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RESEARCH ARTICLE

Impact of age on clinical outcomes and response to serelaxin in patients with acute heart failure: An analysis from the RELAX-AHF-2 trial

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Aims Acute heart failure (AHF) is a major cause of hospitalizations and death in the elderly. However, elderly patients are often underrepresented in randomized clinical trials. We analysed the impact of age on clinical outcomes and response to treatment in patients enrolled in Relaxin in Acute Heart Failure (RELAX-AHF-2), a study that included older patients than in previous AHF trials.

Methods and results The RELAX-AHF-2 randomized patients admitted for AHF to infusion of serelaxin or placebo. We examined the association of pre-specified clinical outcomes and treatment effect according to age categories [(years): <65 ($n = 1411$), 65–74 ($n = 1832$), 75–79 ($n = 1222$), 80–84 ($n = 1156$) and ≥85 ($n = 924$)]. The mean age of the 6545 patients enrolled in RELAX-AHF-2 was 73.0 ± 11 years. The risk of all-cause and cardiovascular (CV) death (all $p < 0.001$) as well as the composite endpoint of CV death or heart failure/renal failure rehospitalization through 180 days ($p = 0.002$) and hospital discharge through day 60 ($p = 0.013$) were all directly associated with age categories. Age remained independently associated with outcomes after adjustment for clinical confounders and the results were consistent when age was analysed continuously. No clinically significant change in treatment effects of serelaxin was observed across age categories for the pre-specified endpoints (interaction $p > 0.05$).

Conclusion Elderly patients are at higher risk of short- and long-term CV outcomes after a hospitalization for AHF. Further efforts are needed to improve CV outcomes in this population.

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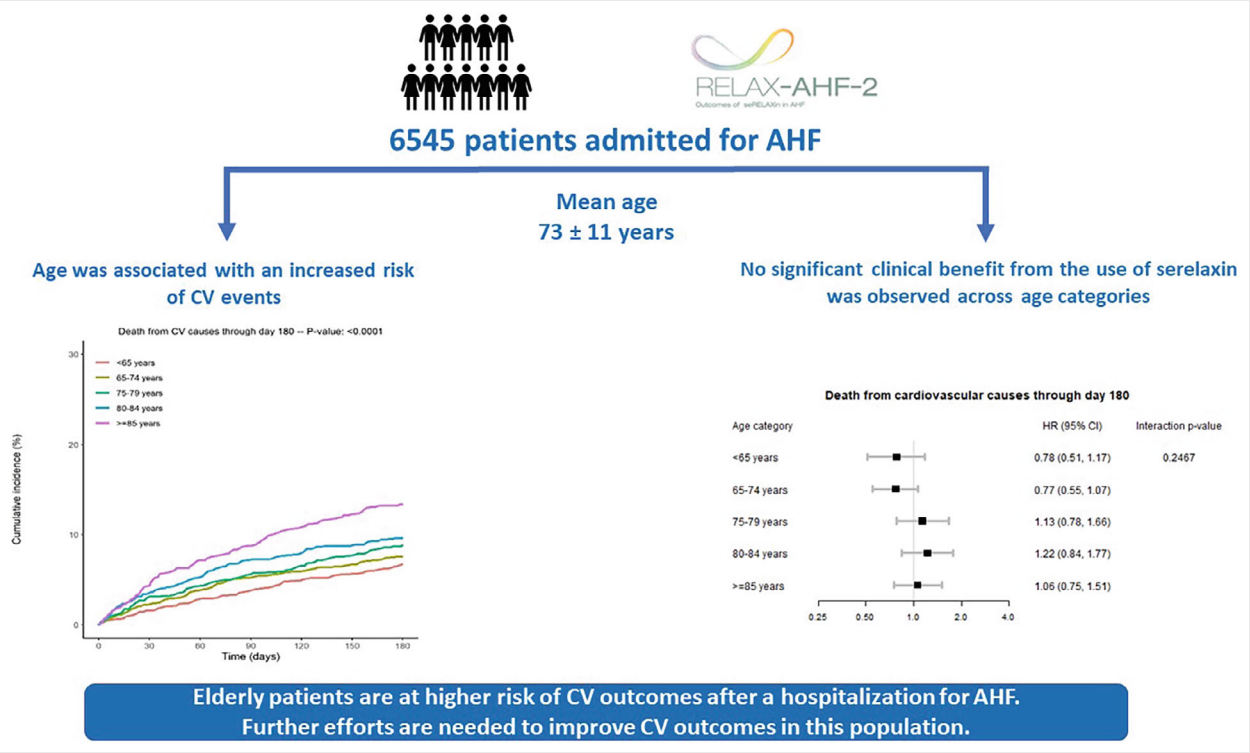
Graphical Abstract



In the RELAX-AHF-2 trial, age was associated with an increased risk of worse cardiovascular (CV) outcomes. No clinically significant change in treatment effects of serelaxin was observed across age categories for the pre-specified endpoints. Further efforts are needed to improve CV outcomes in this population. AHF, acute heart failure; CI, confidence interval; HR, hazard ratio. [Correction added on 8 November 2024, after first online publication: Additional abbreviations have been inserted in this version.]

