Soluble Glycoprotein 130 Predicts Fatal Outcomes in Chronic Heart Failure

Analysis From the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)

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Background—Glycoprotein 130 (gp130) is the common signal-transducing receptor subunit of the interleukin-6 (IL-6) family, which may be involved in the progression of heart failure (HF). We hypothesized that soluble gp130 would provide prognostic information beyond that of IL-6 in a population with HF from the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA).

Methods and Results—The associations of soluble gp130 and IL-6 with morbidity, mortality, and mode of death were assessed by immunoassays in a subset of 1452 patients enrolled in the CORONA trial, which included patients with HF, aged ≥60 years, in New York Heart Association classes II to IV, who had ischemic heart disease and a reduced left ventricular ejection fraction. In multivariable analyses, including C-reactive protein, IL-6, troponin T, and N-terminal pro-B-type natriuretic peptide, elevated soluble gp130 (fifth quintile versus all lower quintiles) was associated with all-cause mortality (hazard ratio, 1.47 [1.11–1.93]; *P*=0.006), cardiovascular mortality (hazard ratio, 1.38 [1.01–1.87]; *P*=0.042), and death from worsening HF (hazard ratio, 1.85 [1.09–3.14]; *P*=0.002), but not with the primary end point (composite of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke; hazard ratio, 1.12 [0.84–1.50]; *P*=0.44). Plasma IL-6 was not associated with outcomes in multivariable analyses.

Conclusions—Marked elevations in soluble gp130 are associated with total and cardiovascular mortality, as well as deaths from worsening HF, in elderly patients with HF of ischemic cause.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00206310. **(*Circ Heart Fail*. 2013;6:91-98.)**

Key Words: heart failure ■ interleukin-6 ■ mortality ■ risk assessment ■ soluble glycoprotein 130

Inflammation is involved in the pathogenesis of heart failure (HF).[1,2] Although an inflammatory response is required for tissue repair after myocardial infarction,[3] prolonged or excessive inflammation may be maladaptive, leading to myocardial dysfunction and left ventricular (LV) remodeling.[4] Thus, although short-lived activation of interleukin-6 (IL-6) and related cytokines may be protective during ischemia, persistent activation of these mediators may lead to the development of cardiac hypertrophy and HF.[5,6] In line with this, increased plasma IL-6 levels, proportional to disease severity, have been shown in patients with chronic HF of both ischemic and nonischemic causes, and high IL-6 concentrations have been associated with increased morbidity and mortality in these patients.[5,7–9] Furthermore, 2 large genetic meta-analyses of >200 000 participants recently proposed a causative link between IL-6 signaling and coronary heart disease.[10,11]

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Within the myocardium, IL-6–type cytokines convey their signals predominantly through the signal transducer and activator of transcription 3 pathway via a glycoprotein 130 (gp130) receptor subunit.[5] The circulating levels of the

Received April 12, 2012; accepted November 29, 2012.

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The online-only Data Supplement is available at http://circheartfailure.ahajournals.org/lookup/suppl/doi:10.1161/CIRCHEARTFAILURE.112.972653/-/DC1.

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common receptor subunit, soluble gp 130 (sgp130), could potentially reflect the activity of the whole IL-6 family, including myocardial activation. We, and others, have reported elevated sgp130 levels in patients with HF,[7,12] but information on the prognostic relevance of sgp130 in HF is still limited.[13] In addition, comparisons of sgp130 and IL-6, as 2 markers of activity in the IL-6 cytokine family, for risk prediction in large HF cohorts are still lacking.

Accordingly, we investigated the association of sgp130 and IL-6 with outcomes in a subset of patients enrolled in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) trial, a large multicenter trial evaluating the effects of rosuvastatin in elderly patients with chronic, systolic HF of ischemic origin.

Methods

Patients and Study Procedures

The design and principal findings of CORONA have been reported in detail.[14] Briefly, patients aged ≥60 years with chronic HF attributed to ischemic heart disease, defined as (1) medical history or ECG signs of myocardial infarction, or (2) other data suggesting an ischemic cause (eg, wall motion disturbances on echocardiography or history of other occlusive atherosclerotic disease [ie, earlier stroke, intermittent claudication, percutaneous coronary intervention]), who were in New York Heart Association classes II to IV, with an LV ejection fraction ≤40% (≤35% if New York Heart Association class II), were eligible for inclusion. The trial complied with the Declaration of Helsinki and was approved by the Ethics Committees of the participating hospitals. All patients provided written informed consent. Patients were randomly assigned to rosuvastatin 10 mg/day or matching placebo, once-daily. The present study was an optional, predefined substudy of the main CORONA trial that included patients from centers capable of collecting the necessary blood samples. Baseline characteristics of the study population according to quintile values of sgp130 are shown in Table 1. Although in general similar to the main CORONA study, there were some modest but significant differences in the baseline characteristics between this substudy and the complete study population (Table I in the online-only Data Supplement).

As a result of limited amounts of serum/plasma, measurement of all biomarkers in all patients was not always possible. A detailed overview of missing biomarker data are given in the Figure in the online-only Data Supplement.

Study Outcomes and Definitions

The primary predefined outcome was the composite of death from cardiovascular (CV) causes, nonfatal myocardial infarction, and nonfatal stroke, analyzed as time to the first event. The secondary predefined outcomes were (1) all-cause mortality, (2) CV mortality (with an additional analysis of cause-specific death from a CV cause), (3) any coronary event (ie, sudden death, fatal or nonfatal myocardial infarction, performance of percutaneous coronary intervention or coronary artery bypass graft surgery, ventricular defibrillation by an implantable cardioverter-defibrillator, resuscitation from cardiac arrest, or hospitalization for unstable angina pectoris), and (4) the number of hospitalizations for CV causes, unstable angina, and worsening of HF (WHF). Details on the definition and adjudication of all outcomes are described elsewhere, as are data on C-reactive protein (CRP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP).[14–17]

Blood Sampling and Biochemical Analyses

Soluble gp130, IL-6, and troponin T (TnT) were measured from blood samples taken after an overnight fast. All other blood samples were nonfasting and analyzed on fresh samples at a central laboratory (Medical Research Laboratories, Zaventem, Belgium). NT-proBNP was analyzed using a commercially available assay (Roche Diagnostics, Basel, Switzerland). An immunonephelometric high-sensitivity method was used to measure CRP (Dade Behring, Atterbury, UK; sensitivity 0.04 mg/L). Plasma IL-6 was measured with a Randox multiplex cytokine high-sensitivity assay (Randox Laboratories Ltd, Crumlin, Co, Antrim, UK) with a detection limit of 0.4 pg/mL and inter- and intra-assay coefficient of variation of <20%. Seventeen patients had undetectable IL-6 levels. Serum TnT was analyzed with a high-sensitivity assay on a Roche Modular E170 platform with a lower detection limit of 3 ng/L (Roche Diagnostics). Serum sgp130 was measured by enzyme immunoassay (R&D Systems, Minneapolis, MN). The detection limit of the assay was 40 pg/mL, with interassay coefficient of variation of 5.9% and intra-assay coefficient of variation for high (1:100 dilutions) and low levels (1:400 dilutions) of 7.8% and 9.4%, respectively. All patients had detectable sgp130 concentrations. Furthermore, sgp130 showed a median intraindividual (n=8) diurnal variation over 3 time points of 8.8% (P=0.37), with no difference between fasting and nonfasting sgp130 levels (P=0.57). When analyzing sgp130 in serum samples over 4-point dilutions from the upper limit of the assay, we found a mean coefficient of variation of 7% (SD 1.7), indicating no, or only minor, matrix effects.

Statistical Analysis

Soluble gp130 was initially evaluated as a log-transformed, continuous variable and found to predict fatal outcomes, with no associations with the primary end point or hospitalizations (Table II in the online-only Data Supplement). A restricted cubic spline analysis with 5 knots revealed nonlinearity of risk for all-cause mortality (significant end point for continuous sgp130 with the highest number of events), with a marked increase in poor outcome per unit increase in sgp130 for those patients with the highest sgp130 concentrations (Figure 1A). The turning point for the restricted cubic spline curve corresponded approximately to the transition between the fourth and the fifth quintile of sgp130. We subsequently dichotomized sgp130 by the fifth versus the fourth lower quintiles in all further analyses. Plasma IL-6 displayed linearity of risk in the restricted cubic spline analysis and was included as a log-transformed, continuous variable in multivariable analyses.

Differences between the top quintile and the bottom 4 quintiles of sgp130 were tested with Student t test for normally distributed baseline variables, Fisher exact test for categorical data, and Wilcoxon rank-sum test for non-normally distributed variables. Trends over sgp130 quintiles were tested with the Cuzick extension of the Wilcoxon rank-sum test, and all baseline variables with a P value for trend <0.05 were included in a multivariable analysis to identify degree of association with sgp130.

