rate of disease progression and increase the risk of death.[12,13]

The hormone relaxin contributes to many of the changes in cardiovascular and renal function observed during pregnancy[14,15] and has vasodilatory, antifibrotic, and antiinflammatory effects and protective effects on end organs.[14] Serelaxin, a recombinant form of human relaxin-2, was developed as a potentially useful therapeutic agent because of both its vasodilatory effects (to relieve congestion) and its direct protective effects on organs. In the Relaxin in Acute Heart Failure (RELAX-AHF) trial, administration of serelaxin resulted in a lower incidence of worsening heart failure during hospitalization and, in an exploratory analysis, lower cardiovascular mortality at 180 days than placebo.[16] However, the RELAX-AHF trial was not designed to show an effect on mortality. The second RELAX-AHF trial (RELAX-AHF-2) was designed to test the hypothesis that early administration of serelaxin in patients admitted for acute heart failure could result in lower cardiovascular mortality at 180 days and a lower incidence of worsening heart failure in the first 5 days than placebo.[17]

Methods

Trial Design and Oversight

RELAX-AHF-2 was a multicenter, randomized, double-blind, placebo-controlled, event-driven trial of serelaxin in addition to standard care in patients with acute heart failure. The trial design has been published previously,[17] and the protocol and statistical analysis plan are available with the full text of this article at NEJM.org. The ethics committee at each trial center approved the trial, and all patients provided written informed consent.

The executive committee, in collaboration with the sponsor (Novartis Pharma), developed and amended the protocol and oversaw the execution of the trial (see the Supplementary Appendix, available at NEJM.org, for listings of committee members and investigators and the role of the sponsor). An independent clinical-events committee, whose members were unaware of the group assignments, adjudicated all deaths and hospitalizations that occurred up to and including day 180. The independent data monitoring committee, supported by an autonomous statistical center that had access to unblinded data, regularly reviewed safety data and also reviewed the results of the interim efficacy analysis. The data were analyzed by the sponsor with verification by statisticians at an independent statistical center. The authors had access to the data and vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol.

Trial Population

Male and female patients (≥18 years of age) were eligible for enrollment in the trial if they were admitted to the hospital for acute heart failure with dyspnea, congestion on chest radiography, elevated plasma concentrations of brain natriuretic peptide or N-terminal pro–brain natriuretic peptide, a systolic blood pressure of at least 125 mm Hg, and mild-to-moderate renal impairment (defined as an estimated glomerular filtration rate of 25 to 75 ml per minute per 1.73 m^2 of body-surface area), and if they were expected to receive intravenous therapy for at least 48 hours. Eligible patients had to be symptomatic after initial treatment with at least 40 mg of furosemide or equivalent, administered intravenously, and had to undergo randomization within 16 hours after either presentation to the hospital or the first intravenous administration of a loop diuretic. Patients who received intravenous nitrates at a dose of 0.1 mg or less per kilogram of body weight per hour were eligible if the systolic blood pressure was more than 150 mm Hg. A full list of eligibility criteria was published previously and is provided in the Supplementary Appendix.[17]

Procedures

Patients were randomly assigned, in a 1:1 ratio with the use of an interactive voice-recognition system, to receive an intravenous infusion of either

The New England Journal of Medicine
Downloaded from nejm.org by IAIN SQUIRE on August 27, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

serelaxin (at a dose of 30 μg per kilogram per day, adjusted according to weight) or matching placebo, beginning no more than 4 hours after randomization and continuing for up to 48 hours (Table S1 in the Supplementary Appendix). If the systolic blood pressure decreased by more than 40 mm Hg from baseline and the absolute value was 100 mm Hg or more in two consecutive measurements 15 minutes apart, the infusion rate was decreased by 50% (as detailed in the protocol). If the systolic blood pressure was below 100 mm Hg in two consecutive measurements 15 minutes apart, the infusion was permanently discontinued. Investigators were encouraged to offer guideline-recommended therapy throughout the course of the trial. After randomization, the investigator could prescribe any additional appropriate medications.

Patients were assessed daily for the first 5 days or until discharge and on days 14, 60, 120 (the assessment on day 120 was performed by telephone), and 180. Signs and symptoms of heart failure were assessed until day 60, and hematologic and clinical chemical variables were assessed locally until day 5. Adverse events were reported from the time the patient gave informed consent until day 5 for nonserious events and until day 14 for serious events.

PRIMARY AND SECONDARY END POINTS

The trial had two primary efficacy end points: death from cardiovascular causes at 180 days and worsening heart failure at 5 days. The trial was initially designed with a single primary end point (death from cardiovascular causes at 180 days). Worsening heart failure at 5 days was changed from a secondary end point to a primary end point in protocol amendment 5, which was finalized on February 18, 2015, after 3140 patients of the total 6600 had undergone randomization.[17] Worsening heart failure was defined as worsening signs or symptoms of heart failure that led to an intensification of treatment for heart failure. Such treatment was defined as initiation or increased dose of intravenous therapy with a diuretic, nitrate, or other medication for heart failure or institution of mechanical support such as mechanical ventilation, ultrafiltration, hemodialysis, an intraaortic balloon pump, or a ventricular-assist device. The end point of worsening heart failure also included death from any cause or rehospitalization for heart failure among patients who had been discharged before day 5.

Secondary efficacy end points included death from any cause at 180 days, the length of the index hospital stay, and death from cardiovascular causes or rehospitalization for heart failure or renal failure at 180 days. Rehospitalization was defined as an unplanned admission to a hospital or a stay in an acute care facility of at least 24 hours.