Keywords Acute heart failure • Age • Comorbidities • Serelaxin

Introduction

The prevalence of heart failure (HF) increases substantially with age and HF represents a major cause of morbidity and mortality in elderly.[1,2] Older HF patients face a higher burden of cardiovascular (CV) risk factors and comorbidities that often remain undertreated in clinical practice.[3,4] This population is also exposed to an excess risk for hospitalization for acute HF (AHF), a marker of an increased risk of rehospitalization and mortality.[5,6] These patients are commonly under-represented in HF clinical trials, representing an unmet clinical need for better understanding the pathophysiology and outcomes of AHF.[7]

Relaxin in Acute Heart Failure (RELAX-AHF-2) is one of the largest trials in patients with AHF and enrolled a high proportion of elderly patients.[8] It therefore gives a major opportunity to evaluate the impact of age on clinical characteristics and outcomes in this population. We analysed the impact of age on clinical characteristics, in-hospital and post-discharge outcomes in patients admitted for AHF as well as the potential treatment effect of serelaxin according to age among patients enrolled in RELAX-AHF-2.

Methods

Study design and population

The rationale and design of the RELAX-AHF-2 trial have been published.[8,9] Briefly, RELAX-AHF-2 was a multicentre, randomized, double-blind, placebo-controlled phase 3 trial that enrolled 6600 hospitalized patients with AHF, of whom 6545 patients were included in the intention-to-treat analysis. The trial included patients ≥18 years old hospitalized for AHF with (i) elevated B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP),[8,9] (ii) systolic blood pressure ≥125 mmHg, (iii) mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥25 and ≤75 ml/min/1.73 m^2 estimated by the Modification of Diet in Renal Disease equation), and (iv) persistent HF symptoms after initial intravenous diuretic treatment equivalent to at least 40 mg of furosemide. Eligible patients were

randomized within 16 h of presentation to receive either intravenous serelaxin for 48 h or matching placebo. All patients signed written informed consent for participation, and the trial protocols were approved by the local institutional review boards or ethics committees at each participating site.

Study outcomes

The study outcomes of the current analysis included: CV death or rehospitalization for HF/renal failure (RF) through day 180, death from CV causes through day 180, rehospitalization for HF/RF through day 180, worsening HF or death from any cause through day 5, death from any cause through day 180, hospital discharge through day 60. Patients enrolled in the study were assessed daily during hospitalization and then at pre-defined clinic visits occurring at days 14, 60 and 180 post-randomization. Rehospitalization criteria included unplanned hospital admission or attendance in an acute care setting for at least 24 h. An independent Clinical Event Committee, unaware of the group assignments, adjudicated all deaths and rehospitalization events through day 180.

Statistical analysis

In the present study, patients were divided into four age categories based on clinical relevance: <65 years, 65–74 years, 75–79 years, 80–84 years, and ≥85 years. Baseline characteristics are presented as mean ± standard deviation across the age groups for continuous data with normal distribution and median (interquartile range [IQR]) for data not normally distributed and as percentage for binary data. The differences between age groups were compared and *p*-values for trend were based on linear regression for continuous variables, logistic regression for binary variables and multinomial regression for nominal variables with more than two categories. Cumulative incidence curves were produced using the one minus Kaplan–Meier estimator for all-cause mortality through day 180, worsening HF through day 5, and the Aalen–Johansen estimator for all other outcomes (to account for death as a competing risk). Cox proportional hazards models were used to calculate hazard ratios (HRs) of age for each outcome not affected by all-cause death as a competing risk and proportional cause-specific hazards models were used to calculate those HRs for all other outcomes. The analyses were performed in the overall population as well as in both treatment arms (placebo and serelaxin groups, online supplementary *Table S1* and *S2*) to prevent the associations from being distorted by possible interactions with the study treatment. Separate models were fitted with age as a categorical variable and age as a continuous variable. In the models where age was entered as a continuous variable, possible non-linearities were assessed using natural cubic splines with knots placed at the first quartile (66 years), median (75 years), and third quartile (81 years) of the age variable. *P*-values for association and linearity were subsequently obtained through likelihood ratio tests. All associations between age and outcomes were analysed unadjusted and adjusted by (considered to be relevant according to clinical judgement) race, region, sex, hypertension, diabetes mellitus, myocardial infarction, stroke or other cerebrovascular event, atrial fibrillation or flutter, alcohol history, number of hospitalizations for HF within previous year, ischaemic cause of HF, left ventricular ejection fraction, NT-proBNP, implantable cardiac defibrillator, HF therapy at baseline, body mass index, systolic and diastolic blood pressure, heart rate, eGFR, bilirubin, haemoglobin. Missing data in the adjustment variables were imputed with the mean for continuous variables and the modes for categorical variables, stratified by age group. Continuous covariates were entered linearly in the adjusted models. The interactions between age and study treatment (serelaxin) effects were also tested. For these analyses, death or CV death, as applicable, was considered part of a composite outcome (and non-CV deaths censored) rather than treating death (or non-CV death) as a competing risk. Interaction *p*-values were calculated using likelihood ratio tests comparing the goodness-of-fit of Cox proportional hazards models fitted to the total study population with and without interaction terms, in both the unadjusted and adjusted models. A two-tailed *p*-value of ≤0.05 was considered statistically significant. All analyses were performed using R statistical software version 4.1.1.

