Fibrosis Marker Syndecan-1 and Outcome in Patients With Heart Failure With Reduced and Preserved Ejection Fraction

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Background—Syndecan-1 is a member of the proteoglycan family involved in cell–matrix interactions. Experimental studies showed that syndecan-1 is associated with inflammation in acute myocardial infarction and remodeling. The goal of this study was to explore the role of syndecan-1 in human heart failure (HF).

Methods and Results—We analyzed plasma syndecan-1 levels in 567 patients with chronic HF. Primary end point was a composite of all-cause mortality and rehospitalization for HF at 18 months. Mean age was 71.0±11.0 years, 38% was women, and mean left ventricular ejection fraction was 32.5±14.0%. Median syndecan-1 levels were 20.1 ng/mL (interquartile range, 13.9–27.7 ng/mL). Patients with higher syndecan-1 levels were more often men, had higher N-terminal probrain-type natriuretic peptide levels, and worse renal function. Multivariable regression analyses showed a positive correlation between syndecan-1 levels and markers of fibrosis and remodeling but no correlation with inflammation markers. Interaction analysis revealed an interaction between left ventricular ejection fraction and syndecan-1 (P=0.047). A doubling of syndecan-1 was associated with an increased risk of the primary outcome in patients with HF with preserved ejection fraction (hazard ratio, 2.10; 95% confidence interval, 1.14–3.86; P=0.017) but not in patients with HF with reduced ejection fraction (hazard ratio, 0.95; 95% confidence interval, 0.71–1.27; P=0.729). Finally, syndecan-1 enhanced risk classification in patients with HF with preserved ejection fraction when added to a prediction model with established risk factors.

Conclusions—In patients with HF, syndecan-1 levels correlate with fibrosis biomarkers pointing toward a role in cardiac remodeling. Syndecan-1 was associated with clinical outcome in patients with HF with preserved ejection fraction but not in patients with HF with reduced ejection fraction. **(*Circ Heart Fail*. 2014;7:457-462.)**

Key Words: fibrosis ■ heart failure ■ prognosis ■ syndecan-1

Extracellular matrix components, particularly proteoglycans, are associated with inflammation, fibrosis, and cardiac remodeling.[1] Members of the syndecan family have been found to be associated with the onset of cardiac fibrosis by functioning as an important target for transforming growth factor-β.[2,3] Experimental studies in mice have shown that syndecan-1 was involved in both inflammation and fibrosis after myocardial injury.[2–4] Syndecan-1 had a protective effect in short-term inflammation postmyocardial infarction resulting in less remodeling through direct extracellular matrix involvement in wound healing.[3,4] However, in the long term it might lead to increased fibrosis and remodeling through the involvement of activated renin–angiotensin–aldosterone system stimulation.[2] The ecto-domain of the transmembrane receptor syndecan-1 protein has been known to shed into the extracellular matrix; consequentially, the ecto-domain of syndecan-1 is measurable in plasma.[5] We recently reported sex-specific differences in biomarker levels in patients with heart failure (HF) related to inflammation and fibrosis.[6] We therefore hypothesized that syndecan-1 might be associated with fibrosis and adverse outcome in patients with HF. In the present study, we aimed to further establish the association between syndecan-1 and markers of inflammation and fibrosis and assess the prognostic value of syndecan-1 in patients with HF with preserved and reduced left ventricular ejection fractions (LVEFs).

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Methods

Patient Population and Study Design

The current study was performed as a substudy of the Coordinating study evaluating Outcomes of Advising and Counseling in Heart Failure (COACH). In brief, 1023 patients were included to participate

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in a prospective randomized disease management study. The rationale and outcomes of this trial have been reported elsewhere.[7–9] Patients with HF with both preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) were included in the study. The cutoff point of LVEF to identify HFpEF was predefined at >40% in the study protocol and similar to a previously published study from this cohort.[9] Samples for biomarker analysis were obtained from a subset of 567 patients, who were representative for the entire study population on baseline characteristics. Before discharge, when patients were stabilized after an acute HF admission, samples were collected. This study complies with the Declaration of Helsinki, local medical ethics committees approved the study, and all patients provided written informed consent.

