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Published in:
Journal of the American College of Cardiology
DOI:
10.1016/j.jacc.2014.05.071

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2014

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Effect of Serelaxin on Mode of Death in Acute Heart Failure

Results From the RELAX-AHF Study

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ABSTRACT

BACKGROUND Little is known about mode of death after acute heart failure (AHF) hospitalization. In the RELAX-AHF (Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure) study, serelaxin, the recombinant form of human relaxin-2, reduced post-discharge mortality at 180 days in selected patients with AHF.

OBJECTIVES The goal of this study was to assess the effect of serelaxin on specific modes of death in patients with AHF.

METHODS The RELAX-AHF study randomized 1,161 patients with AHF to 48 h of therapy with intravenous serelaxin or placebo. Patients were followed for vital status through 180 days. A blinded clinical events committee reviewed all deaths and adjudicated a cause of death on the basis of pre-specified criteria. Cox proportional hazard models were used to assess the effect of serelaxin on each mode of death, on the basis of pre-specified groupings of mode of death.

RESULTS There were 107 deaths (9.3%): 37 (35%) due to HF, 25 (23%) due to sudden death, 15 (14%) due to other cardiovascular (CV) causes, 19 (18%) due to non-CV causes, and 11 (10%) classified as unknown. The treatment effect of serelaxin was most pronounced on other CV deaths (hazard ratio [HR]: 0.29; 95% CI: 0.12 to 0.73; p = 0.005) and sudden death (HR: 0.46; 95% CI: 0.20 to 1.07; p = 0.065). There was no apparent impact of serelaxin treatment on HF deaths or non-CV deaths.

CONCLUSIONS In the RELAX-AHF study, the effects of serelaxin on mortality were primarily driven by reduction in mortality from other CV causes and sudden death, without apparent impact on HF deaths. (Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure [RELAX-AHF]; NCT00520806) (J Am Coll Cardiol 2014;64:1591–8) © 2014 by the American College of Cardiology Foundation.
Heart failure (HF) is among the leading causes of mortality and morbidity worldwide (1,2). Hospitalization for acute HF (AHF) is associated with high post-discharge mortality, typically 10% to 20% by 6 months (3–5). The most common modes of death in patients with HF are death from progressive HF and sudden cardiac death (6,7). Despite the well-recognized mortality risk after AHF hospitalization, relatively little is known about the mode of death in these patients, although HF and sudden cardiac death appear to predominate (8). Understanding the treatment effects of specific therapies on mode of death can provide insight into the mechanism of action of the therapy as well as the pathophysiology of HF generally. Additionally, the time course of various types of post-discharge events may have implications for the frequency and intensity of clinical follow-up.

**METHODS**

The design and primary results of the RELAX-AHF study (9) were published previously (3,10,11). Briefly, the RELAX-AHF study was a double-blind, prospective, multicenter clinical trial that randomized 1,161 patients within 16 h of AHF presentation to either intravenous serelaxin (30 μg/kg/day, n = 581) or matching placebo (n = 580) for up to 48 h. To be eligible for enrollment, patients had to have congestion on chest radiograph, dyspnea at rest or with minimal exertion, elevated natriuretic peptide levels, systolic blood pressure >125 mm Hg, and mild to moderate renal insufficiency. The primary endpoints of the study were dyspnea assessment by change in the visual analog scale from baseline to day 5 and by Likert scale during the first 24 h. All patients were followed to 180 days for the pre-specified efficacy endpoint of cardiovascular (CV) mortality and the safety endpoint of all-cause mortality.

