

# **Supplemental Material**

**Table S1. Normal laboratory ranges for full blood count and serum biochemistry variables.**

<b>Blood biomarkers</b>	<b>Normal range</b>
<b>Full blood count</b>	
Haemoglobin (g/L)	Male: 135 – 170 Female: 110 – 150
WBC x 10 <sup>9</sup> /L	3.5 – 11.0
Platelets x 10 <sup>9</sup> /L	140 - 400
<b>Serum biochemistry</b>	
Sodium (mmol/L)	135 - 145
Potassium (mmol/L)	3.5 – 5.1
Urea (mmol/L)	2.9 – 8.1
Creatinine (µmol/L)	66 – 112
eGFR (ml/min/1.73m <sup>2</sup> )	> 90
Total bilirubin (µmol/L)	> 21
Alanine transaminase (IU/L)	Male: 10 – 50 Female: 10 – 35
Aspartate aminotransferase (IU/L)	Male: 10 – 50 Female: 10 – 35
Alkaline phosphatase (IU/L)	> 129
Gamma GT (IU/L)	5 – 36
Total protein (g/L)	66 – 87
Albumin (g/L)	35 – 50
C-reactive protein (mg/L)	< 5

**Table S2. Baseline characteristics and blood biomarkers for the whole ATTR-CA population, and split by genotype into patients with wtATTR-CA, p.(V142I)-hATTR-CA and non-p.(V142I)-hATTR-CA.**

	wtATTR-CA (n = 1834, 71.5%)	p.(V142I)- hATTR-CA (n = 425, 16.6%)	Non-p.(V142I)- hATTR-CA (n = 307, 12.0%)	wt vs p.(V142I) standardised differences	wt vs non- p.(V142I) standardised differences	p.(V142I) vs non- p.(V142I) standardised differences
<b>Demographics</b>						
Age (years)	78.8 ± 6.6	76.4 ± 7.3	66.4 ± 9.8	0.348	1.489	1.158
Sex (male)	1715 (93.5%)	288 (67.8%)	215 (70.0%)	0.689	0.6375	-0.049
<b>Cardiac biomarkers</b>						
NAC stage						
1	866 (47.2%)	191 (44.9%)	210 (68.4%)	0.045	-0.439	-0.487
2	664 (36.2%)	146 (34.4%)	78 (25.4%)	0.039	0.235	0.196
3	304 (16.6%)	88 (20.7%)	19 (6.2%)	-0.106	0.331	0.435
NT-proBNP (ng/L)	2907 (1499 – 5281)	2850 (1548 – 5704)	1852 (626 – 3714)	-0.087	0.248	0.314
Troponin-T (ng/L)	58 (40 – 84)	73 (49 – 108)	40 (25 – 60)	-0.319	0.418	0.668
Troponin-T >14ng/L	1742 (98.9%)	395 (99.0%)	260 (92.5%)	-0.013	0.316	0.325
Troponin-T >56ng/L	915 (51.9%)	266 (66.7%)	82 (29.2%)	-0.305	0.475	0.808
<b>Full blood count</b>						
Haemoglobin (g/L)	137 (126 – 148)	129 (120 – 140)	134 (124 – 144)	0.447	0.187	-0.295
Anaemia	716 (39.0%)	179 (42.1%)	95 (30.9%)	-0.063	0.170	0.233
WBC x 10 <sup>9</sup> /L	6.8 (5.8 – 6.9)	5.0 (4.2 – 6.1)	6.3 (5.2 – 7.5)	0.855	0.306	-0.610
Platelets x 10 <sup>9</sup> /L	202 (170 – 240)	190 (156 – 233)	208 (179 – 253)	0.158	-0.182	-0.328
Low platelets	263 (14.4%)	91 (21.4%)	33 (10.8%)	-0.184	0.109	0.292
<b>Serum biochemistry</b>						
Sodium (mmol/L)	141 (139 – 143)	141 (139 – 143)	141 (139 – 143)	-0.168	0.013	0.179
Hyponatraemia	114 (6.2%)	15 (3.5%)	22 (7.2%)	0.125	-0.038	-0.162
Potassium (mmol/L)	4.5 (4.3 – 4.8)	4.5 (4.2 – 4.8)	4.4 (4.2 – 4.7)	0.173	0.326	0.134
Urea (mmol/L)	8.9 (6.9 – 11.7)	8.0 (6.2 – 11.0)	6.4 (5.2 – 8.3)	0.108	0.667	0.501
High-urea	1061 (57.9%)	201 (47.3%)	80 (26.1%)	0.212	0.680	0.451
Creatinine (µmol/L)	107 (90 – 131)	110 (92 – 133)	81 (68 – 98)	-0.079	0.571	0.617
eGFR (ml/min/1.73m <sup>2</sup> )	59 (46 – 72)	55 (43 – 67)	80 (64 – 90)	0.256	-0.908	-1.181
eGFR < 60 ml/min/1.73m <sup>2</sup>	953 (52.0%)	261 (61.4%)	57 (18.6%)	-0.192	0.745	0.971
Serum total bilirubin (µmol/L)	12 (10 – 19)	13 (8 – 20)	11 (8 – 15)	-0.070	0.355	0.377
Hyperbilirubinemia	337 (18.4%)	89 (20.9%)	33 (10.7%)	-0.065	0.217	0.281
Alanine transaminase (IU/L)	24 (19 – 31)	27 (20 – 37)	24 (19 – 32)	-0.246	-0.072	0.164
High alanine transaminase	99 (5.4%)	60 (14.1%)	33 (10.7%)	-0.297	-0.197	0.102
Aspartate aminotransferase (IU/L)	29 (24 – 35)	32 (26 – 42)	26 (21 – 31)	-0.265	0.215	0.382
High aspartate aminotransferase	84 (4.6%)	75 (17.6%)	19 (6.2%)	-0.297	-0.071	0.359
Alkaline phosphatase (IU/L)	94 (74 – 143)	97 (76 – 134)	78 (62 – 103)	-0.069	0.375	0.444
High alkaline phosphatase	323 (17.6%)	80 (18.8%)	18 (5.9%)	-0.031	0.371	0.401
GGT (IU/L)	69 (34 – 143)	104 (51 – 209)	33 (18 – 75)	-0.294	0.440	0.716
High GGT	1308 (71.3%)	350 (82.4%)	133 (43.3%)	-0.264	0.590	0.882
Total protein (g/L)	71 (67 – 74)	73 (69 – 76)	68 (65 – 72)	-0.329	0.503	0.799
Albumin (g/L)	44 (42 – 46)	42 (40 – 45)	43 (41 – 46)	0.449	0.247	-0.204
Hypoalbuminemia	16 (0.9%)	17 (4.0%)	5 (1.6%)	-0.204	-0.068	0.144