Results

Patient characteristics

Overall, 6545 patients (59.7% male, 5.10% black) were included in the present analysis. *Table 1* shows the patients' clinical and demographic characteristics stratified by age categories. Mean age was 73.0 ± 11 years and there were 2080 (31.7%) patients aged ≥80 years and 924 (14.1%) aged ≥85 years. Compared with the younger, older patients were more often female, white and enrolled in Western Europe. Older patients were more likely to suffer from hypertension, previous cerebrovascular events and atrial fibrillation. They had lower body mass index, heart rate and renal function and higher left ventricular ejection fraction and NT-proBNP plasma values. With respect to background medical treatment for HF, older patients were less likely to receive evidence-based medical therapy for HF, including beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and mineralocorticoid receptor antagonists, and were on higher doses of diuretics.

Clinical outcomes by age categories

The risks of death from CV causes through day 180 and death from any cause through day 180 increased by age categories ($p < 0.001$ for both), as well as the risk of CV death or rehospitalization for HF/RF through 180 days ($p = 0.002$), but not rehospitalizations for HF/RF through 180 days alone ($p = 0.22$) (*Table 2* and *Figure 1*). Similar results were observed for the hospital discharge through day 60 ($p = 0.013$). No age-related differences were observed for the risk of worsening HF or death from any cause through day 5 ($p = 0.14$). The association of age with outcomes was consistent when analysis was restricted separately to the placebo and serelaxin groups (online supplementary *Table S1* and *S2*).

The association between age and the risk of death from CV causes through day 180 and death from any cause through day 180 remained significant after adjustment for clinical confounders (all $p < 0.001$) and when age was analysed as a continuous variable such that older age was significantly associated with an increased risk of events (fully adjusted HR for each 5 years increase, 1.14, 95% confidence interval [CI] 1.08–1.20, $p < 0.001$, and HR 1.27, 95% CI 1.16–1.40, $p < 0.001$, and HR 1.17, 95% CI 1.12–1.22, $p < 0.001$, respectively) (*Table 2* and *Figure 2*). Similar results were observed for the composite endpoint of CV death or rehospitalization for HF/RF through 180 days ($p = 0.046$ and HR 1.04, 95% CI