**EVENT ADJUDICATION PROCESS.** A clinical events committee composed of 4 cardiologists (G.M.F., J.B., A.F.H., and A.B.M.) with expertise in HF and experience in adjudicating clinical events in trials of CV disease who were blinded to treatment allocation adjudicated all deaths through day 180. For each event, the committee reviewed the case report form, narrative summary provided by the study investigator, and all available relevant source documents from the medical record, including hospital notes, telemetry or implantable cardioverter-defibrillator (ICD) interrogations, discharge summaries, autopsy reports, and death certificates. Definitions for each cause of death were prospectively developed by the clinical events committee and approved by the study executive committee before the start of the study. Specific definitions used for adjudication were as follows:

**HF death:** Deaths occurring in the context of clinically worsening symptoms and/or signs of HF without evidence of another cause of death were classified as HF deaths. Hospitalized patients being actively treated for HF who had a sudden death as the terminal event in the hospital were classified with HF death.

**Sudden cardiac death:** Deaths that occurred unexpectedly in a previously stable patient were adjudicated as sudden cardiac deaths. An unwitnessed death in a patient last seen alive within 72 h who, at that time, did not manifest another life-threatening disease or process was classified as sudden cardiac death.

**Death due to acute coronary syndrome (ACS):** Deaths occurring up to 14 days after a documented acute myocardial infarction (AMI) or by autopsy findings showing recent MI or recent coronary thrombus and when there was no conclusive evidence of another cause of death were classified as deaths due to ACS. Adjudication of MI required creatine kinase-MB >2 × the upper limit of the normal (ULN) or troponin I or T >2 × ULN and either typical clinical presentation consistent with MI or typical electrocardiogram (ECG) changes consisting of new abnormal Q waves in at least 2 consecutive leads or evolving, ischemic ST-segment or T-wave changes in at least 2 consecutive leads, or new left bundle branch block. If death occurred before biochemical confirmation of myocardial necrosis could be obtained, adjudication was on the basis of clinical presentation and ECG evidence.

**Death due to stroke:** Deaths occurring up to 30 days after a suspected or confirmed stroke on
the basis of clinical signs and symptoms as well as neuroimaging and/or autopsy and when there was no conclusive evidence of another cause of death were adjudicated as deaths due to stroke. This category included deaths occurring up to 30 days after a stroke that were either due to the stroke or caused by a complication of the stroke.

Other CV causes of death: Deaths due to another documented CV cause or from complications from a CV intervention were adjudicated as such.

Unknown/presumed CV death: Deaths not attributable to any apparent CV cause or non-CV cause and for which there was no additional relevant information were classified as unknown deaths. For the purpose of the endpoint of CV mortality, these events were presumed to be CV in nature.

Death due to renal failure: Deaths were classified as due to renal failure when the reason for death was primarily due to documented signs, symptoms, or laboratory abnormalities directly related to renal dysfunction; no other acute perturbation was responsible for the death; and/or antemortem therapeutic interventions included those directed toward treatment of renal failure.

Deaths due to non-CV or nonrenal causes: Deaths with a clearly identified non-CV or nonrenal cause as defined previously were adjudicated into specific categories (e.g., malignancy, sepsis).

**STATISTICAL ANALYSIS.** Baseline characteristics were described using appropriate descriptive statistics (percentages, means and SDs, or medians and interquartile ranges depending on the type of variable and its distribution). Because some causes of death were relatively infrequent, deaths were grouped into 4 predefined categories for the purposes of this analysis: HF death, sudden death, other CV death, and non-CV death. Deaths classified as unknown/presumed CV death were included with the other CV deaths for the purposes of analysis. Because these deaths generally occurred out of hospital, a sensitivity analysis was performed with these deaths reclassified as sudden deaths. Fourteen patients with 180-day vital status that was not known (they were followed for less than the required 173 days) were excluded from the comparisons of baseline characteristics between survivors and those who died. Cox proportional hazard models were used to assess the treatment effect of serelaxin on each mode of death.

