Supplementary Material

Worsening renal function in acute heart failure in the context of diuretic response

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Supplementary Table 1. Differences between in- and excluded patients in the current study subsets

	RELAX-AHF-2			PROTECT		
	Study subset N=5,586	Patients without available measurements N=959	P-value	Study subset N=1,698	Patients without available measurements N= 335	P-value
Age	73 ± 11	72 ± 13	**<0.001**	72 (62 – 78)	73 (63 – 80)	0.191
Sex (female), n (%)	2280 (40.8)	357 (37.2)	**0.040**	563 (33.2)	106 (31.6)	0.634
Race (white), n (%)	5265 (94.3)	751 (78.3)	**<0.001**	1628 (95.9)	296 (88.4)	**<0.001**
BMI	29 (25 – 33)	29 (25 – 33)	**0.034**	28 (24 – 32)	28 (25 – 32)	0.220
NYHA classification III/IV, n (%)*	2307 (56.9)	384 (55.3)	**0.007**	1338 (82.8)	243 (78.4)	**<0.001**
Systolic blood pressure (mmHg)	139 (130 – 150)	140 (130 – 153)	0.279	125 (110 – 140)	121 (110 – 135)	0.066
Diastolic blood pressure (mmHg)	80 (70 – 89)	78 (69 – 88)	**0.015**	75 (67 – 80)	70 (62 – 80)	**<0.001**

Heart rate (bpm)	80 (70 – 92)	78 (68 – 90)	**0.004**	80 (70 – 90)	76 (67 – 85)	**<0.001**
LVEF (%)	40 (30 – 50)	35 (27 – 50)	**0.005**	30 (23 – 40)	30 (20 – 40)	1
- <40%	2726 (51.5)	454 (54.1)	0.178	584 (72.2)	114 (68.7)	0.412
- ≥50%	1362 (25.8)	233 (27.8)	0.232	104 (12.9)	26 (15.7)	0.399
HF aetiology, n (%)			1			
Ischemic	2221 (53.8)	386 (53.8)				
Non-Ischemic	1908 (46.2)	332 (46.2)				
History of ischaemic heart disease, n (%)				1187 (70.0)	230 (68.7)	0.664
Previous hospitalisation for heart failure, n (%)**	2821 (54.1)	517 (57.2)	0.096	854 (50.3)	148 (44.2)	**0.047**
No. of hospitalisations for heart failure within previous year, n (%)			**0.001**			0.415
≥3 Hospitalisations	255 (9.2)	73 (14.4)		166 (19.5)	38 (28.1)	

1-2 Hospitalisations	1714 (61.5)	285 (56.1)		684 (80.5)	97 (71.9)	
No hospitalisations	816 (29.3)	150 (29.5)				
Length of hospital stay (days)	7 (6 – 11)	3 (3 – 6)	**<0.001**	8 (6 – 14)	3 (3 – 8)	**<0.001**
ACE/ARB, n (%)	3664 (69.2)	620 (68.4)	0.651	1284 (75.6)	250 (74.6)	1
Beta blocker, n (%)	3952 (74.7)	689 (76.0)	0.408	1289 (75.9)	257 (76.7)	**0.019**
MRA, n (%)	1630 (30.8)	226 (24.9)	**<0.001**	1071 (63.1)	185 (55.2)	**0.019**
Haematocrit (%)	39 (35 – 43)	38 (34 – 42)	**0.002**	40 (36 – 44)	39 (35 – 43)	**0.008**
Haemoglobin (mmol/L)	7.9 (7.0 – 8.8)	7.8 (6.8 – 8.6)	**<0.001**	12.7 (11.3 – 14.1)	12.1 (10.8 – 13.5)	**<0.001**
Sodium (mmol/L)	140 (137 – 142)	140 (137 – 142)	**0.047**	140 (137 – 142)	139 (136 – 141)	**<0.001**
Potassium (mmol/L)	4.3 (3.9 – 4.7)	4.2 (3.9 – 4.7)	**<0.001**	4.2 (3.9 – 4.6)	4.2 (3.8 – 4.6)	0.277
Creatinine (mg/dL)	1.3 (1.1 – 1.6)	1.3 (1.1 – 1.6)	0.266	1.4 (1.1 – 1.8)	1.4 (1.2 – 1.9)	0.081
eGFR (mL/min/1.73m^2)	50 (38 – 62)	51 (40 – 63)	**0.018**	46 (34 – 62)	44 (32 – 57)	**0.011**
BUN (mg/dL)	24 (19 – 32)	24 (18 – 31)	**0.033**	29 (22 – 41)	31 (23 – 45)	0.087
ALAT (U/L)	23 (16 – 36)	25 (17 – 38)	**0.003**	21 (15 – 32)	21 (15 – 31)	0.708
ASAT (U/L)	26 (20 – 36)	27 (21 – 38)	**0.027**	25 (19 – 33)	25 (19 – 33)	0.983

NT-proBNP (ng/L)	5116 (2909 – 9509)	5906 (3247 – 9788)	0.336			
BNP (ng/L)				452 (258 – 814)	407 (237 – 756)	0.364

*Available in 3,438 patients in RELAX-AHF-2 and 1,615 in PROTECT

** Ever in RELAX-AHF-2, in the past year for PROTECT

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ALAT, alanine transaminase; ASAT, aspartate aminotransferase; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; ΔePV, delta estimated plasma volume; Hb, haemoglobin; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N terminal pro brain natriuretic peptide; NYHA, New York Heart Association; WRF, worsening renal function

Supplementary Table 2. Cox regression analysis for presence/absence of WRF and good/poor diuretic response with regards to the combined endpoints*

	Univariable		Adjusted for age, sex, and baseline creatinine		Adjusted model**	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
RELAX-AHF-2						
No WRF + good DR	1.0 (Reference)	Ref	1.0 (Reference)	Ref	1.0 (Reference)	Ref
WRF + good DR	0.99 (0.80 – 1.24)	0.945	0.86 (0.71 – 1.11)	0.289	0.88 (0.68 – 1.14)	0.332
No WRF + poor DR	1.55 (1.37 – 1.76)	**<0.001**	1.43 (1.27 – 1.63)	**<0.001**	1.33 (1.16 – 1.53)	**<0.001**
WRF + poor DR	1.99 (1.66 – 2.38)	**<0.001**	1.74 (1.45 – 2.09)	**<0.001**	1.48 (1.20 – 1.81)	**<0.001**
PROTECT						
No WRF + good DR	1.0 (Reference)	Ref	1.0 (Reference)	Ref	1.0 (Reference)	Ref
WRF + good DR	1.02 (0.66 – 1.58)	0.927	1.02 (0.66 – 1.52)	0.930	1.15 (0.74 – 1.78)	0.548
No WRF + poor DR	1.81 (1.46 – 2.23)	**<0.001**	1.74 (1.41 – 2.15)	<0.001	1.50 (1.20 – 1.86)	**<0.001**
WRF + poor DR	2.45 (1.83 – 3.28)	**<0.001**	2.19 (1.63 – 2.95)	<0.001	2.00 (1.48 – 2.71)	**<0.001**

