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Cause of Death in Patients With Acute Heart Failure



Insights From RELAX-AHF-2

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ABSTRACT

OBJECTIVES This study sought to better understand the discrepant results of 2 trials of serelaxin on acute heart failure (AHF) and short-term mortality after AHF by analyzing causes of death of patients in the RELAX-AHF-2 (Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF-2) trial.

BACKGROUND Patients with AHF continue to suffer significant short-term mortality, but limited systematic analyses of causes of death in this patient population are available.

METHODS Adjudicated cause of death of patients in RELAX-AHF-2, a randomized, double-blind, placebo-controlled trial of serelaxin in patients with AHF across the spectrum of ejection fraction (EF), was analyzed.

RESULTS By 180 days of follow-up, 11.5% of patients in RELAX-AHF-2 died, primarily due to heart failure (HF) (38% of all deaths). Unlike RELAX-AHF, there was no apparent effect of treatment with serelaxin on any category of cause of death. Older patients (≥ 75 years) had higher rates of mortality (14.2% vs. 8.8%) and noncardiovascular (CV) death (27% vs. 19%) compared to younger patients. Patients with preserved EF ($\geq 50\%$) had lower rates of HF-related mortality (30% vs. 40%) but higher non-CV mortality (36% vs. 20%) compared to patients with reduced EF.

CONCLUSIONS Despite previous data suggesting benefit of serelaxin in AHF, treatment with serelaxin was not found to improve overall mortality or have an effect on any category of cause of death in RELAX-AHF-2. Careful adjudication of events in the serelaxin trials showed that older patients and those with preserved EF had fewer deaths from HF or sudden death and more deaths from other CV causes and from noncardiac causes. (Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF [RELAX-AHF-2]; [NCT01870778](https://doi.org/10.1016/j.jchf.2020.09.100)) (J Am Coll Cardiol HF 2020;8:999-1008)
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**ABBREVIATIONS
AND ACRONYMS**

- AHF** = acute heart failure
- CV** = cardiovascular
- EF** = ejection fraction
- HF** = heart failure
- HFpEF** = heart failure with preserved ejection fraction
- HFREF** = heart failure with reduced ejection fraction
- SCD** = sudden cardiac death

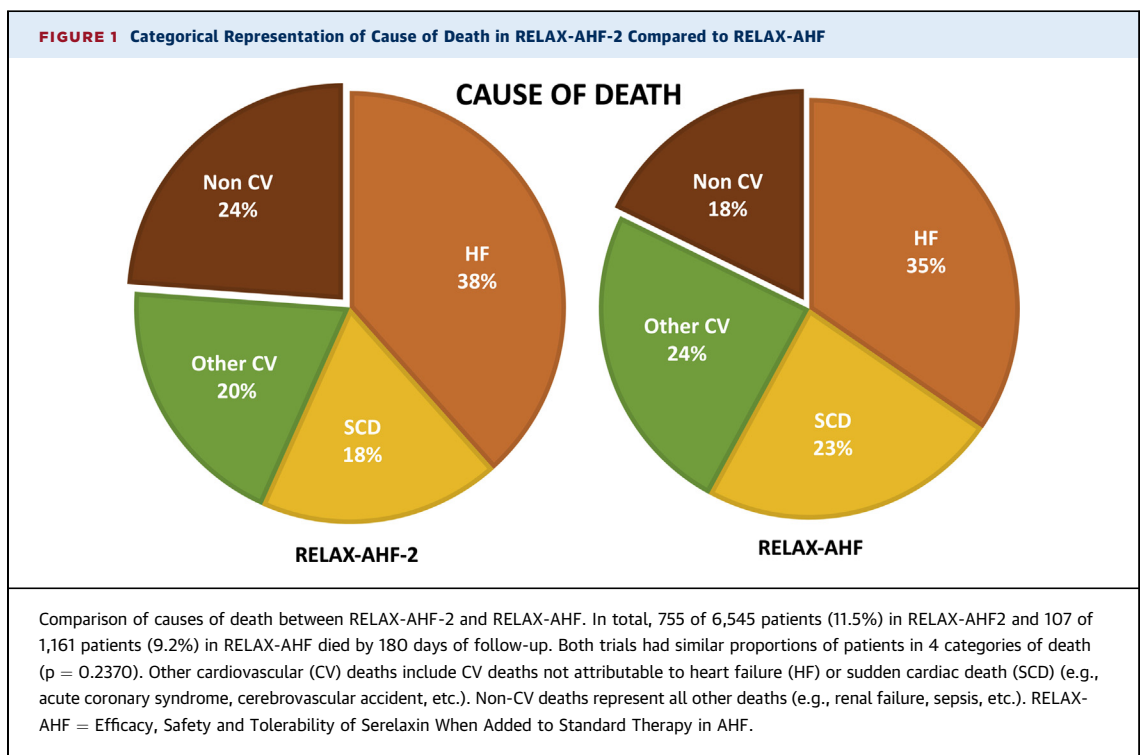
Hospitalization for acute heart failure (AHF) is associated with significant short- and long-term morbidity and mortality, and to date no specific therapy has been developed to improve these outcomes. Given that many patients with heart failure (HF) are older and have a high burden of comorbidities, the period after hospitalization is marked by a variety of competing risks for both cardiovascular (CV) and non-CV events. Improved understanding of the specific causes of mortality after AHF

may help identify strategies for better addressing poor outcomes in these patients.