C-reactive protein (mg/L)	2 (1 – 5)	3 (1 – 7)	1 (1 – 3)	-0.150	0.089	0.205
High c-reactive protein	509 (27.8%)	139 (32.7%)	52 (16.9%)	-0.108	0.262	0.371
<b>Echocardiographic parameters</b>						
IVSd (mm)	16.9 ± 2.5	16.8 ± 2.3 <sup>γ</sup>	16.2 ± 3.1	0.058	0.242	0.197
PWTd (mm)	16.4 ± 2.6	16.5 ± 2.4	15.9 ± 3.1	-0.014	0.189	0.209
RWT	0.77 ± 0.17	0.81 ± 0.18	0.79 ± 0.19	-0.184	-0.094	0.083
LVEF (%)	48.9 ± 10.2	43.7 ± 11.0	50.8 ± 10.9	0.483	-0.189	-0.648
LVEF ≤40%	377 (20.6%)	169 (39.8%)	52 (16.9%)	-0.428	0.093	0.522
Stroke volume (ml)	38.7 ± 13.4	30.8 ± 11.8	36.8 ± 12.7	0.626	0.143	-0.490
Longitudinal strain (%)	-11.1 ± 3.7	-9.7 ± 3.3	-11.9 ± 4.3	-0.400	0.204	0.581
Average E/e'	16.4 ± 6.3	17.9 ± 6.4	17.4 ± 7.7	-0.233	-0.343	0.071

P-values for pairwise comparison:  $\alpha = P < 0.05$  for wtATTR vs. p.(V142I) hATTR,  $\beta = P < 0.05$  for wtATTR vs. non-p.(V142I) hATTR,  $\gamma = P < 0.05$  for p.(V142I) hATTR vs. non-p.(V142I) hATTR

wtATTR-CA = Wild-type transthyretin cardiac amyloidosis; hATTR-CA = Hereditary transthyretin cardiac amyloidosis; WBC = White blood count; NAC = National Amyloidosis Centre; NT-pro-BNP = N-terminal pro B-type natriuretic peptide; eGFR = Estimated glomerular filtration rate; GGT = gamma-glutamyl transferase; IVSd = Interventricular septal thickness in diastole; PWTd = Posterior wall thickness in diastole; RWT = Relative wall thickness; LVEF = Left ventricular ejection fraction.