Survival analyses were conducted using the Cox proportional hazard regression model where sgp130 was included in a version of the 3-stage model described elsewhere,[17] which included mainly clinical variables at step 1 (LV ejection fraction, New York Heart Association class, age, body mass index, diabetes mellitus, sex, intermittent claudication, and heart rate). At step 2, the estimated glomerular filtration rate and apolipoprotein B/apolipoprotein A-1 ratio were included in the model. At stage 3, the log-transformed plasma concentrations of NT-proBNP, IL-6 and CRP were included, and, finally, at stage 4, the log-transformed serum concentration of TnT was included. Harrell C-statistic was calculated for all end points using the multivariable model with and without sgp130, and the difference between the C-statistics was estimated. We calculated C-statistics both without (step 3) and with TnT values (step 4) (Table 2). To correct for overoptimism associated with validating a model in the same material from which it is developed, we implemented a jack-knife cross-validation approach, where predictions for each observation were obtained from models developed on the remaining observations. These cross-validated probabilities were used to calculate jack-knife C-statistics. Recently, calculation of net reclassification improvement (NRI) has been suggested for the evaluation of the prognostic usefulness of a biomarker.[18] In particular, when no established risk categories exist, the use of a category-free NRI has been advocated.[19] We, therefore, calculated the category-free NRI after adding sgp130 to the multivariable model at step 3 and step 4. Confidence intervals and P values for NRI were determined by boot-strapping with

Table 1. Baseline Patient Characteristics

Variable	Total	sgp130 Quintiles					*P*, Trend	*P*, Q5
		First	Second	Third	Fourth	Fifth		
Sgp130 range, ng/mL		106.0–274.2	274.3–317.5	317.6–363.9	364.0–438.1	438.2–786.7		
Age, y	71.8 (6.9)	71.5 (7.3)	71.9 (6.7)	71.7 (6.6)	72.3 (6.9)	71.5 (6.8)	0.810	0.378
Female sex	339 (23.3)	62 (21.3)	71 (24.5)	66 (22.7)	69 (23.8)	71 (24.5)	0.477	0.642
Smoking	175 (12.1)	33 (11.3)	37 (12.8)	38 (13.1)	25 (8.6)	42 (14.5)	0.684	0.159
NYHA Class							0.667	0.162
II	468 (32.2)	99 (34.0)	81 (27.8)	88 (30.6)	115 (39.4)	85 (29.3)		
III	967 (66.6)	186 (63.9)	208 (71.5)	197 (68.4)	172 (58.9)	204 (70.3)		
IV	17 (1.2)	6 (2.1)	2 (0.7)	3 (1.0)	5 (1.7)	1 (0.3)		
Ejection fraction, %	32 (7)	32 (7)	32 (6)	32 (7)	31 (7)	31 (7)	0.026	0.266
BMI, kg/m^2	27.3 (4.6)	27.3 (4.5)	27.3 (4.4)	27.4 (4.7)	27.4 (4.3)	26.9 (5.0)	0.193	0.143
SBP, mm Hg	130 (16.0)	128 (15)	130 (16)	130 (16)	130 (17)	130 (16)	0.156	0.353
DBP, mm Hg	77 (9)	76 (9)	78 (9)	76 (8)	77 (10)	77 (9)	0.649	0.592
Heart rate, bpm	71 (11)	70 (10)	70 (10)	70 (10)	71 (11)	73 (12)	0.006	0.000
Medical history								
Hypertension	1013 (69.8)	183 (62.9)	213 (73.2)	201 (69.8)	206 (70.5)	210 (72.4)	0.054	0.284
Diabetes mellitus	377 (26.0)	57 (19.6)	67 (23.0)	81 (28.1)	85 (29.1)	87 (30.0)	0.001	0.085
Atrial fibrillation/flutter	318 (21.9)	51 (17.5)	62 (21.4)	55 (18.9)	64 (22.1)	86 (29.7)	0.001	0.001
Myocardial infarction	916 (63.1)	172 (59.1)	169 (58.1)	199 (69.1)	189 (64.7)	187 (64.5)	0.052	0.634
PCI or CABG	301 (20.7)	54 (18.6)	73 (25.1)	50 (17.4)	57 (19.5)	67 (23.1)	0.641	0.292
Stroke	173 (11.9)	33 (11.3)	41 (14.1)	36 (12.5)	36 (12.3)	27 (9.3)	0.334	0.155
Intermittent claudication	156 (10.7)	22 (7.6)	35 (12.0)	34 (11.8)	34 (11.6)	31 (10.7)	0.306	1.000
Laboratory measures								
Total cholesterol, mmol/L	5.23 (1.09)	5.27 (0.98)	5.38 (1.05)	5.29 (1.18)	5.14 (1.09)	5.07 (1.14)	0.001	0.006
LDL, mmol/L	3.64 (0.97)	3.58 (0.91)	3.71 (0.88)	3.71 (1.10)	3.64 (1.01)	3.55 (0.95)	0.404	0.072
HDL, mmol/L	1.23 (0.34)	1.22 (0.29)	1.25 (0.36)	1.23 (0.35)	1.23 (0.33)	1.24 (0.37)	0.890	0.603
Triglycerides, mmol/L	2.01 (1.39)	2.07 (1.57)	1.91 (1.02)	1.95 (1.21)	2.02 (1.38)	2.10 (1.69)	0.632	0.212
Apo B/Apo A-1 value	0.89 (0.25)	0.87 (0.24)	0.90 (0.26)	0.92 (0.29)	0.88 (0.23)	0.87 (0.24)	0.807	0.165
$eGFR_{MDRD}$, mL/min per 1.73 m^2	57 (14)	59 (14)	58 (13)	58 (14)	55 (15)	57 (15)	0.016	0.744
CRP, mg/L	3.7 (1.6–7.7)	3.8 (1.8–8.0)	3.4 (1.5–7.2)	3.6 (1.6–8.4)	4.4 (1.7–7.6)	3.4 (1.6–6.8)	0.710	0.294
NT-proBNP, pmol/L	160 (59–341)	135 (53–302)	124 (49–258)	162 (66–333)	186(80–349)	217(73–494)	<0.001	<0.001
IL-6, pg/mL	3.0 (1.9–5.5)	2.8 (1.9–5.0)	2.9 (1.7–5.3)	2.8 (1.8–5.0)	3.0 (2.1–5.7)	3.2 (1.8–6.5)	0.034	0.113
Troponin T, ng/L	13.9 (6.6–25.6)	11.4 (4.6–20.2)	11.5 (4.8–23.1)	13.5 (7.3–25.3)	16.5 (8.6–29.9)	16.3 (7.8–30.8)	<0.001	<0.001
sgp130, ng/mL	339 (286–417)	243 (221–260)	296 (286–307)	339 (329–352)	397 (381–417)	515 (474–587)		
Medications								
Diuretics							0.003	0.121
Thiazide or loop	1105 (76.1)	240 (82.5)	228 (78.4)	213 (74.0)	213 (72.9)	211 (72.8)		
Thiazide and loop	157 (10.8)	16 (5.5)	20 (6.9)	35 (12.2)	45 (15.4)	41 (14.1)		
Aldosterone antagonist	530 (36.5)	95 (32.6)	105 (36.1)	106 (36.8)	104 (35.6)	120 (41.4)	0.057	0.056
ACE inhibitor	1168 (80.4)	224 (77.0)	238 (81.8)	238 (82.6)	238 (81.5)	230 (79.3)	0.549	0.620
ARB	147 (10.1)	29 (10.0)	27 (9.3)	30 (10.4)	32 (11.0)	29 (10.0)	0.754	1.000
β-Blocker	1108 (76.3)	213 (73.2)	225 (77.3)	223 (77.4)	231 (79.1)	216 (74.5)	0.578	0.440
Digitalis glycoside	418 (28.8)	65 (22.3)	78 (26.8)	73 (25.3)	89 (30.5)	113 (39.0)	<0.001	<0.001

Clinical and biochemical baseline characteristics stratified by quintile values of sgp130. CRP, NT-proBNP, IL-6, TnT, and sgp130 are displayed as median value (25th–75th percentiles). Other variables are shown as number (percentage of total) or as mean (SD) where appropriate. ACE indicates angiotensin-converting enzyme; ApoA-1, apolipoprotein A-1; ApoB, apolipoprotein B; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IL-6, interleukin 6; LDL, low-density lipoprotein; MDRD, modification of diet in renal disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; *P*, trend, probability value for trend across all quintiles; *P*, Q5, probability value for fifth quintile compared with all lower quintiles; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; sgp130, soluble glycoprotein 130; and TnT, troponin T.