End Points

The primary end point in this study was defined as the combined end point of all-cause mortality or rehospitalization at 18 months, where rehospitalization was defined as an unplanned overnight hospital stay connected to worsening HF. The secondary end point was defined as all-cause mortality at 3 years. All events were evaluated and adjudicated by an independent end point committee.

Biochemical Analysis

Blood sampling was done before discharge and samples were immediately stored at −80°C until analysis was performed. Levels of multiple fibrosis markers, including syndecan-1, galectin-3, periostin, and ST-2, were measured using a commercially available competitive ELISA (Alere San Diego, Inc, San Diego, CA). Measurements were made with the usage of the luminex platform. Lower limits for the detection of syndecan-1 with this specific ELISA were 2.4 ng/mL; intra- and interassay coefficients of variation are 25% and 25%, respectively. Interleukin-6, C-reactive protein, and transforming growth factor-β1 were measured in a 96-well polystyrene microtiter plate using searchlight proteome arrays, as previously described.[10,11] Measurement of N-terminal probrain-type natriuretic peptide (NT-proBNP) was done using the Elecsys proBNP ELISA (Roche diagnostics, Mannheim, Germany). Estimated glomerular filtration rate was calculated using the modification of diet in renal disease formula.[12]

Statistical Analysis

Data are expressed as mean±SD when normally distributed, as medians with lower and upper quartiles when non-normally distributed or as numbers and percentages when categorical. Baseline characteristics were divided into quartiles of syndecan-1. Intergroup differences were tested using trend analysis. For further analyses, skewed variables were transformed to a 2-log scale to achieve a normal distribution. Risk estimates for the transformed variables should be interpreted as the relative risk if values were doubled (eg, 2–4 mmol/L).

To establish clinical determinants of syndecan-1 levels and its relation to other markers of inflammation and fibrosis, multiple linear regression models were constructed. Variables with a significant univariate association with syndecan-1 (<0.10) were entered in a stepwise backward multivariable model based on the strength of their univariate association.

Univariate and multivariable Cox proportional hazard regression models were used to calculate the predictive value of syndecan-1 on both the primary and the secondary end point. In 2 consecutive multivariable models, syndecan-1 was adjusted for age, sex, the presence of diabetes mellitus, previous HF hospitalizations, LVEF, renal function, levels of NT-proBNP, and finally for galectin-3, periostin, ST-2 levels, and a history of myocardial infarction.

Finally, risk stratification of syndecan-1 levels on top of the COACH risk engine model, as described elsewhere, was tested for both end points using the continuous net reclassification improvement (NRI) and integrated discrimination improvement.[13] As suggested, the continuous NRI is a more objective and versatile measure of improvement in risk prediction compared with the categorical NRI.[14] Variables in the COACH risk model include age, sex, blood pressure, pulse pressure, a prior stroke and myocardial infarction, previous HF hospitalizations, the presence of peripheral artery disease, atrial fibrillation and/or diabetes mellitus, renal function, and levels of NT-proBNP and sodium. All tests were 2 sided, and a P value of <0.05 was considered statistically significant. All statistical analyses were performed using STATA version 11.0 (StataCorp LP, College Station, TX).

Results

Patient Characteristics

Baseline characteristics are described in Table 1. No significant differences with regard to patient characteristics were observed between the original COACH cohort and this substudy (Table in the Data Supplement). Of the 567 patients, 38% was women, 47% was in New York Heart Association class II, and 49% in New York Heart Association class III. Mean LVEF was measured in 460 patients before discharge and was 32.5±14.0%. Patients with higher syndecan-1 levels were more often men, had lower blood pressures, a lower LVEF, and more previous HF-related hospitalizations. In addition, higher levels of NT-proBNP, fibrosis markers, and a worse renal function were observed in patients with higher syndecan-1 levels. Interestingly, no elevated levels of inflammatory markers were observed in patients with higher syndecan-1 levels.