The RELAX-AHF (Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF) and RELAX-AHF-2 studies were global, phase III, randomized clinical trials evaluating the safety and efficacy of serelaxin, a recombinant form of human relaxin-2, in patients hospitalized with AHF (1,2). The hormone relaxin contributes to many of the CV adaptations of pregnancy, including decreased systemic vascular resistance, increased renal blood flow, and augmented cardiac output (3,4). Additional pleiotropic properties possibly include anti-inflammatory, angiogenic, anti-ischemic, and antifibrotic effects (4,5). RELAX-AHF

randomized 1,161 patients with AHF and demonstrated improvement in dyspnea (the primary endpoint) as well as lower CV mortality (1). A subsequent analysis of adjudicated cause of death in these patients revealed that improved survival in the serelaxin arm of RELAX-AHF was primarily mediated by reduction in “other CV deaths” (which itself was largely driven by a reduction in stroke), with a modest reduction in sudden cardiac death (SCD) (6).

These findings led to a larger global trial of 6,545 patients, RELAX-AHF-2, which was designed to test the hypothesis that early administration of serelaxin would reduce CV mortality at 180 days and worsening HF through 5 days compared to placebo (2). Despite the promising findings of RELAX-AHF, RELAX-AHF-2 failed to conclusively demonstrate benefits on either of these outcomes. In the current analysis, our primary goals were to utilize data on adjudicated cause of death from the RELAX-AHF-2 trial to (1) inform understanding of the discrepant results of the RELAX-AHF and RELAX-AHF-2 studies; and (2) identify potential opportunities to better target therapies after AHF hospitalization, especially in previously understudied groups (e.g., the elderly and patients with HF with preserved ejection fraction [HFpEF]).



METHODS

RELAX-AHF-2 was a multicenter, randomized, double-blind, placebo-controlled, event-driven trial that randomized patients admitted to the hospital for AHF with symptoms of dyspnea, congestion on chest radiography, elevation in natriuretic peptide concentrations, systolic blood pressure at least 125mm Hg, and mild-to-moderate renal impairment (estimated glomerular filtration rate 25 to 75 ml/min/1.73 m² body surface area) to serelaxin or matching placebo. The trial design and primary results have been previously reported (2,7). In brief, patients who remained symptomatic after 1 dose of intravenous furosemide (at least 40 mg or equivalent) were eligible for randomization. Randomization occurred within 16 h of presentation or first intravenous administration of loop diuretic in a 1:1 ratio. Patients received either serelaxin at a dose of 30 µg/kg/day or matching placebo, beginning no more than 4 h after randomization, for up to 48 h. Serelaxin dosing was adjusted or discontinued in response to decreases in systolic blood pressure according to protocol. The ethics committee at each participating center approved the study, and patients provided written informed consent.

The trial had 2 primary efficacy endpoints: death from CV causes at 180 days and worsening HF (defined as worsening signs and symptoms of HF necessitating the addition or escalation of HF therapy) at 5 days. Secondary endpoints included death from any cause at 180 days, length of index hospital stay, and a composite of death from CV causes or rehospitalization for HF or renal failure at 180 days.

EVENT ADJUDICATION. A clinical events committee blinded to treatment allocation adjudicated all deaths and hospitalizations that occurred up to 180 days. For each event, the committee reviewed the case report form and all available relevant source documents from the medical record, including hospital notes, discharge summaries, autopsy reports, and death certificates. Definitions of each cause of death were previously developed by the clinical events committee and approved by the study executive committee. Specific event definitions and the adjudication process were generally the same in both RELAX-AHF studies. Specific definitions used to adjudicate deaths are summarized in Supplemental Appendix A (1,6).

STATISTICAL ANALYSIS. Baseline characteristics are described using appropriate descriptive statistics (percentage, mean ± SD, or median [interquartile range] depending on the type of variable and its

TABLE 1 Cause of Death in RELAX-AHF-2

	Serelaxin (n = 3,274)	Placebo (n = 3,271)	Total (N = 6,545)
All	367 (11.2)	388 (11.9)	755 (11.5)
CV	285 (8.7)	290 (8.9)	575 (8.8)
HF or cardiogenic shock	133 (4.1)	157 (4.8)	290 (4.4)
Sudden cardiac death	68 (2.0)	70 (2.1)	138 (2.1)
Other	84 (2.6)	63 (1.9)	147 (2.2)
Cerebrovascular accident	21 (0.6)	12 (0.4)	33 (0.5)
Acute coronary syndrome	16 (0.5)	9 (0.3)	25 (0.4)
Procedure complication	6 (0.2)	13 (0.4)	19 (0.3)
Systemic or pulmonary embolism	6 (0.2)	4 (0.1)	10 (0.1)
Peripheral arterial disease	2 (0.1)	0 (0.0)	2 (0.0)
Presumed CV/unknown	33 (1.0)	25 (0.8)	58 (0.9)
Non-CV	82 (2.5)	98 (3.0)	180 (2.8)
Infectious	29 (0.9)	31 (1.0)	60 (0.9)
Pulmonary	18 (0.6)	25 (0.8)	43 (0.7)
Malignancy	9 (0.3)	21 (0.6)	30 (0.5)
Gastrointestinal	8 (0.2)	7 (0.2)	15 (0.2)
Renal	6 (0.2)	5 (0.2)	11 (0.2)
Neurological	5 (0.2)	2 (0.1)	7 (0.1)
Other	7 (0.2)	7 (0.2)	14 (0.2)