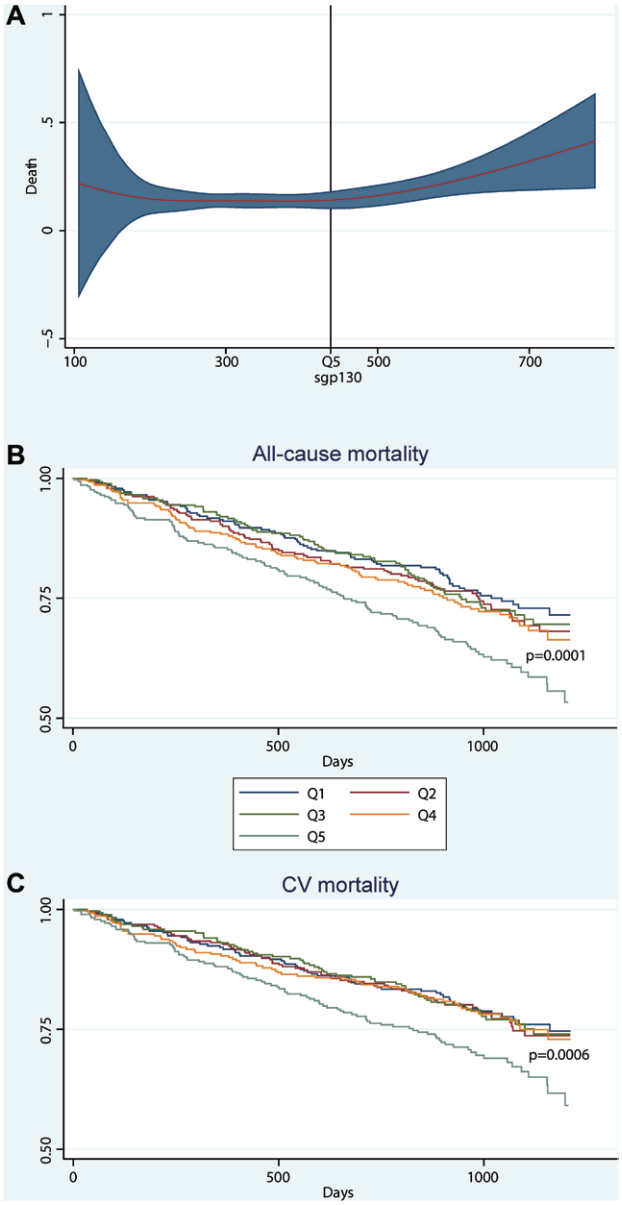

Figure 1. Restricted cubic spline analysis showed nonlinearity of risk for all-cause mortality, with increasing risk from approximately Q5 (**A**); fitted curve with 95% confidence interval. Kaplan–Meier curves for all-cause (**B**) and cardiovascular (CV; **C**) mortality according to quintile sgp130 concentration. Q1 indicates lowest quintile serum sgp130; and Q5, highest quintile serum sgp130. Patients with the highest sgp130 levels (Q5) displayed markedly reduced survival compared with all lower quintiles (Q1–4); *P*=0.0001 for all-cause mortality, *P*=0.0006 for CV mortality.

2000 repetitions. A 2-sided $P<0.05$ was considered to be significant, except for interaction terms, for which $P<0.10$ were accepted. All statistical analyses were performed using STATA version 11 for Windows (StataCorp, College Station, TX).

Results

Serum sgp130 was measured at baseline and at 3 months in 1452 patients. Patients in the top quintile of sgp130 were more likely to be in atrial fibrillation, take digoxin, and had slightly higher heart rates (Table 1). They also had lower cholesterol and higher NT-proBNP and TnT. In addition, patients in higher quintiles had more diabetes mellitus, slightly worse renal function, lower LV ejection fraction, and were more likely to be taking loop and thiazide diuretics in combination. In multivariable regression modeling, diabetes mellitus, digitalis use, use of loop and thiazide diuretics combined, and TnT remained associated with sgp130. TnT was the strongest determinant of sgp130, but explained only ≈2.5% of the variation in baseline sgp130 concentration.

IL-6 and sgp130 Levels and Association With Outcomes

During a median follow-up of 955 (25th–75th percentiles, 817–1103) days, 411 patients reached a primary end point and 425 patients died. Kaplan–Meier plots for all-cause and CV mortality revealed a markedly reduced survival for patients in sgp130 Q5 compared with all lower quintiles combined (Figure 1B and 1C).

When adjusting for demographic and clinical variables (step 1) in a 4-step multivariable analysis, sgp130 was associated with all-cause mortality, death because of CV causes, including death from WHF, and hospitalization because of WHF. However, sgp130 was associated with neither the primary nor the coronary end point (Table 2). The inclusion of medications and extended medical history in an expanded Cox model did not alter these associations substantially (Table III in the online-only Data Supplement). The associations with mortality remained significant after adjusting for apolipoprotein B/apolipoprotein A-1 ratio and estimated glomerular filtration rate (step 2). After correcting for NT-proBNP, IL-6 and CRP (step 3), and TnT (step 4) sgp130 remained a strong predictor for overall mortality and death from CV causes, including death from WHF, with little change in hazard ratio from the unadjusted model (Table 2). Importantly, although related to sgp130, log-transformed, continuous IL-6 showed no association with any of the end points after adjustment for CRP and NT-proBNP (Table IV in the online-only Data Supplement).

Although area under curve analyses revealed limited discriminatory value of sgp130 alone (Table 3), addition of sgp130 in the multivariable analyses did not substantially alter effects of other variables (Table V in the online-only Data Supplement), suggesting incremental value of sgp130 and a noncompeting relationship to conventional risk factors and established biomarkers. This finding is further underscored by highly significant continuous NRIs for both all-cause (NRI 0.24; $P<0.001$) and CV mortality (NRI 0.22; $P=0.006$) when sgp130 was added to the multivariable models in step 3 (Figure 2 and Table 2). However, when accounting for TnT (step 4), sgp130 did not enhance risk prediction for any end points (Table 2). Finally, sgp130 used as a continuous variable carried similar prognostic information in models adjusted for clinical variables alone, but when adjusted for NT-proBNP, the association with CV death was of only borderline significance ($P=0.06$), and significance for all outcomes was lost after adjusting for TnT (Table II in the online-only Data Supplement).

Effect of Rosuvastatin Treatment on IL-6- and sgp130 Levels and Clinical Outcomes

Plasma IL-6 and serum sgp130 concentrations were similar at baseline and 3-month follow-up (continuous variable) both in patients assigned to placebo and rosuvastatin ($P=0.99$ and

Table 2. Multivariable Analyses: Effects of sgp130 on Outcomes

sgp130, Quintiles		Events	HR (95% CI)	*P*	Wald	C Index, Δ*	NRI
Primary end point							
Step 1†	n=1449	411	1.19 (0.95–1.50)	0.137	2.21		
Step 2‡	n=1434	408	1.22 (0.97–1.54)	0.091	2.85		
Step 3§	n=1183	314	1.22 (0.93–1.59)	0.154	2.04	<–0.0001 (0.96)	0.14 (0.067)
Step 4‖	n=1015	270	1.12 (0.84–1.50)	0.438	0.60	0.0007 (0.49)	0.04 (0.61)
All-cause mortality							
Step 1		425	1.40 (1.12–1.74)	0.003	9.06		
Step 2		422	1.43 (1.15–1.78)	0.001	10.20		
Step 3		322	1.54 (1.20–1.98)	0.001	11.20	0.0047 (0.15)	0.24 (<0.001)
Step 4		275	1.47 (1.11–1.93)	0.006	7.42	–0.0043 (0.16)	0.16 (0.051)
Death from CV cause							
Step 1		346	1.38 (1.08–1.76)	0.009	6.76		
Step 2		344	1.41 (1.10–1.80)	0.006	7.60		
Step 3		263	1.47 (1.11–1.95)	0.007	7.17	0.0035 (0.25)	0.22 (0.006)
Step 4		225	1.38 (1.01–1.87)	0.042	4.12	–0.0026 (0.33)	0.11 (0.19)
Death from WHF							
Step 1		102	1.98 (1.31–2.99)	0.001	10.40		
Step 2		102	2.00 (1.32–3.04)	0.001	10.50		
Step 3		78	2.25 (1.39–3.66)	0.001	10.80	0.0140 (0.11)	0.32 (0.090)
Step 4		69	1.85 (1.09–3.14)	0.023	5.15	–0.0060 (0.47)	0.18 (0.39)
Sudden death							
Step 1		196	1.07 (0.75–1.51)	0.714	0.13		
Step 2		194	1.09 (0.77–1.55)	0.620	0.25		
Step 3		150	1.21 (0.82–1.79)	0.340	0.91	<–0.0001 (0.97)	0.19 (0.068)
Step 4		129	1.25 (0.83–1.90)	0.286	1.14	<–0.0001 (0.99)	0.075 (0.42)
Coronary end point							
Step 1		332	1.00 (0.76–1.31)	0.984	<0.001		
Step 2		327	0.99 (0.75–1.30)	0.955	0.003		
Step 3		254	1.00 (0.73–1.36)	0.989	<0.001	–0.002 (<0.001)	–0.09 (0.29)
Step 4		212	0.95 (0.67–1.01)	0.759	0.094	0.0017 (0.025)	–0.053 (0.35)
Hospitalization, CV causes							
Step 1		611	1.14 (0.94–1.39)	0.190	1.72		
Step 2		605	1.12 (0.92–1.37)	0.242	1.37		
Step 3		491	1.03 (0.82–1.28)	0.825	0.049	–0.001 (<0.001)	<0.01 (0.92)
Step 4		417	1.00 (0.79–1.28)	0.977	<0.001	0.0012 (<0.001)	–0.013 (0.85)
Hospitalization from WHF							
Step 1		329	1.30 (1.01–1.68)	0.042	4.15		
Step 2		327	1.28 (0.99–1.66)	0.057	3.62		
Step 3		268	1.18 (0.89–1.58)	0.258	1.28	–0.0006 (0.64)	0.07 (0.36)
Step 4		232	1.23 (0.91–1.68)	0.181	1.79	0.0007 (0.70)	0.05 (0.52)

Soluble gp130, dichotomized by fifth (Q5) versus all lower quintiles (Q1–4), as a predictor of outcome. All hazard ratios (HR) are given as HR (95% confidence interval). ApoA-1 indicates apolipoprotein A-1; ApoB, apolipoprotein B; C index, Δ, difference in C index between adjusted models with and without inclusion of sgp130, corresponding (*P* value); CRP, C-reactive protein; CV, cardiovascular; LVEF, left ventricular ejection fraction; NRI, net reclassification improvement calculated from C indexes for adjusted models with and without inclusion of sgp130, corresponding (*P* value); NYHA, New York Heart Association; and WHF, worsening heart failure.

*C index, Δ: difference in C index between adjusted models with and without inclusion of sgp130, corresponding *P* value.

The models are adjusted as follows: †Step 1: LVEF, NYHA functional class, age, body mass index, diabetes mellitus, sex, intermittent claudication and heart rate.