STATISTICAL ANALYSIS

RELAX-AHF-2 was an event-driven trial. After accounting for one interim analysis, we determined that 547 confirmed cardiovascular deaths would be needed to give the trial 80% power to detect a 22% lower relative risk of death from cardiovascular causes in the serelaxin group than in the placebo group. Assuming that 9% of patients in the placebo group would die by day 180 (as observed in the RELAX-AHF trial[13]), we calculated that approximately 6800 patients would need to be enrolled. With the use of a multiple-testing procedure, we determined that the sample size of 6800 patients would give the trial 80% power to detect a 20% lower relative risk of worsening heart failure in the serelaxin group than in the placebo group, assuming that 12.2% of patients in the placebo group would have worsening heart failure (on the basis of results from the RELAX-AHF trial).

An interim efficacy analysis of cardiovascular death was planned after at least 60% (or 329) of the planned total confirmed deaths from cardiovascular causes had occurred. A Lan–DeMets spending function approximating an O'Brien–Fleming stopping boundary was used to control the overall two-sided alpha level at 4% for the end point of death from cardiovascular causes (adjusted $P=0.0384$). The results of the interim analysis did not cross the stopping boundary (details are provided in the Supplementary Appendix).

Primary and secondary efficacy end points, with the exception of death from any cause, were compared between groups on an intention-to-treat basis with the use of a sequentially rejective multiple-testing procedure[18] to control the overall two-sided alpha level at 5% (with adjustment for the interim analysis). At 180 days, the time to cardiovascular death was compared between groups with a log-rank test, with four fifths of

The New England Journal of Medicine
Downloaded from nejm.org by IAIN SQUIRE on August 27, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

the alpha assigned to that end point (final adjusted P=0.0372). The time to worsening heart failure through day 5 was compared between groups with the use of Gehan's generalized Wilcoxon test, with one fifth of the alpha assigned to that end point (final adjusted P=0.0094). If the test of either or both of the primary end points was significant, death from any cause would be tested independently at the two-sided 5% significance level.

RESULTS

PATIENTS

From October 2, 2013, to February 1, 2017, a total of 7554 patients at 546 centers in 35 countries were screened. Of these patients, 954 did not meet the criteria for randomization (the most frequent reasons are listed in Table S2 in the Supplementary Appendix). A total of 6600 patients underwent randomization: 3298 were assigned to the serelaxin group, and 3302 to the placebo group. A total of 55 patients underwent randomization in error and did not take the trial drug or were enrolled at a site that was closed because of Good Clinical Practice violations and were therefore prospectively omitted from all analyses before the end of the trial. Accordingly, 3274 patients assigned to receive serelaxin and 3271 assigned to receive placebo were included in the intention-to-treat analysis (Fig. S1 in the Supplementary Appendix). The groups were balanced with respect to baseline characteristics (Table 1, and Table S3 in the Supplementary Appendix).

TRIAL INTERVENTION AND FOLLOW-UP

Patients underwent randomization a median of 5.3 hours after the first intravenously administered dose of a loop diuretic, and serelaxin or placebo was initiated a median of 0.5 hours after randomization. The median duration of infusion was 48.0 hours in both groups. A total of 40 patients in the serelaxin group and 55 patients in the placebo group did not receive the infusion. The mean blood pressure was lower among patients in the serelaxin group than among those in the placebo group after 30 minutes of infusion and remained lower for 3 days (Fig. 1, and Table S4 in the Supplementary Appendix).

Infusions were permanently discontinued in 717 patients (21.9%) in the serelaxin group and in 512 patients (15.7%) in the placebo group (Tables S5 and S6 in the Supplementary Appendix). The most common reason for discontinuation was a decrease in systolic blood pressure that met the criteria for discontinuation in accordance with the protocol (18.5% of patients in the serelaxin group and 12.5% in the placebo group); in addition, 1.3% of patients in the serelaxin group and 1.4% in the placebo group prematurely discontinued infusions because of adverse events. Concomitant medications during the trial are shown in Tables S7 through S9, and the number of patients who received diuretics intravenously and the mean dose per patient are shown in Table S10, in the Supplementary Appendix.

Patients in the serelaxin group were followed for a mean (±SD) of 167.6±38.2 days, and patients in the placebo group for 166.5±40.0 days. Vital status at the end of follow-up was unknown for 16 patients (8 patients in each group [0.2%]), and 2 patients in the placebo group were lost to follow-up.

PRIMARY AND KEY SECONDARY END POINTS

At day 180, adjudicated death from cardiovascular causes (one of the two primary end points) had occurred in 285 patients (8.7%) in the serelaxin group and in 290 (8.9%) in the placebo group (hazard ratio, 0.98; 95% confidence interval [CI], 0.83 to 1.15; P=0.77). At day 5, worsening heart failure (the other primary end point) had occurred in 227 patients (6.9%) in the serelaxin group and in 252 (7.7%) in the placebo group (hazard ratio, 0.89; 95% CI, 0.75 to 1.07; P=0.19) (Table 2 and Fig. 2A and 2B). Analysis of both primary end points in the per-protocol population showed similar results (Table S11 in the Supplementary Appendix). Subgroup analyses of both primary end points are shown in Figure S2 in the Supplementary Appendix.