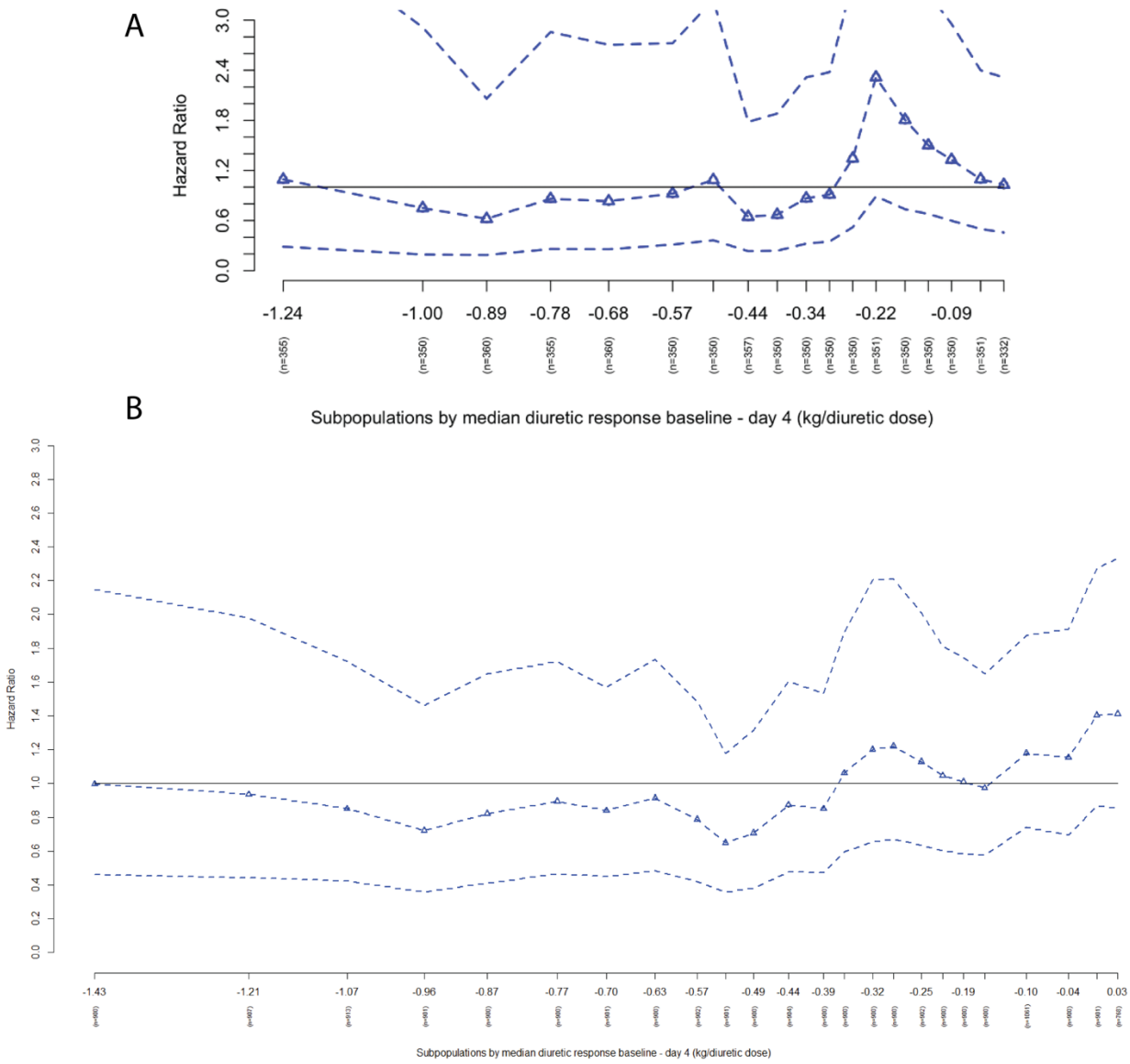
*180-day CV death or heart/renal failure hospitalisation in RELAX-AHF-2 and 60-day death from any cause or cardiovascular or renal hospitalisation in PROTECT.

**RELAX-AHF-2: adjusted for age, sex, baseline creatinine, actual study treatment, asthma/bronchitis/chronic obstructive pulmonary disease, atrial fibrillation/flutter, blood urea nitrogen, cerebrovascular accident, composite of N terminal pro brain natriuretic peptide or brain natriuretic peptide Z-score, depression, oedema, grouped geographical region, haemoglobin, known history of diabetes mellitus, peripheral arterial occlusive disease, prior heart failure hospitalisation, respiratory rate, sodium, and systolic blood pressure.[28]

PROTECT: Adjusted for age, sex, baseline creatinine, treatment allocation, previous heart failure hospitalisation, peripheral oedema, SBP, sodium, urea, creatinine, and albumin.[27]

Abbreviations: CI, confidence interval; DR, diuretic response; HR, hazard ratio; WRF, worsening renal function.

Supplementary Figure 1. Sensitivity analysis STEPP plots of worsening renal function (≥0.3 mg/dL and ≥25% creatinine increase) by diuretic response with regards to combined endpoints*

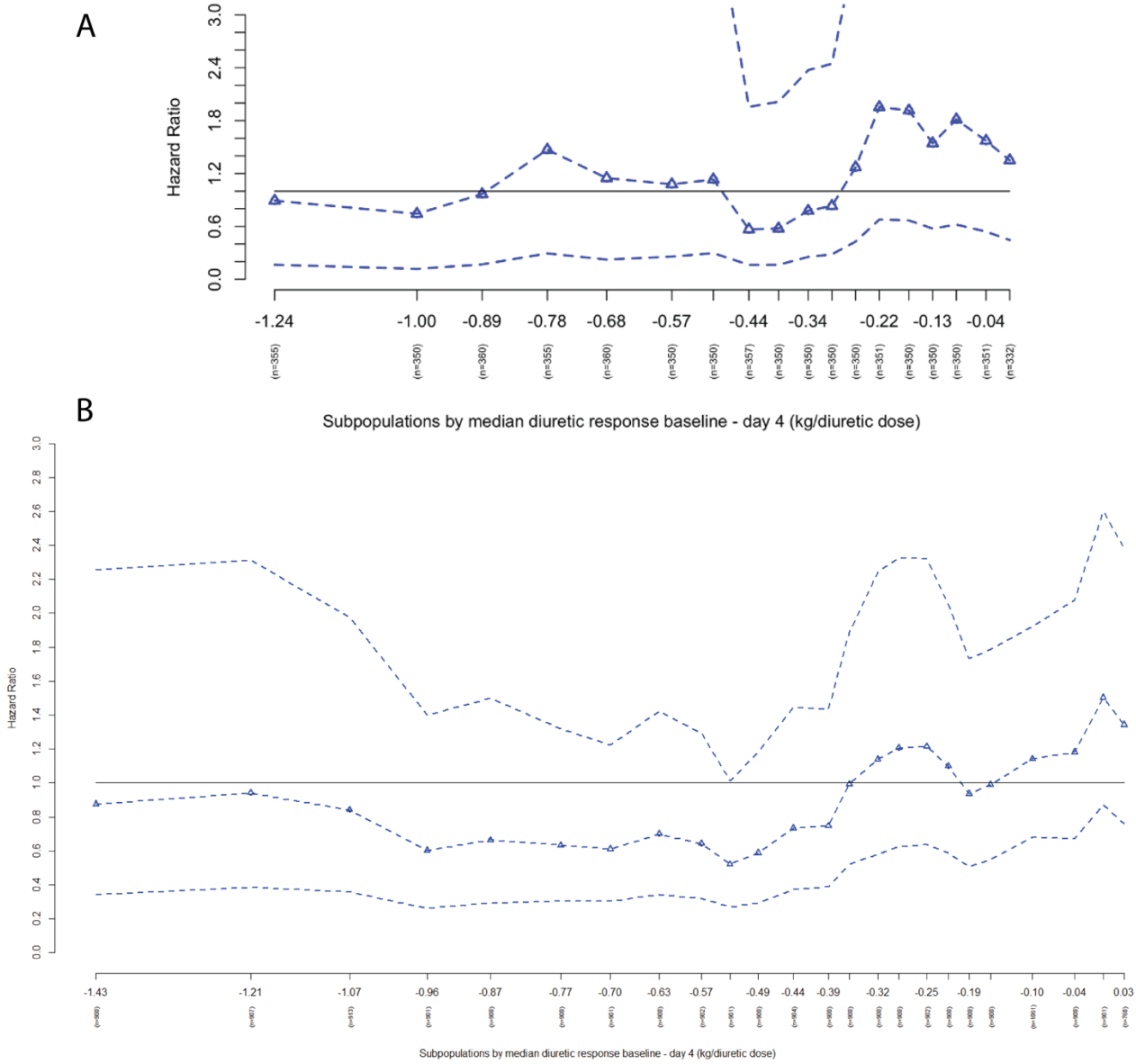


STEPP plots show the hazard ratio of WRF relative to no WRF across a continuum of subpopulations of diuretic response. A) PROTECT, P=0.269; B) RELAX-AHF-2, P=0.079.