Predictors of Syndecan-1 Levels in HF

To assess whether syndecan-1 was associated with fibrosis or inflammation, a multivariable regression analysis was performed as shown in Table 2. A clear positive association was found relating to fibrotic and remodeling markers, including periostin, galectin-3, and ST-2 (all P<0.001). No correlation could be observed between syndecan-1 and the inflammatory markers high sensitive-C-reactive protein (P=0.635) and interleukin-6 (P=0.838). A negative correlation was observed between syndecan-1 and renal function (P=0.009). Furthermore, sex was found to be a predictor of syndecan-1 levels (P=0.029).

Syndecan-1 and Clinical Outcome in HF

After 18 months, 240 patients reached the combined end point and 234 patients died after 3 years. In univariate analysis, a doubling of syndecan-1 levels showed a significant increase risk for both the combined end point (hazard ratio [HR], 1.20; 95% confidence interval [CI], 1.05–1.37; P=0.005) and for all-cause mortality after 3 years (HR, 1.27; 95% CI, 1.12–1.44; P<0.001; Table 3). However, when adjusting for age, sex, presence of diabetes mellitus, previous HF hospitalizations, LVEF, renal function, and NT-proBNP, syndecan-1 was no longer significantly associated with both end points. Interaction analysis showed an interaction between syndecan-1 and LVEF for both the combined end point (P=0.047) and 3-year mortality (P=0.003). Consequently, patients were subdivided into those with preserved LVEF (n=107) and reduced LVEF (n=353). Within these subgroups, 143 patients with HFrEF and 50 patients with HFpEF reached the primary combined end point at 18 months. Furthermore, 142 patients with HFrEF and 44 patients with HFpEF reached the secondary end point at 3 years. The interaction among HFrEF, HFpEF, and syndecan-1 levels is shown in the Figure. This figure depicts

Table 1. Baseline Characteristics of All 567 Patients at Discharge, Divided Into Quartiles of Syndecan-1 (ng/mL)