**Table S3. Blood biomarkers split by National Amyloidosis Centre disease stage.**

	NAC stage 1 (n = 1267, 49.4%)	NAC stage 2 (n = 888, 34.6%)	NAC stage 3 (n = 411, 16.0%)	1 vs 2 standardised differences	1 vs 3 standardised differences	2 vs 3 standardised differences
<b>Full blood count</b>						
Haemoglobin (g/L)	138 (128 – 148)	135 (124 – 146)	126 (115 – 139)	0.204	0.632	0.408
Anaemia	390 (30.8%)	367 (41.3%)	233 (56.7%)	-0.221	-0.541	-0.311
WBC x 10 <sup>9</sup> /L	6.5 (5.4 – 7.8)	6.6 (5.4 – 7.9)	6.4 (5.2 – 7.8)	-0.059	0.008	0.063
Platelets x 10 <sup>9</sup> /L	206 (175 – 247)	197 (162 – 238)	189 (156 – 232)	0.146	0.283	0.125
Low platelets	137 (10.8%)	162 (18.3%)	88 (21.5%)	-0.214	-0.292	-0.078
<b>Serum biochemistry</b>						
Sodium (mmol/L)	141 (139 – 143)	141 (138 – 143)	140 (138 – 142)	0.122	0.230	0.098
Hyponatraemia	54 (4.3%)	67 (7.5%)	30 (7.3%)	-0.140	-0.130	0.009
Potassium (mmol/L)	4.5 (4.3 – 4.8)	4.5 (4.2 – 4.8)	4.6 (4.3 – 5.0)	-0.016	-0.238	-0.208
Urea (mmol/L)	7.1 (5.8 – 8.7)	9.3 (7.3 – 11.6)	14.5 (11.5 – 19.2)	-0.754	-1.770	-1.200
High-urea	397 (31.3%)	557 (62.7%)	388 (94.4%)	-0.662	-1.722	-0.836
Creatinine (µmol/L)	93 (79 – 107)	110 (94 – 126)	160 (144 – 184)	-0.591	-2.069	-1.289
Serum total bilirubin (µmol/L)	11 (8 – 11)	15 (10 – 21)	14 (10 – 21)	-0.370	-0.329	0.032
Hyperbilirubinemia	155 (12.2%)	209 (23.5%)	95 (32.1%)	-0.298	-0.288	0.010
Alanine transaminase (IU/L)	25 (19 – 33)	25 (20 – 34)	23 (18 – 30)	-0.034	0.083	0.120
High alanine transaminase	90 (7.1%)	71 (8.0%)	31 (7.5%)	-0.034	-0.017	0.017
Aspartate aminotransferase (IU/L)	28 (23 – 34)	30 (25 – 37)	29 (24 – 37)	-0.255	-0.190	-0.043
High aspartate aminotransferase	67 (5.3%)	66 (7.4%)	45 (10.9%)	-0.034	-0.208	-0.122
Alkaline phosphatase (IU/L)	83 (67 – 106)	102 (77 – 137)	114 (87 – 155)	-0.419	-0.609	-0.252
High alkaline phosphatase	115 (9.1%)	190 (21.4%)	116 (28.2%)	-0.348	-0.507	-0.158
GGT (IU/L)	48 (26 – 107)	88 (44 – 184)	108 (55 – 210)	-0.358	-0.501	-0.191
High GGT	738 (58.2%)	707 (79.6%)	346 (84.2%)	-0.474	-0.598	-0.119
Albumin (g/L)	44 (42 – 46)	43 (41 – 45)	43 (41 – 45)	0.270	0.350	0.081
Hypoalbuminemia	9 (0.7%)	17 (1.9%)	12 (2.9%)	-0.106	-0.166	-0.065
C-reactive protein (mg/L)	2 (1 – 4)	3 (1 – 6)	4 (2 – 8)	-0.195	-0.331	-0.133
High c-reactive protein	242 (19.1%)	281 (31.6%)	177 (43.1%)	-0.291	-0.536	-0.238
NT-proBNP (ng/L)	1468 (846 – 2155)	4533 (3374 – 6494)	6952 (4703 – 10981)	-1.306	-1.548	-0.669
Troponin-T (ng/L)	43 (29 – 60)	69 (51 – 94)	104 (74 – 146)	-0.680	-1.146	-0.603
Troponin-T > 14ng/L	1163 (96.5%)	841 (99.6%)	393 (100.0%)	-0.229	-0.269	-0.084
Troponin-T > 56ng/L	355 (29.5%)	565 (66.9%)	342 (87.0%)	-0.809	-1.436	-0.491
<b>Echocardiographic parameters</b>						
IVSd (mm)	16.3 ± 2.6	17.3 ± 2.4	17.2 ± 2.4	-0.391	-0.324	0.065
PWTd (mm)	15.8 ± 2.6	16.9 ± 2.4	16.8 ± 2.6	-0.432	-0.354	0.066
RWT	0.75 ± 0.17	0.80 ± 0.18	0.81 ± 0.19	-0.334	-0.403	-0.077
LVEF (%)	51.0 ± 9.5	45.8 ± 10.7	44.9 ± 11.3	0.507	0.578	0.081
LVEF ≤40%	185 (14.6%)	270 (30.4%)	143 (34.8%)	-0.385	-0.481	-0.094
Stroke volume (ml)	39.7 ± 13.7	35.5 ± 12.5	33.0 ± 12.9	0.322	0.509	0.202
Longitudinal strain (%)	-12.2 ± 3.8	-9.8 ± 3.2	-9.5 ± 3.3	-0.696	-0.784	-0.099
Average E/e'	15.6 ± 5.9	17.9 ± 6.9	18.1 ± 6.9	-0.363	-0.400	-0.035

P-values for pairwise comparison:  $\alpha = P < 0.01$  for NAC stage 1 vs. NAC stage 2,  $\beta = P < 0.01$  NAC stage 1 vs. NAC stage 3,  $\gamma = P < 0.01$  NAC stage 2 vs NAC stage 3.

WBC = White blood count; NAC = National Amyloidosis Centre; NT-pro-BNP = N-terminal pro B-type natriuretic peptide; eGFR = Estimated glomerular filtration rate; GGT = gamma-glutamyl transferase; IVSd = Interventricular septal thickness in diastole; PWTd = Posterior wall thickness in diastole; RWT = Relative wall thickness; LVEF = Left ventricular ejection fraction.