‡Step 2: All variables from step 1, as well as ApoB/Apo A-1 ratio and estimated glomerular filtration rate.

§Step 3: All variables from step 2, as well as NT-proBNP, IL-6, and CRP.

‖Step 4: All variables from step, 3 as well as troponin T.

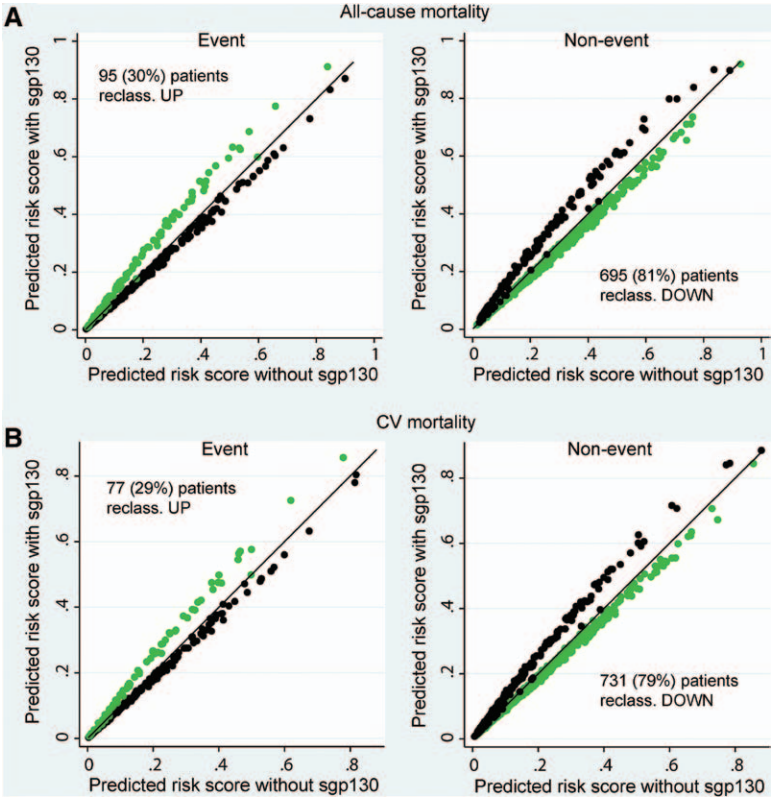

Figure 2. Net reclassification improvements (NRIs) of sgp130 on all-cause (**A**) and cardiovascular (CV; **B**) mortality at step 3; NRI 0.24, *P*<0.001 for all-cause mortality and NRI 0.22, *P*=0.006 for CV mortality. Ideally, all patients with events are reclassified upward (higher risk), and all patients without events are reclassified downward (lower risk). Green dots indicate improved risk estimation.

0.36, respectively). No interaction was observed between neither IL-6 nor sgp130 and treatment group. Furthermore, sgp130 performed similarly in multivariable analyses in both the total (Table 2) and the placebo arm (Table VI in the online-only Data Supplement) of the study population.

Discussion

In this post hoc analysis of CORONA, we found that serum concentrations of sgp130, but not IL-6, were associated with fatal outcomes in a large population of elderly patients with chronic systolic HF of ischemic origin.

We, and others, have demonstrated elevated levels of sgp130 in HF patients, with increasing levels according to disease severity.[7,12,20] However, few patients (n<100 in each study) were included in these reports. Gwechenberger et al[13] also reported an association between sgp130 and WHF, independently of NT-proBNP, in a small HF population of mixed cause. We now show, in a large population of HF patients with many events, that serum levels of sgp130 are associated with all-cause and CV mortality, including death from WHF, even after adjusting for NT-proBNP, CRP, IL-6, and TnT. To our knowledge, this is the first large-scale evaluation of the predictive power of sgp130 in HF.

The ability to reflect several upstream pathogenic pathways is a desirable feature of a biomarker.[21] The capacity of sgp130 to mirror the activity of several IL-6–related cytokines, of which many have been implicated in the pathogenesis of HF,[5,6] may account for its association with fatal outcomes in this analysis. In contrast to IL-6, sgp130 was associated with all fatal outcomes, except for sudden death, in the fully

Table 3. Area Under Curve: sgp130 vs NT-proBNP

End Point	sgp130, Q5	*P*	NT-proBNP	*P*	IL-6	*P*
Primary end point	0.522 (0.501–0.543)	0.042	0.676 (0.646–0.707)	<0.001	0.590 (0.561–0.617)	<0.001
All-cause mortality	0.537 (0.516–0.559)	0.001	0.691 (0.662–0.720)	<0.001	0.612 (0.584–0.641)	<0.001
Death from CV causes	0.536 (0.513–0.560)	0.003	0.707 (0.675–0.739)	<0.001	0.608 (0.577–0.640)	<0.001
Death from WHF	0.576 (0.529–0.623)	0.002	0.753 (0.700–0.808)	<0.001	0.661 (0.609–0.713)	<0.001
Sudden death	0.511 (0.481–0.540)	0.475	0.688 (0.644–0.733)	<0.001	0.574 (0.531–0.618)	0.001
Hospitalization for CV causes	0.518 (0.500–0.535)	0.040	0.617 (0.592–0.642)	<0.001	0.566 (0.548–0.590)	<0.001
Hospitalization for WHF	0.534 (0.510–0.558)	0.005	0.692 (0.661–0.723)	<0.001	0.614 (0.584–0.645)	<0.001
Coronary end point	0.504 (0.482–0.526)	0.729	0.643 (0.608–0.677)	<0.001	0.561 (0.528–0.594)	<0.001

AUC (95% CI) of sgp130 as a categorical (top quintile versus lower four quintiles) variable compared with AUC of NT-proBNP and IL-6 for all end points. AUC indicates area under curve; CI, confidence interval; CV, cardiovascular; IL-6, interleukin-6; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sgp130, soluble glycoprotein 130; and WHF, worsening heart failure.

adjusted Cox model. This suggests that sgp130 might better reflect IL-6–type activity than IL-6 itself. From a practical point of view, IL-6 circulates at low levels (<10 pg/mL), often just above the detection limit of the assay, whereas sgp130 circulates at high concentrations (>100 ng/mL), making it more suitable as a clinical biomarker.

Soluble gp130 acts as a decoy receptor (R) for IL-6/sIL-6Rα complexes, when present in molar excess.[22] We hypothesize that sgp130 expression might be a compensatory response to limit IL-6 trans-signaling. In line with this, we suggest that considerably elevated sgp130 levels in patients with HF may reflect markedly enhanced gp130/signal transducer and activator of transcription 3 signaling in these patients. Although gp130-mediated signaling may confer cardioprotective properties through compensatory hypertrophy, tissue repair, and reduced apoptosis,[23] continuous and markedly increased activation of this signaling, potentially reflected by increased sgp130 levels, might have deleterious effects.[24] It is conceivable that the nonlinear risk increase seen for sgp130 in the present study may reflect a shift from compensatory to detrimental gp130-mediated signaling in relation to particularly high levels of sgp130.

In contrast to its association with fatal end points, sgp130 was not associated with the primary end point that included contributions from multiple disease mechanisms (ie, HF/LV remodeling, atherosclerotic/vascular disease, intracranial hemorrhage). It is unlikely that the prognostic usefulness of sgp130 for all aforementioned disease mechanisms would be equally prominent. In fact, experimental studies suggest that inhibition of IL-6 trans-signaling could reduce rather than enhance atherogenesis.[25] The association between sgp130 levels and atherosclerosis may, therefore, be more complex, which again could influence its lack of association with the primary end point.

Recent evidence supports targeting of IL-6 signaling as a therapeutic strategy for reducing CV disease.[10,11] The novel fusion protein sgp130Fc, which mimics natural, circulating sgp130, selectively inhibits IL-6 trans-signaling.[26] We hypothesize that measurements of sgp130 might be used to stratify patients most likely to benefit from sgp130Fc therapy, on the basis of ongoing, excessive IL-6 trans-signaling. The first human phase I study of sgp130Fc in chronic inflammatory diseases is scheduled for this year,[26] and it is tempting to suggest that similar studies should be performed in chronic HF.

Herein, we demonstrate that sgp130 is associated with all-cause and CV mortality and death from WHF also after multivariable adjustment. Applying sgp130 concentrations to adjusted multivariable models without TnT resulted in significant continuous NRIs for all-cause and CV mortality. However, sgp130 did not enhance risk prediction in our study population when TnT was accounted for. Area under curve analyses favored NT-proBNP as the best single marker for all end points and also demonstrated limited isolated discriminatory power of sgp130 (Table 3). Still, new biomarkers might offer information on pathophysiological processes poorly reflected by today's state-of-the-art biomarkers, despite having lower receiver operating characteristics. Although NT-proBNP, and potentially also TnT, is a strong predictor of adverse outcome in patients with HF, it is unlikely that these biomarkers could reflect all pathogenic pathways that are involved in this complex disorder.

The present study examined multiple end points in a large HF population with a considerable number of events. However, for some subgroup analyses, including the interaction of sgp130 with rosuvastatin, there were relatively few events, and, therefore, these data should be interpreted cautiously. The discriminatory properties of sgp130 alone (Table 3) were limited in our population, implying that at present, the clinical usefulness of sgp130 is questionable. Also, not all markers (eg, TnT) were analyzed in all patients, which may have influenced the power of our analyses. In addition, we used a cut point derived from an analysis of one end point (all-cause mortality) on all other outcomes, which may have influenced the results. However, continuous sgp130 performed similarly to this cut point in the Cox regression, and the risk of substantially skewing the results in favor of all-cause mortality, therefore, seems limited. Our study was performed in trial patients aged ≥60 years, with LV systolic dysfunction and ischemic heart disease and a low prevalence of non-CV comorbidity (eg, chronic obstructive pulmonary disease). Thus, the results may not apply to all patients with HF. Also, we could not include an acknowledged HF risk model (eg, Seattle HF risk score) in the multivariable analyses as we did not have all the requisite variables. Finally, there is a need for more standardized methods for measuring sgp130, with an established normal range, before it is ready for use in clinical practice.