Variable	All (n=567)	Q1 (n=141)	Q2 (n=143)	Q3 (n=142)	Q4 (n=141)	*P* Value (Trend)
Syndecan-1, ng/mL (min–max)	2.4–393.0	2.4–13.9	14.0–20.1	20.2–27.6	27.7–393.0	NA
Demographics and clinical signs						
Age, y	71.0±11.0	70.3±11.5	70.6±11.5	72.3±9.7	71.0±11.0	0.544
Female sex, %	38.1	48.2	39.2	31.0	34.0	0.004
BMI, kg/m^2	26.1 (23.5–29.5)	26.7 (24.0–29.9)	26.8 (23.9–30.1)	25.9 (23.9–29.0)	25.8 (23.1–29.4)	0.079
Systolic BP, mm Hg	118.2±21.2	122.2±23.2	120.4±20.4	116.7±20.4	113.3±19.5	<0.001
Heart rate, beats per minute	74.3±13.1	74.6±12.2	73.8±12.3	75.0±15.6	73.8±11.7	0.355
LVEF, %	32.5±14.0	33.0±13.8	34.2±13.8	32.6±14.7	30.0±13.4	0.036
Previous HF hospitalization	34.4	28.4	32.2	35.9	41.1	0.026
NYHA class, II/III/IV, %	46.6/49.8/3.6	56.8/39.6/3.6	41.3/57.3/1.4	43.9/51.8/4.3	44.7/50.3/5.0	0.087
Medical history, %						
Myocardial infarction	40.9	35.5	39.8	43.7	44.7	0.110
Stroke	15.3	12.1	21.7	16.9	10.6	0.524
Hypertension	42.3	37.6	51.1	38.0	42.6	0.876
Atrial fibrillation of flutter	46.0	38.3	47.6	48.6	49.7	0.054
Diabetes mellitus	30.5	32.2	31.5	27.5	31.9	0.762
COPD	28.0	29.1	21.0	33.8	28.4	0.606
Laboratory						
Hemoglobin, g/dL	13.1±2.0	13.3±2.2	13.2±2.1	13.0±1.9	13.0±1.8	0.533
Sodium, mmol/L	139±4	139±4	139±4	139±5	138±4	0.142
NT-proBNP, pg/dL	2534 (1314–5869)	1943 (1039–3398)	2346 (1072–4590)	3242 (1706–6779)	3957 (1641–9429)	<0.001
High-sensitive CRP, mg/L	2.3 (0.9–5.1)	2.3 (0.8–5.3)	2.0 (0.7–5.0)	2.2 (0.8–4.9)	2.9 (1.6–6.0)	0.073
IL-6, pg/mL	12.0 (6.9–24.5)	12.0 (6.1–21.6)	11.2 (6.4–20.4)	11.9 (6.7–25.6)	15.4 (8.2–29.6)	0.081
ST-2, ng/mL	2.5 (1.4–5.4)	1.2 (0.7–1.9)	2.1 (1.4–4.7)	3.1 (2.1–5.4)	4.8 (2.7–8.6)	<0.001
Galectin-3, ng/mL	25.6 (21.2–32.1)	21.1 (16.6–25.5)	25.0 (21.1–30.1)	28.0 (23.0–32.8)	31.1 (25.1–39.7)	<0.001
Periostin, ng/mL	4.7 (3.4–6.6)	3.3 (2.3–4.4)	4.4 (3.4–5.6)	5.2 (3.8–7.1)	6.6 (5.2–8.9)	<0.001
TGF-β, ng/mL	51.0 (35.8–75.0)	69.0 (41.5–97.0)	49.6 (35.8–67.8)	46.8 (28.9–62.7)	45.8 (33.4–66.2)	<0.001
Creatinine, μmol/L	127.4±54	110.6±38.1	128.3±52.0	134.7±57.7	138.3±62.4	<0.001
eGFR, mL/min per 1.73 m^2	53.9±20.2	59.7±20.8	53.1±19.6	50.9±17.9	52.0±21.3	0.001
<60, %	61.4	51.1	62.2	63.0	69.1	0.016
BUN, mmol/L	11.1 (8.3–15.8)	9.8 (7.5–13.6)	11.6 (8.9–17.5)	11.5 (8.3–15.4)	12.0 (8.9–18.3)	0.002
Treatment at discharge, %						
ACE inhibitor or ARB	82.0	83.7	79.8	83.8	80.9	0.888
β-Blocker	66.7	61.5	62.4	66.9	75.9	0.010
Diuretic	95.6	94.3	95.1	96.8	97.2	0.235
MRA	54.8	59.6	51.8	53.5	54.6	0.486
Statin	38.8	36.2	42.7	37.3	39.0	0.866
Digoxin	32.6	29.8	31.5	37.3	31.9	0.487

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HF, heart failure; IL-6, interleukin-6; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NA, not applicable; NT-proBNP, N-terminal probrain-type natriuretic peptide; NYHA, New York Heart Association; and TGF-β, transforming growth factor-β.

how an increase in syndecan-1 levels poses a much stronger increase in risk for patients with HFpEF than in patients with HFrEF (Figure). There was no interaction among syndecan-1, sex, and the primary end point (*P*=0.232). An interaction was found for syndecan-1 and sex for the secondary end point (*P*=0.017). When subdividing patients with HFpEF by sex, a significant predictive value was found for syndecan-1 levels in female patients with HFpEF (HR, 8.44; 95% CI, 2.18–32.70; *P*=0.002), but not in males with HFpEF (HR, 1.08; 95% CI, 0.52–2.25; *P*=0.843). Syndecan-1 was not associated with an increased risk for either the primary end point (HR, 0.95; 95% CI, 0.71–1.27; *P*=0.729) or the secondary end point (HR, 1.11; 95% CI, 0.83–1.78; *P*=0.477) in patients with HFrEF (Table 3). A strong predictive value was found for doubling of syndecan-1 in patients with HFpEF for the combined end point (HR, 1.30; 95% CI, 1.05–1.61; *P*=0.016) and for 3-year mortality (HR, 1.52; 95% CI, 1.22–1.90; *P*<0.001; Table 3). This association remained statistically significant in

