Administration of serelaxin to patients with acute heart failure: are there any differences across RELAX-AHF subgroups?

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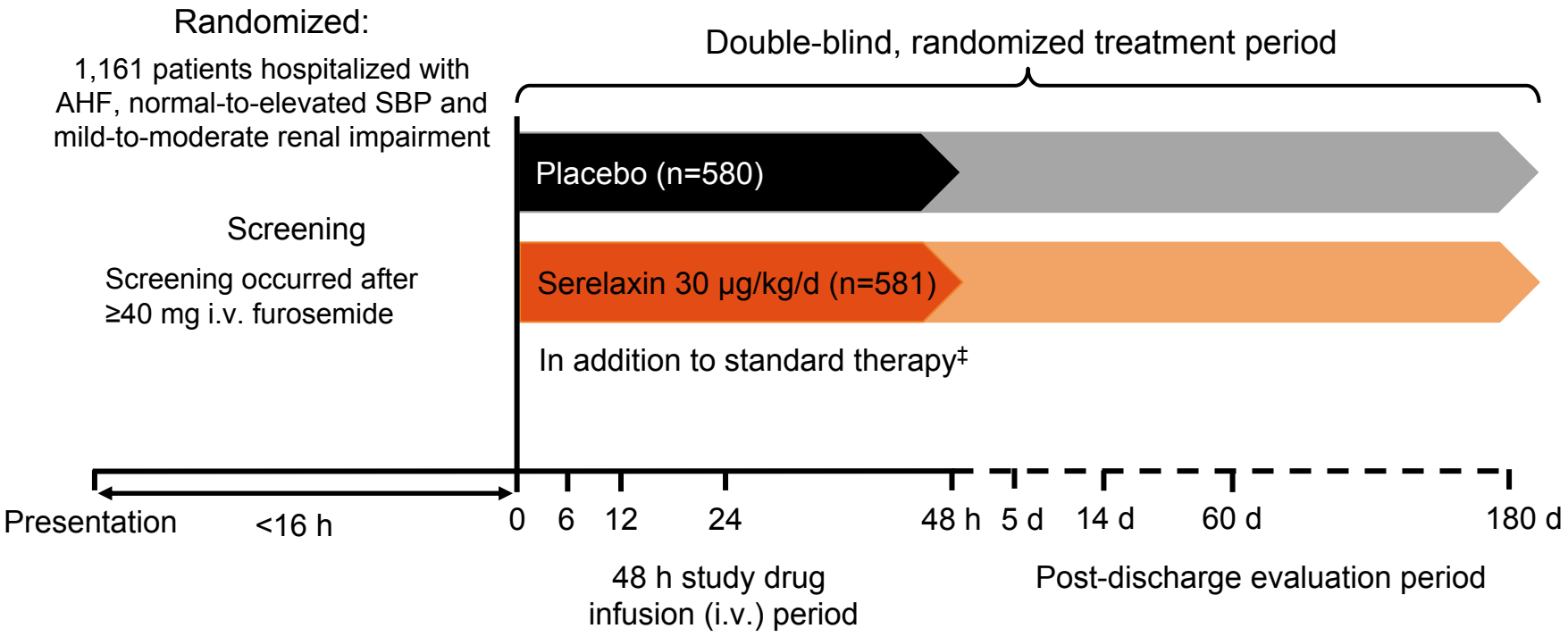
Disclosures

- M.M. received consulting income from Novartis, Amgen, Bayer, Daiichi-Sankyo, Servier and Trevena and received speaker honoraria from Abbott Vascular and Novartis
- P.P. received consulting income from Abbott Vascular, Amgen, Bayer, J&J, Novartis, Servier, Cardiorentis, Vifor, Cibiem, Momentum Research and Respicardia; received speaker honoraria from Abbott Vascular, Novartis, Servier, Vifor, Pfizer, Merck-Serono and Boehringer Ingelheim and received research grant support from Vifor
- G.C. and B.D. are employees of Momentum Research, which has received research grants from Novartis, Corthera Inc. (a Novartis Company), Sorbent Therapeutics, ChanRx, Amgen, Cardio3 Biosciences, Trevena and Anexon and have received travel support from Momentum Research
- G.M.F. received consulting income from Novartis, Amgen, Otsuka and Trevena; received research grant support from Amgen and Otsuka; received payment for participation in review activities (e.g. data monitoring boards, endpoint committee, etc.) from Novartis and received payment for development of educational presentations from Novartis
- G.F. received consulting income from Corthera Inc. (a Novartis company), Bayer and Cardiorentis; received speaker honoraria from Novartis and received research grant support from Amgen, Nanosphere and the European Union
- B.H.G. received consulting income from Novartis, Celladon and Zensun; received payment for participation in review activities (e.g. data monitoring boards, endpoint committee, etc.) from St. Jude's Medical, Actelion, Amgen, Bayer and Gambro; and received payment for development of educational presentations from Novartis
- T.A.H. and T.S. are employees of Novartis, and receive salary and stock options from Novartis Pharmaceuticals Corporation and Novartis Pharma AG, respectively
- E.U. was former employee of the sponsor, Corthera Inc. (a Novartis Company)
- A.A.V. received consulting income from Novartis; received speaker honoraria from Novartis and received research grant support from Novartis
- J.R.T. received consulting income from Novartis, Trevena and Amgen/Cytokinetics and received research grant support from Novartis and Amgen/Cytokinetics

RELAX-AHF: study design

- A Phase III, multicentre, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of serelaxin, in addition to standard therapy, in subjects hospitalized for AHF



‡Standard therapy permitted at physician's discretion
AHF=acute heart failure; d=day; h=hour; i.v.=intravenous; SBP=systolic blood pressure
Teerlink et al. Lancet 2013;381:29–39; Ponikowski et al. Am Heart J 2012;163:149–55; ClinicalTrials.gov identifier: NCT00520806