In conclusion, serum sgp130 was associated with fatal outcomes in patients with chronic systolic HF of ischemic cause, but did not seem to predict vascular events, and sgp130 did not enhance risk prediction when TnT was accounted for. Nonetheless, our findings may suggest a role for sustained activation of the gp130/signal transducer and activator of transcription 3 signaling pathway in the pathogenesis of HF, and the role of IL-6–related cytokines as a target for therapy in HF should be explored further. Furthermore, larger studies in more heterogeneous HF populations have to be performed before advocating implementation of sgp130 as a biomarker in clinical practice.

Sources of Funding

This study was supported by a grant from an anonymous benefactor. The CORONA study was funded by AstraZeneca.

Disclosures

J.K., J.J.V.M., J.G.F.C., and L.G. were on the CORONA steering committee and have received lecture fees from AstraZeneca. J.J.V.M. and J.G.F.C. have received research grants from AstraZeneca. The other authors have no conflicts to report.

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CLINICAL PERSPECTIVE

Soluble glycoprotein 130 (sgp130) is a decoy receptor for the central proinflammatory cytokine interleukin-6 (IL-6), a marker associated with heart failure (HF) development and myocardial remodeling. IL-6 was also recently causally implicated as a mediator in the pathogenesis of coronary heart disease, and several experimental studies suggest targeting of IL-6 signaling as a therapeutic strategy for reducing cardiovascular disease. Soluble gp130 has been suggested to reflect the activity of IL-6–related cytokines. To determine the role of circulating sgp130 in the prediction of fatal and nonfatal outcomes in HF, we investigated serum levels of sgp130 in a large contemporary cohort of older patients with systolic HF, receiving modern pharmacological therapy, randomly assigned to statin therapy or placebo in a double-blind fashion. Sgp130 independently predicted fatal outcomes and improved risk prediction after adjustment for conventional risk markers, as well as C-reactive protein, IL-6, and N-terminal pro-B-type natriuretic peptide. However, when also accounting for troponin T, sgp130 remained independently predictive of mortality, but no longer provided incremental value in risk assessment as assessed by net reclassification improvement scores. In contrast, IL-6 was not associated with any end points after multivariable adjustment. Our data support involvement of IL-6 type signaling in chronic HF and suggest that serum sgp130 might partly reflect unmodified biological events in HF progression. Measurements of sgp130 might be used in risk stratification of patients with HF and possibly also to identify patients most likely to benefit from IL-6 inhibition.

Soluble Glycoprotein 130 Predicts Fatal Outcomes in Chronic Heart Failure: Analysis From the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)

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Circ Heart Fail. 2013;6:91-98; originally published online December 10, 2012;
doi: 10.1161/CIRCHEARTFAILURE.112.972653
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3289. Online ISSN: 1941-3297

SUPPLEMENTAL MATERIAL

Soluble Glycoprotein 130 Predicts Fatal Outcomes In Chronic Heart Failure: Analysis From The Controlled Rosuvastatin Multinational Trial In Heart Failure (CORONA)

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Supplemental Table I. Baseline differences between total CORONA population and sgp130 sub-study.

CRP and NT-proBNP are displayed as median value (25^{th}-75^{th} percentiles). Other variables are shown as number (percentage of total) or as mean (standard deviation) where appropriate.

Variable	**CORONA Total study** n=5011	**CORONA sgp130 sub-study** n=1452	***P*-value**
Age	72.7 (7.1)	71.8 (6.9)	<0.001
Sex (female)	1180 (23.5)	339 (23.3)	0.888
NYHA class			0.002
II	1857 (37.1)	468 (32.2)	
III	3081 (61.5)	967 (66.6)	
IV	73 (1.5)	17 (1.2)	
LVEF (%)	31 (6)	32 (7)	<0.001
BMI (kg/m^2)	27.2 (4.5)	27.3 (4.6)	0.657
SBP (mmHg)	129 (16)	130 (16)	0.526
DBP (mmHg)	76 (9)	77 (9)	0.002
Heart rate (b.p.m)	72 (11)	71 (11)	0.017
Smoking	528 (10.5)	175 (12.1)	0.114
Medical history			
Prior MI	3006 (60.0)	916 (63.1)	<0.001
Prior PCI or CABG	1229 (24.5)	301 (20.7)	<0.001
Hypertension	3175 (63.4)	1013 (69.8)	<0.001
Diabetes Mellitus	1477 (29.5)	377 (26.0)	0.009
Stroke	624 (12.5)	173 (11.9)	0.618
Intermittent Claudication	637 (12.7)	156 (10.7)	0.046
COPD	109 (2.2)	29 (2.0)	0.757
Biochemistry			

Total Cholesterol (mmol/L)	5.17 (1.08)	5.23 (1.09)	0.068
LDL (mmol/L)	3.55 (0.94)	3.64 (0.97)	0.002
HDL (mmol/L)	1.23 (0.35)	1.23 (0.34)	0.993
Triglycerides (mmol/L)	2.00 (1.28)	2.01 (1.39)	0.817
Apo B/Apo A-1 value	0.87 (0.25)	0.89 (0.25)	0.082
$eGFR_{MDRD}$ (mL/min/1.73 m^2)	57.1 (14.4)	57.4 (14.2)	0.458
NT-proBNP (pmol/L)	173 (73-368)	160 (59-341)	0.032
CRP (mg/L)	3.5 (1.6-7.5)	3.7 (1.6-7.7)	0.207
Medication			
Diuretics			<0.001
None	677 (13.5)	190 (13.1)	
Loop OR Thiazide	3977 (79.4)	1105 (76.1)	
Loop AND Thiazide	357 (7.1)	157 (10.8)	
Aldosterone antagonist	1906 (38.0)	530 (36.5)	0.296
ACE-inhibitor	3981 (79.4)	1168 (80.4)	0.416
ARB	637 (12.7)	147 (10.1)	0.008
Beta blocker	3722 (74.3)	1108 (76.3)	0.123
Digitalis glycoside	1618 (32.3)	418 (28.8)	0.011

NYHA, New York Heart Association; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ApoB, apolipoprotein B; ApoA-1, apolipoprotein A-1; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; CRP, C-reactive protein; NT-proBNP, amino-terminal pro-brain natriuretic peptide; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker.

Supplemental Table II. Multivariable analyses – effects of continuous sgp130 on outcomes.

log gp130, continuous variable		Events	HR	(95% CI)	*p*-value	Wald
Primary endpoint						
Unadjusted	n=1452	411	1.50	(1.08 - 2.08)	0.016	5.78
*Step 1**	n=1449	411	1.32	(0.95 - 1.85)	0.100	2.70
Step 2†	n=1434	408	1.32	(0.94 - 1.85)	0.112	2.52
Step 3‡	n=1196	311	1.25	(0.84 - 1.85)	0.275	1.19
Step 4§	n=1015	270	0.98	(0.64 - 1.49)	0.912	0.012
All-cause mortality						
Unadjusted		425	1.91	(1.38 - 2.64)	0.000	15.4
Step 1		425	1.65	(1.19 - 2.29)	0.003	8.89
Step 2		422	1.64	(1.17 - 2.29)	0.004	8.27
Step 3		322	1.75	(1.19 - 2.59)	0.004	8.07
Step 4		275	1.37	(0.90 - 2.08)	0.146	2.11
Death from CV cause						
Unadjusted		346	1.77	(1.24 - 2.53)	0.002	9.70
Step 1		346	1.53	(1.06 - 2.20)	0.023	5.16
Step 2		344	1.51	(1.04 - 2.19)	0.031	4.67
Step 3		263	1.52	(0.99 - 2.34)	0.058	3.59

Step 4	225	1.19	(0.75 - 1.90)	0.466	0.53
Death from WHF					
Unadjusted	102	3.02	(1.58 - 5.79)	0.001	11.1
Step 1	102	2.51	(1.28 - 4.90)	0.007	7.21
Step 2	102	2.51	(1.27 - 4.94)	0.008	7.08
Step 3	78	3.26	(1.50 - 7.08)	0.003	8.90
Step 4	69	1.90	(0.83 - 4.37)	0.129	2.30
Sudden death					
Unadjusted	196	1.33	(0.82 - 2.15)	0.244	1.36
Step 1	196	1.19	(0.73 - 1.93)	0.489	0.48
Step 2	194	1.15	(0.70 - 1.90)	0.574	0.32
Step 3	150	1.09	(0.61 - 1.94)	0.782	0.077
Step 4	129	1.00	(0.54 - 1.88)	0.991	0.00014
Coronary endpoint					
Unadjusted	332	1.16	(0.80 - 1.68)	0.425	0.64
Step 1	332	1.07	(0.74 - 1.56)	0.712	0.14
Step 2	327	1.01	(0.69 - 1.48)	0.949	0.0041
Step 3	254	0.89	(0.57 - 1.37)	0.590	0.29
Step 4	212	0.76	(0.47 - 1.23)	0.265	1.24
Hospitalization, CV causes					
Unadjusted	613	1.59	(1.22 - 2.08)	0.001	11.4

Step 1	611	1.47	(1.12 - 1.94)	0.006	7.45
Step 2	605	1.41	(1.06 - 1.86)	0.017	5.67
Step 3	491	1.20	(0.87 - 1.64)	0.270	1.22
Step 4	417	1.07	(0.76 - 1.50)	0.717	0.13
Hospitalization from WHF					
Unadjusted	330	1.86	(1.29 - 2.68)	0.001	10.9
Step 1	329	1.67	(1.14 - 2.43)	0.008	7.03
Step 2	327	1.58	(1.08 - 2.32)	0.018	5.57
Step 3	268	1.32	(0.85 - 2.05)	0.213	1.55
Step 4	232	1.19	(0.74 - 1.89)	0.470	0.52

The models are adjusted as follows: **Step 1:* LVEF, NYHA functional class, age, body mass index, diabetes mellitus, sex, intermittent claudication and heart rate. †*Step 2:* All variables from Step 1 as well as ApoB/Apo A-1 ratio and estimated glomerular filtration rate. ‡*Step 3:* all variables from Step 2 as well as NT-proBNP, IL-6 and CRP. §*Step 4:* All variables from Step 3 as well as troponin T. CV, cardiovascular; WHF, worsening heart failure.