Values are n (%). Cause of death in RELAX-AHF-2 by treatment arm with etiologies of "other" CV and non-CV death.
 CV = cardiovascular; HF = heart failure; RELAX-AHF-2 = Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF-2.

distribution). Deaths were grouped into pre-defined categories, similar to those used for the cause of death analysis of RELAX-AHF (6). CV causes of death included HF, SCD, and other CV death. Other CV deaths included cerebrovascular events (ischemic, hemorrhagic, or unknown stroke), acute coronary syndrome, systemic or pulmonary embolism, CV procedure complication, or presumed/unknown CV death. The final category of non-CV deaths included all other causes of death (e.g., sepsis, malignancy, renal failure, etc.).

Cox proportional hazards models were used to assess the treatment effect of serelaxin on each cause of death (based on cause-specific hazards). All patients were included in these models with follow-up time censored at the last date known alive until 180 days or date of death from another mode, and hazard ratios with associated 95% confidence intervals estimated from these models are presented. The p values from the log-rank test are presented. Chi-square tests were used to determine differences between cause-of-death categories in the 2 RELAX-AHF-2. The Fine and Gray subdistribution hazard competing risk model was fitted to obtain the cumulative incidence function for each cause of death for both RELAX trials. SAS release 9.4 (SAS Institute, Inc., Cary, North Carolina) was used for analyses.

TABLE 2 Demographics of Patients by Vital Status and Cause of Death

	Survivors (n = 5,790)	Nonsurvivors (n = 755)	HF Death (n = 290)	Sudden Death (n = 138)	Other CV Death (n = 147)	Non-CV Death (n = 180)
Age, yrs	72.6 ± 11.2	76.2 ± 10.5	76.7 ± 10.2	73.2 ± 12.0	75.4 ± 10.5	78.4 ± 9.4
Weight, kg	84.5 ± 20.0	81.5 ± 20.8	82.2 ± 20.5	83.7 ± 22.9	78.8 ± 19.2	80.9 ± 20.8
SBP, mm Hg*	146.4 ± 16.8	144.4 ± 15.8	141.8 ± 14.4	145.9 ± 17.2	145.3 ± 16.8	146.9 ± 15.4
DBP, mm Hg*	82.4 ± 14.2	80.1 ± 13.4	77.9 ± 12.5	83.3 ± 14.1	82.3 ± 14.8	79.6 ± 12.6
Heart rate, beats/min*	83.5 ± 17.1	83.7 ± 16.5	83.7 ± 15.7	82.4 ± 16.6	84.9 ± 17.2	83.7 ± 17.3
Respiratory rate, breaths/min*	21.8 ± 4.5	22.6 ± 5.3	22.4 ± 4.8	23.3 ± 5.9	22.8 ± 5.0	22.4 ± 5.7
Most recent EF, %	39.9 ± 13.8	39.3 ± 14.4	38.6 ± 13.9	38.2 ± 14.5	41.0 ± 16.5	40.2 ± 13.7
Number of admissions for HF in past year	1.1 ± 1.2	1.3 ± 1.2	1.4 ± 1.3	1.1 ± 1.0	1.2 ± 1.1	1.2 ± 1.2
Men	3,450 (59.6)	458 (60.7)	171 (59.0)	94 (68.1)	81 (55.1)	112 (62.2)
White	5,307 (91.7)	709 (93.9)	273 (94.1)	127 (92.0)	139 (94.6)	170 (94.4)
EF <40%	1,364/2,772 (49.2)	195/366 (53.3)	84/152 (55.3)	37/71 (52.1)	32/65 (49.2)	42/78 (53.8)
Admitted to hospital for HF in past year	2,896/5,397 (53.7)	442/718 (61.6)	191/280 (68.2)	88/134 (65.7)	71/138 (51.4)	92/166 (55.4)
Medical history						
Asthma	261 (4.5)	38 (5.0)	17 (5.9)	9 (6.5)	6 (4.1)	6 (3.3)
Blood transfusion	446 (7.7)	71 (9.4)	27 (9.3)	12 (8.7)	12 (8.2)	20 (11.1)
Bronchitis	447 (7.7)	60 (7.9)	28 (9.7)	9 (6.5)	12 (8.2)	11 (6.1)
CABG	833 (14.4)	128 (17.0)	54 (18.6)	16 (11.6)	23 (15.6)	35 (19.4)
Cardiac pacemaker insertion	727 (12.6)	115 (15.2)	46 (15.9)	7 (5.1)	16 (10.9)	46 (25.6)
Cardiac resynchronization therapy	219 (3.8)	35 (4.6)	16 (5.5)	6 (4.3)	6 (4.1)	7 (3.9)
Cerebrovascular accident	870 (15.0)	138 (18.3)	51 (17.6)	27 (19.6)	25 (17.0)	35 (19.4)
Chronic obstructive pulmonary disease	891 (15.4)	150 (19.9)	60 (20.7)	22 (15.9)	27 (18.4)	41 (22.8)
Depression	544 (9.4)	79 (10.5)	31 (10.7)	12 (8.7)	14 (9.5)	22 (12.2)
Hyperlipidemia	2,955 (51.0)	356 (47.2)	135 (46.6)	63 (45.7)	72 (49.0)	86 (47.8)
Hypertension	5,191 (89.7)	684 (90.6)	263 (90.7)	121 (87.7)	136 (92.5)	164 (91.1)
Hyperthyroidism	198 (3.4)	22 (2.9)	8 (2.8)	2 (1.4)	2 (1.4)	10 (5.6)
Hypothyroidism	626 (10.8)	78 (10.3)	31 (10.7)	11 (8.0)	17 (11.6)	19 (10.6)
Implantable defibrillator insertion	508 (8.8)	68 (9.0)	26 (9.0)	15 (10.9)	12 (8.2)	15 (8.3)
Ischemic heart disease	1,875 (32.4)	269 (35.6)	116 (40.0)	49 (35.5)	53 (36.1)	51 (28.3)
Percutaneous coronary intervention	1,379 (23.8)	193 (25.6)	71 (24.5)	41 (29.7)	36 (24.5)	45 (25.0)
Peripheral arterial disease	740 (12.8)	137 (18.1)	49 (16.9)	26 (18.8)	20 (13.6)	42 (23.3)
Diabetes mellitus	2,637/5,787 (45.6)	376/755 (49.8)	150/290 (51.7)	63/138 (45.7)	78/147 (53.1)	85/180 (47.2)
eGFR (ml/min)	52 ± 14.3	46.1 ± 14.0	44.5 ± 13.3	48.6 ± 14.4	47.1 ± 14.3	45.8 ± 14.5
NT-proBNP (pg/ml)	5,800 (3,444-9,008)	9,006 (4,702-13,509)	9,006 (4,919-13,509)	9,006 (4,631-13,509)	9,006 (4,593-13,509)	7,821 (4,332-13,509)