*180-day CV death or heart/renal failure hospitalisation in RELAX-AHF-2 and 60-day death from any cause or cardiovascular or renal hospitalisation in PROTECT.

Abbreviations: STEPP, subpopulation treatment effect pattern plot.

Supplementary Figure 2. Sensitivity analysis STEPP plots of worsening renal function (≥ 30% eGFR decrease) by diuretic response with regards to combined endpoints*

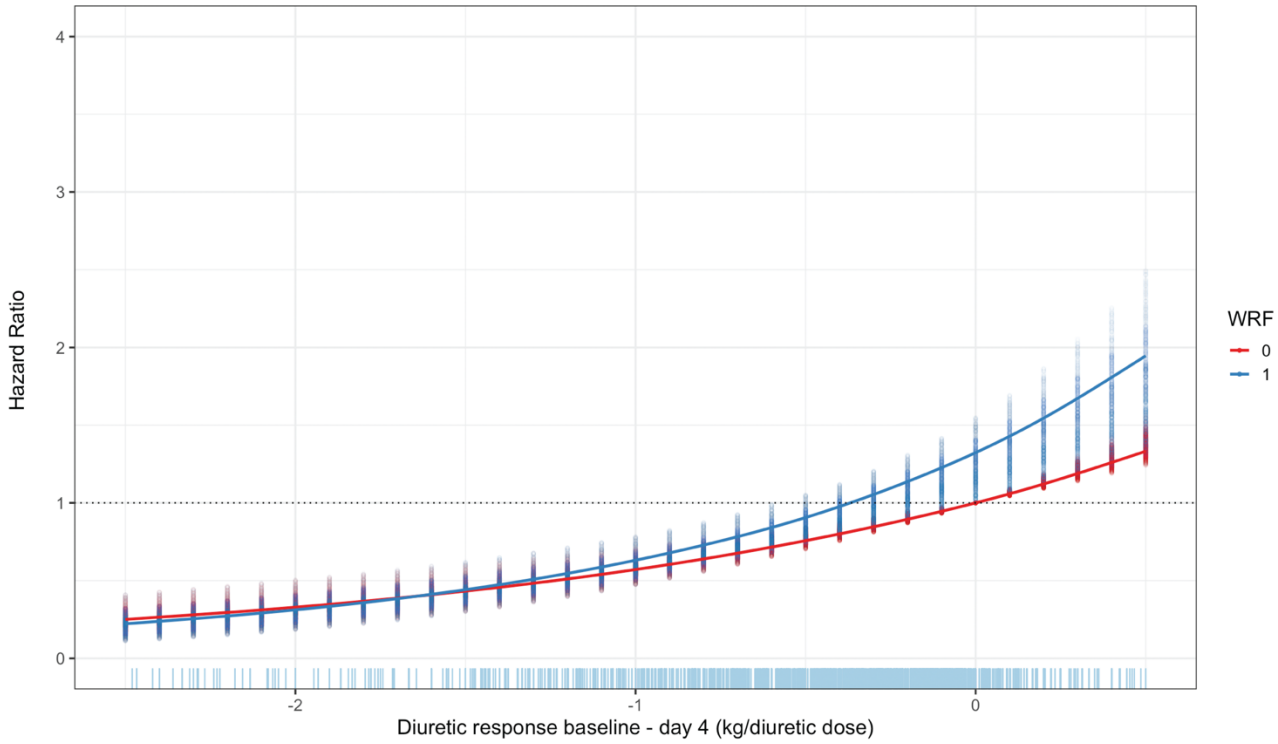


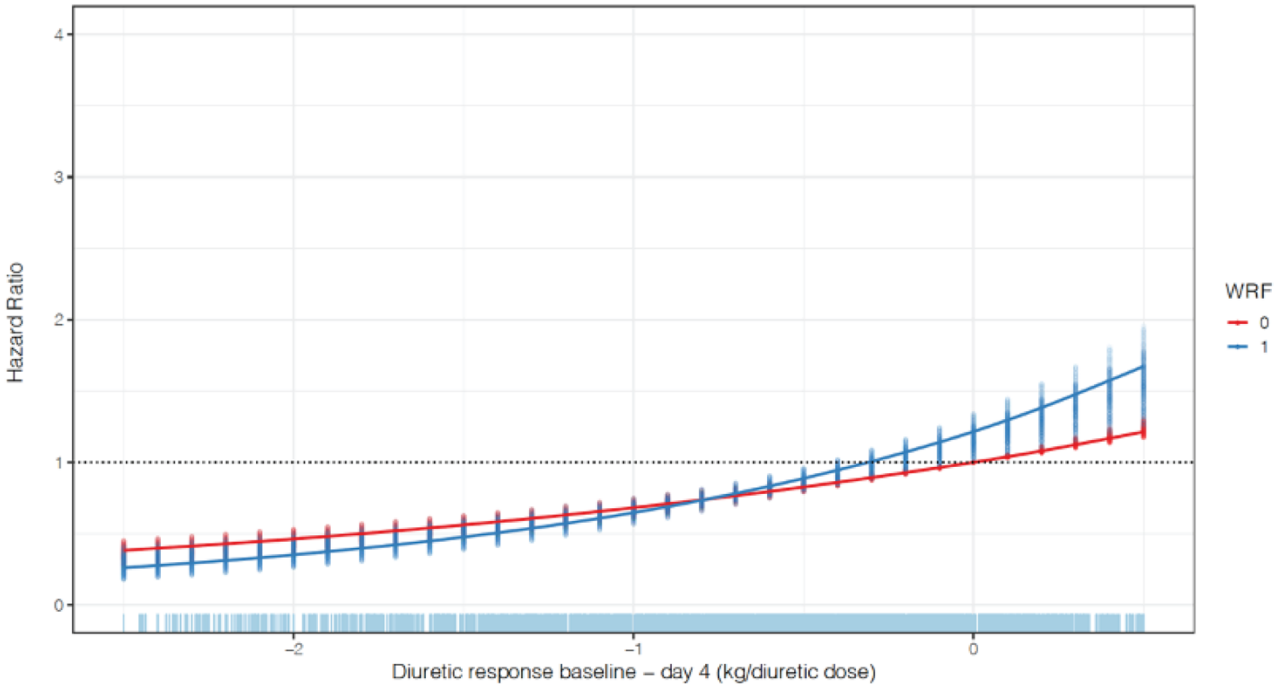
STEPP plots show the hazard ratio of WRF relative to no WRF across a continuum of subpopulations of diuretic response. A) PROTECT, P=0.421; B) RELAX-AHF-2, P=0.026.

*180-day CV death or heart/renal failure hospitalisation in RELAX-AHF-2 and 60-day death from any cause or cardiovascular or renal hospitalisation in PROTECT.

Abbreviations: STEPP, subpopulation treatment effect pattern plot.