Table 2. Clinical Variables Associated With Syndecan-1 (per Doubling) in Chronic Heart Failure

Variables	Univariate β	*P* Value	Multivariable β	*P* Value
Demographics and clinical signs				
Age, y	−0.008	0.854	…	…
Female sex, %	−0.092	0.027	−0.125	0.029
BMI, kg/m^2	−0.100	0.020	…	…
Systolic BP (per 5 mm Hg)	−0.141	0.001	…	…
Heart rate, beats per minute	−0.058	0.171	…	…
LVEF, %	−0.054	0.249	…	…
Previous HF hospitalization	0.091	0.031	…	…
NYHA class, II/III/IV, %	0.085	0.043	…	…
Medical history, %				
Myocardial infarction	0.039	0.358	…	…
Stroke	−0.030	0.474	…	…
Hypertension	−0.002	0.963	…	…
Atrial fibrillation	0.087	0.037	…	…
Diabetes mellitus	−0.021	0.619	…	…
COPD	0.013	0.765	…	…
Laboratory				
Hemoglobin, g/dL	0.024	0.670	…	…
Sodium, mmol/L	−0.048	0.259	…	…
NT-proBNP (per doubling)	0.230	<0.001	…	…
High-sensitive CRP (per doubling)	0.021	0.635	…	…
IL-6 (per doubling)	0.009	0.838	…	…
ST-2 (per doubling)	0.622	<0.001	0.230	<0.001
Galectin-3 (per doubling)	0.499	<0.001	0.357	<0.001
Periostin (per doubling)	0.634	<0.001	0.516	<0.001
TGF-β (per doubling)	−0.024	0.573	…	…
eGFR (per 5 mL/min per 1.73 m^2)	−0.111	0.009	−0.027	<0.001
BUN (per doubling)	0.112	0.011	…	…
Treatment at discharge, %				
ACE inhibitor or ARB	−0.042	0.312	…	…
β-Blocker	0.099	0.018	…	…
Diuretic	0.073	0.081	…	…
MRA	−0.009	0.833	…	…
Statin	−0.015	0.718	…	…
Digoxin	0.008	0.845	…	…

Values are standardized β coefficients. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HF, heart failure; IL-6, interleukin 6; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal probrain-type natriuretic peptide; NYHA, New York Heart Association; and TGF-β, transforming growth factor β.

the multivariable corrected model for both the combined end point (HR, 2.10; 95% CI, 1.14–3.86; *P*=0.017) and the 3-year mortality (HR, 2.00; 95% CI, 1.01–3.98; *P*=0.044).

Table 3. Hazard Ratios in Predicting the Combined End Point (HF Hospitalizations or All-Cause Mortality at 18 Months) or All-Cause Mortality at 3 Years in Overall HF and Divided Into HFrEF and HFpEF