Values are mean ± SD, n (%), n/N, or median (interquartile range Q1-Q3). Baseline demographics of survivors and nonsurvivors, with nonsurvivors further characterized by cause of death. *Vital signs at screening visit.

CABG = coronary artery bypass grafting; DBP = diastolic blood pressure; EF = ejection fraction; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure; other abbreviations as in Table 1.

RESULTS

Of the 6,545 patients included in the intention-to-treat analysis of RELAX-AHF-2, 755 (11.5%) died within 180 days. The majority of deaths were due to CV causes (n = 575; 76% of total deaths), attributable most commonly to HF (n = 290; 38% of total deaths), followed by “other CV death” (n = 147; 20% of total deaths) and SCD (n = 138; 18% of total deaths) (Figure 1). By comparison, 107 of 1,161 of patients (9.2%) in RELAX-AHF died by 180 days of follow-up. Both trials had similar

proportions of patients in the 4 categories of death (p = 0.2370). In RELAX-AHF-2, among the 147 patients classified as having “other CV death” (i.e., not from HF or SCD), 33 had cerebrovascular accidents, 25 had acute coronary syndromes, 19 deaths were related to CV procedures, and 58 were classified as unknown/presumed CV death (Table 1). Overall, 180 patients (24% of total deaths; 2.8% of the trial population) died of non-CV causes, including 60 infection, 43 pulmonary cause (including pneumonia), 30 malignancy, and 11 renal failure (Table 1).

Baseline characteristics of survivors and non-survivors by cause of death are outlined in **Table 2**. Nonsurvivors were older, more frequently had previous hospitalization for HF in the preceding year, and had a higher burden of comorbidities, including history of coronary bypass surgery, cerebrovascular accident, obstructive pulmonary disease, and peripheral arterial disease. They also had worse renal function (lower estimated glomerular filtration rate) and higher natriuretic peptide levels.

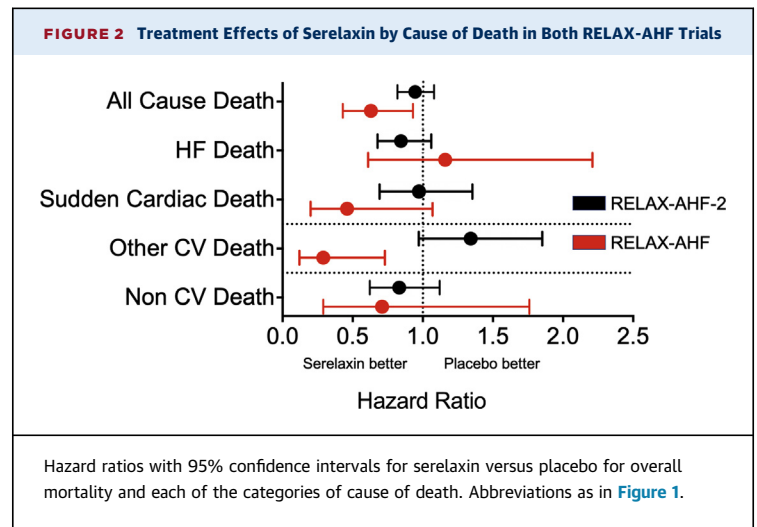
There was no apparent effect of treatment with serelaxin on any category of cause of death (**Figures 2 and 3, Supplemental Table 1**) in RELAX-AHF-2. Patients in RELAX-AHF had a numerically higher proportions of deaths in the SCD and other CV death categories, whereas patients in RELAX-AHF-2 had a numerically higher proportion of deaths due to non-CV causes (**Figure 1**).