Supplementary Figure 3. Interaction plots for presence or absence of WRF (≥0.3 mg/dL creatinine increase) by diuretic response with regards to combined endpoints*

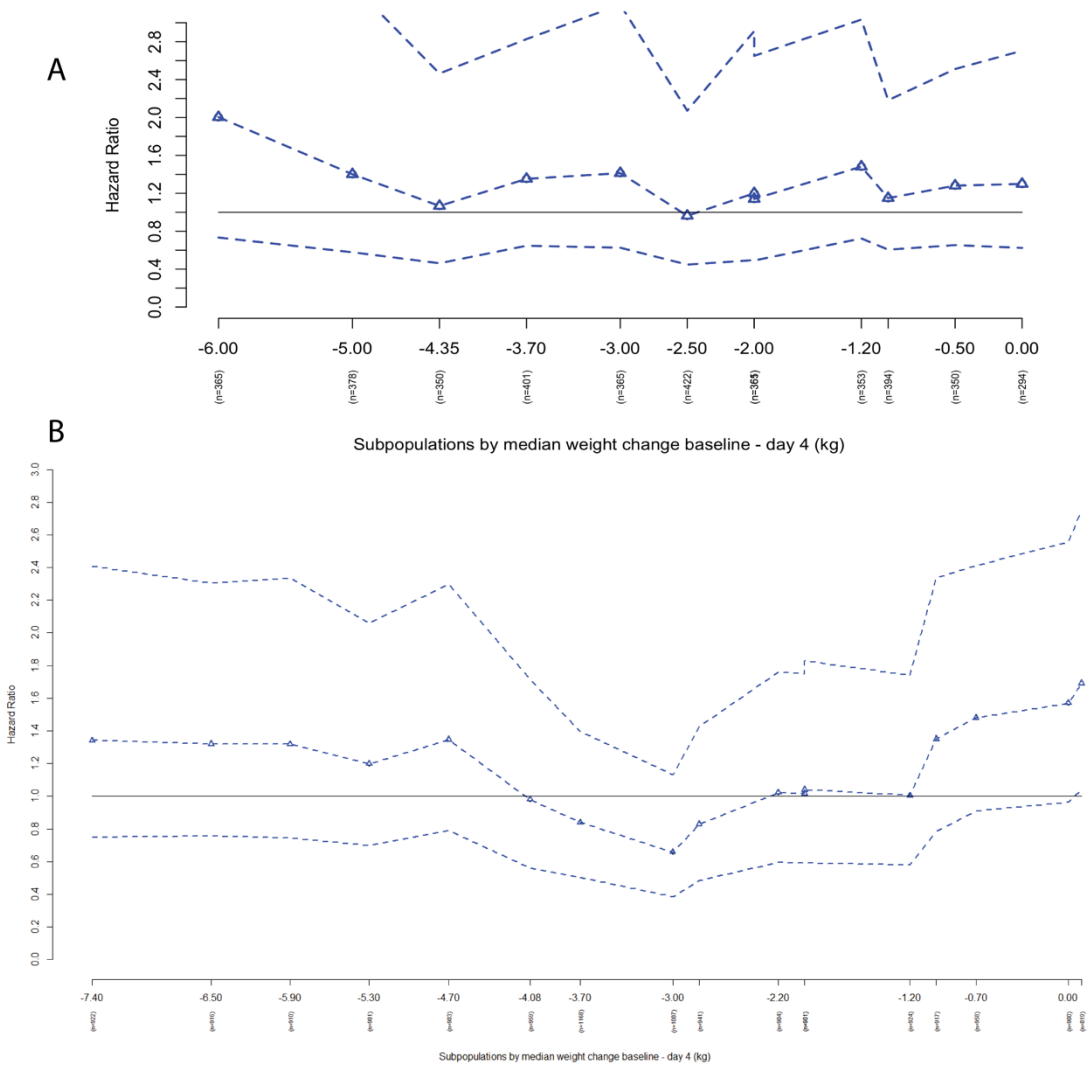




*180-day CV death or heart/renal failure hospitalisation in RELAX-AHF-2 and 60-day death from any cause or cardiovascular or renal hospitalisation in PROTECT.

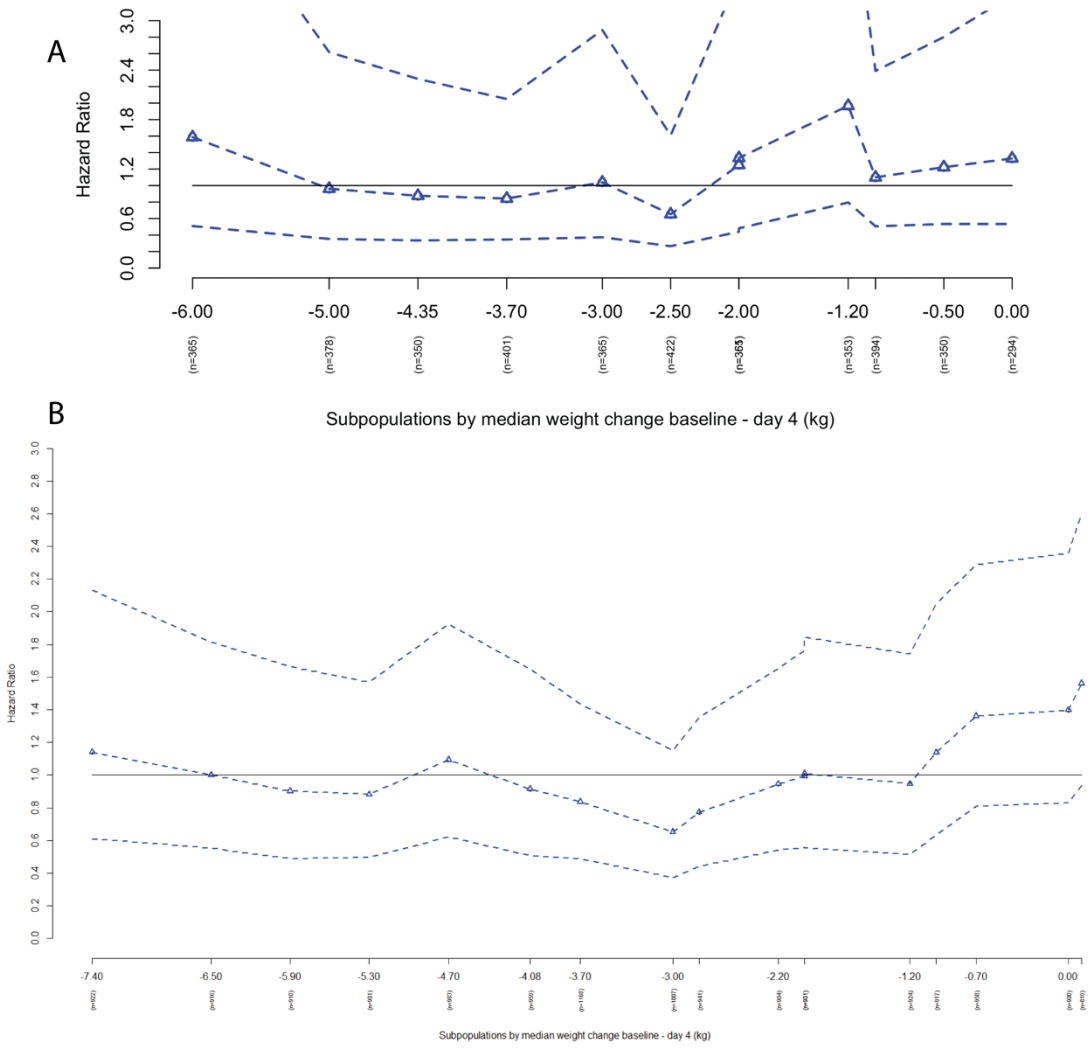
Upper: PROTECT, P=0.128; lower: RELAX-AHF-2, P=0.075

Supplementary Figure 4. STEPP plots of worsening renal function (≥0.3 mg/dL creatinine increase) by crude weight change with regards to combined endpoints*



STEPP plots show the hazard ratio of presence of WRF relative to no WRF across a continuum of overlapping subpopulations of weight change. Each triangle indicates the hazard ratio corresponding with the median weight change of that subpopulation, with the dashed lines representing the 95% confidence interval of the hazard ratio. A) PROTECT, P=0.774; B) RELAX-AHF-2, P=0.006. *180-day CV death or heart/renal failure hospitalisation in RELAX-AHF-2 and 60-day death from any cause or cardiovascular or renal hospitalisation in PROTECT.