Table 1 Baseline characteristics according to age categories

	<65 years (n = 1411)	65–74 years (n = 1832)	75–79 years (n = 1222)	80–84 years (n = 1156)	≥85 years (n = 924)	p-value
Male sex	1027 (72.8)	1225 (66.9)	675 (55.2)	586 (50.7)	395 (42.7)	<0.001
Black race	207 (14.7)	72 (3.9)	24 (2)	17 (1.5)	14 (1.5)	<0.001
Region						<0.001
Eastern Europe	633 (44.9)	915 (49.9)	573 (46.9)	460 (39.8)	249 (26.9)	
Western Europe	280 (19.8)	537 (29.3)	467 (38.2)	511 (44.2)	507 (54.9)	
Latin America	182 (12.9)	189 (10.3)	110 (9)	92 (8)	69 (7.5)	
North America	300 (21.3)	175 (9.6)	67 (5.5)	79 (6.8)	75 (8.1)	
Other	16 (1.1)	16 (0.87)	5 (0.41)	14 (1.2)	24 (2.6)	
Medical history						
Hypertension	1214 (86)	1654 (90.3)	1105 (90.4)	1060 (91.7)	842 (91.1)	<0.001
Diabetes mellitus	652 (46.2)	997 (54.4)	575 (47.1)	482 (41.7)	307 (33.2)	<0.001
Myocardial infarction	401 (28.4)	672 (36.7)	432 (35.4)	357 (30.9)	282 (30.5)	0.81
Stroke or other cerebrovascular event	179 (12.7)	290 (15.8)	205 (16.8)	168 (14.5)	166 (18)	0.0072
Chronic kidney disease	793 (56.3)	1217 (66.5)	909 (74.5)	865 (74.9)	726 (78.6)	< 0.001
AF/flutter	449 (31.8)	949 (51.8)	749 (61.3)	748 (64.7)	570 (61.7)	<0.001
History of heart failure	1029/1410 (73)	1399/1832 (76.4)	937/1221 (76.7)	830/1154 (71.9)	659/924 (71.3)	0.077
Previous hospitalization for heart failure	750/1324 (56.6)	979/1724 (56.8)	638/1144 (55.8)	534/1068 (50)	437/855 (51.1)	<0.001
Ischaemic cause of heart failure	469/1027 (45.7)	819/1397 (58.6)	555/935 (59.4)	435/830 (52.4)	329/658 (50)	0.41
Ejection fraction at index hospitalization	33.7 ± 13.2	38 ± 13.5	40.1 ± 13.4	41.9 ± 13.4	43.9 ± 13.7	<0.001
Ejection fraction ≤40%	920/1342 (68.6)	962/1731 (55.6)	554/1149 (48.2)	447/1074 (41.6)	297/832 (35.7)	<0.001
NYHA class 1 month before admission						0.094
I/II	419/1013 (41.4)	585/1376 (42.5)	381/919 (41.5)	373/813 (45.9)	300/628 (47.8)	
III	479/1013 (47.3)	643/1376 (46.7)	436/919 (47.4)	364/813 (44.8)	262/628 (41.7)	
IV	115/1013 (11.4)	148/1376 (10.8)	102/919 (11.1)	76/813 (9.3)	66/628 (10.5)	
Treatment						
Cardiac resynchronization therapy	43 (3)	101 (5.5)	55 (4.5)	43 (3.7)	12 (1.3)	0.0074
Implantable cardiac defibrillator	142 (10.1)	223 (12.2)	123 (10.1)	56 (4.8)	32 (3.5)	<0.001
ACEi or ARB	1141 (80.9)	1436 (78.4)	940 (76.9)	879 (76)	664 (71.9)	<0.001
Beta-blocker	1214 (86)	1569 (85.6)	1023 (83.7)	914 (79.1)	698 (75.5)	<0.001
Aldosterone antagonist	865 (61.3)	1031 (56.3)	674 (55.2)	561 (48.5)	379 (41)	<0.001
Oral loop diuretics	773 (54.8)	1068 (58.3)	731 (59.8)	703 (60.8)	616 (66.7)	<0.001
Digoxin	261 (18.5)	391 (21.3)	269 (22)	240 (20.8)	174 (18.8)	0.79
IV nitrates at randomization	87 (6.2)	97 (5.3)	58 (4.7)	64 (5.5)	54 (5.8)	0.74
Randomized to receive serelaxin 30 μg/kg/day	686 (48.6)	922 (50.3)	626 (51.2)	558 (48.3)	482 (52.2)	0.33
Physiological measures						
BMI (kg/m^2)	32.5 ± 7.3	30.6 ± 6.2	29.5 ± 5.8	28.1 ± 5.3	26.6 ± 4.6	<0.001
SBP (mmHg)	147.3 ± 17.7	145.1 ± 16.7	145.9 ± 15.7	146.7 ± 16.7	146.4 ± 16.3	0.87
Heart rate (bpm)	88.4 ± 16.7	83.4 ± 17.1	81.8 ± 16.5	81.6 ± 17.3	80.8 ± 16.4	<0.001
NT-proBNP (ng/L)	5906.3 [3420.9–9005.8]	5771.2 [3308.9–9413]	6110.9 [3614.3–9772]	6293.5 [3698.9–10 551.7]	6860.4 [3907–12 723.2]	<0.001
eGFR (ml/min/1.73 m^2)	55.7 ± 14.6	52 ± 14.4	49.8 ± 13.8	49.2 ± 14	47.8 ± 13.7	<0.001
Haemoglobin (g/L)	133 ± 20.7	127.9 ± 19.8	124.3 ± 18.3	123.3 ± 18.4	121.4 ± 17.9	<0.001

Values are *n* (%), mean ± standard deviation, or median [interquartile range].
AF, atrial fibrillation; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IV, intravenous; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure.

1.01–1.07, $p = 0.018$), while no significant relationship was found between age and rehospitalization for HF/RF through 180 days alone (*Table 2*). The association between age, by category groups, and hospital discharge through day 60 remained significant also after adjustment at multivariable analysis ($p = 0.024$), as younger patients showed lower time to hospital discharge compared to the elderly.

Interaction between age and study treatment

The effect of serelaxin, compared with placebo, was analysed across age categories for all the pre-specified outcomes (*Figure 3*). No clinically significant treatment effect modification was observed for the analysed endpoints, except for a numerical reduction in CV death in the younger patients treated with serelaxin which did not reach statistical significance (p for interaction = 0.24 across age categories).