AGE AND CAUSE OF DEATH. The mean age of patients enrolled in RELAX-AHF-2 was approximately 73 years, and more than one-half of patients were ≥ 75 years old ($n = 3,302$), allowing unique insight into cause of death in older patients with AHF. To further understand this relationship, we analyzed cause of death in older versus younger patients (**Table 3**). As expected, the age group ≥ 75 years had higher mortality ($n = 468$; 14.2% of cohort) than the younger group of patients ($n = 287$; 8.8% of cohort). The distribution of cause of death also differed by age group, with more SCD seen in younger patients and more non-CV deaths in older patients.

CAUSE OF DEATH IN HFpEF VERSUS HFrEF. RELAX-AHF-2 enrolled a heterogeneous AHF population across the spectrum of left ventricular EF. To better understand how differences in EF have an impact on cause of death after AHF, we assessed cause of death based on preserved EF ($\geq 50\%$; $n = 1,595$) versus reduced EF ($< 50\%$; $n = 4,533$) in patients in RELAX-AHF-2 (**Table 4**) in whom EF was available at enrollment ($n = 6,128$). By 180 days of follow-up, 498 patients (11.0%) with heart failure with reduced ejection fraction (HFrEF) died, and 183 patients (11.5%) with HFpEF died. Patients with reduced versus preserved EF had significantly different proportions of patients in each category of death, with HFrEF patients having more HF deaths (40% vs. 30%) and HFpEF patients having more non-CV deaths (36% vs. 20%) ($p < 0.0001$).

DISCUSSION

Improved insight into the specific causes of death after AHF can inform understanding of the results of specific clinical trials and provide direction for new