All patients were included in these models with follow-up time censored at the last date known alive or date of death from another mode, and hazard ratios (HRs) with associated 95% confidence intervals (CIs) estimated from these models are presented. The p values from the log-rank test are presented. Because event rates were low, an analysis taking competing risks into account on the basis of methods of Fine and Gray (12) resulted in nearly identical results. The heterogeneity of serelaxin’s effect on the different categories of modes of death was tested by constructing a 3-df chi-square test from estimates of the 4 log HRs and their covariance matrix obtained using the Wei-Lin-Weissfeld method (13). SAS release 9.2 (SAS Institute, Inc., Cary, North Carolina) was used for analyses.

**RESULTS**

Of the 1,161 patients enrolled in RELAX-AHF, there were 14 with an unknown 180-day vital status. A total of 107 patients (9.3%) died. Of the 107 deaths, 88 (82%) were CV and 19 (18%) were non-CV. Within the category of CV death, 37 (35%) were due to HF, 25 (23%) were classified as sudden cardiac death, and 26

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**FIGURE 1 Categories for Mode of Death**

Categories for causes of death in the RELAX-AHF (Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure) study are shown. Contiguous slices sum to the more general categories of cardiovascular (CV) death and non-CV death. The subcategory other CV death includes deaths due to acute coronary syndromes or CV procedures and those classified as unknown/presumed CV.
(24%) were classified as other CV death (Figure 1). Baseline characteristics for survivors compared with those for each of the 4 analysis categories are shown in Table 1. Of the deaths classified as other CV death, 2 were due to ACS, 4 were due to stroke, 9 were related to CV procedures, and 11 were adjudicated as unknown/presumed CV. There were no deaths due to renal failure. The deaths adjudicated into each specific category for serelaxin and placebo are shown in Table 2.

**EFFECT OF SERELAXIN TREATMENT ON SPECIFIC MODES OF DEATH.** As reported previously, serelaxin treatment was associated with a substantial decrease in the rate of CV death (HR: 0.63; 95% CI: 0.41 to 0.96; p = 0.028) and all-cause death (HR: 0.63; 95% CI: 0.43 to 0.93; p = 0.020) (3). The treatment effect of serelaxin was most pronounced on other CV death (HR: 0.29; 95% CI: 0.12 to 0.73; p = 0.005) and sudden death (HR: 0.46; 95% CI: 0.20 to 1.07; p = 0.065) (Central Illustration). There was no apparent impact of serelaxin treatment on HF deaths (HR: 1.16; 95% CI: 0.61 to 2.21; p = 0.655) or non-CV deaths (HR: 0.71; 95% CI: 0.29 to 1.76; p = 0.548). Kaplan-Meier curves for each of the 4 primary categories of mode of death are shown in Figure 2. In an alternate sensitivity analysis, when unknown deaths were reclassified as sudden death, results were generally similar, although the HR for the effect of serelaxin on sudden death reached statistical significance (HR: 0.49; 95% CI: 0.25 to 0.98; p = 0.039).

Because the other CV death category included a variety of causes of death, we assessed these individually (Table 2). The most notable difference in this category was regarding death from stroke, which showed 1 death (0.2%) in the serelaxin group compared with 8 deaths (1.5%) with placebo. Of these

<table>
<thead>
<tr>
<th>TABLE 1 Baseline Characteristics by Vital Status and Mode of Death</th>
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<tbody>
<tr>
<td><strong>Baseline Characteristics</strong></td>
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<tr>
<td>Age, yrs</td>
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<td>Weight, kg</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
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<tr>
<td>Heart rate, beats/min</td>
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<tr>
<td>Respiratory rate, breaths/min</td>
</tr>
<tr>
<td>Most recent ejection fraction, %</td>
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<tr>
<td>No. of admissions for HF in past year</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Ejection fraction &lt;40%</td>
</tr>
<tr>
<td>Admitted to hospital for HF in past year</td>
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<tr>
<td>Medical history</td>
</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Hyperlipidemia</td>
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<tr>
<td>Stroke</td>
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<tr>
<td>Cigarette smoking</td>
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<td>Peripheral vascular disease</td>
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<tr>
<td>Mitral regeneration</td>
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<td>Ischemic heart disease</td>
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<tr>
<td>Pacemaker</td>
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<tr>
<td>Biventricular pacing</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
</tr>
<tr>
<td>Chronic lung disease</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>NT-proBNP, ng/l</td>
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<tr>
<td>Tropinin T, μg/l</td>
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</tbody>
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Values are mean ± SD, n (%), or geometric mean (95% CI).