Safety outcomes

Online supplementary *Table S3* shows the occurrence of the pre-specified adverse events of interest according to age category. Overall, adverse effects became more common with increasing age, although the absolute increase was modest across the age groups. Hypokalaemia and cardiac failure were the most common

Table 2 Clinical outcomes according to age in the overall population

Outcome	*n* (%)	Participants with event/100 patient-years	Unadjusted HR (95% CI)	*p*-value	Fully adjusted HR (95% CI)	*p*-value
CV death or rehospitalization for HF/RF through day 180						
<65 years	315 (22.3)	52.1 (46.5–58.2)	Reference	0.002	Reference	0.046
65–74 years	432 (23.6)	55.9 (50.8–61.5)	1.07 (0.93–1.24)		1.01 (0.87–1.18)	
75–79 years	307 (25.1)	60.4 (53.8–67.6)	1.15 (0.99–1.35)		1.07 (0.90–1.28)	
80–84 years	286 (24.7)	59.8 (53.1–67.1)	1.14 (0.97–1.34)		1.10 (0.92–1.32)	
≥85 years	267 (28.9)	73.2 (64.6–82.5)	1.39 (1.18–1.63)		1.31 (1.07–1.59)	
Continuous per 5-year increase	–	–	1.04 (1.02–1.07)	<0.001	1.04 (1.01–1.07)	0.018
Death from CV causes through day 180						
<65 years	94 (6.7)	13.9 (11.3–17.1)	Reference	<0.001	Reference	<0.001
65–74 years	139 (7.6)	16.2 (13.6–19.1)	1.16 (0.89–1.50)		1.05 (0.80–1.38)	
75–79 years	108 (8.8)	19.0 (15.6–22.9)	1.36 (1.03–1.79)		1.26 (0.94–1.70)	
80–84 years	111 (9.6)	21.1 (17.4–25.4)	1.50 (1.14–1.98)		1.51 (1.11–2.06)	
≥85 years	123 (13.3)	30.2 (25.1–36.0)	2.13 (1.63–2.79)		2.17 (1.58–2.98)	
Continuous per 5-year increase	–	–	1.13 (1.08–1.17)	<0.001	1.14 (1.08–1.20)	<0.001
Rehospitalization for HF/RF through day 180						
<65 years	255 (18.1)	42.2 (37.2–47.7)	Reference	0.22	Reference	0.64
65–74 years	347 (18.9)	44.9 (40.3–49.9)	1.06 (0.90–1.25)		1.00 (0.84–1.19)	
75–79 years	232 (19.0)	45.7 (40.0–51.9)	1.08 (0.90–1.29)		0.97 (0.80–1.19)	
80–84 years	209 (18.1)	43.7 (38.0–50.0)	1.03 (0.86–1.24)		0.96 (0.77–1.18)	
≥85 years	193 (20.9)	52.9 (45.7–60.9)	1.24 (1.03–1.50)		1.11 (0.89–1.39)	
Continuous per 5-year increase	–	–	1.02 (0.99–1.04)	0.15	1.00 (0.97–1.04)	0.87
Worsening HF or death from any cause through day 5						
<65 years	85 (6.0)	449.2 (358.8–555.4)	Reference	0.14	Reference	0.24
65–74 years	129 (7.0)	529.5 (442.1–629.2)	1.18 (0.90–1.55)		1.08 (0.81–1.44)	
75–79 years	96 (7.9)	592.6 (480.0–723.7)	1.32 (0.98–1.77)		1.23 (0.89–1.70)	
80–84 years	98 (8.5)	641.8 (521.0–782.1)	1.43 (1.07–1.91)		1.42 (1.02–1.99)	
≥85 years	71 (7.7)	578.8 (452.1–730.1)	1.29 (0.94–1.76)		1.30 (0.89–1.89)	
Continuous per 5-year increase	–	–	1.06 (1.01–1.10)	0.009	1.06 (1.00–1.12)	0.04
Death from any cause through day 180						
<65 years	111 (7.9)	16.5 (13.5–19.8)	Reference	<0.001	Reference	<0.001
65–74 years	176 (9.6)	20.5 (17.6–23.7)	1.24 (0.98–1.57)		1.11 (0.87–1.42)	
75–79 years	137 (11.2)	24.1 (20.2–28.5)	1.46 (1.14–1.87)		1.32 (1.01–1.73)	
80–84 years	160 (13.8)	30.4 (25.9–35.5)	1.84 (1.44–2.34)		1.75 (1.33–2.30)	
≥85 years	171 (18.5)	42.0 (35.9–48.7)	2.52 (1.98–3.20)		2.37 (1.79–3.15)	
Continuous per 5-year increase	–	–	1.17 (1.13–1.21)	<0.001	1.17 (1.12–1.22)	<0.001
Hospital discharge through day 60						
<65 years	1392 (98.7)	4065.9 (3855.1–4285.2)	Reference	0.013	Reference	0.024
65–74 years	1800 (98.3)	4025.6 (3841.8–4216.0)	0.99 (0.93–1.06)		1.06 (0.98–1.14)	
75–79 years	1195 (97.8)	3833.9 (3619.6–4057.6)	0.92 (0.85–0.99)		0.97 (0.89–1.06)	
80–84 years	1120 (96.9)	3752.8 (3536.2–3979.2)	0.90 (0.83–0.97)		0.95 (0.87–1.04)	
≥85 years	897 (97.1)	4053.2 (3792.3–4327.4)	1.00 (0.92–1.09)		1.05 (0.95–1.16)	
Continuous per 5-year increase	–	–	0.98 (0.97–1.00)	0.006	0.99 (0.98–1.01)	0.40