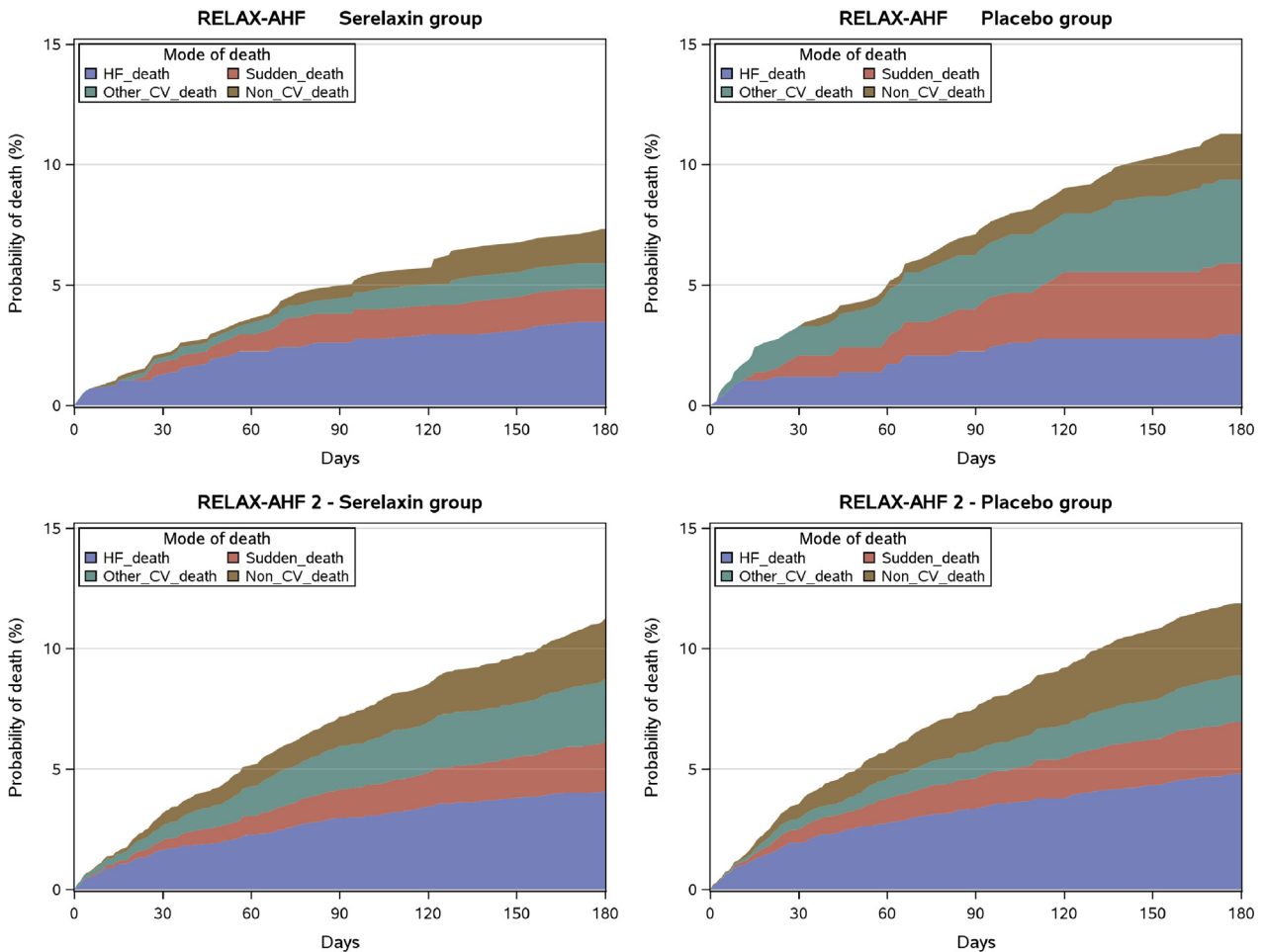


therapeutic interventions. We aimed to use adjudicated cause of death data from the RELAX-AHF-2 study to better understand the discrepant results of the RELAX-AHF and RELAX-AHF-2 studies and identify potential opportunities to better target therapies in patients with AHF (**Central Illustration**).

Unlike RELAX-AHF, in which treatment with serelaxin reduced 180-day all-cause and CV mortality, primarily through reduction in “other CV deaths,” serelaxin use did not have a significant impact on any cause of death in RELAX-AHF-2. Multiple potential explanations for the different results from RELAX-AHF and RELAX-AHF-2 include differences in patient population, investigative sites, trial design, and the play of chance. In a previously published analysis, the reduction in stroke deaths observed in RELAX-AHF was postulated to be due to improved blood pressure control or favorable vascular changes, and putative mechanisms for a marginal reduction in SCD including reduction in ischemia or contribution of additional pleotropic effects of serelaxin, including anti-inflammatory, antifibrotic, and vasodilatory properties (6). We did not confirm a treatment effect of serelaxin on these specific causes of death in RELAX-AHF-2, suggesting that it is unlikely that serelaxin therapy conferred an important benefit with regard to these endpoints. Despite the intention to enroll similar patients, patients in RELAX-AHF-2 had a 33% higher rate of non-CV death (24% vs. 18% of total deaths) than patients in RELAX-AHF. The higher incidence of non-CV death in RELAX-AHF-2 suggests that these patients may have had higher non-CV (and thus were less modifiable with a HF intervention) competing risk than patients in RELAX-AHF.

IMPLICATIONS FOR MANAGEMENT OF AHF AND FUTURE TRIALS. In comparison to chronic HF, the

FIGURE 3 Competing Risk Analysis of Both RELAX-AHF Trials



Competing risk analysis demonstrates probability of dying from each cause of death over follow-up for serelaxin and placebo arms of RELAX-AHF and RELAX-AHF-2. Abbreviations as in [Figure 1](#).

period after an AHF hospitalization is a higher risk period, sometime termed the “vulnerable phase” (8). In comparison to patients with chronic HF, patients with AHF have higher short-term event rates and a higher proportion of HF deaths versus other causes of death (9). In RELAX-AHF-2, patients had a 180-day mortality of 11.5% after AHF hospitalization, with a large proportion of deaths due to HF (38%). Similarly, causes of death in the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) trial were predominantly related to HF (41%) and SCD (26%) (10). To our knowledge, the current analysis is the largest to date examining adjudicated cause of death in patients after AHF hospitalization and supports previous data indicating

that a significant portion of early deaths after AHF are HF-related (11).

Similar to other trials of AHF, the findings observed in RELAX-AHF-2 suggest that short-term therapies are unlikely to have a lasting impact on long-term mortality compared to standard of care (12,13). However, a hospitalization for AHF may be an opportune time to initiate (or titrate) chronic guideline-directed medical therapy, a strategy that has generated some evidence of clinical benefit (14-17).

IMPLICATIONS FOR HF MANAGEMENT IN THE ELDERLY. Older patients with HF tend to have a greater burden of comorbidities and other competing risks than do younger patients with HF. With an average age of 73 years, which is older than in many comparable AHF

studies (68 years in TRUE-HF [Efficacy and Safety of Ularitide for the Treatment of Acute Decompensated Heart Failure] and 67 years in ASCEND-HF [Double-Blind, Placebo-Controlled, Multicenter Acute Study of Clinical Effectiveness of Nesiritide in Subjects With Decompensated Heart Failure]), the RELAX-AHF-2 program provided a unique opportunity to assess cause of death in older patients with HF (12,13). Compared to previous studies assessing cause of death in AHF patients with HFpEF (13.2% at median follow-up of 9.9 months) and across the spectrum of EF (11.9% at 6 months), our rate of non-CV death at 180 days was higher (24%) (10,11), which may be attributable to the more contemporary nature of and improved standard of HF care within our trial, but also inclusion of a more elderly population. Our study demonstrates that older patients in RELAX-AHF-2, in particular, had significantly higher proportions of non-CV death compared to younger patients (27% vs. 19%) and lower relative and absolute rates of CV death. Hospitalization for AHF may represent an opportunity to coordinate multimodal care for elderly patients with additional comorbidities in order to mitigate some non-CV deaths (18).