Summary of the RELAX-AHF results

- Serelaxin, compared with placebo:
  - improved the primary efficacy endpoint of dyspnoea relief through Day 5 assessed by the Visual Analogue Scale AUC (p=0.007)
  - provided a numerical increase of the proportion of patients reporting moderately or markedly improved dyspnoea (Likert scale) at 6, 12 and 24 hours (p=0.70)
  - had no effect on secondary efficacy endpoints (CV death or rehospitalization for HF or renal failure through Day 60, or days alive and out of hospital to Day 60)
  - reduced CV (efficacy endpoint) and all-cause 180 Day mortality (safety endpoint) by 37% (HRs [95%CIs], 0.63 [0.41, 0.96], p=0.028 and 0.63 [0.43, 0.93], p=0.02, respectively)

AHF=acute heart failure; AUC=area under the curve; CI=confidence interval; CV=cardiovascular; HF=heart failure; HR=hazard ratio; SBP=systolic blood pressure

Teerlink et al. Lancet 2013;381:29–39

RELAX-AHF: subgroup analyses

- Patients hospitalized for AHF differ with respect to many clinical characteristics
- The aim of the present analysis is to compare the effects of serelaxin versus placebo in multiple pre-specified and other subgroups of interest, with respect to:
  - the two primary endpoints of dyspnoea relief (VAS and Likert scale)
  - the secondary endpoint of cardiovascular (CV) death or rehospitalization for heart failure or renal failure through day 60
  - CV death and all-cause death through day 180
- The possible differential effect of serelaxin was tested using a separate regression model for each outcome and covariate

AHF=acute heart failure

Patients' characteristics at baseline

Characteristic	Placebo (N=580)	Serelaxin (N=581)
Male, %	62	63
Age, %		
≥65 years	79	75
≥75 years	49	46
Region, %		
Eastern Europe	49	48
Western Europe	17	18
South America	6	6
North America	10	10
Israel	18	18
Race, %		
White / Caucasian	95	94
Other	5	6
Hospitalization for heart failure in past year, %	31	37
Systolic blood pressure ≥140 mmHg, (N) %	(N=578) 51	(N=577) 48
Heart rate ≥80 bpm, %	49	46
LVEF <40%, (N) %	(N=539) 55	(N=552) 55
History of ischaemic heart disease, %	53	51
History of ICD or CRT, %	24	26
History of diabetes mellitus, %	47	48
History of atrial fibrillation, %	53	51
Atrial fibrillation at screening, (N) %	(N=579) 42	(N=580) 40

CRT=cardiac resynchronization therapy; ICD= implantable cardioverter defibrillator; LVEF=left ventricular ejection fraction

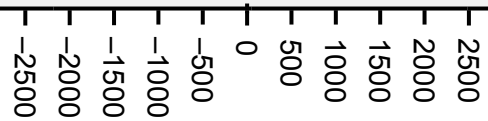
Patients' characteristics at baseline (continued)

Characteristic	Placebo (N=580)	Serelaxin (N=581)
ACEI/ARB use at baseline, %	69	67
Beta-blocker use at baseline, %	70	67
Mineralocorticoid receptor antagonist use at baseline, %	30	33
Intravenous nitrates at baseline, %	7	7
Lymphocytes at baseline ≤12%, (N) %	(N=536) 24	(N=535) 21
Troponin T at baseline, (N) %	(N=541)	(N=541)
≤0.024 µg/L	31	33
0.025–0.045 µg/L	36	34
>0.045 µg/L	33	33
NT-proBNP at baseline, (N) %	(N=551)	(N=550)
<5000 ng/L	51	52
≥5000 ng/L	49	48
≤3346 ng/L	34	32
3347–7281 ng/L	32	35
>7281 ng/L	34	33
Cystatin C at baseline, (N) %	(N=551)	(N=550)
≤1.26 mg/L	33	34
1.27–1.65 mg/L	35	33
>1.65 mg/L	33	33
eGFR at baseline, (N) %	(N=568)	(N=564)
<60 ml/min/1.73m^2	72	73
<50 ml/min/1.73m^2	48	48

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; eGFR=estimated glomerular filtration rate; NT-proBNP=N-terminal prohormone B-type natriuretic peptide

RELAX-AHF subgroup analyses: Dyspnoea VAS AUC by general baseline characteristics

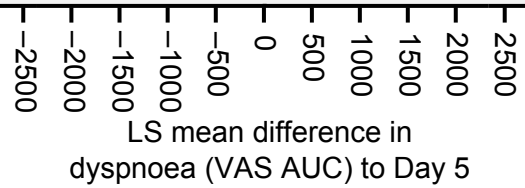
Subgroup		Placebo Mean (SD)	Serelaxin Mean (SD)	LS mean difference Estimate (95%CI)	Interaction P value
Total population		2308 (3082)	2756 (2588)	448 (120, 775)	
Gender	Male	2194 (3129)	2635 (2585)	441 (26, 855)	0.92
	Female	2491 (3003)	2965 (2586)	474 (–61, 1009)	
Age	<65 years	2325 (3210)	2635 (2583)	310 (–381, 1001)	0.65
	≥65 years	2304 (3052)	2796 (2592)	492 (119, 866)	
	<75 years	2484 (3042)	2676 (2482)	192 (–260, 644)	0.11
	≥75 years	2125 (3118)	2850 (2711)	725 (249, 1202)	
Region	Eastern Europe	2236 (3046)	2509 (2478)	273 (–197, 743)	0.85
	Western Europe	1924 (2853)	2503 (2919)	579 (–201, 1358)	
	South America	2771 (3441)	3675 (3058)	904 (–419, 2226)	
	North America	2428 (3337)	2878 (2752)	449 (–594, 1493)	
	Israel	2644 (3123)	3295 (2132)	651 (–117, 1419)	
Race	White / Caucasian	2325 (3032)	2701 (2533)	376 (38, 713)	0.10
	Other	1967 (3996)	3563 (3235)	1596 (199, 2994)	
HF past year hospitalization	Yes	2241 (3231)	2729 (2502)	488 (–75, 1051)	0.88
	No	2338 (3016)	2771 (2641)	433 (28, 838)	
Time to randomization	<6 h	2178 (2910)	2797 (2587)	620 (139, 1100)	0.34
	≥6 h	2418 (3221)	2718 (2594)	300 (–149, 749)	



AUC=area under the curve; HF=heart failure; LS=least squares; VAS=visual analogue scale; SD=standard deviation

RELAX-AHF subgroup analyses: Dyspnoea VAS AUC by clinical signs and comorbidities