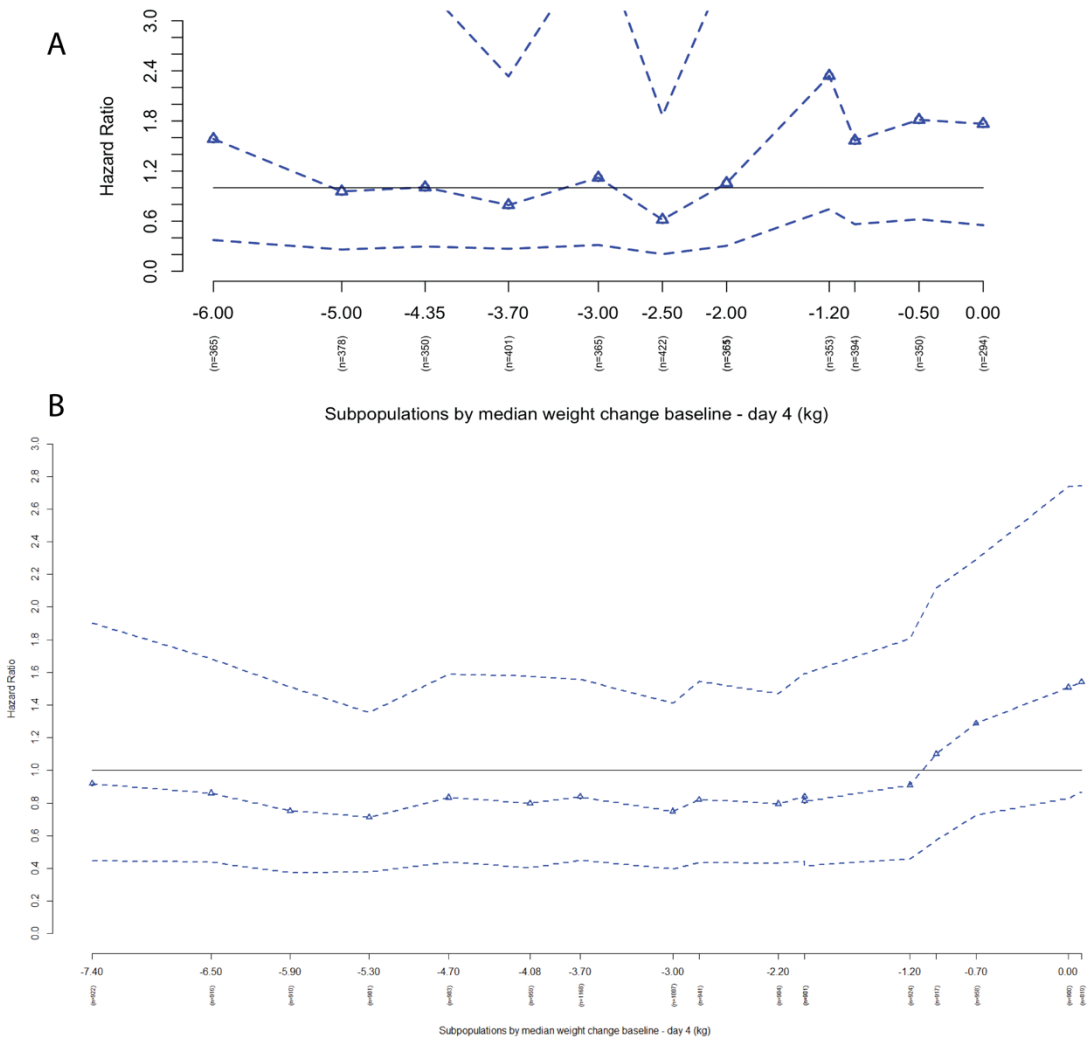
Supplementary Figure 5. STEPP plots of worsening renal function (≥0.3 mg/dL and ≥25% creatinine increase) by crude weight change with regards to combined endpoints*



STEPP plots show the hazard ratio of presence of WRF relative to no WRF across a continuum of overlapping subpopulations of weight change. Each triangle indicates the hazard ratio corresponding with the median weight change of that subpopulation, with the dashed lines representing the 95% confidence interval of the hazard ratio. A) PROTECT, P=0.371; B) RELAX-AHF-2, P=0.044.

*180-day CV death or heart/renal failure hospitalisation in RELAX-AHF-2 and 60-day death from any cause or cardiovascular or renal hospitalisation in PROTECT.

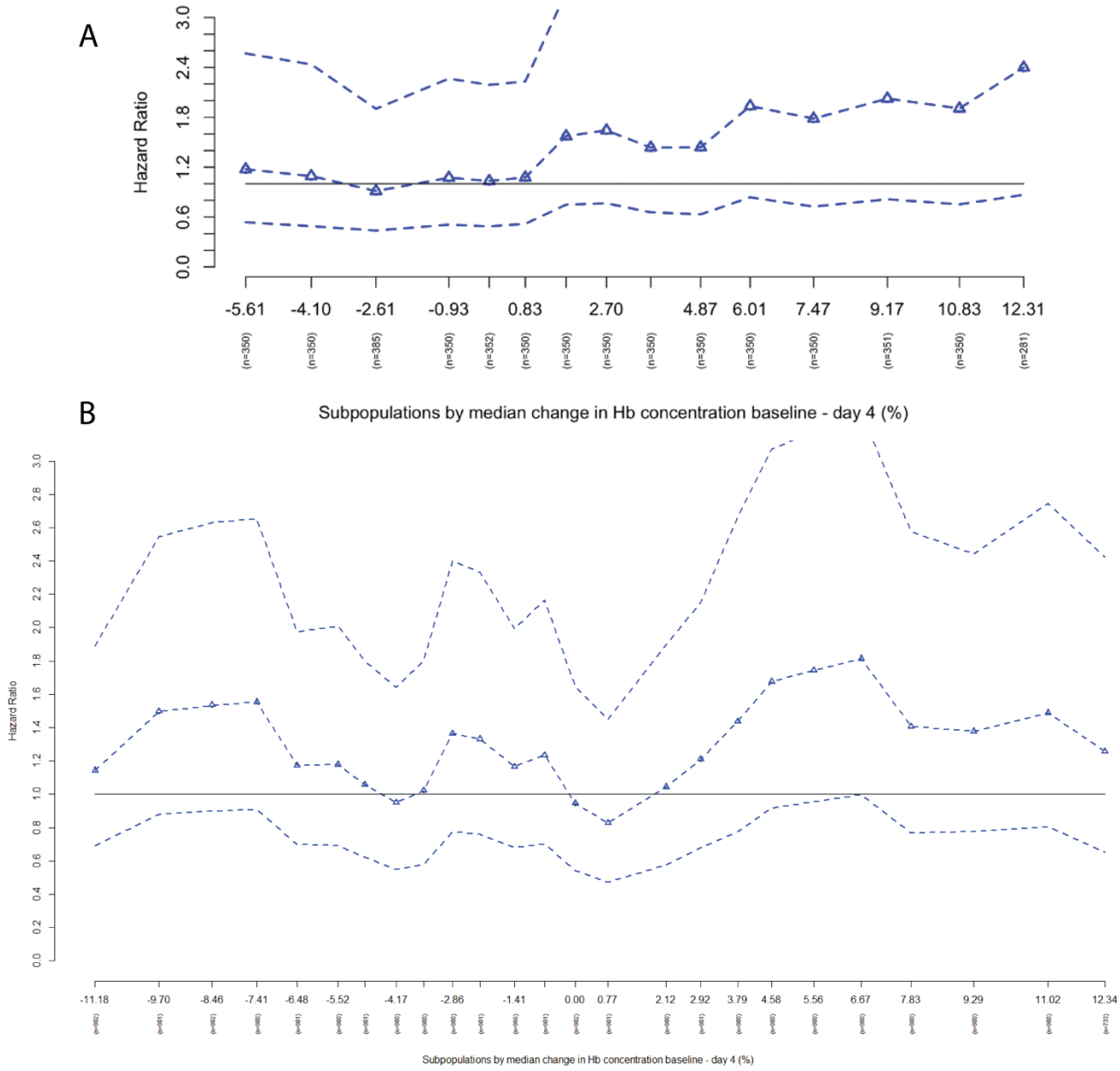
Supplementary Figure 6. STEPP plots of worsening renal function (≥30% eGFR decrease) by crude weight change with regards to combined endpoints*



STEPP plots show the hazard ratio of presence of WRF relative to no WRF across a continuum of overlapping subpopulations of weight change. Each triangle indicates the hazard ratio corresponding with the median weight change of that subpopulation, with the dashed lines representing the 95% confidence interval of the hazard ratio. A) PROTECT, P=0.394; B) RELAX-AHF-2, P=0.212.