Younger patients had more from SCD (24% vs. 15%). A recent trial assessing the benefit of implantable cardioverter-defibrillators in patients with non-ischemic cardiomyopathy with depressed EF found that prophylactic implantable cardioverter-defibrillator insertion in this population was not associated with long-term reduction in mortality (19). However, when assessed specifically by age, younger patients with fewer comorbidities tended to derive benefit whereas older patients with more comorbidities did not (20). Although these findings are in a different population, our analysis supports their plausibility.

IMPLICATIONS FOR MANAGEMENT OF HFpEF. Patients with HFpEF account for a growing proportion of patients hospitalized with AHF (21). Although RELAX-AHF-2 enrolled mostly patients with reduced EF (74%), those with preserved EF had a similar incidence of 180-day mortality (11.0% vs. 11.5%) but with significantly different proportions of patients in each category of death. Patients with HFpEF had a higher proportion of patients with HF death (40% vs. 30%), whereas those with HFpEF had a higher proportion of patients with non-CV death (36% vs. 20%).

Our findings are in line with previous studies, demonstrating that (1) patients have higher short-term mortality post-AHF, regardless of EF (11); (2) long-term mortality is similar between HFpEF and HFpEF patients post-AHF (22); but (3) patients with

TABLE 3 Cause of Death by Age in RELAX-AHF-2

	Age <75 yrs (n = 287)	Age ≥75 yrs (n = 468)	p Value* (<75 yrs vs. ≥75 yrs)
HF death	103 (36)	187 (40)	0.0014
SCD	70 (24)	68 (15)	
Other CV death	60 (21)	87 (19)	
Non-CV death	54 (19)	126 (27)	
Total	287 (100)	468 (100)	

Values are n (%), unless otherwise indicated. In RELAX-AHF-2, 8.8% (287 of 3,243) of patients age <75 years and 14.2% (468 of 3,302) of patients age ≥75 years died. These groups had significantly different proportions of patients in the 4 categories of cause of death, with a higher proportion of sudden death at age <75 years and a higher proportion of non-CV death at age ≥75 years. *Based on Chi-square test.
 SCD = sudden cardiac death; other abbreviations as in Table 1.

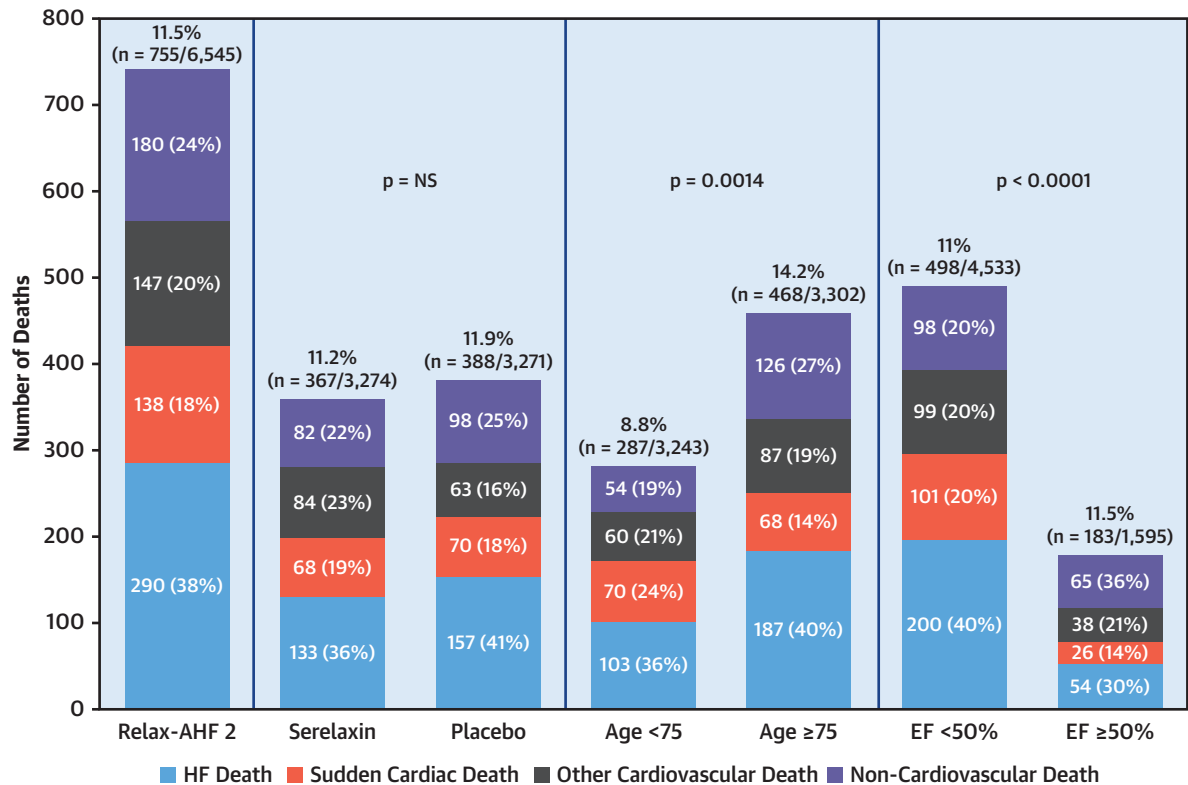
HFpEF tend to have higher rates of CV and HF readmissions, whereas patients with HFpEF tend to have more non-CV readmissions and non-CV death (22-24). Within our HFpEF group, rates of non-CV death (36%) were similar to those in the CHARM-Preserved (Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity) trial (29%) (25), I-Preserve (Irbesartan in Heart Failure With Preserved Ejection Fraction Study) trial (30%) (26), and TOPCAT (Spironolactone for Heart Failure with Preserved Ejection Fraction) trial (28%) (27). In the EVEREST trial, which enrolled patients with EF ≤40%, non-CV death accounted for only 13.2% of deaths during follow-up. In totality, these findings demonstrate that patients with both HFpEF and HFpEF have significant short-term mortality, with a higher contribution of non-CV causes in those with HFpEF.