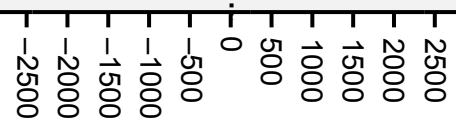
Subgroup		Placebo Mean (SD)	Serelaxin Mean (SD)	LS mean difference Estimate (95%CI)	Interaction P value
Total population		2308 (3082)	2756 (2588)	448 (120, 775)	
SBP	<140 mmHg	2207 (3026)	2642 (2580)	436 (–27, 899)	0.82
	≥140 mmHg	2403 (3139)	2916 (2592)	513 (47, 980)	
Heart rate	<80 bpm	2496 (3106)	2837 (2551)	341 (–111, 793)	0.54
	≥80 bpm	2112 (3050)	2660 (2633)	548 (72, 1024)	
LVEF	<40%	2266 (3043)	2644 (2467)	378 (–71, 828)	0.83
	≥40%	2400 (2981)	2855 (2697)	454 (–41, 949)	
History of IHD	Yes	2391 (3118)	2704 (2664)	313 (–142, 769)	0.40
	No	2215 (3044)	2809 (2511)	594 (121, 1067)	
History of ICD or CRT	Yes	1921 (3511)	2829 (2479)	908 (256, 1559)	0.11
	No	2432 (2924)	2729 (2629)	297 (–82, 676)	
History of DM	Yes	2286 (3217)	2999 (2584)	713 (238, 1188)	0.13
	No	2328 (2963)	2531 (2576)	204 (–248, 655)	
History of AF	Yes	1905 (3199)	2524 (2642)	619 (167, 1071)	0.26
	No	2754 (2888)	2998 (2513)	243 (–226, 713)	
AF at screening	Yes	1959 (3136)	2501 (2593)	541 (32, 1050)	0.59
	No	2567 (3025)	2926 (2579)	359 (–68, 786)	



AF=atrial fibrillation; AUC=area under the curve; CRT=cardiac resynchronization therapy; DM=diabetes mellitus; ICD=implantable cardioverter defibrillator; IHD=ischaemic heart disease; LS=least squares; LVEF=left ventricular ejection fraction; SBP=systolic blood pressure; SD=standard deviation; VAS=visual analogue scale

RELAX-AHF subgroup analyses: Dyspnoea VAS AUC by baseline therapies

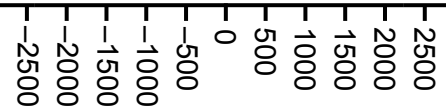
Subgroup		Placebo Mean (SD)	Serelaxin Mean (SD)	LS mean difference Estimate (95%CI)	Interaction P value
Total population		2308 (3082)	2756 (2588)	448 (120, 775)	
ACEI/ARB	Yes	2402 (2933)	2646 (2586)	244 (–154, 641)	0.08
	No	2102 (3384)	2980 (2585)	878 (300, 1456)	
Beta-blocker	Yes	2272 (2988)	2638 (2503)	366 (–30, 762)	0.52
	No	2393 (3300)	2991 (2742)	598 (14, 1182)	
Mineralo-corticoid receptor antagonist	Yes	2406 (3066)	2512 (2314)	106 (–480, 691)	0.16
	No	2266 (3092)	2876 (2708)	610 (214, 1006)	
Intravenous nitrates	Yes	2210 (3708)	3018 (3597)	808 (–435, 2050)	0.56
	No	2316 (3032)	2737 (2504)	421 (81, 761)	



ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; AUC=area under the curve; LS=least squares; SD=standard deviation; VAS=visual analogue scale

RELAX-AHF subgroup analyses: Dyspnoea VAS AUC by biomarkers at baseline

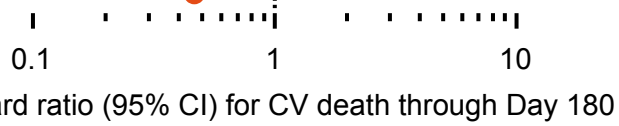
Subgroup		Placebo Mean (SD)	Serelaxin Mean (SD)	LS mean difference Estimate (95%CI)	Interaction P value
Total population		2308 (3082)	2756 (2588)	448 (120, 775)	
Lymphocytes	≤12%	2149 (3209)	2488 (3021)	339 (–387, 1065)	0.87
	>12%	2405 (3007)	2812 (2486)	407 (21, 793)	
Troponin T	≤0.024 µg/L	2808 (2980)	3126 (2494)	318 (–289, 925)	0.91
	0.025–0.045 µg/L	2031 (2962)	2527 (2718)	496 (–81, 1072)	
	>0.045 µg/L	2335 (3317)	2707 (2563)	372 (–223, 967)	
NT-proBNP	<5000 ng/L	2444 (2991)	2782 (2529)	338 (–132, 808)	0.69
	≥5000 ng/L	2321 (3183)	2798 (2661)	477 (–8, 961)	
	≤3346 ng/L	2452 (2747)	2879 (2326)	426 (–158, 1011)	0.39
	3347–7281 ng/L	2253 (3391)	2939 (2770)	686 (102, 1270)	
	>7281 ng/L	2434 (3125)	2539 (2633)	106 (–479, 691)	
Cystatin C	≤1.26 mg/L	2567 (2980)	2904 (2421)	337 (–244, 919)	0.96
	1.27–1.65 mg/L	2102 (3484)	2502 (2920)	400 (–180, 980)	
	>1.65 mg/L	2497 (2712)	2955 (2397)	458 (–130, 1046)	
eGFR	<60 ml/min/1.73 m^2	2270 (2947)	2774 (2546)	504 (113, 895)	0.55
	≥60 ml/min/1.73 m^2	2524 (3369)	2804 (2746)	280 (–350, 910)	
	<50 ml/min/1.73 m^2	2353 (3036)	2754 (2580)	401 (–80, 882)	0.83
	≥50 ml/min/1.73 m^2	2331 (3107)	2807 (2622)	476 (17, 935)	



AUC=area under the curve; eGFR=estimated glomerular filtration rate; LS=least squares; NT-proBNP=N-terminal prohormone B-type natriuretic peptide; SD=standard deviation; VAS=visual analogue scale