**Table S4. Blood biomarkers split by NYHA class.**

	NYHA class I (n = 1267,	NYHA class II (n = 1531,	NYHA class III (n = 515	NYHA class IV (n = 38	P-value
<b>Full blood count</b>					
Haemoglobin (g/L)	137 (126 – 147) <sup>βγ</sup>	137 (126 – 147) <sup>δϵ</sup>	132 (120 – 143) <sup>ϕ</sup>	127 (111 – 134)	<0.001
Anaemia	111 (34.2%) <sup>βγ</sup>	570 (37.2%) <sup>δϵ</sup>	226 (43.9%)	23 (60.5%)	<0.001
WBC x 10 <sup>9</sup> /L	6.5 (5.3 – 7.7) <sup>γ</sup>	6.6 (5.4 – 7.9) <sup>δϵ</sup>	6.2 (5.1 – 7.6) <sup>ϕ</sup>	5.2 (4.1 – 6.9)	<0.001
Platelets x 10 <sup>9</sup> /L	204 (174 – 254) <sup>δ</sup>	201 (167 – 239) <sup>ε</sup>	197 (166 – 231) <sup>ϕ</sup>	191 (161 – 244)	0.022
Low platelets	37 (11.4%)	238 (15.6%)	87 (17.0%)	4 (10.5%)	0.126
<b>Serum biochemistry</b>					
Sodium (mmol/L)	141 (139 – 143)	141 (139 – 143)	141 (138 – 143)	141 (139 – 143)	0.339
Hyponatraemia	15 (4.6%)	78 (5.1%)	38 (7.4%)	2 (5.3%)	0.216
Potassium (mmol/L)	4.5 (4.2 – 4.8)	4.5 (4.2 – 4.8)	4.5 (4.2 – 4.9)	4.3 (4.0 – 4.6)	0.007
Urea (mmol/L)	6.9 (5.6 – 8.6) <sup>αβγ</sup>	8.5 (6.6 – 11.1) <sup>δϵ</sup>	9.6 (7.2 – 12.8)	10.9 (7.2 – 16.3)	<0.001
Uraemia	94 (28.9%) <sup>αβγ</sup>	800 (52.3%) <sup>δ</sup>	331 (64.3%)	26 (68.4%)	<0.001
Creatinine (μmol/L)	93 (79 – 111) <sup>αβγ</sup>	105 (87 – 127) <sup>δϵ</sup>	113 (94 – 141)	140 (103 – 176)	<0.001
Serum total bilirubin (μmol/L)	11 (8 – 16) <sup>αβγ</sup>	13 (9 – 18) <sup>δ</sup>	14 (9 – 21)	18 (11 – 23)	<0.001
Hyperbilirubinemia	37 (11.4%) <sup>βγ</sup>	263 (17.2%) <sup>δ</sup>	122 (23.7%)	27 (71.1%)	<0.001
Alanine transaminase (IU/L)	25 (19 – 33) <sup>βγ</sup>	25 (19 – 33)	24 (18 – 32)	19 (13 – 26)	<0.001
High alanine transaminase	22 (6.8%)	108 (7.1%)	51 (9.9%)	1 (2.6%)	0.101
Aspartate aminotransferase (IU/L)	27 (22 – 34) <sup>γ</sup>	29 (24 – 36) <sup>ε</sup>	29 (24 – 36) <sup>ϕ</sup>	31 (24 – 39)	0.004
High aspartate aminotransferase	17 (5.2%)	94 (6.1%) <sup>δ</sup>	53 (10.3%)	4 (10.5%)	0.005
Alkaline phosphatase (IU/L)	81 (64 – 105) <sup>αβγ</sup>	92 (73 – 139) <sup>δϵ</sup>	102 (77 – 142)	119 (89 – 164)	<0.001
High alkaline phosphatase	24 (7.4%) <sup>αβγ</sup>	243 (15.9%) <sup>δ</sup>	114 (77.9%)	12 (31.6%)	<0.001
GGT (IU/L)	40 (23 – 102) <sup>αβγ</sup>	69 (33 – 139) <sup>δϵ</sup>	97 (44 – 184)	104 (53 – 212)	<0.001
High GGT	171 (52.6%) <sup>αβγ</sup>	1085 (70.9%) <sup>δ</sup>	402 (78.1%)	32 (84.2%)	<0.001
Albumin (g/L)	44 (42 – 46) <sup>βγ</sup>	44 (42 – 46) <sup>δϵ</sup>	43 (41 – 45) <sup>ϕ</sup>	41 (38 – 43)	<0.001
Hypoalbuminemia	1 (0.3%) <sup>βγ</sup>	13 (0.8%) <sup>δϵ</sup>	15 (2.9%)	3 (7.9%)	<0.001
C-reactive protein (mg/L)	2 (1 – 3) <sup>αβγ</sup>	2 (1 – 5) <sup>δϵ</sup>	3 (1 – 6) <sup>ϕ</sup>	7 (4 – 13)	<0.001
High c-reactive protein	59 (18.2%) <sup>αβγ</sup>	386 (25.2%) <sup>δϵ</sup>	181 (35.1%) <sup>ϕ</sup>	26 (68.4%)	<0.001
NT-proBNP (ng/L)	1438 (578 – 2715) <sup>αβγ</sup>	2605 (1404 – 4716) <sup>δϵ</sup>	4203 (2162 – 7476)	5918 (3445 – 10351)	<0.001
Troponin-T (ng/L)	42 (26 – 64) <sup>αβγ</sup>	57 (38 – 81) <sup>δϵ</sup>	75 (49 – 109)	106 (69 – 168)	<0.001
Troponin-T > 14ng/L	290 (93.5%) <sup>αβ</sup>	1450 (98.6%)	484 (99.4%)	29 (96.7%)	<0.001
Troponin-T > 56ng/L	95 (30.6%) <sup>αβγ</sup>	743 (50.5%) <sup>δϵ</sup>	318 (65.3%)	24 (80.0%)	<0.001
<b>Echocardiographic parameters</b>					
IVSd (mm)	16.3 ± 2.6 <sup>αβ</sup>	16.9 ± 2.5	17.1 ± 2.2	17.4 ± 2.3	<0.001
PWTd (mm)	15.8 ± 2.6 <sup>αβγ</sup>	16.5 ± 2.5	16.7 ± 2.4	17.1 ± 2.2	<0.001
LVEF (%)	51.0 ± 9.5 <sup>αβγ</sup>	48.7 ± 10.2 <sup>δϵ</sup>	44.1 ± 11.2	40.5 ± 10.5	<0.001
LVEF ≤40%	33 (10.2%) <sup>αβ</sup>	326 (21.3%) <sup>δϵ</sup>	195 (37.9)	18 (47.4%)	<0.001
Longitudinal strain (%)	-12.3 ± 3.8 <sup>αβγ</sup>	-11.1 ± 3.7 <sup>δϵ</sup>	-9.8 ± 3.4 <sup>ϕ</sup>	-7.9 ± 2.9	<0.001
Average E/e'	15.6 ± 5.9 <sup>αβ</sup>	16.6 ± 6.4 <sup>δ</sup>	18.1 ± 7.0	18.4 ± 8.6	<0.001