In accordance with the multiple-testing procedure, the key secondary end points were not tested for significance; hazard ratios and unadjusted 95% confidence intervals are shown in Table 2. At 180 days, the incidence of death from any cause was similar in the serelaxin group and the placebo group (11.2% and 11.9%, respectively), as was the incidence of death from cardiovascular causes or rehospitalization for heart failure or renal failure (24.3% and 24.9%, respectively) (Fig. 2C, and Fig. S3 in the Supplementary

The New England Journal of Medicine
Downloaded from nejm.org by IAIN SQUIRE on August 27, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

Table 1. Selected Characteristics of the Patients in the Intention-to-Treat Population at Baseline.*

Characteristic	Serelaxin Group (N=3274)	Placebo Group (N=3271)
Age — yr	73.1±11.2	72.8±11.2
Age group — no. (%)		
<75 yr	1608 (49.1)	1635 (50.0)
≥75 yr	1666 (50.9)	1636 (50.0)
Male sex — no. (%)	1978 (60.4)	1930 (59.0)
Race — no. (%)†		
White	3017 (92.2)	2999 (91.7)
Black	163 (5.0)	171 (5.2)
Other or missing data	94 (2.9)	101 (3.1)
Weight — kg	84.0±20.0	84.3±20.2
Body-mass index‡	29.8±6.4	29.8±6.3
Systolic blood pressure — mm Hg	146.3±16.9	146.1±16.5
Diastolic blood pressure — mm Hg	82.2±14.2	82.0±13.9
Heart rate — beats/min	83.5±17.0	83.5±17.1
Respiratory rate — breaths/min	22.0±4.6	21.9±4.6
Temperature — °C	36.5±0.4	36.5±0.4
History of heart failure — no./total no. (%)	2411/3272 (73.7)	2443/3269 (74.7)
Previous hospitalization for heart failure — no./total no. (%)	1647/3066 (53.7)	1691/3049 (55.5)
No. of hospitalizations for heart failure within previous 1 yr	1.1±1.2	1.2±1.2
Ischemic cause of heart failure — no./total no. (%)	1313/2409 (54.5)	1294/2438 (53.1)
Ejection fraction at index hospitalization — %§	39.3±13.9	38.5±13.7
Ejection fraction ≤40% — no./total no. (%)	1571/3074 (51.1)	1609/3054 (52.7)
NYHA class 1 mo before admission — no./total no. (%)		
I	116/2365 (4.9)	94/2384 (3.9)
II	914/2365 (38.6)	934/2384 (39.2)
III	1089/2365 (46.0)	1095/2384 (45.9)
IV	246/2365 (10.4)	261/2384 (10.9)
Intravenous nitrates at randomization — no. (%)	179 (5.5)	181 (5.5)
Median BNP level (IQR) — ng/liter¶	1095 (741–1715)	1200 (773–1992)
Median NT-proBNP level (IQR) — ng/liter‖	6153 (3613–10,387)	6035 (3485–9567)
eGFR — ml/min/1.73 m^2**	51.3±14.3	51.3±14.5
Median time from either presentation or first intravenous loop diuretic, whichever occurred earlier, to randomization (IQR) — hr	7.1 (4.9–11.1)	6.9 (4.9–11.0)
Median time from presentation to randomization (IQR) — hr	7.0 (4.9–11.0)	6.9 (4.9–10.9)
Median time from first intravenous loop diuretic to randomization (IQR) — hr	5.3 (3.1–9.5)	5.2 (3.1–9.3)
Median time from randomization to administration of serelaxin or placebo (IQR) — hr	0.5 (0.3–1.0)	0.5 (0.3–1.0)

* Plus–minus values are means ±SD. There were no significant between-group differences in the listed characteristics ($P<0.05$). Additional baseline characteristics are shown in Table S4 in the Supplementary Appendix. Percentages may not total 100 because of rounding. BNP denotes brain natriuretic peptide, IQR interquartile range, NT N-terminal, and NYHA New York Heart Association.

† Race was reported by the patient.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Data were available for 3074 patients in the serelaxin group and 3054 patients in the placebo group.

¶ Data were available for 654 patients in the serelaxin group and 652 patients in the placebo group.

‖ Data were available for 2631 patients in the serelaxin group and 2630 patients in the placebo group.

** Estimated glomerular filtration rate (eGFR) was calculated with the use of the simplified Modification of Diet in Renal Disease formula, which takes into account age, sex, race, and serum creatinine level.[19]

The New England Journal of Medicine
Downloaded from nejm.org by IAIN SQUIRE on August 27, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

Appendix). The median length of stay during the index hospitalization was also similar in the two groups (6.8 days in the serelaxin group and 6.9 days in the placebo group).

SAFETY

A similar percentage of patients in each group had at least one adverse event in the first 5 days (53.1% in the serelaxin group and 52.1% in the placebo group) (Table 3). Adverse events and serious adverse events that occurred up to and including day 14 were also similar in the two groups; 55.3% in the serelaxin group and 54.5% in the placebo group had an adverse event, and 12.6% and 13.1%, respectively, had a serious adverse event. Additional information about adverse events and laboratory data that were collected for safety analyses are provided in Tables S12 through S14 in the Supplementary Appendix.