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; RF, renal failure.
Adjusted for race, region, sex, hypertension, diabetes mellitus, myocardial infarction, stroke or other cerebrovascular event, atrial fibrillation/flutter, alcohol history, number of hospitalizations for HF within previous year, ischaemic cause of heart failure, left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide, implantable cardiac defibrillator, HF therapy at baseline, body mass index, systolic and diastolic blood pressure, heart rate, estimated glomerular filtration rate, bilirubin, haemoglobin.

pre-specified safety outcomes observed in the elderly compared to the younger, without any significant interaction with treatment (*p* for interaction 0.48 and 0.29, respectively).

Discussion

This post-hoc analysis of the RELAX-AHF-2 trial showed that in a contemporary population admitted for AHF, the prevalence of elderly patients is high. Age is a major independent risk factor for mortality, either CV or non-CV, in patients hospitalized for AHF. No significant treatment effect modification of serelaxin was observed across age categories, highlighting the unmeet clinical need to improve CV outcomes in this population.

The present analysis showed a two-fold increased risk of CV death in patients aged ≥85 years, and a 14% increased risk for each 5-year increase, after accounting for clinical confounders. The

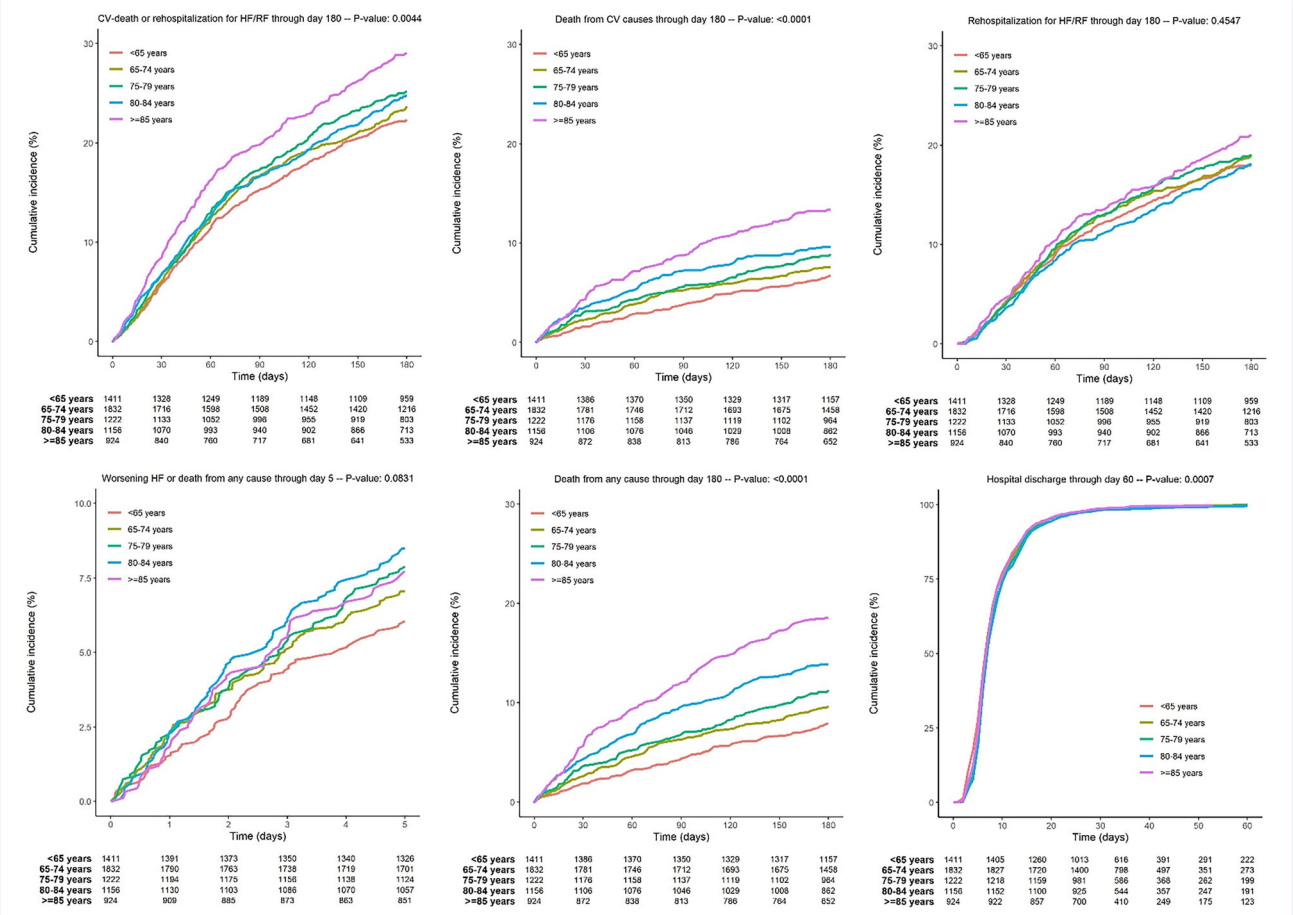


Figure 1 Cumulative incidence curves of each endpoint and stacked bar chart for length of in-hospital stay across age categories. CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; RF, renal failure.