RELAX-AHF subgroup analyses: CV death by general characteristics at baseline

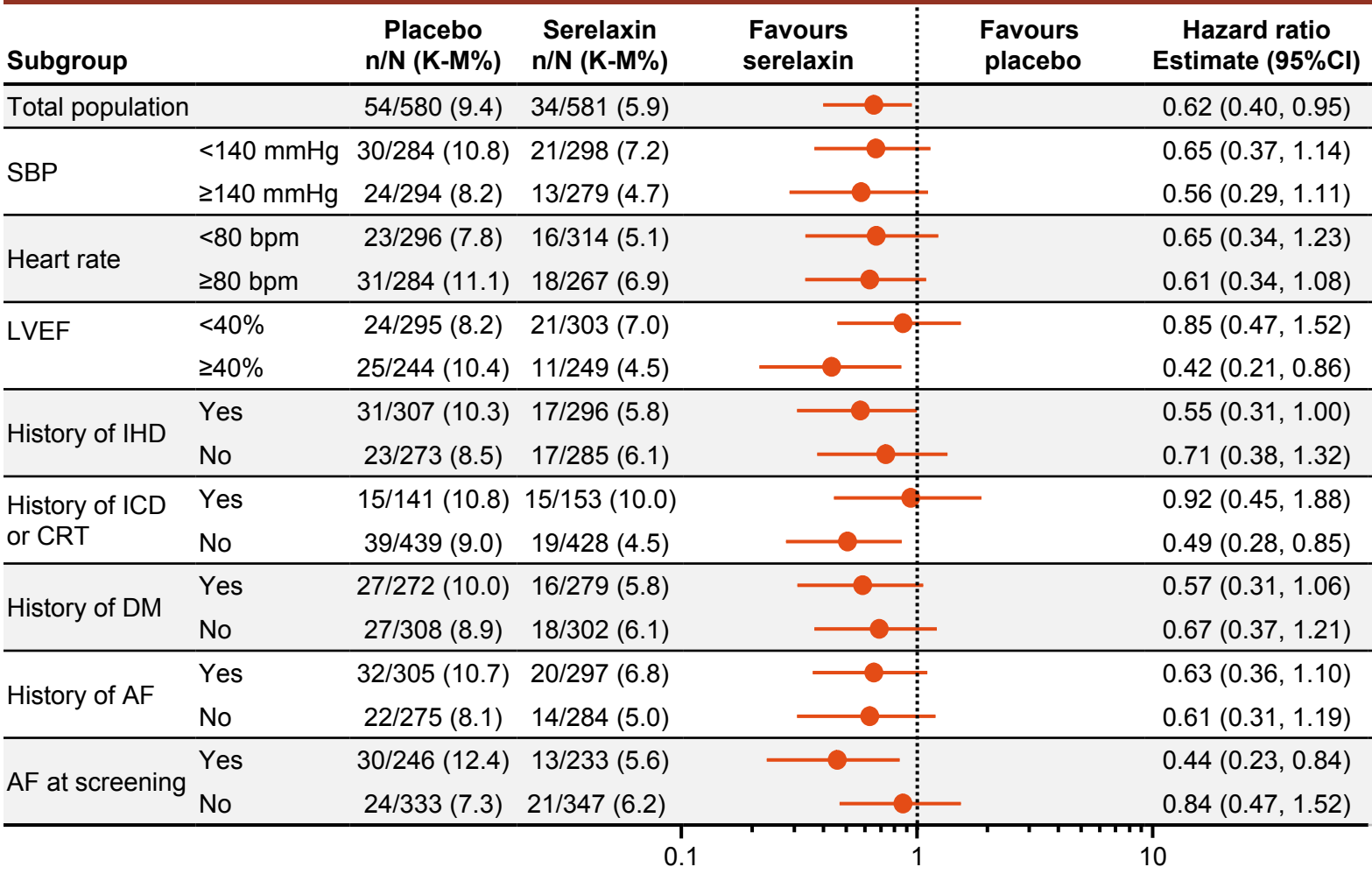
Subgroup		Placebo n/N (K-M%)	Serelaxin n/N (K-M%)	Hazard ratio Estimate (95%CI)	Interaction P-value
Total population		54/580 (9.4)	34/581 (5.9)	0.62 (0.40, 0.95)	
Gender	Male	32/357 (9.1)	25/368 (6.9)	0.75 (0.44, 1.26)	0.23
	Female	22/223 (10.0)	9/213 (4.3)	0.42 (0.19, 0.92)	
Age	<65 years	9/119 (7.6)	9/145 (6.3)	0.82 (0.33, 2.07)	0.50
	≥65 years	45/461 (9.9)	25/436 (5.8)	0.58 (0.35, 0.94)	
	<75 years	18/296 (6.1)	20/315 (6.5)	1.05 (0.55, 1.98)	**0.03**
	≥75 years	36/284 (12.9)	14/266 (5.3)	0.40 (0.22, 0.74)	
Region	Eastern Europe	32/282 (11.5)	22/280 (7.9)	0.68 (0.40, 1.18)	0.75
	Western Europe	7/101 (7.1)	2/103 (2.0)	0.27 (0.06, 1.30)	
	South America	4/37 (10.9)	3/34 (8.8)	0.82 (0.18, 3.65)	
	North America	4/55 (7.3)	4/59 (6.9)	0.91 (0.23, 3.64)	
	Israel	7/105 (6.8)	3/105 (2.9)	0.43 (0.11, 1.66)	
Race	White / Caucasian	51/552 (9.4)	32/544 (6.0)	0.63 (0.40, 0.98)	0.76
	Other	3/28 (10.7)	2/37 (5.5)	0.47 (0.08, 2.81)	
Hospitalization for HF in past year	Yes	13/181 (7.2)	19/216 (9.0)	1.26 (0.62, 2.54)	**0.01**
	No	41/399 (10.4)	15/365 (4.1)	0.39 (0.21, 0.70)	
Time to randomization	<6 h	23/266 (8.7)	20/275 (7.4)	0.84 (0.46, 1.53)	0.16
	≥6 h	31/314 (10.0)	14/306 (4.6)	0.45 (0.24, 0.85)	