Syndecan-1 (per Doubling)	Combined End Point, HR (95% CI)	*P* Value	All-Cause Mortality, HR (95% CI)	*P* Value
Overall HF (n=567)				
Univariate	1.20 (1.05–1.37)	0.005	1.27 (1.12–1.44)	<0.001
Model 1	1.21 (1.06–1.40)	0.004	1.29 (1.13–1.48)	<0.001
Model 2	1.08 (0.91–1.28)	0.385	1.11 (0.93–1.33)	0.238
Model 3	1.08 (0.84–1.39)	0.563	1.21 (0.94–1.56)	0.143
HFrEF (n=353)				
Univariate	1.12 (0.95–1.33)	0.180	1.17 (1.00–1.39)	0.050
Model 1	1.12 (0.94–1.33)	0.223	1.18 (1.00–1.41)	0.055
Model 2	0.98 (0.80–1.21)	0.901	1.04 (0.84–1.28)	0.721
Model 3	0.95 (0.71–1.27)	0.729	1.11 (0.83–1.48)	0.477
HFpEF (n=107)				
Univariate	1.30 (1.05–1.61)	0.016	1.52 (1.22–1.90)	<0.001
Model 1	1.33 (1.07–1.66)	0.009	1.54 (1.23–1.93)	<0.001
Model 2	1.37 (1.01–1.86)	0.046	1.45 (1.02–2.08)	0.040
Model 3	2.10 (1.14–3.86)	0.017	2.00 (1.01–3.98)	0.044

Model 1 is adjusted for age and sex. Model 2 is adjusted for model 1+presence of diabetes mellitus, previous HF hospitalizations, left ventricular ejection fraction (only in overall HF), renal function, and N-terminal probrain-type natriuretic peptide levels. Model 3 is adjusted for model 2+levels of galectin-3, ST-2 and periostin, and prior myocardial infarction. CI indicates confidence interval; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and HR, hazard ratio.

Finally, NRI and integrated discrimination improvement showed a significant additive value for the combined primary end point in patients with HFpEF, when syndecan-1 was added on top of variables of the COACH risk engine model. This additive value was not observed in patients with HFrEF (Table 4).

Discussion

This study aimed to extend the knowledge of syndecan-1 plasma levels by assessing the role of syndecan-1 in patients with HF. The findings of this study have demonstrated that syndecan-1 is associated with fibrotic and remodeling markers galectin-3, periostin, and ST-2, whereas no correlation with

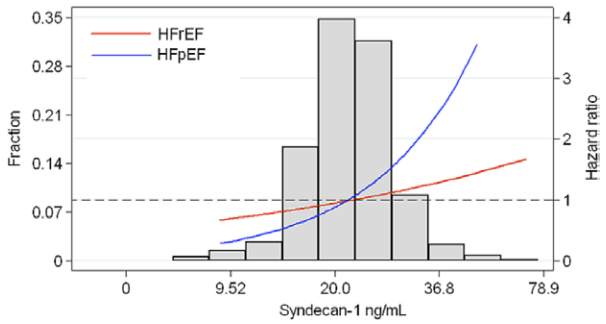

Figure. Graphical depiction of the risk estimates for the primary end point in patients with heart failure with preserved ejection fraction (HFpEF) vs heart failure with reduced ejection fraction (HFrEF). The distribution of (log2-transformed) syndecan-1 is depicted in gray bars in the background.

Table 4. Risk Stratification Improvement of Syndecan-1 Levels on Top of Established Clinical Risk Factors for Both End Points in Patients with HFrEF and HFpEF

Syndecan-1 (per Doubling)	NRI*	*P* Value	IDI	*P* Value
HFrEF (n=353)				
Combined end point	0.026	0.816	0.001	0.674
3-y all-cause mortality	0.006	0.952	0.001	0.517
HFpEF (n=107)				
Combined end point	0.485	0.016	0.031	0.026
3-y all-cause mortality	0.031	0.560	0.029	0.060

HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IDI, integrated discrimination improvement; and NRI, net reclassification improvement.

*Coordinating study evaluating Outcomes of Advising and Counseling in Heart Failure risk engine model includes age, sex, blood pressure, pulse pressure, history of stroke and of myocardial infarction, presence of atrial fibrillation, peripheral artery disease and diabetes mellitus, renal function, levels of N-terminal probrain-type natriuretic peptide sodium, and previous heart failure hospitalization.

inflammation markers was observed, confirming earlier published experimental in vitro results in a human clinical setting.[2] In addition, this study identified syndecan-1 as a specific predictor for clinical outcome in patients with HFpEF, but not in patients with HFrEF.