P-values for pairwise comparison:  $\alpha = P < 0.05$  for NYHA class I vs. NYHA class II,  $\beta = P < 0.05$  for NYHA class I vs. NYHA class III,  $\gamma = P < 0.05$  for NYHA class I vs. NYHA class IV,  $\delta = 0.05$  for NYHA class II vs. NYHA class III,  $\epsilon =$  NYHA class II vs. NYHA class IV,  $\phi =$  NYHA class III vs. NYHA class IV

NYHA = New York Heart Association; WBC = White blood count; NAC = National Amyloidosis Centre; NT-pro-BNP = N-terminal pro B-type natriuretic peptide; eGFR = Estimated glomerular filtration rate; GGT = gamma-glutamyl transferase; IVSd = Interventricular septal thickness in diastole; PWTd = Posterior wall thickness in diastole; LVEF = Left ventricular ejection fraction.

**Table S5. Blood biomarkers split by left ventricular ejection fraction.**

	<b>LVEF ≤40%</b> (n=598, 23.3%)	<b>LVEF &gt;40%</b> (n=1968, 76.7%)	<b>P-value</b>
<b>Full blood count</b>			
Haemoglobin (g/L)	136 (123 – 146)	135 (125 – 146)	0.283
Anaemia	229 (38.3%)	761 (38.7%)	0.869
WBC x 10 <sup>9</sup> /L	6.4 (5.1 – 7.8)	6.6 (5.4 – 7.8)	0.014
Platelets x 10 <sup>9</sup> /L	196 (161 – 241)	141 (139 – 143)	0.050
Low platelets	106 (17.3%)	281 (14.3%)	0.041
<b>Serum biochemistry</b>			
Sodium (mmol/L)	141 (138 – 143)	141 (139 – 143)	0.525
Hyponatraemia	40 (6.7%)	111 (5.6%)	0.340
Potassium (mmol/L)	4.5 (4.2 – 4.8)	4.5 (4.2 – 4.8)	0.915
Urea (mmol/L)	9.2 (7.0 – 11.9)	8.2 (6.4– 10.9)	<0.001
Uraemia	365 (61.0%)	977 (49.6%)	<0.001
Creatinine (µmol/L)	112 (93 – 137)	103 (86 – 125)	<0.001
eGFR (ml/min/1.73m <sup>2</sup> )	55 (44 – 69)	61 (48 – 76)	<0.001
eGFR < 60 ml/min/1.73m <sup>2</sup>	352 (58.9%)	919 (46.7%)	<0.001
Serum total bilirubin (µmol/L)	15 (11 – 22)	12 (9 – 18)	<0.001
Hyperbilirubinemia	158 (26.4%)	301 (15.3%)	<0.001
Alanine transaminase (IU/L)	25 (19 – 34)	24 (9 – 18)	0.604
High alanine transaminase	56 (9.4%)	136 (6.9%)	0.046
Aspartate aminotransferase (IU/L)	30 (25 – 38)	28 (19 – 32)	<0.001
High aspartate aminotransferase	66 (11.0%)	112 (5.7%)	<0.001
Alkaline phosphatase (IU/L)	101 (78 – 143)	90 (71 – 120)	<0.001
High alkaline phosphatase	140 (23.4%)	281 (14.3%)	<0.001
GGT (IU/L)	96 (47 – 207)	62 (30 – 127)	<0.001
High GGT	481 (80.4%)	1310 (66.6%)	<0.001
Albumin (g/L)	43 (41 – 45)	44 (42 – 46)	<0.001
Hypoalbuminemia	12 (2.0%)	26 (1.3%)	0.224
C-reactive protein (mg/L)	3 (1 – 7)	2 (1 – 3)	<0.001
High c-reactive protein	202 (33.8%)	498 (25.3%)	<0.001
NT-proBNP (ng/L)	4114 (2466 – 7201)	2379 (1219 – 4521)	<0.001
Troponin-T (ng/L)	73 (48 – 104)	54 (37 – 79)	<0.001
Troponin-T > 14ng/L	572 (99.7%)	1827 (97.7%)	0.002
Troponin-T > 56ng/L	375 (65.6%)	887 (47.4%)	<0.001
<b>Echocardiographic parameters</b>			
IVSd (mm)	17.0 ± 2.5	16.7 ± 2.6	0.026
PWTd (mm)	16.6 ± 2.6	16.3 ± 2.6	0.016
LVEF (%)	33.6 ± 5.4	52.9 ± 7.1	<0.001
Longitudinal strain (%)	-8.0 ± 2.6	-11.9 ± 3.6	<0.001
Average E/e'	18.1 ± 7.1	16.4 ± 6.3	<0.001

LVEF = Left ventricular ejection fraction; WBC = White blood count; NT-pro-BNP = N-terminal pro B-type natriuretic peptide; eGFR = Estimated glomerular filtration rate; GGT = gamma-glutamyl transferase; IVSd = Interventricular septal thickness in diastole; PWTd = Posterior wall thickness in diastole; LVEF = Left ventricular ejection fraction