Supplemental Table III. Multivariable analyses – effects of extended medical history and medication.

sgp130, quintiles		Primary endpoint	All-cause mortality	Death from CV causes	Death from WHF	Sudden death	Coronary endpoint	Hospitalization, CV causes	Hospitalization from WHF
Unadjusted	HR	1.29	1.54	1.52	2.27	1.15	1.06	1.21	1.44
*Step 1**		1.19	1.40	1.38	1.98	1.07	1.00	1.14	1.30
Step 2†		1.22	1.43	1.41	2.00	1.09	0.99	1.12	1.28
Step 3‡		1.20	1.51	1.45	2.28	1.17	0.97	1.02	1.17
Step 4§		1.12	1.47	1.38	1.85	1.25	0.95	1.00	1.23
Step 5‖									
sgp130	HR	1.13	1.50	1.42	1.89	1.33	0.97	0.97	1.17
	CI	(0.85 - 1.52)	(1.13 - 1.98)	(1.04 - 1.94)	(1.10 - 3.23)	(0.87 - 2.02)	(0.68 - 1.37)	(0.76 - 1.24)	(0.86 - 1.60)
	p-value	0.400	0.004	0.026	0.020	0.182	0.855	0.810	0.323
	Wald	0.71	8.11	4.96	5.37	1.78	0.033	0.058	0.98
Implanted pacemaker		0.51	0.58	0.52	0.36	0.46	0.55	1.19	1.46
		(0.32 - 0.81)	(0.38 - 0.90)	(0.31 - 0.85)	(0.13 - 1.05)	(0.24 - 0.90)	(0.33 - 0.91)	(0.88 - 1.60)	(0.99 - 2.14)
		0.004	0.015	0.010	0.063	0.024	0.021	0.256	0.055
		8.13	5.97	6.68	3.47	5.11	5.31	1.29	3.69
Atrial Fibrillation/Flutter		1.05	1.17	1.14	1.63	0.89	0.96	1.33	1.45
		(0.81 - 1.35)	(0.91 - 1.50)	(0.86 - 1.50)	(0.98 - 2.73)	(0.62 - 1.29)	(0.72 - 1.28)	(1.08 - 1.63)	(1.10 - 1.91)
		0.730	0.215	0.359	0.060	0.550	0.767	0.007	0.009
		0.12	1.54	0.84	3.53	0.36	0.088	7.25	6.80
Previous PCI or CABG		0.74	0.76	0.68	0.42	0.85	1.12	1.03	0.86
		(0.53 - 1.04)	(0.54 - 1.06)	(0.47 - 1.01)	(0.17 - 1.04)	(0.53 - 1.38)	(0.79 - 1.58)	(0.80 - 1.32)	(0.60 - 1.22)
		0.085	0.100	0.054	0.060	0.516	0.528	0.807	0.400
		2.97	2.70	3.72	3.54	0.42	0.40	0.059	0.71
Hypertension		1.15	1.04	1.06	0.94	1.31	1.37	1.33	1.51
		(0.86 - 1.54)	(0.79 - 1.38)	(0.77 - 1.46)	(0.53 - 1.68)	(0.86 - 2.01)	(0.98 - 1.92)	(1.05 - 1.68)	(1.09 - 2.08)
		0.334	0.776	0.710	0.831	0.214	0.065	0.018	0.012
		0.93	0.081	0.14	0.045	1.55	3.40	5.57	6.27

Previous MI	1.19 (0.91 - 1.57) 0.209 1.91	1.13 (0.86 - 1.49) 0.368 0.95	1.10 (0.82 - 1.49) 0.522 1.15	1.27 (0.73 - 2.19) 0.395 0.017	0.86 (0.58 - 1.28) 0.451 0	1.02 (0.75 - 1.39) 0.897 0.032	1.27 (1.02 - 1.58) 0.036 0.13	1.45 (1.08 - 1.95) 0.015 0.23
COPD	0.37 (0.09 - 1.51) 0.166 1.91	0.56 (0.18 - 1.79) 0.331 0.95	0.46 (0.11 - 1.89) 0.284 1.15	1.11 (0.25 - 4.99) 0.896 0.017	0 (0 - 0) 0 0	0.90 (0.28 - 2.89) 0.858 0.032	1.14 (0.55 - 2.36) 0.722 0.13	0.79 (0.30 - 2.06) 0.628 0.23
Beta-blocker	1.04 (0.75 - 1.43) 0.830 0.046	0.87 (0.64 - 1.18) 0.378 0.78	0.91 (0.64 - 1.28) 0.578 0.31	0.60 (0.33 - 1.08) 0.088 2.91	1.37 (0.82 - 2.28) 0.234 1.42	1.08 (0.75 - 1.57) 0.670 0.18	1.17 (0.91 - 1.51) 0.227 1.46	1.25 (0.88 - 1.78) 0.219 1.51
Aldosterone-antagonist	1.29 (1.00 - 1.65) 0.047 3.95	1.28 (1.00 - 1.63) 0.052 3.77	1.32 (1.00 - 1.73) 0.047 3.93	1.95 (1.17 - 3.24) 0.010 6.64	1.17 (0.81 - 1.67) 0.402 0.70	1.09 (0.82 - 1.44) 0.552 0.35	1.05 (0.86 - 1.28) 0.637 0.22	1.34 (1.03 - 1.75) 0.031 4.64
ACE-inhibitor	1.22 (0.83 - 1.81) 0.306 1.05	1.55 (1.05 - 2.30) 0.029 4.78	1.46 (0.95 - 2.24) 0.086 2.95	1.35 (0.65 - 2.80) 0.419 0.65	1.22 (0.70 - 2.13) 0.489 0.48	1.19 (0.76 - 1.87) 0.438 0.60	0.89 (0.65 - 1.20) 0.433 0.61	0.78 (0.52 - 1.15) 0.208 1.58
Angiotensin II receptor blocker	0.88 (0.50 - 1.53) 0.643 0.21	0.99 (0.57 - 1.73) 0.979 0.00070	0.83 (0.44 - 1.58) 0.568 0.33	1.16 (0.39 - 3.43) 0.787 0.073	0.72 (0.31 - 1.68) 0.453 0.56	0.90 (0.48 - 1.67) 0.733 0.12	0.95 (0.64 - 1.42) 0.806 0.060	0.75 (0.43 - 1.31) 0.313 1.02
Diuretics	1.14 (0.87 - 1.50) 0.338 0.92	1.02 (0.77 - 1.33) 0.911 0.013	1.15 (0.85 - 1.55) 0.367 0.81	1.22 (0.68 - 2.19) 0.502 0.45	1.27 (0.86 - 1.86) 0.229 1.45	0.99 (0.73 - 1.34) 0.946 0.0046	0.97 (0.78 - 1.20) 0.783 0.076	1.01 (0.76 - 1.35) 0.950 0.0039

The models are adjusted as follows: *_Step 1_(n=1449): LVEF, NYHA functional class, age, body mass index, diabetes mellitus, sex, intermittent claudication and heart rate. †_Step 2_(n=1434): All variables from Step 1 as well as ApoB/Apo A-1 ratio and estimated glomerular filtration rate. ‡_Step 3_(n=1183): All variables from Step 2 as well as NT-proBNP, IL-6 and CRP. §_Step 4_(n=1015): All variables from Step 3 as well as troponin T. ‖_Step 5_(n=1015): All variables from Step 4 as well as extended medical history and medications. sgp130, soluble glycoprotein 130; CV, cardiovascular; WHF, worsening heart failure; COPD, chronic obstructive pulmonary disease; ACE, angiotensin converting enzyme; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction; HR, hazard ratio; CI, 95% confidence interval.

Supplemental Table IV. Multivariable analyses - Association of IL-6 with outcomes.

Serum IL-6 (log-transformed, continuous variable) as a predictor of outcomes. All Hazard Ratios (HR) are given as HR (95% confidence interval), corresponding *p*-value. Net Reclassification Improvement (NRI); calculated from C-indexes for adjusted models with and without inclusion of IL-6, corresponding (*p*-value).