Syndecan-1 is a heparan-sulfate proteoglycan that functions as an important cell receptor in the extracellular matrix and is found on the cell surfaces of almost all cell types. As such, it is involved in a wide array of processes in human (patho)physiology.[15] Animal models showed that syndecan-1 is associated with inflammation in the acute phase postmyocardial infarction.[3,4] Furthermore, in vitro and in vivo studies have provided evidence for the involvement of syndecan-1 in fibrosis and remodeling after angiotensin-II–induced HF through the transforming growth factor-β/Smad-3 pathway. These studies demonstrated an increase of syndecan-1 expression in the heart after angiotensin-II infusion in which the ecto-domain of syndecan-1 plays a key role in the onset of fibrosis; blockage of the ecto-domain led to a diminished effect of angiotensin-II stimulation resulting in less collagen disposition.[2] Shedding of the ecto-domain, leading to increased levels of soluble levels of the ecto-domain of syndecan-1 in plasma, may be part of a protective mechanism in HF. The correlation of shedding and detectable plasma levels is currently unknown. One may speculate that the loss of its ecto-domain might inhibit the function of the syndecan-1 receptor in activating the Smad-3/transforming growth factor-β pathway. Moreover, the soluble ecto-domain has been suggested to retain its binding properties, reducing the bioavailability of syndecan-1 receptor ligands.[16]

The ecto-domain of the syndecan-1 protein has been shown to shed under the influence of matrix metalloproteinases and tissue inhibitors of metalloproteinases.[17] Previous studies have shown the subtle balance between matrix metalloproteinases and tissue inhibitors of metalloproteinases to be primarily responsible for the cleavage of the syndecan-1 ecto-domain from the cell surface; a balance that has readily been shown to be disturbed in HF, leading to measurable levels of the syndecan-1 ecto-domain in plasma.[17–19] In addition, cellular syndecan-1 levels have been shown to be increased in wild-type mice in a HF model after angiotensin-II stimulation, the relative increase of shedding of the ecto-domain of syndecan-1 has, however, not been shown.[2] To determine whether the shedding of the ecto-domain of syndecan-1 has a protective or harmful effect, additional evidence for the relative share of shedding of the syndecan-1 ecto-domain to the possible increased expression of syndecan-1 on a cellular level during HF is needed. Furthermore, HFpEF-induced fibrosis might be altered by directly or indirectly influencing the activity of the syndecan-1 receptor through syndecan-1 receptor antagonists or through decreasing the bioavailability of syndecan-1 and possibly increasing the presence of soluble syndecan-1 by influencing the tissue inhibitors of metalloproteinase/matrix metalloproteinase balance. However, more research has to be done to unravel the specific ligand(s) of syndecan-1 and how these relate to HF.

Interestingly, Cox regression analysis showed that levels of syndecan-1 were related to clinical outcome in patients with HFpEF, but not in patients with HFrEF, which is independent of other known HF risk factors and the earlier reported correlation between sex and syndecan-1 levels.[6] In addition, syndecan-1 showed prognostic value by adding it to known risk factors in HF as defined in the COACH risk model for the primary end point for patients with HFpEF. Significant added value was not observed in NRI/integrated discrimination improvement analysis for the secondary end point; however, this could be explained by the nature of the COACH risk model, which is particularly designed for the primary end point in the COACH trial.[13] This is of particular interest because syndecan-1 seems to be a marker for collagen turnover, which is suggested to play a central role in the pathophysiology of HFpEF.[20] As such, this study shows that syndecan-1 has both prognostic value for the combined end point at 18 months and all-cause mortality at 3 years. This may indicate a possible biological involvement of syndecan-1 in the pathophysiological process of HFpEF on short- and long-term follow-up, suggesting an ongoing involvement of syndecan-1 throughout the progression of HFpEF. In addition, a significant interaction for syndecan-1, sex, and the secondary end point was found, as reported earlier.[6] When dividing patients with HFpEF by sex, a significant predictive value was found for female patients but not for male patients. The results with regard to sex should, however, be critically interpreted because of the small size of the sex subgroups in the HFpEF population and the accompanying wide CIs, especially because no interaction was observed for syndecan-1, sex, and the primary end point. Additional research is needed to explore its role as a possible new marker in the treatment of patients with HFpEF. However, our observations are in line with a previous study published by our group, where we showed that the fibrotic biomarker galectin-3 has particular value in patients with HFpEF.[11] Herein, we also found an interaction between the association of syndecan-1 and clinical outcome. This study provides further support for such an association between collagen and HFpEF, but less so for HFrEF.