**Table S6. Correlation between stroke volume and blood biomarkers.**

Correlation with stroke volume (ml)		
	Correlation coefficient	P-value
Haemoglobin (g/L)	0.011	0.620
Sodium (mmol/L)	0.016	0.481
Urea (mmol/L)	-0.102	<0.001
Serum total bilirubin ( $\mu\text{mol/L}$ )	-0.158	<0.001
Alanine transaminase (IU/L)	-0.005	<0.810
Aspartate aminotransferase (IU/L)	-0.178	<0.001
Alkaline phosphatase (IU/L)	-0.162	<0.001
GGT (IU/L)	-0.181	<0.001
Albumin (g/L)	0.132	<0.001
C-reactive protein (mg/L)	-0.132	<0.001
Troponin-T (ng/L)	-0.174	<0.001

**Table S7. Multivariable linear regression assessing the independent relationship between blood biomarkers and stroke volume.**

<b>Multivariable linear regression model</b>		
<b>Stroke volume (ml)</b>	<b>Coefficient 95%(CI)</b>	<b>P-value</b>
NAC stage 1 disease	Ref	
NAC stage 2 disease	-3.38 (-4.79 to -1.97)	<0.001
NAC stage 3 disease	-6.14 (-8.38 to -3.90)	<0.001
Haemoglobin (g/L)	-0.03 (-0.07 to 0.01)	0.091
Sodium (mmol/L)	-0.11 (-0.29 to 0.06)	0.210
Urea (mmol/L)	0.12 (-0.05 to 0.29)	0.168
Serum total bilirubin ( $\mu$ mol/L)	-0.14 (-0.21 to -0.07)	<0.001
Alanine transaminase (IU/L)	0.00 (-0.04 to 0.04)	0.998
Alkaline phosphatase (IU/L)	0.00 (-0.02 to 0.01)	0.834
GGT (IU/L)	-0.01 (-0.01 to 0.00)	0.070
Albumin (g/L)	0.43 (0.24 to 0.62)	<0.001
C-reactive protein (mg/L)	-0.02 (-0.08 to 0.03)	0.396
Troponin-T (ng/L)	-0.01 (-0.02 to 0.01)	0.227

NAC = National Amyloidosis Centre; GGT = gamma-glutamyl transferase.

**Table S8. Univariable Cox proportional hazards regression analysis of risk of death in the overall ATTR-CA population.**

<b>Univariable Cox regression of continuous variables</b>		
	<b>HR (95%CI)</b>	<b>P-value</b>
Haemoglobin (g/L)	0.99 (0.98-0.99)	<0.001
Platelets x 10 <sup>9</sup> /L	1.00 (0.99-1.00)	0.006
Sodium (mmol/L)	0.94 (0.93-0.96)	<0.001
Urea (mmol/L)	1.10 (1.09-1.11)	<0.001
Total bilirubin (µmol/L)	1.02 (1.02-1.03)	<0.001
ALT (IU/L)	1.00 (0.99-1.00)	0.307
AST (IU/L)	1.01 (1.01-1.01)	<0.001
ALP (IU/L)	1.00 (1.00-1.01)	<0.001
GGT (IU/L)	1.00 (1.00-1.00)	<0.001
Albumin (g/L)	0.93 (0.91-0.94)	<0.001
CRP (mg/L)	1.01 (1.01-1.01)	<0.001
Troponin-T (ng/L)	1.01 (1.00-1.01)	<0.001
<b>Univariable Cox regression of z-score standardised continuous variables</b>		
	<b>HR (95%CI)</b>	<b>P-value</b>
Haemoglobin (g/L)	0.79 (0.74-0.84)	<0.001
Platelets x 10 <sup>9</sup> /L	0.91 (0.85-0.97)	0.006
Sodium (mmol/L)	0.82 (0.77-0.87)	<0.001
Urea (mmol/L)	1.56 (1.49-1.64)	<0.001
Total bilirubin (µmol/L)	1.22 (1.16-1.28)	<0.001
ALT (IU/L)	0.97 (0.91-1.03)	0.307
AST (IU/L)	1.14 (1.09-1.18)	<0.001
ALP (IU/L)	1.28 (1.22-1.34)	<0.001
GGT (IU/L)	1.26 (1.20-1.32)	<0.001
Albumin (g/L)	0.77 (0.72-0.82)	<0.001
CRP (mg/L)	1.13 (1.08-1.18)	<0.001
Troponin-T (ng/L)	1.32 (1.29-1.36)	<0.001
<b>Univariable Cox regression of dichotomous variables</b>		
	<b>HR (95%CI)</b>	<b>P-value</b>
Anaemia	1.59 (1.40-1.80)	<0.001
Low platelets	1.25 (1.05-1.48)	0.010
Hyponatraemia	1.80 (1.42-2.28)	<0.001
Uraemia	2.06 (1.8-2.36)	<0.001
Hyperbilirubinemia	1.77 (1.5-2.05)	<0.001
High ALT	0.99 (0.78-1.25)	0.915
High AST	1.55 (1.24-1.95)	<0.001
High ALP	1.98 (1.71-2.30)	<0.001
High GGT	1.70 (1.46-1.98)	<0.001
Hypoalbuminemia	3.39 (2.31-4.97)	<0.001
High CRP	1.66 (1.45-1.89)	<0.001
Troponin-T >56ng/L	2.75 (2.36-3.19)	<0.001

HR = Hazard ratio; CI = Confidence interval; ALT = alanine transaminase; AST = Aspartate aminotransferase; ALP = Alkaline phosphatase; GGT = gamma-glutamyl transferase; CRP = C-reactive protein.