HF=heart failure

RELAX-AHF subgroup analyses: CV death by clinical signs and comorbidities

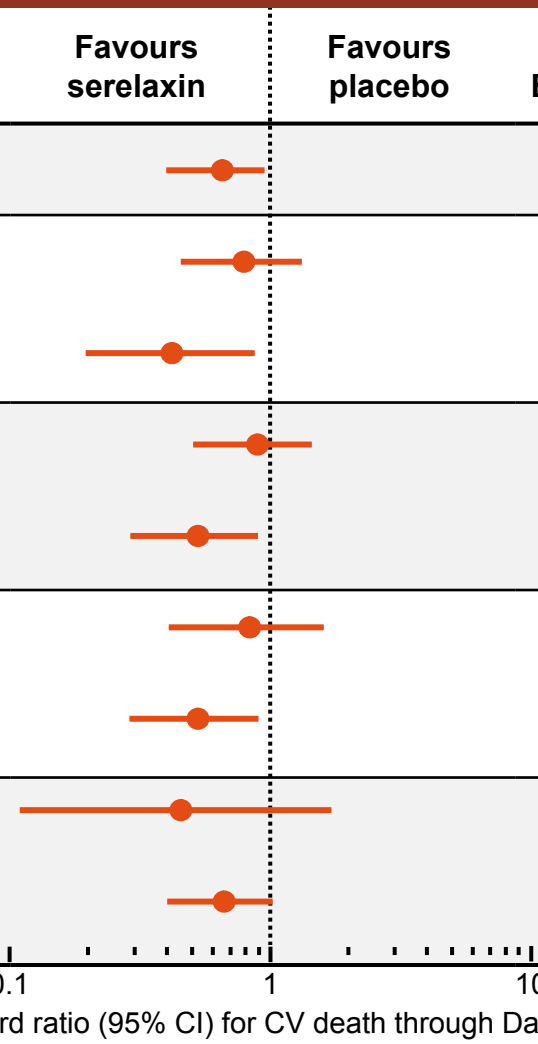
Subgroup		Placebo n/N (K-M%)	Serelaxin n/N (K-M%)	Hazard ratio Estimate (95%CI)	Interaction P-value
Total population		54/580 (9.4)	34/581 (5.9)	0.62 (0.40, 0.95)	
SBP	<140 mmHg	30/284 (10.8)	21/298 (7.2)	0.65 (0.37, 1.14)	0.74
	≥140 mmHg	24/294 (8.2)	13/279 (4.7)	0.56 (0.29, 1.11)	
Heart rate	<80 bpm	23/296 (7.8)	16/314 (5.1)	0.65 (0.34, 1.23)	0.88
	≥80 bpm	31/284 (11.1)	18/267 (6.9)	0.61 (0.34, 1.08)	
LVEF	<40%	24/295 (8.2)	21/303 (7.0)	0.85 (0.47, 1.52)	0.14
	≥40%	25/244 (10.4)	11/249 (4.5)	0.42 (0.21, 0.86)	
History of IHD	Yes	31/307 (10.3)	17/296 (5.8)	0.55 (0.31, 1.00)	0.58
	No	23/273 (8.5)	17/285 (6.1)	0.71 (0.38, 1.32)	
History of ICD or CRT	Yes	15/141 (10.8)	15/153 (10.0)	0.92 (0.45, 1.88)	0.17
	No	39/439 (9.0)	19/428 (4.5)	0.49 (0.28, 0.85)	
History of DM	Yes	27/272 (10.0)	16/279 (5.8)	0.57 (0.31, 1.06)	0.73
	No	27/308 (8.9)	18/302 (6.1)	0.67 (0.37, 1.21)	
History of AF	Yes	32/305 (10.7)	20/297 (6.8)	0.63 (0.36, 1.10)	0.95
	No	22/275 (8.1)	14/284 (5.0)	0.61 (0.31, 1.19)	
AF at screening	Yes	30/246 (12.4)	13/233 (5.6)	0.44 (0.23, 0.84)	0.14
	No	24/333 (7.3)	21/347 (6.2)	0.84 (0.47, 1.52)	



AF=atrial fibrillation; AUC=area under the curve;
CRT=cardiac resynchronization therapy;
DM=diabetes mellitus; ICD=implantable cardioverter defibrillator;
IHD=ischaemic heart disease; LVEF=left ventricular ejection fraction; SBP=systolic blood pressure

RELAX-AHF subgroup analyses: CV death by baseline therapies

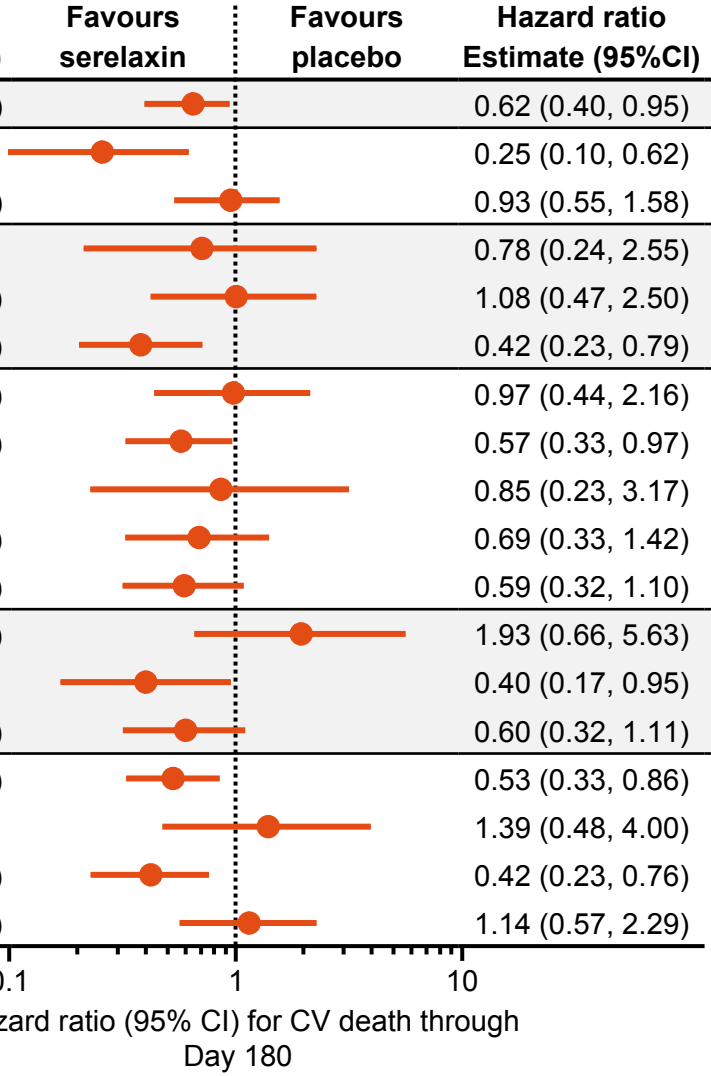
Subgroup		Placebo n/N (K-M%)	Serelaxin n/N (K-M%)	Hazard ratio Estimate (95%CI)	Interaction P-value
Total population		54/580 (9.4)	34/581 (5.9)	0.62 (0.40, 0.95)	
ACEI/ARB	Yes	32/398 (8.1)	24/390 (6.2)	0.76 (0.45, 1.30)	0.19
	No	22/182 (12.3)	10/191 (5.3)	0.41 (0.20, 0.88)	
Beta-blocker	Yes	32/407 (8.0)	26/387 (6.8)	0.85 (0.50, 1.42)	**0.04**
	No	22/173 (12.7)	8/194 (4.2)	0.31 (0.14, 0.71)	
Mineralo-corticoid receptor antagonist	Yes	18/173 (10.5)	16/192 (8.5)	0.81 (0.41, 1.59)	0.30
	No	36/407 (9.0)	18/389 (4.7)	0.51 (0.29, 0.89)	
Intravenous nitrates	Yes	7/42 (17.0)	3/39 (7.8)	0.44 (0.11, 1.70)	0.60
	No	47/538 (8.8)	31/542 (5.8)	0.65 (0.41, 1.02)	



ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker

RELAX-AHF subgroup analyses: CV death by biomarkers at baseline

Subgroup		Placebo n/N (K-M%)	Serelaxin n/N (K-M%)	Hazard ratio Estimate (95%CI)	Interaction P-value
Total population		54/580 (9.4)	34/581 (5.9)	0.62 (0.40, 0.95)	
Lymphocytes	≤12%	25/127 (20.2)	6/110 (5.6)	0.25 (0.10, 0.62)	**0.01**
	>12%	28/409 (6.9)	27/425 (6.4)	0.93 (0.55, 1.58)	
Troponin T	≤0.024 µg/L	6/165 (3.7)	5/176 (2.8)	0.78 (0.24, 2.55)	
	0.025–0.045 µg/L	11/196 (5.7)	11/182 (6.1)	1.08 (0.47, 2.50)	0.19
	>0.045 µg/L	32/180 (18.0)	14/175 (8.2)	0.42 (0.23, 0.79)	
NT-proBNP	<5000 ng/L	12/279 (4.3)	12/288 (4.2)	0.97 (0.44, 2.16)	0.28
	≥5000 ng/L	37/272 (13.9)	21/262 (8.1)	0.57 (0.33, 0.97)	
	≤3346 ng/L	5/190 (2.7)	4/177 (2.3)	0.85 (0.23, 3.17)	
	3347–7281 ng/L	17/174 (9.9)	13/194 (6.8)	0.69 (0.33, 1.42)	0.87
	>7281 ng/L	27/187 (14.8)	16/179 (9.0)	0.59 (0.32, 1.10)	
Cystatin C	≤1.26 mg/L	5/180 (2.8)	10/189 (5.4)	1.93 (0.66, 5.63)	
	1.27–1.65 mg/L	18/191 (9.7)	7/180 (3.9)	0.40 (0.17, 0.95)	0.07
	>1.65 mg/L	26/180 (14.6)	16/181 (8.9)	0.60 (0.32, 1.11)	
eGFR	<60 ml/min/1.73 m^2	46/408 (11.5)	25/409 (6.2)	0.53 (0.33, 0.86)	0.11
	≥60 ml/min/1.73 m^2	6/160 (3.8)	8/155 (5.2)	1.39 (0.48, 4.00)	
	<50 ml/min/1.73 m^2	37/272 (13.9)	16/268 (6.1)	0.42 (0.23, 0.76)	**0.03**
	≥50 ml/min/1.73 m^2	15/296 (5.1)	17/296 (5.8)	1.14 (0.57, 2.29)	



eGFR=estimated glomerular filtration rate;
NT-proBNP=N-terminal prohormone B-type natriuretic peptide

Summary

- The effects of serelaxin versus placebo were homogenous across multiple subgroups with respect to the endpoints of the study, including 180-day CV mortality
- Potentially larger mortality benefits were seen in the patients with:
  - older age
  - no previous HF hospitalization
  - not treated with beta-blockers at the time of randomization
  - signs of inflammation (lymphopenia)
  - more severe renal impairment
- The present study is underpowered for the subgroup analyses, particularly for mortality data. These results must be considered as hypothesis-generating.

RELAX-AHF subgroups analysis: Simultaneous publication in the *European Heart Journal*

European Heart Journal
doi:10.1093/eurheartj/eht371

FASTTRACK CLINICAL RESEARCH

Heart failure/cardiomyopathy

Effects of serelaxin in subgroups of patients with acute heart failure: results from RELAX-AHF

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Received 5 July 2013; revised 8 August 2013; accepted 9 August 2013

Study Organization

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- **Steering Committee:** KF Adams (US), M Dorobantu (RO), L Grinfeld (AR), G Jondeau (FR), A Marmor (IL), J Masip (ES), PS Pang (US), K Werdan (DE)
- **DSMB:** BM Massie-Chair (US), M Böhm (DE), E Davis (US), G Francis (US), S Goldstein (US)
- **Sponsor:** Corthera Inc. (a Novartis affiliate company)
- **Coordinating Center:** Momentum Research Inc.