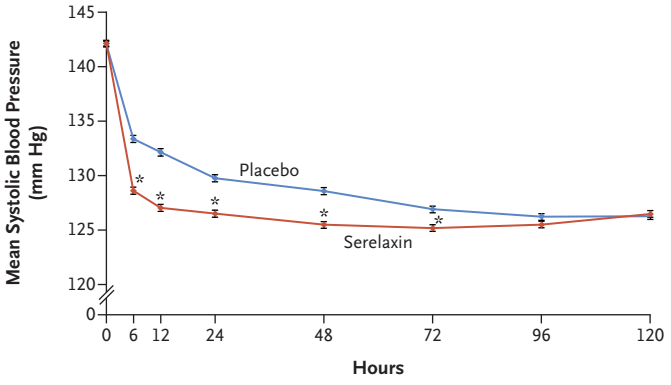


Figure 1. Systolic Blood Pressure through 120 Hours According to Group.
Asterisks indicate time points at which the between-group difference was significant (P<0.05) (see also Table S4 in the Supplementary Appendix). I bars indicate standard errors.

DISCUSSION

In the RELAX-AHF-2 trial, a 48-hour infusion of serelaxin in patients with acute heart failure did not result in a lower incidence of death from cardiovascular causes at 180 days or worsening heart failure at 5 days than placebo. In addition, serelaxin was not associated with a shorter length of index hospital stay or a lower incidence of rehospitalization for heart failure or renal failure than placebo. Administration of serelaxin resulted in a greater reduction in blood pressure than did placebo, which is consistent with a pharmacologic effect.

The RELAX-AHF-2 trial was prospectively powered to evaluate the effect of serelaxin on death from cardiovascular causes at 180 days. However, it did not replicate the benefit of serelaxin with respect to cardiovascular mortality

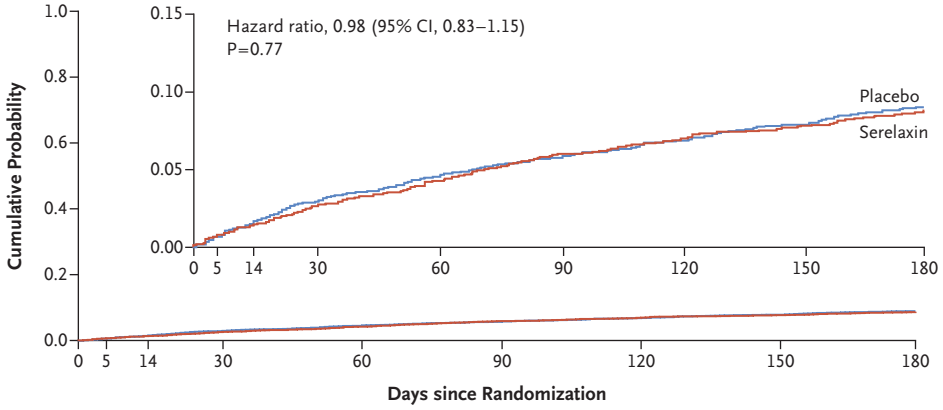
Table 2. Protocol-Specified Efficacy End Points.

End Point	Serelaxin Group (N=3274)	Placebo Group (N=3271)	Hazard Ratio or Mean Difference (95% CI)*	P Value
Primary efficacy end points — no. (%)				
Death from cardiovascular causes at 180 days	285 (8.7)	290 (8.9)	0.98 (0.83 to 1.15)	0.77†
Worsening heart failure at 5 days	227 (6.9)	252 (7.7)	0.89 (0.75 to 1.07)	0.19‡
Key secondary efficacy end points				
Death from any cause at 180 days — no. (%)	367 (11.2)	388 (11.9)	0.94 (0.81 to 1.08)	
Median length of index hospital stay (IQR) — days§	6.8 (5.0 to 10.0)	6.9 (5.0 to 10.0)	–0.183 (–0.645 to 0.280)¶	
Composite of death from cardiovascular causes or rehospitalization for heart failure or renal failure at 180 days — no. (%)	794 (24.3)	813 (24.9)	0.97 (0.88 to 1.07)	
Death from cardiovascular causes	285 (8.7)	290 (8.9)	0.98 (0.83 to 1.15)	
Rehospitalization for heart failure or renal failure	604 (18.4)	632 (19.3)	0.95 (0.85 to 1.06)	

* The 95% confidence intervals have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible.
† The P value was calculated with the use of the log-rank test.
‡ The P value was calculated with the use of Gehan's generalized Wilcoxon test.
§ The length of stay for patients who were still in the hospital on day 60 was truncated at 60 days, and the value for patients who died in the hospital was imputed as 61 days.
¶ The value is the mean difference between the groups; the 95% confidence interval was calculated with the use of the bootstrap method.

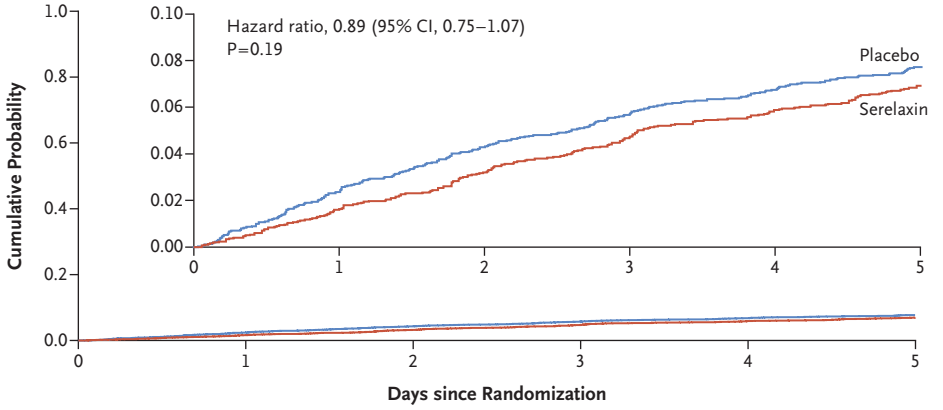
The New England Journal of Medicine
Downloaded from nejm.org by IAIN SQUIRE on August 27, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