*180-day CV death or heart/renal failure hospitalisation in RELAX-AHF-2 and 60-day death from any cause or cardiovascular or renal hospitalisation in PROTECT.

Supplementary Figure 7. STEPP plots of worsening renal function (≥ 0.3 mg/dL creatinine increase) by haemoglobin change with regards to combined endpoints*

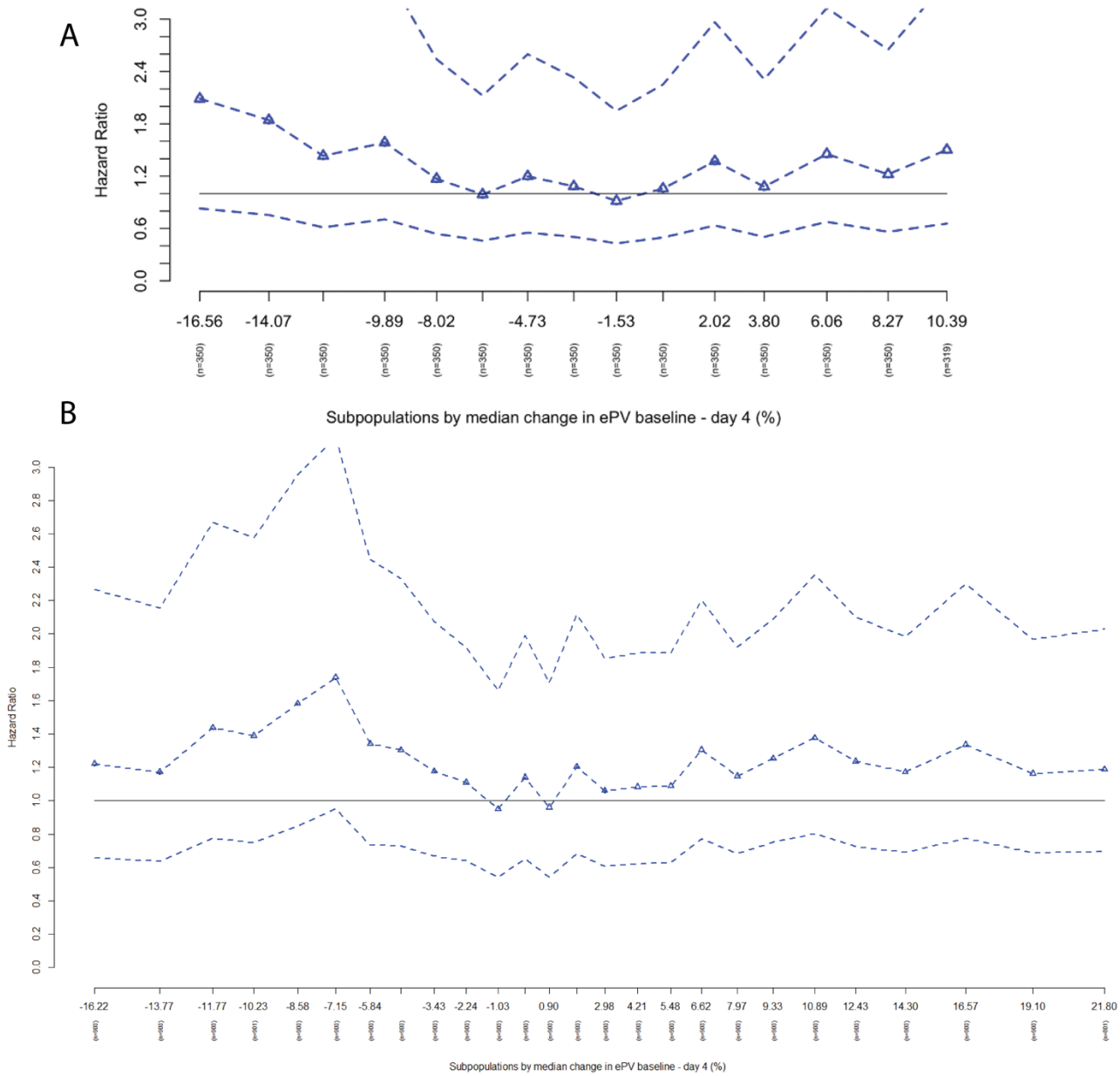


STEPP plots show the hazard ratio of WRF relative to no WRF across a continuum of subpopulations of haemoglobin change. A) PROTECT, P=0.274; B) RELAX-AHF-2, P=0.186.

*180-day CV death or heart/renal failure hospitalisation in RELAX-AHF-2 and 60-day death from any cause or cardiovascular or renal hospitalisation in PROTECT.

Abbreviations: STEPP, subpopulation treatment effect pattern plot.

Supplementary Figure 8. STEPP plots of worsening renal function (≥ 0.3 mg/dL creatinine increase) by ΔePV with regards to combined endpoints*