**Table S9. Multivariable Cox proportional hazards regression analysis of risk of death in the overall ATTR-CA population.**

<b>Multivariable Cox regression analysis of z-score standardised continuous variables</b>					
<b>Patients not censored for the start date of clinical trials and disease modifying therapy</b>			<b>Patients censored for the start date of clinical trials and disease modifying therapy</b>		
<b>Variable</b>	<b>HR (95%CI)</b>	<b>P-value</b>	<b>Variable</b>	<b>HR (95%CI)</b>	<b>P-value</b>
Haemoglobin (g/L)	0.88 (0.2-0.94)	<0.001	Haemoglobin (g/L)	0.88 (0.81-0.94)	0.001
Sodium (mmol/L)	0.90 (0.84-0.96)	0.003	Sodium (mmol/L)	0.92 (0.86-0.99)	0.021
Urea (mmol/L)	1.32 (1.24-1.41)	<0.001	Urea (mmol/L)	1.30 (1.22-1.39)	<0.001
Total bilirubin (µmol/L)	1.15 (1.09-1.22)	<0.001	Total bilirubin (µmol/L)	1.15 (1.08-1.22)	<0.001
ALP (IU/L)	1.00 (0.92-1.08)	0.933	ALP (IU/L)	1.00 (0.92-1.08)	0.906
GGT (IU/L)	1.06 (0.97-1.14)	0.183	GGT (IU/L)	1.05 (0.96-1.14)	0.287
Albumin (g/L)	0.88 (0.82-0.94)	<0.001	Albumin (g/L)	0.88 (0.82-0.95)	0.001
CRP (mg/L)	1.03 (0.97-1.10)	0.274	CRP (mg/L)	1.04 (0.98-1.10)	0.250
Troponin-T (ng/L)	1.24 (1.19-1.29)	<0.001	Troponin-T (ng/L)	1.24 (1.19-1.29)	<0.001
Harrell's c	0.712 (0.694-0.731)	<0.001	Harrell's c	0.711 (0.691-0.731)	<0.001

HR = Hazard ratio; CI = Confidence interval; ALP = Alkaline phosphatase; GGT = gamma-glutamyl transferase; CRP = C-reactive protein.

**Table S10. Multivariable Cox proportional hazards regression analyses of risk of death in the overall ATTR-CA population adjusting for furosemide equivalent dose and stroke volume.**

<b>Multivariable Cox regression analysis in the overall population adjusting for furosemide dose</b>					
<b>Patients not censored for the start date of clinical trials and disease modifying therapy</b>			<b>Patients censored for the start date of clinical trials and disease modifying therapy</b>		
<b>Variable</b>	<b>HR (95%CI)</b>	<b>P-value</b>	<b>Variable</b>	<b>HR (95%CI)</b>	<b>P-value</b>
Furosemide (mg/24hrs)	1.00 (1.00-1.00)	<0.001	Furosemide (mg/24hrs)	1.00 (1.00-1.00)	<0.001
Anaemia	1.22 (1.06-1.40)	0.004	Anaemia	1.20 (1.04-1.38)	0.015
Hyponatraemia	1.66 (1.29-2.13)	<0.001	Hyponatraemia	1.72 (1.32-2.22)	<0.001
Uraemia	1.36 (1.16-1.58)	<0.001	Uraemia	1.36 (1.15-1.59)	<0.001
Hyperbilirubinemia	1.30 (1.10-1.53)	0.002	Hyperbilirubinemia	1.28 (1.08-1.51)	0.005
High ALP	1.20 (1.01-1.42)	0.041	High ALP	1.18 (0.98-1.41)	0.067
High GGT	1.13 (0.95-1.33)	0.164	High GGT	1.11 (0.93-1.33)	0.237
Hypoalbuminemia	1.52 (0.99-2.33)	0.054	Hypoalbuminemia	1.57 (1.02-2.40)	0.039
High CRP	1.17 (1.02-1.36)	0.030	High CRP	1.15 (0.99-1.34)	0.064
Troponin-T >56ng/L	1.99 (1.68-2.33)	<0.001	Troponin-T >56ng/L	1.90 (1.60-2.25)	<0.001
Harrell's c	0.700 (0.682-0.718)	<0.001	Harrell's c	0.698 (0.79-0.717)	<0.001
<b>Multivariable Cox regression analysis in the overall population adjusting for stroke volume</b>					
<b>Patients not censored for the start date of clinical trials and disease modifying therapy</b>			<b>Patients censored for the start date of clinical trials and disease modifying therapy</b>		
<b>Variable</b>	<b>HR (95%CI)</b>	<b>P-value</b>	<b>Variable</b>	<b>HR (95%CI)</b>	<b>P-value</b>
Stroke volume (ml)	0.98 (0.97-0.99)	<0.001	Stroke volume (ml)	0.98 (0.97-0.99)	<0.001
Anaemia	1.28 (1.10-1.49)	0.001	Anaemia	1.26 (1.08-1.47)	0.004
Hyponatraemia	1.68 (1.27-2.21)	<0.001	Hyponatraemia	1.63 (1.23-2.17)	0.001
Uraemia	1.43 (1.21-1.68)	<0.001	Uraemia	1.44 (1.21-1.70)	<0.001
Hyperbilirubinemia	1.22 (1.03-1.46)	0.023	Hyperbilirubinemia	1.21 (1.01-1.45)	0.041
High ALP	1.29 (1.07-1.55)	0.006	High ALP	1.25 (1.04-1.52)	0.018
High GGT	1.04 (0.86-1.25)	0.708	High GGT	1.01 (0.83-1.23)	0.908
Hypoalbuminemia	1.42 (0.85-2.34)	0.177	Hypoalbuminemia	1.47 (0.89-2.44)	0.134
High CRP	1.10 (0.94-1.28)	0.248	High CRP	1.11 (0.95-1.30)	0.200
Troponin-T >56ng/L	2.09 (1.75-2.50)	<0.001	Troponin-T >56ng/L	1.93 (1.61-2.31)	<0.001
Harrell's c	0.705 (0.686-0.724)	<0.001	Harrell's c	0.697 (0.676-0.717)	<0.001

HR = Hazard ratio; CI = Confidence interval; ALP = Alkaline phosphatase; GGT = gamma-glutamyl transferase; CRP = C-reactive protein.