A Death from Cardiovascular Causes



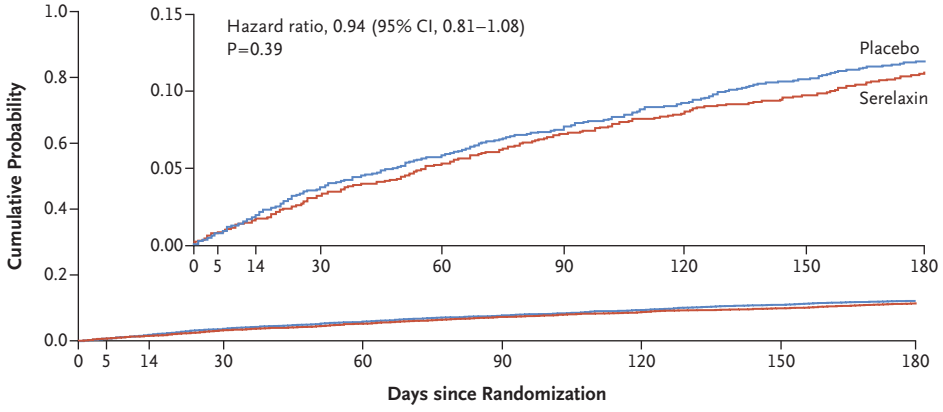
No. at Risk								
Placebo	3271 3244 3210	3149	3080	3018	2962	2912	2545
Serelaxin	3274 3247 3218	3165	3100	3032	2988	2949	2548

B Worsening Heart Failure



No. at Risk						
Placebo	3271	3190	3128	3081	3047	3016
Serelaxin	3274	3219	3166	3117	3078	3043

C Death from Any Cause



No. at Risk								
Placebo	3271 3244 3210	3149	3080	3018	2962	2912	2545
Serelaxin	3274 3247 3218	3165	3100	3032	2988	2949	2548

The New England Journal of Medicine
Downloaded from nejm.org by IAIN SQUIRE on August 27, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

Figure 2 (facing page). Efficacy End Points.

Panel A shows Kaplan–Meier estimates of the probability of death from cardiovascular causes. At day 180, death from cardiovascular causes had occurred in 285 patients in the serelaxin group and in 290 patients in the placebo group. Panel B shows Kaplan–Meier estimates of the probability of worsening heart failure during the first 5 days. At 5 days, worsening heart failure had occurred in 227 patients in the serelaxin group and in 252 patients in the placebo group. Panel C shows Kaplan–Meier estimates of the probability of death from any cause. At day 180, death from any cause had occurred in 367 patients in the serelaxin group and in 388 patients in the placebo group. In each panel, the inset shows the same data on an enlarged y axis.

Table 3. Most Frequent Adverse Events up to and Including Day 5.*

Event	Serelaxin Group (N=3257)	Placebo Group (N=3248)	P Value†
	no. (%)		
Hypokalemia	263 (8.1)	242 (7.5)	0.35
Cardiac failure	192 (5.9)	215 (6.6)	0.23
Muscle spasms	80 (2.5)	49 (1.5)	0.006
Hypotension	77 (2.4)	65 (2.0)	0.32
Headache	74 (2.3)	92 (2.8)	0.15
Constipation	70 (2.1)	57 (1.8)	0.25
Urinary tract infection	63 (1.9)	68 (2.1)	0.65

* Shown are events that occurred in at least 2% of patients in either group.
† P values were calculated with the use of the Cochran–Mantel–Haenszel test.

that was seen in the previous RELAX-AHF trial.[16] One explanation for these disparate results is that the result in the RELAX-AHF trial was due to chance. The P value for the between-group comparison of death from cardiovascular causes (an exploratory outcome) in the RELAX-AHF trial was 0.028, without correction for multiple testing. The RELAX-AHF-2 trial was specifically designed to determine whether this result could be confirmed; therefore, death from cardiovascular causes was a primary end point. The RELAX-AHF-2 trial was also more than five times larger than the previous trial. The negative result for the end point of death from cardiovascular causes in the RELAX-AHF-2 trial is therefore consistent with the conclusion that the result in the RELAX-AHF trial was a chance finding. Other trials of intravenous vasodilator therapy during hospitalization for acute heart failure (such as ularitide in TRUE-AHF [Trial of Ularitide Efficacy and Safety in Acute Heart Failure][20] and nesiritide in ASCEND-HF [Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure][21]) have also failed to show a benefit with respect to postdischarge cardiovascular mortality. Although these previous trials evaluated the administration of natriuretic peptides, which have a different mechanism of action than serelaxin, the results suggest that short-term interventions in patients with acute heart failure may not influence long-term outcomes.