Endpoint		**HR**	**(95% CI)**	***p*-value**	**NRI**	***p*-value**
Primary endpoint						
Unadjusted	n=1452	1.35	(1.23-1.49)	<0.001		
*Step 1**	n=1449	1.28	(1.16-1.41)	<0.001		
Step 2†	n=1434	1.25	(1.13-1.38)	<0.001		
Step 3‡	n=1196	1.02	(0.88-1.19)	0.758	-0.11	0.37
All-cause mortality						
Unadjusted		1.44	(1.32-1.58)	<0.001		
*Step 1**		1.35	(1.23-1.48)	<0.001		
Step 2†		1.34	(1.22-1.47)	<0.001		
Step 3‡		1.11	(0.95-1.28)	0.185	-0.02	0.78
Death from CV cause						
Unadjusted		1.42	(1.28-1.57)	<0.001		
*Step 1**		1.32	(1.19-1.47)	<0.001		
Step 2†		1.30	(1.17-1.45)	<0.001		
Step 3‡		1.05	(0.89-1.24)	0.569	-0.11	0.38
Death from WHF						
Unadjusted		1.62	(1.37-1.93)	<0.001		
*Step 1**		1.46	(1.22-1.75)	<0.001		
Step 2†		1.45	(1.21-1.74)	<0.001		
Step 3‡		1.27	(0.95-1.68)	0.103	-0.03	0.90
Sudden death						
Unadjusted		1.29	(1.12-1.49)	<0.001		
*Step 1**		1.23	(1.06-1.42)	0.005		

Step 2†	1.21	(1.04-1.40)	0.014		
Step 3‡	0.91	(0.72-1.15)	0.435	0.15	0.19
Coronary endpoint					
Unadjusted	1.23	(1.10-1.38)	<0.001		
*Step 1**	1.18	(1.05-1.32)	0.006		
Step 2†	1.14	(1.01-1.28)	0.031		
Step 3‡	0.95	(0.79-1.13)	0.555	0.08	0.37
Hospitalization, CV causes					
Unadjusted	1.23	(1.13-1.34)	<0.001		
*Step 1**	1.17	(1.07-1.27)	<0.001		
Step 2†	1.15	(1.06-1.26)	0.001		
Step 3‡	1.07	(0.94-1.21)	0.306	0.02	0.75
Hospitalization from WHF					
Unadjusted	1.40	(1.26-1.55)	<0.001		
*Step 1**	1.29	(1.16-1.43)	<0.001		
Step 2†	1.27	(1.14-1.42)	<0.001		
Step 3‡	1.09	(0.93-1.29)	0.270	0.02	0.85

The models are adjusted as follows: **Step 1:* LVEF, NYHA functional class, age, body mass index, diabetes mellitus, sex, intermittent claudication and heart rate. †*Step 2:* All variables from Step 1 as well as ApoB/Apo A-1 ratio and estimated glomerular filtration rate. ‡*Step 3:* all variables from Step 2 as well as NT-proBNP and CRP. CV, cardiovascular; WHF, worsening heart failure.

Supplemental Table V. Multivariable analyses – effects of sgp130 on variables.

Fully adjusted multivariable models (Step 4) with extended medical history and medications for all-cause mortality, CV mortality and death from WHF, with and without inclusion of fifth quintile (Q5) sgp130 concentration.

Variables		All-cause Mortality		CV Mortality		Death from WHF	
		sgp130		sgp130		sgp130	
		Without	With	Without	With	Without	With
Ejection fraction (x 100)	HR	0.99	0.99	0.98	0.98	1.00	1.00
	CI	(0.97 - 1.01)	(0.97 - 1.01)	(0.96 - 1.01)	(0.96 - 1.01)	(0.96 - 1.05)	(0.96 - 1.05)
	p-value	0.219	0.198	0.143	0.135	0.880	0.956
	Wald	1.51	1.66	2.15	2.23	0.02	<0.01
Age (x 10)		1.06	1.07	1.05	1.06	1.70	1.73
		(0.86 - 1.29)	(0.87 - 1.31)	(0.84 - 1.31)	(0.84 - 1.32)	(1.10 - 2.62)	(1.12 - 2.69)
		0.597	0.514	0.680	0.628	0.018	0.014
		0.28	0.43	0.17	0.24	5.62	6.02
Heart rate (x 1/10)		0.97	0.97	0.94	0.94	1.04	1.05
		(0.86 - 1.10)	(0.86 - 1.10)	(0.82 - 1.08)	(0.82 - 1.08)	(0.82 - 1.33)	(0.82 - 1.34)
		0.681	0.627	0.397	0.359	0.732	0.713
		0.17	0.24	0.72	0.84	0.12	0.14
Female sex		0.89	0.90	0.97	0.98	2.06	1.98
		(0.63 - 1.25)	(0.64 - 1.26)	(0.67 - 1.41)	(0.67 - 1.41)	(1.13 - 3.79)	(1.08 - 3.64)
		0.511	0.529	0.881	0.898	0.019	0.027
		0.43	0.40	0.02	0.02	5.50	4.91

Diabetes Mellitus	1.26	1.22	1.19	1.16	1.53	1.43
	(0.96 - 1.66)	(0.93 - 1.61)	(0.88 - 1.61)	(0.86 - 1.57)	(0.90 - 2.59)	(0.84 - 2.43)
	0.093	0.148	0.254	0.337	0.117	0.192
	2.82	2.09	1.30	0.92	2.46	1.70
Intermittent Claudication	1.40	1.39	1.28	1.28	1.14	1.18
	(0.98 - 1.99)	(0.97 - 1.99)	(0.85 - 1.93)	(0.84 - 1.93)	(0.48 - 2.73)	(0.49 - 2.84)
	0.068	0.072	0.244	0.249	0.763	0.708
	3.34	3.23	1.36	1.33	0.091	0.14
BMI	0.94	0.94	0.95	0.95	0.96	0.96
	(0.91 - 0.97)	(0.91 - 0.97)	(0.91 - 0.98)	(0.91 - 0.98)	(0.90 - 1.02)	(0.90 - 1.02)
	<0.001	<0.001	0.001	0.001	0.233	0.224
	13.0	13.0	10.2	10.2	1.42	1.48
NYHA III	1.13	1.11	1.10	1.09	1.08	1.06
	(0.84 - 1.52)	(0.83 - 1.50)	(0.79 - 1.52)	(0.79 - 1.51)	(0.58 - 2.02)	(0.56 - 2.00)
	0.411	0.472	0.570	0.601	0.815	0.848
	0.67	0.52	0.32	0.27	0.06	0.04
NYHA IV	1.26	1.40	1.19	1.31	0.76	0.93
	(0.55 - 2.89)	(0.61 - 3.23)	(0.48 - 2.94)	(0.53 - 3.25)	(0.15 - 3.81)	(0.18 - 4.72)
	0.587	0.433	0.704	0.561	0.743	0.929
	0.29	0.62	0.14	0.34	0.11	<0.01
eGFR	0.99	0.99	0.99	0.99	1.01	1.01

	(0.98 - 1.00)	(0.98 - 1.00)	(0.98 - 1.01)	(0.98 - 1.00)	(0.99 - 1.03)	(0.99 - 1.03)
	0.179	0.109	0.284	0.195	0.213	0.318
	1.81	2.57	1.15	1.68	1.55	1.00
	1.33	1.35	1.52	1.53	2.20	2.32
Apo B/Apo A-1 ratio	(0.79 - 2.23)	(0.80 - 2.28)	(0.86 - 2.67)	(0.87 - 2.71)	(0.81 - 5.98)	(0.84 - 6.38)
	0.284	0.254	0.149	0.141	0.120	0.103
	1.15	1.30	2.08	2.16	2.41	2.66
	1.44	1.41	1.53	1.51	1.51	1.47
NT-proBNP	(1.25 - 1.66)	(1.23 - 1.63)	(1.30 - 1.79)	(1.29 - 1.77)	(1.14 - 2.02)	(1.10 - 1.96)
	<0.001	<0.001	<0.001	<0.001	0.005	0.009
	24.7	22.5	27.4	25.6	8.03	6.82
	1.15	1.18	1.16	1.18	1.06	1.11
CRP	(1.01 - 1.31)	(1.04 - 1.35)	(1.00 - 1.33)	(1.02 - 1.36)	(0.83 - 1.35)	(0.86 - 1.43)
	0.029	0.013	0.049	0.028	0.645	0.417
	4.77	6.12	3.86	4.81	0.21	0.66
	1.01	1.00	0.94	0.93	1.21	1.17
IL-6	(0.85 - 1.19)	(0.84 - 1.18)	(0.78 - 1.14)	(0.77 - 1.13)	(0.88 - 1.66)	(0.85 - 1.61)
	0.927	0.977	0.557	0.489	0.242	0.337
	<0.01	<0.01	0.34	0.48	1.37	0.92
	1.48	1.46	1.49	1.47	1.76	1.71
TnT	(1.25 - 1.76)	(1.23 - 1.74)	(1.23 - 1.80)	(1.22 - 1.78)	(1.25 - 2.50)	(1.20 - 2.43)
	<0.001	<0.001	<0.001	<0.001	0.001	0.003