CV = cardiovascular; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; NT-proBNP = N-terminal pro-B-type natriuretic peptide.
stroke deaths, 3 occurred within the first 8 days after randomization (all 3 in placebo-treated patients), and the remainder were 35 days or greater from randomization.

Given the relatively modest total number of events (107 deaths), we performed formal statistical testing for heterogeneity as described previously.

This analysis could not rule out the possibility that the variability observed in the effect of serelaxin on mode of death was due to chance ($p = 0.08$), suggesting that results this extreme or greater for a differential effect on mode of death would be expected to occur 8% of the time by chance alone.

**TIMING OF DEATHS FROM RANDOMIZATION.** The distribution of deaths over the follow-up period is shown in **Figure 3**. Forty-nine of 107 deaths (46%) occurred within 60 days of randomization, 20 in patients randomized to serelaxin and 29 in patients randomized to placebo. In general, early deaths were much more likely to be CV in nature, with only 1 of 31 (3%) non-CV deaths within 30 days of randomization. HF deaths were roughly evenly distributed across the follow-up time period.

**DISCUSSION**

Understanding mode of death and timing of events in patients with HF can provide insight into the mechanism of treatment effect of novel therapies. In the RELAX-AHF study, patients receiving serelaxin demonstrated a significant improvement in both all-cause and CV mortality at 180 days. The current analysis suggests that the primary treatment effects of serelaxin were on other CV events and sudden death, rather than deaths from HF.
Prior data assessing the impact of other acute therapies on mode of death are limited, in part because AHF therapies with a demonstrable effect on mortality have not previously been identified. The most detailed previous data on mode of death in AHF comes from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan) trial (8). Overall mortality in the EVEREST trial was significantly higher than that observed in RELAX-AHF (26.1% over a median follow-up of 9.9 months for EVEREST vs. 9.3% at 6 months for RELAX-AHF). Although the EVEREST trial had a longer follow-up period than the RELAX-AHF study, patient characteristics are the most likely explanation for these differences in outcome. The EVEREST trial required a history of chronic HF and an ejection fraction ≥40% for entry, whereas the RELAX-AHF trial allowed patients with AHF (including those with de novo HF) regardless of ejection fraction. Consistent with these inclusion characteristics, HF death was substantially more common than sudden death in the EVEREST trial (which included only those patients with impaired left ventricular systolic function), whereas the incidence of HF death and sudden death were similar in the RELAX-AHF trial. Additionally, the RELAX-AHF study required elevated blood pressure (systolic blood pressure >125 mm Hg) for study entry, whereas the EVEREST trial only excluded those patients with systolic blood pressure <90 mm Hg. Higher systolic blood pressure at presentation was previously demonstrated to be a favorable prognostic finding in AHF and potentially selects patients at lower risk of dying from HF (14,15).

Many deaths in clinical trials occur outside the hospital, and details that can provide clues to the specific cause of death may be unavailable. The framework for classifying these “unknown” deaths may significantly influence the results of mode of death analyses. These deaths are typically categorized as CV, given the overall burden of CV mortality in patients with HF. In the current study, we further subclassified these unknown deaths into either other CV or alternatively, in a sensitivity analysis, into the sudden death category. Our overall results were not fundamentally changed by the reclassification of these events, with the exception that the treatment effect of serelaxin on sudden death frequency became nominally statistically significant (p = 0.039) after reclassification.