**Table S11. Multivariable Cox proportional hazards regression analysis of risk of death in the overall ATTR-CA population.**

<b>Multivariable Cox regression analysis for patient with a LVEF ≤40%</b>					
<b>Patients not censored for the start date of clinical trials and disease modifying therapy</b>			<b>Patients censored for the start date of clinical trials and disease modifying therapy</b>		
<b>Variable</b>	<b>HR (95%CI)</b>	<b>P-value</b>	<b>Variable</b>	<b>HR (95%CI)</b>	<b>P-value</b>
Age (years)	1.03 (1.01-1.05)	<0.001	Age (years)	1.03 (1.01-1.05)	0.001
hATTR-CA	1.47 (1.14-1.89)	0.003	hATTR-CA	1.44 (1.10-1.87)	0.007
NAC stage 1	ref		NAC stage 1	ref	
NAC stage 2	1.46 (1.05-2.02)	0.025	NAC stage 2	1.50 (1.06-2.12)	0.022
NAC stage 3	1.73 (1.17-2.57)	0.005	NAC stage 3	1.66 (1.11-2.49)	0.015
Anaemia	1.39 (1.08-1.81)	0.012	Anaemia	1.43 (1.10-1.87)	0.008
Hyponatraemia	2.51 (1.62-3.87)	<0.001	Hyponatraemia	2.52 (1.62-3.93)	<0.001
Uraemia	0.97 (0.71-1.32)	0.851	Uraemia	0.91 (0.66-1.25)	0.562
Hyperbilirubinemia	1.18 (0.89-1.56)	0.242	Hyperbilirubinemia	1.18 (0.89-1.57)	0.260
High ALP	1.39 (1.05-1.86)	0.023	High ALP	1.34 (1.00-1.81)	0.049
High GGT	0.90 (0.79-1.32)	0.871	High GGT	0.89 (0.62-1.28)	0.546
Hypoalbuminemia	1.14 (0.49-2.64)	0.766	Hypoalbuminemia	1.24 (0.53-2.87)	0.622
High CRP	1.02 (0.79-1.32)	0.871	High CRP	1.06 (0.82-1.38)	0.638
Troponin-T>56ng/L	1.64 (1.18-2.29)	0.003	Troponin-T>56ng/L	1.72 (1.22-2.44)	0.002
Harrell's c	0.709 (0.676-0.740)	<0.001	Harrell's c	0.712 (0.79-0.745)	<0.001
<b>Multivariable Cox regression analysis for patient with a LVEF 40%</b>					
<b>Patients not censored for the start date of clinical trials and disease modifying therapy</b>			<b>Patients censored for the start date of clinical trials and disease modifying therapy</b>		
<b>Variable</b>	<b>HR (95%CI)</b>	<b>P-value</b>	<b>Variable</b>	<b>HR (95%CI)</b>	<b>P-value</b>
Age (years)	1.02 (1.01-1.04)	<0.001	Age (years)	1.02 (1.01-1.03)	0.004
hATTR-CA	1.58 (1.31-1.91)	<0.001	hATTR-CA	1.56 (1.28-1.91)	<0.001
NAC stage 1	ref		NAC stage 1	ref	
NAC stage 2	1.58 (1.30-1.93)	<0.001	NAC stage 2	1.57 (1.27-1.93)	<0.001
NAC stage 3	1.94 (1.51-2.50)	<0.001	NAC stage 3	2.08 (1.60-2.70)	<0.001
Anaemia	1.11 (0.94-1.31)	0.206	Anaemia	1.08 (0.91-1.29)	0.368
Hyponatraemia	1.43 (1.04-1.96)	0.028	Hyponatraemia	1.51 (1.08-2.10)	0.015
Uraemia	1.33 (1.09-1.61)	0.004	Uraemia	1.37 (1.12-1.68)	0.002
Hyperbilirubinemia	1.39 (1.13-1.72)	0.002	Hyperbilirubinemia	1.35 (1.08-1.69)	0.007
High ALP	1.06 (0.85-1.32)	0.604	High ALP	1.06 (0.85-1.69)	0.594
High GGT	1.15 (0.94-1.40)	0.166	High GGT	1.14 (0.92-1.40)	0.227
Hypoalbuminemia	1.95 (1.18-3.22)	0.009	Hypoalbuminemia	1.93 (1.16-3.20)	0.011
High CRP	1.19 (1.00-1.42)	0.054	High CRP	1.15 (0.96-1.38)	0.123
Troponin-T>56ng/L	1.72 (1.42-2.09)	<0.001	Troponin-T>56ng/L	1.61 (1.31-1.97)	<0.001
Harrell's c	0.719 (0.699-0.740)	<0.001	Harrell's c	0.714 (0.693-0.736)	<0.001

LVEF = Left ventricular ejection fraction; hATTR-CA = Hereditary transthyretin cardiac amyloidosis; NAC = National Amyloidosis Centre; HR = Hazard ratio; CI = Confidence interval; ALP = Alkaline phosphatase; GGT = gamma-glutamyl transferase; CRP = C-reactive protein.