RELAX-AHF Investigators

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BACK-UP SLIDES

RELAX-AHF: key inclusion criteria

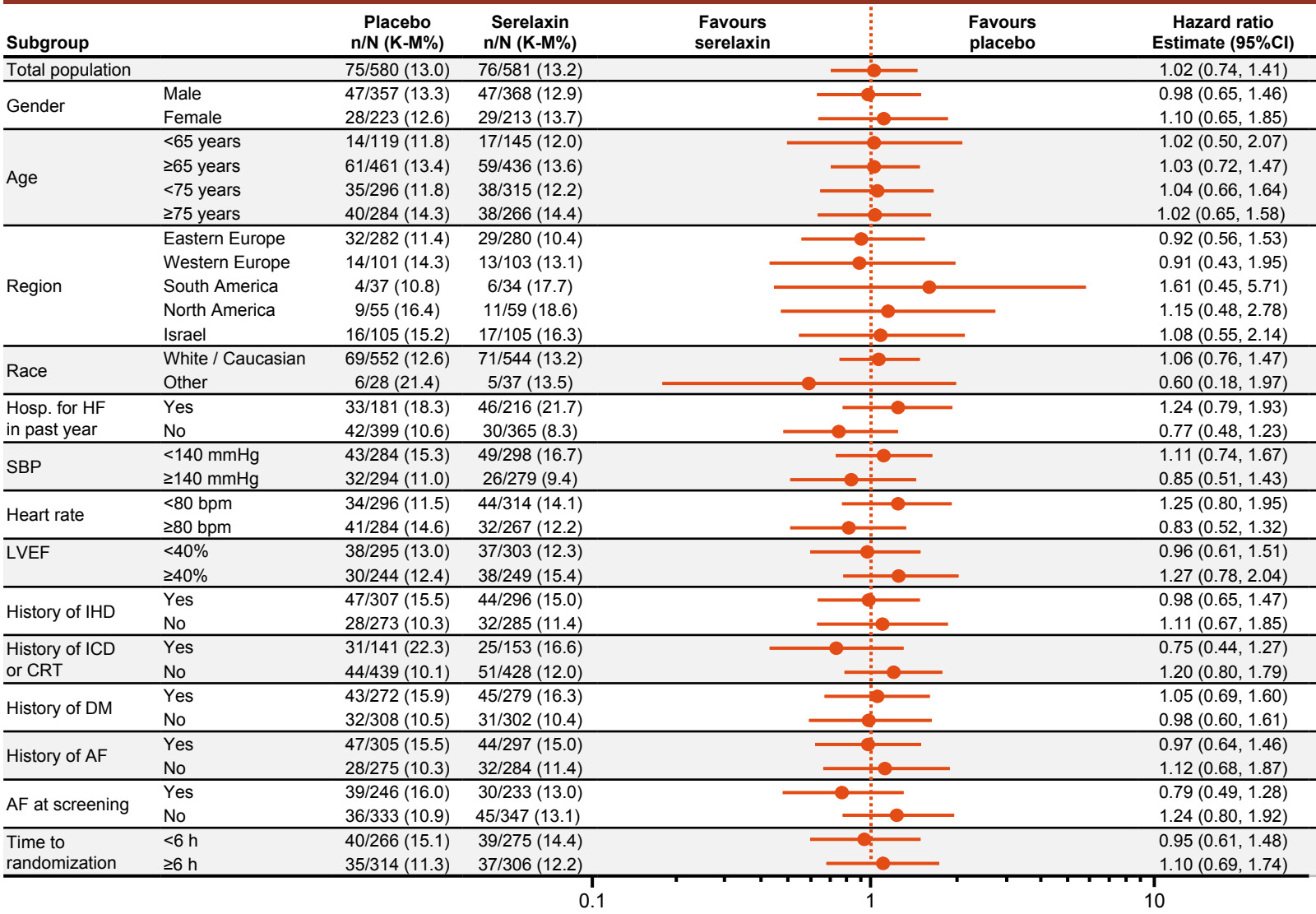
- SBP >125 mmHg
- Hospitalized for AHF, defined as including all of the following at screening:
  - dyspnoea at rest or with minimal exertion
  - pulmonary congestion by chest X-ray
  - BNP ≥350 pg/mL or NT-proBNP ≥1400 pg/mL
- Able to be randomized within 16 hours from hospital presentation (including the ED)
- Received i.v. furosemide ≥40 mg (or equivalent) between presentation to the hospital and screening
- Mild-to-moderate renal impairment (eGFR 30–75 mL/min/1.73 m^2)

AHF=acute heart failure; BNP=B-type natriuretic peptide; ED=emergency department; eGFR =estimated glomerular filtration rate; i.v.=intravenous; NT-proBNP=N-terminal pro B-type natriuretic peptide; SBP=systolic blood pressure

Teerlink et al. Lancet 2013;381:29–39; Ponikowski et al. Am Heart J 2012;163:149–55

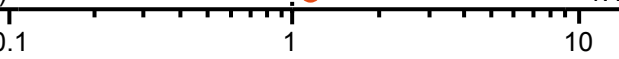
RELAX-AHF subgroup analyses: CV death or rehospitalization for HF or RF through Day 60