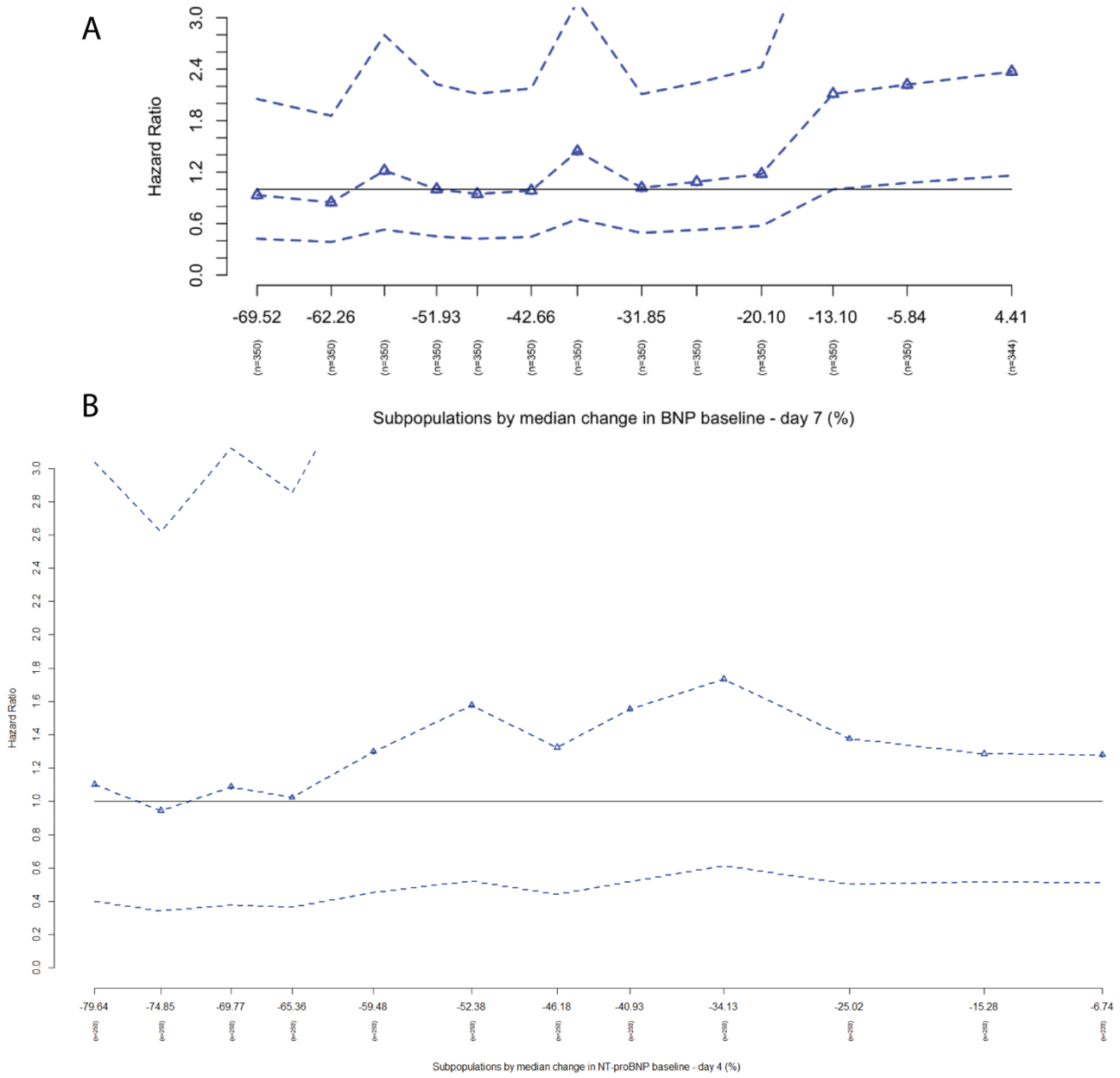


STEPP plots show the hazard ratio of WRF relative to no WRF across a continuum of subpopulations of ΔePV. A) PROTECT, P=0.302; B) RELAX-AHF-2, P=0.456.

*180-day CV death or heart/renal failure hospitalisation in RELAX-AHF-2 and 60-day death from any cause or cardiovascular or renal hospitalisation in PROTECT.

Abbreviations: STEPP, subpopulation treatment effect pattern plot.

Supplementary Figure 9. STEPP plots of worsening renal function (≥0.3 mg/dL creatinine increase) by (NT-pro)BNP change with regards to combined endpoints*



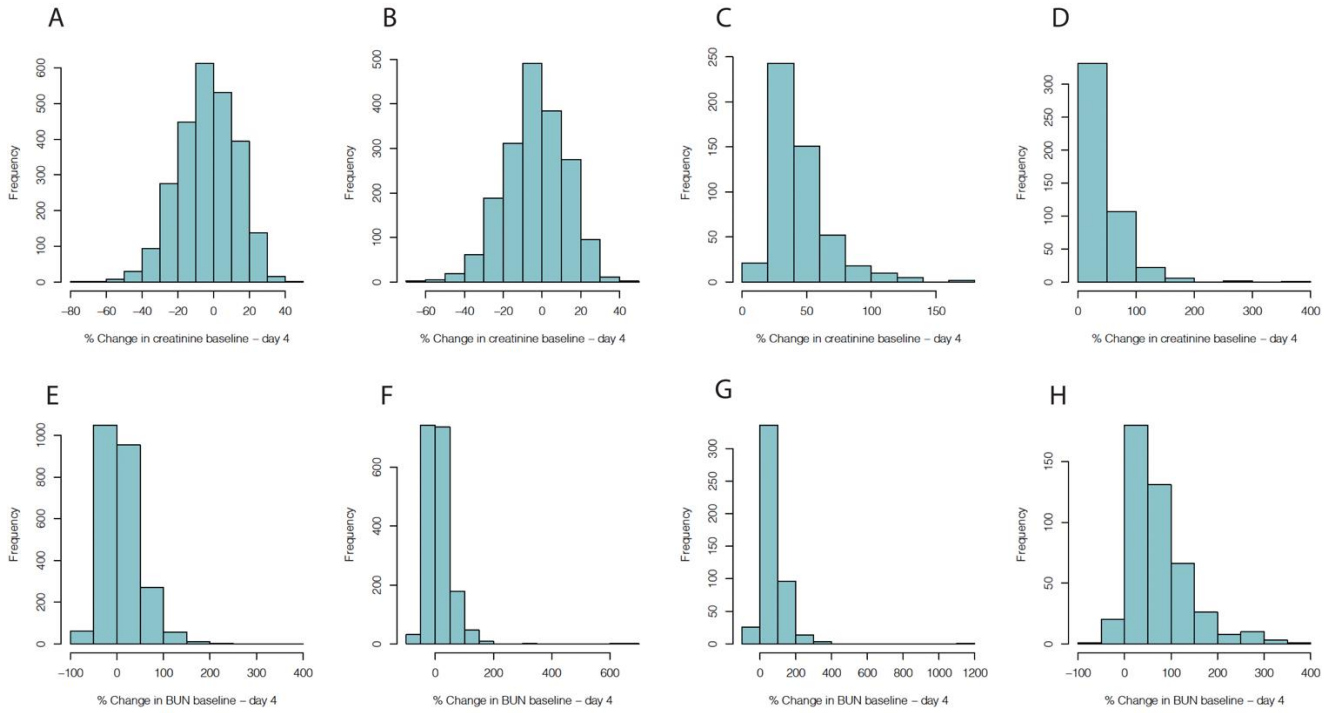
STEPP plots show the hazard ratio of WRF relative to no WRF across a continuum of subpopulations of (NT-pro)BNP. A) PROTECT, P=0.088; B) RELAX-AHF-2, P=0.741.

*180-day CV death or heart/renal failure hospitalisation in RELAX-AHF-2 and 60-day death from any cause or cardiovascular or renal hospitalisation in PROTECT.

Abbreviations: STEPP, subpopulation treatment effect pattern plot.

N=1,209 in PROTECT and N=797 in RELAX-AHF-2.