However, differences in patient characteristics between the two RELAX-AHF trials might also have been responsible for the different results. The entry criteria in the RELAX-AHF-2 trial were nearly identical to those in the RELAX-AHF trial, but patients with worse renal function could be enrolled in the current trial, and there was a higher threshold for natriuretic peptides. These differences should have resulted in higher cardiovascular mortality among enrolled patients. Yet, death from cardiovascular causes occurred in 9.6% (95% CI, 7.5 to 12.3) of patients in the placebo group in the RELAX-AHF trial and in 8.9% (95% CI, 8.1 to 10.5) in the placebo group in the RELAX-AHF-2 trial. In contrast, the rate of death from noncardiovascular causes was higher in this trial than in the RELAX-AHF trial (3.0% vs. 1.7%). Thus, potential differences in the patient populations and their risk profiles may have contributed to the different outcomes of the two trials.

The repeated failure of short-term interventions to improve outcomes in acute heart failure has focused attention on aspects of clinical trial design.[22] The timing of therapy, the imprecision of the diagnosis of acute heart failure, and the failure to align the mechanism of action of the drug being evaluated with the patient population that is most likely to benefit from it have been identified as potential problems. Some studies have suggested that earlier treatment of patients may result in greater relief of symptoms.[23] However, no difference in treatment effect according to the time to randomization was observed in either the RELAX-AHF trial or ASCEND-HF.[24,25]

In-hospital worsening heart failure appears to be a clinically meaningful event associated with adverse outcomes.[26] Its clinical importance has been shown in retrospective analyses of patient databases and intervention trials.[4,6,26-30] In the RELAX-AHF trial, serelaxin resulted in 47% fewer

The New England Journal of Medicine
Downloaded from nejm.org by IAIN SQUIRE on August 27, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

events of worsening heart failure in the first 5 days than placebo. In the RELAX-AHF-2 trial, however, the lower incidence of worsening heart failure in the serelaxin group was not significant. Despite the higher plasma concentrations of natriuretic peptides at screening among patients in the RELAX-AHF-2 trial than among those in the RELAX-AHF trial, the percentage of patients with worsening heart failure in the placebo group was substantially lower in the RELAX-AHF-2 trial than in the previous trial (7.7% vs. 12.2%). Because in the power calculations for the RELAX-AHF-2 trial we assumed that 12.2% of patients in the placebo group would have worsening heart failure, this trial had less power than anticipated to detect a difference in this end point. The percentage of patients in the placebo group with worsening heart failure may have been lower in the RELAX-AHF-2 trial than in the previous trial because the patients in the RELAX-AHF-2 trial may have been at a lower risk for worsening heart failure or because of underreporting by investigators, random variability in the two populations, or other factors.

Drug-induced hypotension has been a major cause of failure in previous trials in acute heart failure.[5,31] Consequently, the protocol for symptom relief was designed to mitigate the risk of clinically significant hypotension by enrolling patients with a systolic blood pressure of at least 125 mm Hg and providing guidelines for dose reduction or discontinuation in the event of hypotension.[32] Approximately 18.5% of patients in the serelaxin group discontinued treatment for this reason, as compared with 12.5% in the placebo group. Although this approach effectively avoided hypotension-related adverse events, it also resulted in a smaller number of patients who were treated for a full 48 hours with serelaxin. However, no interaction between efficacy and the treatment duration was found.

In conclusion, the RELAX-AHF-2 trial evaluated the effect of serelaxin in patients with acute heart failure. Serelaxin treatment resulted in a significantly greater reduction in blood pressure than placebo, a finding consistent with a pharmacologic effect of serelaxin. However, serelaxin did not result in lower cardiovascular mortality at 180 days or a smaller percentage of patients with worsening heart failure at 5 days than placebo. The incidence of adverse events was similar in the two groups.

Supported by Novartis Pharma.

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

We thank Chien-Wei Chen (Novartis Pharmaceuticals) for statistical support, Vajhula Sarma (Novartis Healthcare) for graphical support, and Laoighse Mulrane (Novartis Ireland) for editorial logistics support.

APPENDIX

The authors' full names and academic degrees are as follows: Marco Metra, M.D., John R. Teerlink, M.D., Gad Cotter, M.D., Beth A. Davison, Ph.D., G. Michael Felker, M.D., M.H.S., Gerasimos Filippatos, M.D., Barry H. Greenberg, M.D., Peter S. Pang, M.D., Piotr Ponikowski, M.D., Ph.D., Adriaan A. Voors, M.D., Ph.D., Kirkwood F. Adams, M.D., Stefan D. Anker, M.D., Ph.D., Alexandra Arias-Mendoza, M.D., Patricio Avendaño, M.D., Fernando Bacal, M.D., Ph.D., Michael Böhm, M.D., Guillermo Bortman, M.D., Ph.D., John G.F. Cleland, M.D., Alain Cohen-Solal, M.D., Ph.D., Maria G. Crespo-Leiro, M.D., Ph.D., Maria Dorobantu, M.D., Ph.D., Luis E. Echeverría, M.D., Roberto Ferrari, M.D., Ph.D., Sorel Goland, M.D., Eva Goncalvesová, M.D., Ph.D., Assen Goudev, M.D., D.Sc., Lars Køber, M.D., D.Sci., Juan Lema-Osores, M.D., Phillip D. Levy, M.D., M.P.H., Kenneth McDonald, M.D., Pravin Manga, Ph.D., Béla Merkely, M.D., Ph.D., Christian Mueller, M.D., Burkert Pieske, M.D., Jose Silva-Cardoso, M.D., Ph.D., Jindřich Špinar, M.D., Iain Squire, M.B., Ch.B., M.D., Janina Stępińska, M.D., Ph.D., Walter Van Mieghem, M.D., Dirk von Lewinski, M.D., Gerhard Wikström, M.D., Ph.D., Mehmet B. Yilmaz, M.D., Nicole Hagner, M.A., Thomas Holbro, Ph.D., Tsushung A. Hua, Ph.D., Shalini V. Sabarwal, Pharm.D., Thomas Severin, M.D., Peter Szecsödy, M.D., and Claudio Gimpelewicz, M.D.