Subgroup		Placebo n/N (K-M%)	Serelaxin n/N (K-M%)	Hazard ratio Estimate (95%CI)	Interaction P value
Total population		75/580 (13.0)	76/581 (13.2)	1.02 (0.74, 1.41)	
Gender	Male	47/357 (13.3)	47/368 (12.9)	0.98 (0.65, 1.46)	0.73
	Female	28/223 (12.6)	29/213 (13.7)	1.10 (0.65, 1.85)	
Age	<65 years	14/119 (11.8)	17/145 (12.0)	1.02 (0.50, 2.07)	0.99
	≥65 years	61/461 (13.4)	59/436 (13.6)	1.03 (0.72, 1.47)	
	<75 years	35/296 (11.8)	38/315 (12.2)	1.04 (0.66, 1.64)	0.95
	≥75 years	40/284 (14.3)	38/266 (14.4)	1.02 (0.65, 1.58)	
Region	Eastern Europe	32/282 (11.4)	29/280 (10.4)	0.92 (0.56, 1.53)	0.93
	Western Europe	14/101 (14.3)	13/103 (13.1)	0.91 (0.43, 1.95)	
	South America	4/37 (10.8)	6/34 (17.7)	1.61 (0.45, 5.71)	
	North America	9/55 (16.4)	11/59 (18.6)	1.15 (0.48, 2.78)	
	Israel	16/105 (15.2)	17/105 (16.3)	1.08 (0.55, 2.14)	
Race	White / Caucasian	69/552 (12.6)	71/544 (13.2)	1.06 (0.76, 1.47)	0.37
	Other	6/28 (21.4)	5/37 (13.5)	0.60 (0.18, 1.97)	
Hosp. for HF in past year	Yes	33/181 (18.3)	46/216 (21.7)	1.24 (0.79, 1.93)	0.15
	No	42/399 (10.6)	30/365 (8.3)	0.77 (0.48, 1.23)	
SBP	<140 mmHg	43/284 (15.3)	49/298 (16.7)	1.11 (0.74, 1.67)	0.44
	≥140 mmHg	32/294 (11.0)	26/279 (9.4)	0.85 (0.51, 1.43)	
Heart rate	<80 bpm	34/296 (11.5)	44/314 (14.1)	1.25 (0.80, 1.95)	0.22
	≥80 bpm	41/284 (14.6)	32/267 (12.2)	0.83 (0.52, 1.32)	
LVEF	<40%	38/295 (13.0)	37/303 (12.3)	0.96 (0.61, 1.51)	0.41
	≥40%	30/244 (12.4)	38/249 (15.4)	1.27 (0.78, 2.04)	
History of IHD	Yes	47/307 (15.5)	44/296 (15.0)	0.98 (0.65, 1.47)	0.70
	No	28/273 (10.3)	32/285 (11.4)	1.11 (0.67, 1.85)	
History of ICD or CRT	Yes	31/141 (22.3)	25/153 (16.6)	0.75 (0.44, 1.27)	0.17
	No	44/439 (10.1)	51/428 (12.0)	1.20 (0.80, 1.79)	
History of DM	Yes	43/272 (15.9)	45/279 (16.3)	1.05 (0.69, 1.60)	0.83
	No	32/308 (10.5)	31/302 (10.4)	0.98 (0.60, 1.61)	
History of AF	Yes	47/305 (15.5)	44/297 (15.0)	0.97 (0.64, 1.46)	0.65
	No	28/275 (10.3)	32/284 (11.4)	1.12 (0.68, 1.87)	
AF at screening	Yes	39/246 (16.0)	30/233 (13.0)	0.79 (0.49, 1.28)	0.18
	No	36/333 (10.9)	45/347 (13.1)	1.24 (0.80, 1.92)	
Time to randomization	<6 h	40/266 (15.1)	39/275 (14.4)	0.95 (0.61, 1.48)	0.66
	≥6 h	35/314 (11.3)	37/306 (12.2)	1.10 (0.69, 1.74)	



RELAX-AHF subgroup analyses: CV death or rehospitalization for HF or RF through Day 60

Subgroup		Placebo n/N (K-M%)	Serelaxin n/N (K-M%)	Hazard ratio Estimate (95%CI)	Interaction P value
Total population		75/580 (13.0)	76/581 (13.2)	1.02 (0.74, 1.41)	
ACEI/ARB use at baseline	Yes	42/398 (10.6)	51/390 (13.2)	1.27 (0.84, 1.91)	0.09
	No	33/182 (18.3)	25/191 (13.2)	0.71 (0.42, 1.19)	
Beta-blocker use at baseline	Yes	46/407 (11.4)	49/387 (12.8)	1.14 (0.76, 1.71)	0.32
	No	29/173 (16.8)	27/194 (14.1)	0.82 (0.49, 1.38)	
MRA use at baseline	Yes	21/173 (12.2)	32/192 (17.0)	1.44 (0.83, 2.50)	0.12
	No	54/407 (13.4)	44/389 (11.4)	0.85 (0.57, 1.26)	
IV nitrates at baseline	Yes	8/42 (19.5)	5/39 (12.8)	0.63 (0.21, 1.93)	0.38
	No	67/538 (12.5)	71/542 (13.3)	1.07 (0.77, 1.49)	
Lymphocytes at baseline	≤12%	27/127 (21.6)	15/110 (13.8)	0.61 (0.32, 1.14)	0.13
	>12%	44/409 (10.8)	49/425 (11.6)	1.09 (0.73, 1.64)	
Troponin T at baseline	≤0.024 µg/L	17/165 (10.4)	15/176 (8.5)	0.81 (0.41, 1.63)	0.75
	0.025–0.045 µg/L	23/196 (11.8)	24/182 (13.2)	1.15 (0.65, 2.03)	
	>0.045 µg/L	30/180 (16.8)	30/175 (17.5)	1.04 (0.63, 1.73)	
NT-proBNP at baseline	<5000 ng/L	29/279 (10.4)	32/288 (11.2)	1.08 (0.65, 1.79)	0.91
	≥5000 ng/L	42/272 (15.6)	42/262 (16.1)	1.04 (0.68, 1.60)	
	≤3346 ng/L	18/190 (9.5)	10/177 (5.7)	0.58 (0.27, 1.26)	0.16
	3347–7281 ng/L	22/174 (12.7)	34/194 (17.8)	1.45 (0.85, 2.47)	
	>7281 ng/L	31/187 (16.8)	30/179 (16.8)	1.01 (0.61, 1.68)	
Cystatin C at baseline	≤1.26 mg/L	13/180 (7.3)	16/189 (8.6)	1.19 (0.57, 2.47)	0.89
	1.27–1.65 mg/L	22/191 (11.7)	20/180 (11.2)	0.95 (0.52, 1.74)	
	>1.65 mg/L	36/180 (20.1)	38/181 (21.1)	1.08 (0.69, 1.71)	
eGFR at baseline	<60 ml/min/1.73m^2	59/408 (14.6)	53/409 (13.1)	0.90 (0.62, 1.30)	0.31
	≥60 ml/min/1.73m^2	14/160 (8.8)	18/155 (11.7)	1.35 (0.67, 2.72)	
	<50 ml/min/1.73m^2	46/272 (17.1)	40/268 (15.2)	0.89 (0.58, 1.35)	0.42
	≥50 ml/min/1.73m^2	27/296 (9.2)	31/296 (10.5)	1.16 (0.69, 1.95)	



Hazard ratio (95%CI) for CV death or rehospitalization due to heart failure or renal failure through Day 60

MRA=mineralocorticoid receptor antagonist