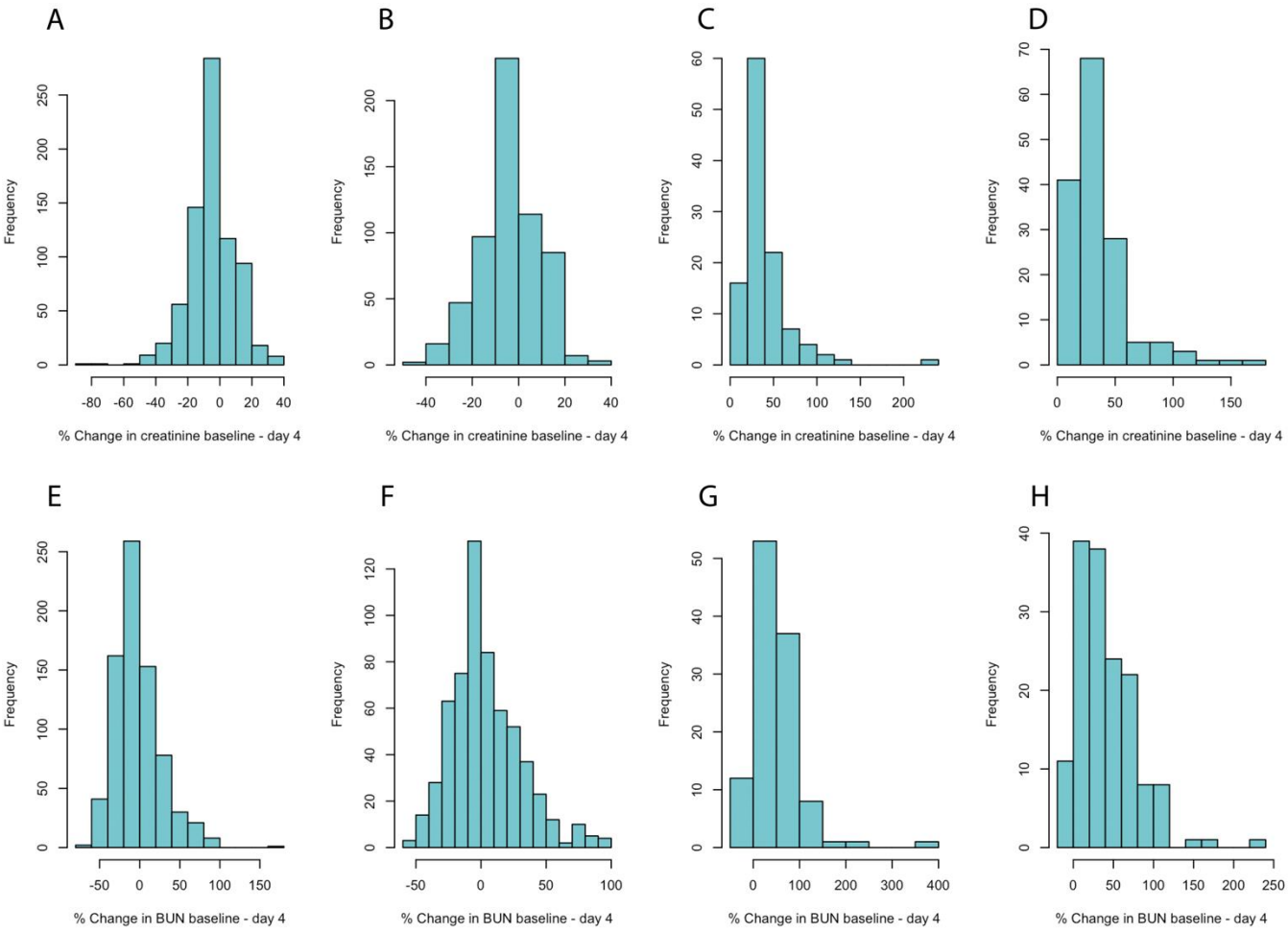
Supplementary Figure 10. Overview of the magnitude of percentage change in creatinine and BUN according to presence/absence of WRF and good/poor diuretic response in RELAX-AHF-2.



Upper panel: percentage change in creatinine between baseline and day 4 in A) patients without WRF and a good diuretic response, B) patients without WRF and a poor diuretic response, C) patients with WRF and a good diuretic response, and D) patients with WRF and a poor diuretic response. Lower panel: percentage change in BUN between baseline and day 4 in E) patients without WRF and a good diuretic response, F) patients without WRF and a poor diuretic response, G) patients with WRF and a good diuretic response, and H) patients with WRF and a poor diuretic response.

Abbreviations: BUN, blood urea nitrogen; WRF, worsening renal function

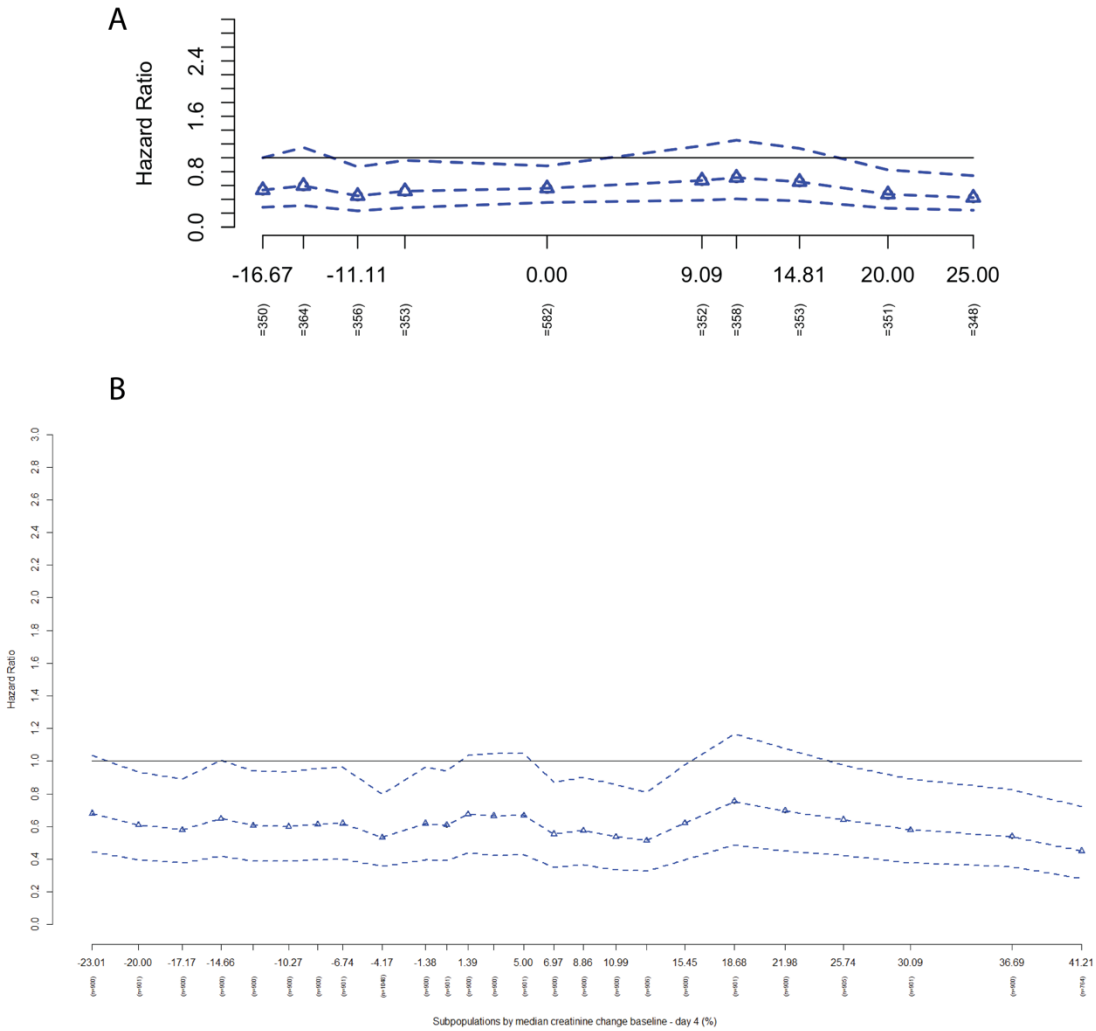
Supplementary Figure 11. Overview of the magnitude of percentage change in creatinine and BUN according to presence/absence of WRF and good/poor diuretic response in PROTECT



Upper panel: percentage change in creatinine between baseline and day 4 in A) patients without WRF and a good diuretic response, B) patients without WRF and a poor diuretic response, C) patients with WRF and a good diuretic response, and D) patients with WRF and a poor diuretic response. Lower panel: percentage change in BUN between baseline and day 4 in E) patients without WRF and a good diuretic response, F) patients without WRF and a poor diuretic response, G) patients with WRF and a good diuretic response, and H) patients with WRF and a poor diuretic response.

Abbreviations: BUN, blood urea nitrogen; WRF, worsening renal function

Supplementary Figure 12. STEPP plots for good diuretic response by percentage serum creatinine change with regards to combined endpoints*



STEPP plots show the hazard ratio of good diuretic response relative to poor diuretic response across a continuum of subpopulations of percentage change in serum creatinine. A) PROTECT, P=0.449; B) RELAX-AHF-2, P=0.403.

*180-day CV death or heart/renal failure hospitalisation in RELAX-AHF-2 and 60-day death from any cause or cardiovascular or renal hospitalisation in PROTECT.