Heterogeneity of the tested population is a commonly postulated reason for failure of previous HFpEF trials. Biopsy studies indicate that a substantial proportion of these patients may have cardiac amyloidosis (28) or represent other distinct phenogroups that may have different risk profiles and

TABLE 4 Cause of Death by EF in RELAX-AHF-2

	EF <50% (n = 498)	EF ≥50% (n = 183)	p Value*
HF death	200 (40)	54 (30)	<0.0001
SCD	101 (20)	26 (14)	
Other CV death	99 (20)	38 (21)	
Non-CV death	98 (20)	65 (36)	
Total	498 (100)	183 (100)	

Values are n (%), unless otherwise indicated. Patients with reduced EF (<50%; n = 4,533) vs. preserved EF (≥50%; n = 1,595) had significantly different proportions of patients in the 4 categories of cause of death. Patients with EF <50% had a significantly higher proportion of patients with HF death, whereas those with EF ≥50% had significantly higher proportion of patients with non-CV death. *Based on Chi-square test.
 Abbreviations as in Tables 1 to 3.

CENTRAL ILLUSTRATION Causes of Death in the Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF-2 Study

Loungani, R.S. et al. *J Am Coll Cardiol HF*. 2020;8(12):999-1008.

In an analysis of adjudicated cause of death in a large, contemporary, heterogeneous acute heart failure (AHF) population across the spectrum of ejection fraction (EF), 180-day mortality was 11.5% and was primarily due to heart failure (HF) (38% of all deaths). Older patients had higher rates of death than younger patients (14.2% vs. 8.8%) and suffered more from non cardiovascular (CV) death. Patients with preserved EF had rates of death similar to those with reduced EF (11.5% vs. 11.0%) but also had more non-CV death. RELAX-AHF-2 = Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in AHF-2.

responses to treatment (29-31). Patients with HFpEF tend to have a higher burden of non-CV comorbidities than those with HFrEF, and HFpEF phenogroups with a high prevalence of these comorbidities tend to fare clinically worse (24,29,30,32). Combined with evidence that HFpEF patients have more non-CV hospitalization and death, clinical care and future trials should incorporate strategies focused on mitigating these comorbidities to improve outcomes. Trials assessing the impact of sodium glucose cotransporter 2 inhibitors (Dapagliflozin Evaluation to Improve the LIVES of Patients With PReserved Ejection Fraction Heart Failure [DELIVER]; NCT03619213) and intravenous iron (Effect of IV Iron in Patients With

Heart Failure With Preserved Ejection Fraction [FAIR-HFpEF]; NCT03074591) on outcomes in HFpEF patients are ongoing. Furthermore, routine preventative care strategies—optimal control of diabetes, recommended cancer screening, vaccine administration—all are important adjuncts to HF care and may play a role in reducing morbidity and mortality in these patients.

CONCLUSIONS

Our analysis of cause of death in RELAX-AHF-2 did not identify an effect of serelaxin on any specific cause of death in the population studied. An

increased rate of non-CV death, in older patients and in those with HFpEF in particular, may limit the impact of CV focused therapies on mortality in this population, highlighting the need for a multilayered approach that optimizes chronic HF therapy and addresses both CV and non-CV morbidities for improving long-term outcomes after AHF.

AUTHOR DISCLOSURES

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In an analysis of adjudicated cause of death in a large, contemporary, heterogeneous AHF population across the spectrum of EF, 180-day mortality was 11.5% and was primarily due to HF (38% of all deaths). Temporary infusion of serelaxin did not have an apparent treatment effect on any category of cause of death. Older patients (≥ 75 years) and patients with HF with preserved EF ($\geq 50\%$) tended to have higher rates of non-CV death.

TRANSLATIONAL OUTLOOK: Post-discharge strategies utilizing a multimodal approach to optimize chronic HF therapy and address important non-CV comorbidities may mitigate high rates of mortality following an episode of AHF and should be tested in future trials.

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KEY WORDS acute heart failure, cause of death, mortality, serelaxin, vulnerable phase

APPENDIX For a supplemental appendix outlining the death definitions and a supplemental table, please see the online version of this paper.