The authors' affiliations are as follows: Cardiology, Department of Medical and Surgical Specialties, Radiologic Sciences, and Public Health, University of Brescia, Brescia (M.M.), Centro Cardiologico Universitario di Ferrara, University of Ferrara, Ferrara (R.F.), and Maria Cecilia Hospital, GVM Care and Research, Cotignola (R.F.) — all in Italy; the Section of Cardiology, San Francisco Veterans Affairs Medical Center and School of Medicine, University of California, San Francisco, San Francisco (J.R.T.), and the Division of Cardiology, University of California, San Diego, La Jolla (B.H.G.) — all in California; Momentum Research (G.C., B.A.D.) and the Division of Cardiology, Duke University School of Medicine (G.M.F.), Durham, and the University of North Carolina, Chapel Hill (K.F.A.) — all in North Carolina; the School of Medicine, University of Cyprus, Nicosia, Cyprus (G.F.); the School of Medicine, National and Kapodistrian University of Athens, Athens (G.F.); the Department of Emergency Medicine, Indiana University School of Medicine, and the Regenstrief Institute, Indianapolis (P.S.P.); the Department of Heart Diseases, Medical University, Military Hospital, Wrocław (P.P.), and Instytut Kardiologii, Warsaw (J.S.) — both in Poland; University of Groningen, Groningen, the Netherlands (A.A.V.); the Department of Internal Medicine and Cardiology, German Center for Cardiovascular Research partner site Berlin (S.D.A., B.P.), and Berlin Institute of Health Center for Regenerative Therapies (S.D.A.), Charité Universitätsmedizin Berlin–Campus Virchow Klinikum, Berlin, and Saarland University, Universitätsklinikum des Saarlandes Homburg, Homburg (M.B.) — all in Germany; the Coronary Care and Emergency Department, Instituto Nacional de Cardiología Ignacio Chávez, Mexico City (A.A.-M.); Hospital Clínico de la Fuerza Aérea de Chile, Las Condes, Chile (P.A.); the Heart Transplantation Department, Heart Institute (InCor), University of São Paulo, and Hospital Israelita Albert Einstein, São Paulo (F.B.); Sanatorio de la Trinidad Mitre, Buenos Aires (G.B.); the Robertson Centre for Biostatistics and Clini-

The New England Journal of Medicine
Downloaded from nejm.org by IAIN SQUIRE on August 27, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

cal Trials, University of Glasgow, Glasgow (J.G.F.C.), National Heart and Lung Institute, Imperial College, London (J.G.F.C.), and the Department of Cardiovascular Sciences, University of Leicester, and National Institute for Health Research Biomedical Research Centre, Glenfield Hospital, Leicester (I.S.) — all in the United Kingdom; Cardiology Department, Hôpital Lariboisière and Université de Paris, Paris (A.C.-S.); Complejo Hospitalario Universitario A Coruña, Universidade da Coruña, Centro de Investigación Biomédica en Red Enfermedades Cardiovasculares, La Coruña, Spain (M.G.C.-L.); Carol Davila University of Medicine and Pharmacy, Bucharest, Romania (M.D.); Heart Failure and Heart Transplant Clinic, Fundación Cardiovascular de Colombia, Floridablanca, Colombia (L.E.E.); Heart Institute, Kaplan Medical Center, Rehovot, Hebrew University, Jerusalem (S.G.); National Cardiovascular Institute, Bratislava, Slovakia (E.G.); Medical University of Sofia, Tzaritza Ioanna University Hospital, Sofia, Bulgaria (A.G.); the Department of Cardiology, Rigshospitalet, University of Copenhagen, Copenhagen (L.K.); Internal Medicine–Cardiology, Internal Medicine Department, Hospital Nacional Arzobispo Loayza, Lima, Peru (J.L.-O.); Wayne State University School of Medicine and Cardiovascular Research Institute, Detroit (P.D.L.); the School of Medicine and Medical Sciences and St. Vincent's University Hospital, University College Dublin, Dublin (K.M.); the Department of Internal Medicine, University of Witwatersrand, Johannesburg (P.M.); Heart and Vascular Center, Semmelweis University, Budapest, Hungary (B.M.); the Department of Cardiology and Cardiovascular Research Institute Basel, University Hospital Basel, University of Basel (C.M.), and Novartis Pharma (T.H., T.S., P.S., C.G.), Basel, Switzerland; CINTESIS, Porto University Medical School, São João Medical Center, Porto, Portugal (J.S.-C.); University Hospital Brno and Medical Faculty Masaryk University, Brno, Czech Republic (J.Š.); University Hasselt, Hasselt, Belgium (W.V.M.); the Division of Cardiology, Department of Internal Medicine, Medical University of Graz, Graz, Austria (D.L.); the Institute of Medical Sciences, Uppsala University, Uppsala University Hospital, Uppsala, Sweden (G.W.); Dokuz Eylül University, Faculty of Medicine, Department of Cardiology, Izmir, Turkey (M.B.Y.); and Novartis Pharmaceuticals, East Hanover, NJ (N.H., T.H., T.A.H., S.V.S.).