prognostic role of age among patients with AHF was shown by previous reports from clinical trials and observational registries and confirmed by the present analysis.[6,10–14] RELAX-AHF-2 was rather unique among HF trials as more than 30% of the enrolled patients were ≥80 years old with a mean age of 73 ± 11 years. In comparison, in the Trial of Ularitide Efficacy and Safety in Acute Heart Failure (TRUE-AHF), mean age was of 68 ± 11 years and in the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF), the only larger trial enrolling patients with AHF, median age was 67 years (IQR 56–76).[15,16] A dichotomous relationship between age and risk of death was found in ASCEND-HF with a decrease in the risk of death or rehospitalization to a nadir at the age of 55 years and a progressive increase at older ages.[14] Such an increased risk of death at ages <55 years was not found in the present analysis as this young age subgroup was under-represented in RELAX-AHF-2, likely because of its inclusion criteria. On the other hand, our analysis confirms and extends previous data showing that the age-dependent risk of death persists also in the context of large AHF trials enrolling predominantly elderly patients.[6,10–12]

Given the relevant healthcare costs related to hospitalization for AHF and the increasing prevalence of this condition among the elderly, early adoption of treatment regimens, potentially improving CV outcomes and shortening the length of hospitalization stay may be of critical importance. Nevertheless, our data were consistent with the main findings of RELAX-AHF-2 that failed to show a significant effect of serelaxin on either primary endpoint.[17–20] Although we found a trend for CV mortality reduction in the younger group randomized to serelaxin, results should be interpreted cautiously given the lower rate of death in this subgroup compared to the elderly. More efforts are required to improve outcomes, especially among elderly patients with AHF who show a distinctive pathophysiological phenotype, complex comorbidity profile, and unique management of HF medication that may justify different treatment response.[21] Most importantly, guideline-recommended HF treatment is significantly underused in a significant portion of otherwise suitable older HF patients. Although many landmark HF trials upon which current treatment guidelines are based mostly include younger patients, it has never been clearly shown an interaction between HF treatment and age, discouraging their use in this population.[22] From this perspective, attention should be adopted to