**FIGURE 2** Kaplan-Meier Curves by Specific Categories of Mode of Death for Serelaxin Versus Placebo

Numbers below the x-axis reflect the number of patients at risk. CI = confidence interval; HF = heart failure.
What would be the potential mechanisms of a reduction in sudden death frequency with serelaxin therapy? Multiple putative mechanisms contribute to sudden death in patients with HF, including ischemia, myocardial fibrosis, increased sympathetic tone, neurohormonal activation, electrolyte abnormalities, and adverse effects of drug therapies. In addition to its vasodilatory effects, in experimental models, serelaxin modulates a variety of relevant biological pathways, including having anti-inflammatory, anti-fibrotic, and proangiogenic properties (16). Whether the relatively brief duration of therapy (48 h) used in the RELAX-AHF study was sufficient to modulate these pathways to a degree likely to have downstream effects on the risk of sudden death is unknown. Serelaxin treatment in the RELAX-AHF trial was associated with a decreased pattern of myocardial injury, as reflected by troponin elevations (11). Given the known association between ischemic injury and subsequent mortality in HF (16,17), subsequent risk of sudden death could potentially be affected. Microfoci of ischemia could potentially predispose patients to ventricular arrhythmias, and prior data from autopsy series suggest that many sudden deaths in patients with HF are actually related to ACS (18,19). Serelaxin therapy was also associated with less aggressive use of diuretics, and diuretic therapy has previously been linked to the risk of sudden death in chronic HF (20). Use of ICDs may also impact overall rates of sudden death—the use of ICDs was relatively low in the RELAX-AHF study overall (13%), owing, in part, to the inclusion of patients with preserved ejection fraction (for whom ICD therapy is generally not indicated) and to substantial enrollment in Europe, where ICD usage rates are lower than in North America. It is, however, notable that 4 of 25 patients (16%) with deaths classified as sudden death had ICDs.

One unexpected finding of the current analysis was the marked difference in rate of fatal stroke between serelaxin and placebo (1 death in the serelaxin group vs. 8 deaths in the placebo group). Prior data on stroke rates in patients with AHF are sparse. In the PROTECT (Placebo-Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) trial of rolofylline in AHF, overall stroke rates were approximately 1% at 60 days, and there was a significant increase in stroke associated with randomization to rolofylline (HR: 3.49; p = 0.043) (21). The potential mechanisms of the observed decrease in fatal stroke frequency with serelaxin are speculative, but serelaxin was associated with controlled decrease in blood pressure over the 48-h treatment period, which could have contributed to reduction in stroke risk. However, only 3 of the stroke events occurred within the first 35 days of therapy, and a direct link between short-term serelaxin treatment and later stroke mortality appears unlikely. Alternatively, given the low number of events (9 fatal strokes overall at 180 days), this finding could potentially be related to chance alone.

**STUDY LIMITATIONS.** Important limitations of this analysis relate to the number of deaths and associated statistical power. There were only 107 deaths in the RELAX-AHF study within 180 days, and many causes of death, including ACS and stroke, had relatively few events and thus limited statistical power to make inferences about the impact of serelaxin therapy on specific modes of death. Thus, there is the possibility that these findings were due to chance, which could not be excluded by formal statistical testing for heterogeneity of effect. Although centralized blinded adjudication of events is considered the “gold standard” for assessment of endpoints in clinical trials, in many cases, detailed information about the cause of out-of-hospital death is limited. In an attempt to minimize the number of deaths classified as unknown, our pre-specified definition of sudden death was relatively broad, including patients last seen alive up to 72 h before death. The RELAX-AHF study did use standard best practices for clinical event adjudication, including the use of a blinded
endpoint committee of experienced HF physicians as well as pre-specified standardized definitions for events.

CONCLUSIONS

Treatment of patients with AHF with serelaxin was associated with significant improvements in CV mortality at 180 days. This effect was primarily driven by improvements in death frequency from other CV causes and sudden death, rather than from HF. These observations will require reassessment in upcoming larger trials with greater numbers of events.

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KEY WORDS cause of death, heart failure, relaxin, sudden cardiac death