REFERENCES

1. Weatherley BD, Milo-Cotter O, Felker GM, et al. Early worsening heart failure in patients admitted with acute heart failure — a new outcome measure associated with long-term prognosis? Fundam Clin Pharmacol 2009;23:633-9.
2. Torre-Amione G, Milo-Cotter O, Kaluski E, et al. Early worsening heart failure in patients admitted for acute heart failure: time course, hemodynamic predictors, and outcome. J Card Fail 2009; 15:639-44.
3. 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.
4. Metra M, Teerlink JR, Felker GM, et al. Dyspnoea and worsening heart failure in patients with acute heart failure: results from the Pre-RELAX-AHF study. Eur J Heart Fail 2010;12:1130-9.
5. Packer M, Colucci W, Fisher L, et al. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. JACC Heart Fail 2013;1:103-11.
6. Mentz RJ, Metra M, Cotter G, et al. Early vs. late worsening heart failure during acute heart failure hospitalization: insights from the PROTECT trial. Eur J Heart Fail 2015;17:697-706.
7. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure: problems and perspectives. J Am Coll Cardiol 2013;61:391-403.
8. Kristensen SL, Jhund PS, Køber L, et al. Comparison of outcomes after hospitalization for worsening heart failure, myocardial infarction, and stroke in patients with heart failure and reduced and preserved ejection fraction. Eur J Heart Fail 2015;17:169-76.
9. Solomon SD, Dobson J, Pocock S, et al. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. Circulation 2007;116:1482-7.
10. Ahmed A, Allman RM, Fonarow GC, et al. Incident heart failure hospitalization and subsequent mortality in chronic heart failure: a propensity-matched study. J Card Fail 2008;14:211-8.
11. Abrahamsson P, Swedberg K, Borer JS, et al. Risk following hospitalization in stable chronic systolic heart failure. Eur J Heart Fail 2013;15:885-91.
12. Harjola VP, Mullens W, Banaszewski M, et al. Organ dysfunction, injury and failure in acute heart failure: from pathophysiology to diagnosis and management — a review on behalf of the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail 2017;19:821-36.
13. 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.
14. Du XJ, Bathgate RA, Samuel CS, Dart AM, Summers RJ. Cardiovascular effects of relaxin: from basic science to clinical therapy. Nat Rev Cardiol 2010;7:48-58.
15. Bathgate RA, Halls ML, van der Westhuizen ET, Callander GE, Kocan M, Summers RJ. Relaxin family peptides and their receptors. Physiol Rev 2013;93:405-80.
16. 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.
17. Teerlink JR, Voors AA, Ponikowski P, et al. Serelaxin in addition to standard therapy in acute heart failure: rationale and design of the RELAX-AHF-2 study. Eur J Heart Fail 2017;19:800-9.
18. Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Stat Med 2009;28:586-604.
19. Swart MJ, Bekker AM, Malan JJ, Meiring A, Swart Z, Joubert G. The simplified modification of diet in renal disease equation as a predictor of renal function after coronary artery bypass graft surgery. Cardiovasc J Afr 2010;21:9-12.
20. Packer M, O'Connor C, McMurray JJV, et al. Effect of ularitide on cardiovascular mortality in acute heart failure. N Engl J Med 2017;376:1956-64.
21. 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.
22. Mebazaa A, Longrois D, Metra M, et al. Agents with vasodilator properties in acute heart failure: how to design successful trials. Eur J Heart Fail 2015;17:652-64.
23. Peacock WF IV, Fonarow GC, Emerman CL, Mills RM, Wynne J. Impact of early initiation of intravenous therapy for acute decompensated heart failure on outcomes in ADHERE. Cardiology 2007;107: 44-51.
24. Metra M, Ponikowski P, Cotter G, et al. Effects of serelaxin in subgroups of patients with acute heart failure: results from RELAX-AHF. Eur Heart J 2013;34:3128-36.
25. Wong YW, Mentz RJ, Felker GM, et al. Nesiritide in patients hospitalized for acute heart failure: does timing matter? Implication for future acute heart failure trials. Eur J Heart Fail 2016;18:684-92.
26. Butler J, Gheorghiade M, Kelkar A, et al. In-hospital worsening heart failure. Eur J Heart Fail 2015;17:1104-13.
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.

The New England Journal of Medicine
Downloaded from nejm.org by IAIN SQUIRE on August 27, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.

28. Cotter G, Metra M, Davison BA, et al. Worsening heart failure, a critical event during hospital admission for acute heart failure: results from the VERITAS study. Eur J Heart Fail 2014;16:1362-71.
29. 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.
30. Davison BA, Metra M, Cotter G, et al. Worsening heart failure following admission for acute heart failure: a pooled analysis of the PROTECT and RELAX-AHF studies. JACC Heart Fail 2015;3:395-403.
31. Erdmann E, Semigran MJ, Nieminen MS, et al. Cinaciguat, a soluble guanylate cyclase activator, unloads the heart but also causes hypotension in acute decompensated heart failure. Eur Heart J 2013; 34:57-67.
32. Cotter G, Metra M, Davison BA, et al. Systolic blood pressure reduction during the first 24 h in acute heart failure admission: friend or foe? Eur J Heart Fail 2018; 20:317-22.
Copyright © 2019 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org by IAIN SQUIRE on August 27, 2019. For personal use only. No other uses without permission.
Copyright © 2019 Massachusetts Medical Society. All rights reserved.