	20.7	18.9	17.3	16.0	10.3	8.84
Pacemaker	0.60	0.58	0.52	0.52	0.38	0.36
	(0.39 - 0.92)	(0.38 - 0.90)	(0.32 - 0.87)	(0.31 - 0.85)	(0.13 - 1.10)	(0.13 - 1.05)
	0.018	0.014	0.012	0.010	0.075	0.062
	5.55	6.00	6.37	6.72	3.18	3.49
Atrial fibrillation/flutter	1.17	1.16	1.12	1.11	1.50	1.49
	(0.91 - 1.52)	(0.90 - 1.50)	(0.84 - 1.49)	(0.84 - 1.48)	(0.89 - 2.54)	(0.88 - 2.52)
	0.223	0.259	0.439	0.465	0.131	0.135
	1.48	1.27	0.60	0.53	2.28	2.24
Previous MI	1.18	1.14	1.14	1.12	1.45	1.36
	(0.89 - 1.55)	(0.86 - 1.50)	(0.84 - 1.54)	(0.82 - 1.51)	(0.83 - 2.51)	(0.78 - 2.36)
	0.249	0.352	0.401	0.481	0.190	0.283
	1.33	0.87	0.71	0.50	1.72	1.15
Previous PCI	0.76	0.76	0.69	0.69	0.44	0.43
	(0.54 - 1.06)	(0.54 - 1.06)	(0.47 - 1.01)	(0.47 - 1.01)	(0.18 - 1.06)	(0.18 - 1.05)
	0.104	0.102	0.056	0.055	0.067	0.062
	2.65	2.67	3.66	3.67	3.36	3.47
Hypertension	1.05	1.04	1.06	1.06	0.93	0.94
	(0.79 - 1.39)	(0.78 - 1.38)	(0.77 - 1.46)	(0.77 - 1.45)	(0.52 - 1.68)	(0.53 - 1.68)
	0.750	0.786	0.701	0.726	0.820	0.836
	0.10	0.07	0.15	0.12	0.05	0.04

COPD	0.57	0.56	0.47	0.46	1.08	1.02
	(0.18 - 1.81)	(0.18 - 1.79)	(0.11 - 1.91)	(0.11 - 1.89)	(0.24 - 4.95)	(0.22 - 4.68)
	0.341	0.330	0.289	0.282	0.921	0.978
	0.91	0.95	1.13	1.16	<0.01	<0.01
Digitalis glycoside	1.09	1.05	1.14	1.11	1.61	1.52
	(0.84 - 1.41)	(0.81 - 1.37)	(0.86 - 1.52)	(0.83 - 1.49)	(0.96 - 2.71)	(0.91 - 2.57)
	0.541	0.701	0.364	0.468	0.069	0.113
	0.37	0.15	0.82	0.53	3.31	2.52
ACE-inhibitor	1.51	1.55	1.41	1.45	1.22	1.35
	(1.01 - 2.24)	(1.04 - 2.30)	(0.92 - 2.17)	(0.94 - 2.24)	(0.58 - 2.54)	(0.64 - 2.82)
	0.043	0.030	0.119	0.089	0.600	0.429
	4.10	4.73	2.43	2.89	0.27	0.62
Angiotension II receptor blocker	1.00	0.99	0.83	0.82	1.08	1.10
	(0.57 - 1.75)	(0.57 - 1.72)	(0.43 - 1.58)	(0.43 - 1.56)	(0.36 - 3.23)	(0.37 - 3.28)
	0.990	0.966	0.570	0.549	0.898	0.869
	<0.01	<0.01	0.32	0.36	0.02	0.03
Beta-blocker	0.86	0.87	0.90	0.91	0.63	0.62
	(0.64 - 1.17)	(0.64 - 1.19)	(0.64 - 1.28)	(0.64 - 1.29)	(0.34 - 1.15)	(0.34 - 1.12)
	0.346	0.384	0.573	0.594	0.129	0.111
	0.89	0.76	0.32	0.28	2.30	2.54
Aldosterone antagonist	1.28	1.27	1.31	1.30	1.85	1.87
	(1.00 - 1.64)	(0.99 - 1.63)	(1.00 - 1.73)	(0.99 - 1.71)	(1.11 - 3.08)	(1.12 - 3.12)

	0.051	0.060	0.052	0.060	0.018	0.016
	3.81	3.55	3.77	3.55	5.58	5.77
Diuretics	1.02	1.01	1.14	1.13	1.17	1.14
	(0.77 - 1.34)	(0.77 - 1.33)	(0.84 - 1.55)	(0.84 - 1.54)	(0.64 - 2.14)	(0.63 - 2.07)
	0.899	0.945	0.388	0.416	0.601	0.672
	0.02	<0.01	0.75	0.66	0.27	0.18
Q5 sgp130		1.49		1.41		1.80
		(1.13 - 1.97)		(1.03 - 1.92)		(1.05 - 3.10)
		0.005		0.031		0.033
		7.86		4.64		4.52

HR, Hazard ratio; CI, 95% Confidence interval for HR; Wald, Wald score; BMI, Body mass index; NYHA, New York Heart Association functional class; eGFR, estimated glomerular filtration rate; Apo B, apolipoprotein B; Apo A-1, apolipoprotein A-1; NT-proBNP, log-transformed amino-terminal pro B-type natriuretic peptide; CRP, log-transformed C-reactive protein; IL-6, log-transformed interleukin 6; TnT, log-transformed troponin T; MI, myocardial infarction; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease; ACE, angiotensin converting enzyme; Q5 sgp130, fifth quintile soluble glycoprotein 130 concentration.

Supplemental Table VI. Multivariable analyses – effects of sgp130 on outcomes in placebo arm of sub-study.

sgp130, quintiles		Events	HR	(95% CI)	*p*-value	Wald
Primary endpoint						
Unadjusted	n=720	214	1.15	(0.82 - 1.62)	0.404	0.70
*Step 1**	n=719	214	1.07	(0.76 - 1.51)	0.697	0.15
Step 2†	n=712	212	1.07	(0.76 - 1.51)	0.697	0.15
Step 3‡	n=586	162	1.17	(0.78 - 1.73)	0.451	0.57
Step 4§	n=508	143	1.17	(0.77 - 1.78)	0.459	0.55
All-cause mortality						
Unadjusted		223	1.46	(1.07 - 1.99)	0.019	5.55
Step 1		223	1.32	(0.96 - 1.82)	0.086	2.96
Step 2		220	1.33	(0.96 - 1.84)	0.082	3.02
Step 3		167	1.57	(1.08 - 2.27)	0.018	5.62
Step 4		143	1.64	(1.11 - 2.44)	0.014	6.05
Death from CV cause						
Unadjusted		178	1.32	(0.92 - 1.89)	0.129	2.31
Step 1		178	1.20	(0.83 - 1.73)	0.338	0.92
Step 2		176	1.21	(0.83 - 1.75)	0.320	0.99
Step 3		134	1.38	(0.90 - 2.11)	0.141	2.16
Step 4		117	1.51	(0.97 - 2.37)	0.071	3.26
Death from WHF						
Unadjusted		55	2.17	(1.23 - 3.85)	0.008	7.06
Step 1		55	1.87	(1.04 - 3.39)	0.038	4.31
Step 2		55	1.84	(1.01 - 3.36)	0.046	3.99
Step 3		41	2.86	(1.41 - 5.80)	0.004	8.47
Step 4		37	2.71	(1.31 - 5.59)	0.007	7.26
Sudden death						

Unadjusted	102	0.84	(0.48 - 1.45)	0.529	0.40
Step 1	102	0.76	(0.44 - 1.33)	0.340	0.91
Step 2	100	0.79	(0.45 - 1.37)	0.397	0.72
Step 3	77	0.87	(0.47 - 1.62)	0.661	0.19
Step 4	67	1.06	(0.55 - 2.04)	0.864	0.029
Coronary endpoint					
Unadjusted	164	0.76	(0.49 - 1.19)	0.233	1.42
Step 1	164	0.71	(0.45 - 1.11)	0.130	2.30
Step 2	161	0.73	(0.47 - 1.14)	0.168	1.90
Step 3	126	0.80	(0.48 - 1.33)	0.389	0.74
Step 4	108	0.68	(0.38 - 1.21)	0.192	1.71
Hospitalization, CV causes					
Unadjusted	310	1.14	(0.86 - 1.52)	0.348	0.88
Step 1	309	1.04	(0.78 - 1.38)	0.812	0.056
Step 2	305	1.04	(0.78 - 1.39)	0.797	0.066
Step 3	245	1.08	(0.78 - 1.49)	0.650	0.21
Step 4	213	1.04	(0.73 - 1.47)	0.837	0.042
Hospitalization from WHF					
Unadjusted	167	1.54	(1.08 - 2.20)	0.017	5.65
Step 1	167	1.32	(0.92 - 1.89)	0.138	2.20
Step 2	166	1.32	(0.91 - 1.90)	0.139	2.19
Step 3	135	1.59	(1.06 - 2.38)	0.024	5.07
Step 4	118	1.61	(1.04 - 2.47)	0.031	4.64

The models are adjusted as follows: **Step 1:* LVEF, NYHA functional class, age, body mass index, diabetes mellitus, sex, intermittent claudication and heart rate. †*Step 2:* All variables from Step 1 as well as ApoB/Apo A-1 ratio and estimated glomerular filtration rate. ‡*Step 3:* all

variables from Step 2 as well as NT-proBNP, IL-6 and CRP. §*Step 4:* All variables from Step 3 as well as troponin T. CV, cardiovascular; WHF, worsening heart failure.

Supplemental Figure Legends

Supplemental Figure.

Patient selection for sub-study analyses. The total CORONA population consisted of 5011 patients, in which NT-proBNP and CRP was measured in 3664 and 4961 patients respectively. The predefined cytokine sub-study consisted of 1480 patients. Due to limited plasma/serum, all parameters could not be analyzed in all patients. The number of patients with sgp130, NT-proBNP, IL-6, CRP and TnT measurements was 1015.

Supplemental Figure.