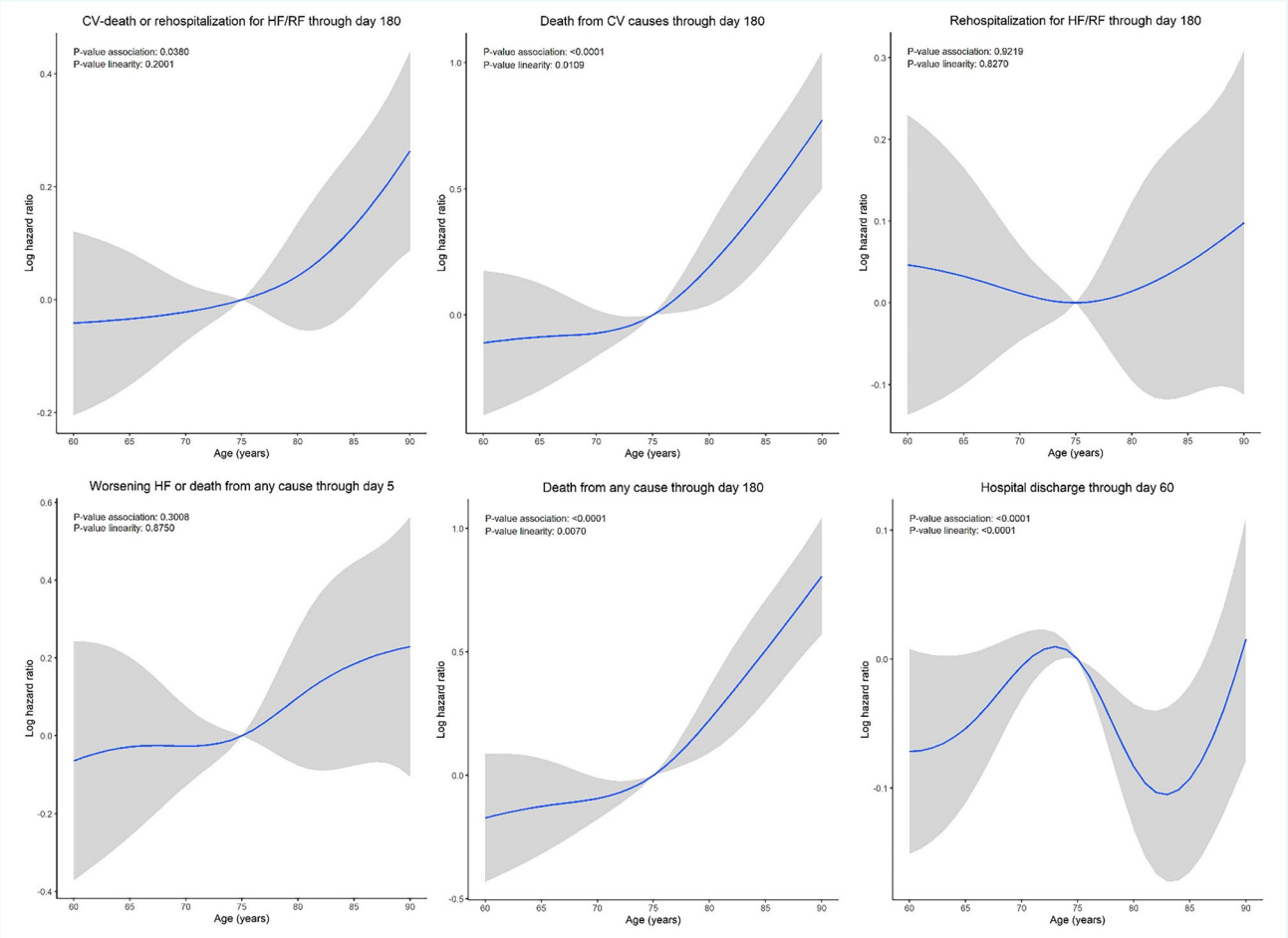


Figure 2 Continuous association of age (hazard ratio [line] and 95% confidence intervals [shaded area]) for each endpoint. CV, cardiovascular; HF, heart failure; RF, renal failure.

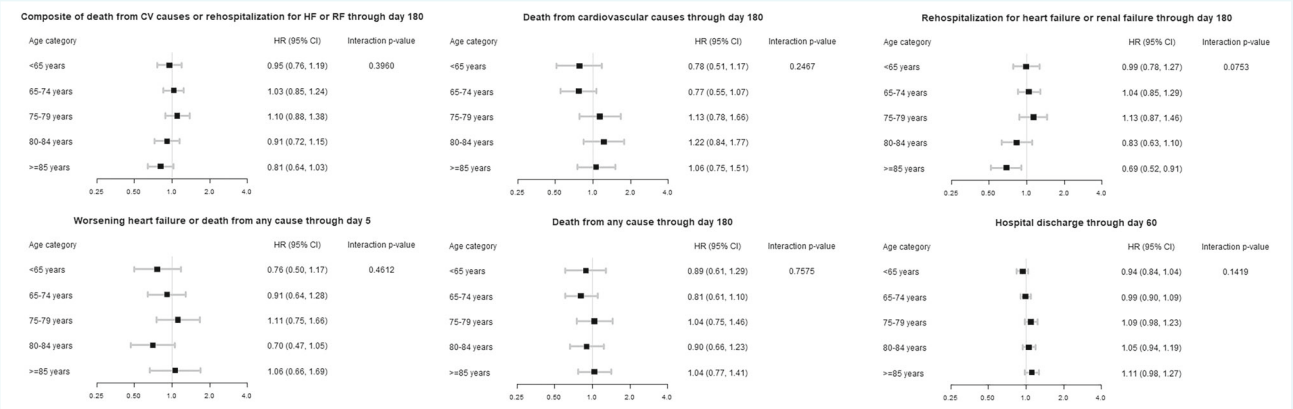


Figure 3 Forest plots of treatment effect of serelaxin versus placebo for each endpoint, according to age categories. CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; RF, renal failure.

optimize HF medical treatment in older patients and overcome potential misperception regarding contraindications and lack of tolerability of these drugs.[23] At the same time early intervention aimed to detect and treat AHF patients who may be more suitable of pharmacological treatment is advocated to ameliorate the short- and consequentially long-term outcomes.

The present study is based on post-hoc analysis of data from a clinical trial, therefore residual confounders could not be excluded in the association between age and outcomes as well as regarding the treatment effect of age. In RELAX-AHF-2, patients were followed up for 180 days. Thus, the associations between age and CV outcomes should be interpreted taking into consideration the relatively short period of follow-up, potentially influencing the risk of rehospitalization for HF, as well as the potential late effects of serelaxin treatment. RELAX-AHF-2 may have suffered from the limitations that may come from large trials where the inclusion of large number of patients may lead to a less selected patient population with consequent dilution of study drug effects.

Conclusion

In a large contemporary population of patients admitted for AHF, we found a high prevalence of elderly patients. Age represents an independent predictor of increased mortality and HF hospitalization in patients admitted for AHF. No significant clinical benefit from the use of serelaxin was observed across age subgroup categories. Further studies in better selected older patients with AHF are warranted to improve CV outcomes in this population.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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