Limitations

This is a post hoc analysis, warranting the possibility of a selection bias. Furthermore, the relatively small number of

patients limits the prognostic value of syndecan-1 in HFpEF in this study. Sampling of patients in the COACH trial was performed at time of discharge, when patients were already recompensated. As such, this study includes patients who, at time of sampling, cover a gray area between acute and chronic HF. Furthermore, measurements of syndecan-1 were plagued by relatively high intra- and interassay coefficients of 25% and 25%, respectively, providing for possible variations between measurements. The findings reported in this study should not be regarded as providing evidence for a causal relationship, but should be seen in a more exploratory context. With regard to the role of syndecan-1 in patients with HFpEF, more research is needed in populations in which solely patients with HFpEF are included.

Conclusions

In patients with HF, syndecan-1 levels strongly correlate with other fibrosis markers pointing toward a role in cardiac fibrosis and remodeling. Syndecan-1 was independently associated with clinical outcome in patients with HFpEF but not in patients with HFrEF.

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Disclosures

None.

References

1. Schellings MW, Pinto YM, Heymans S. Matricellular proteins in the heart: possible role during stress and remodeling. *Cardiovasc Res*. 2004;64:24–31.
2. Schellings MW, Vanhoutte D, van Almen GC, Swinnen M, Leenders JJ, Kubben N, van Leeuwen RE, Hofstra L, Heymans S, Pinto YM. Syndecan-1 amplifies angiotensin II-induced cardiac fibrosis. *Hypertension*. 2010;55:249–256.
3. Vanhoutte D, Schellings MW, Götte M, Swinnen M, Herias V, Wild MK, Vestweber D, Chorianopoulos E, Cortés V, Rigotti A, Stepp MA, Van de Werf F, Carmeliet P, Pinto YM, Heymans S. Increased expression of syndecan-1 protects against cardiac dilatation and dysfunction after myocardial infarction. *Circulation*. 2007;115:475–482.
4. Lei J, Xue SN, Wu W, Zhou SX, Zhang YL, Yuan GY, Wang JF. Increased level of soluble syndecan-1 in serum correlates with myocardial expression in a rat model of myocardial infarction. *Mol Cell Biochem*. 2012;359:177–182.
5. Alexopoulou AN, Multhaupt HA, Couchman JR. Syndecans in wound healing, inflammation and vascular biology. *Int J Biochem Cell Biol*. 2007;39:505–528.
6. Meyer S, van der Meer P, van Deursen VM, Jaarsma T, van Veldhuisen DJ, van der Wal MH, Hillege HL, Voors AA. Neurohormonal and clinical sex differences in heart failure. *Eur Heart J*. 2013;34:2538–2547.
7. Jaarsma T, Van Der Wal MH, Hogenhuis J, Lesman I, Luttik ML, Veeger NJ, Van Veldhuisen DJ. Design and methodology of the COACH study: a multicenter randomised Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure. *Eur J Heart Fail*. 2004;6:227–233.
8. Jaarsma T, van der Wal MH, Lesman-Leegte I, Luttik ML, Hogenhuis J, Veeger NJ, Sanderman R, Hoes AW, van Gilst WH, Lok DJ, Dunselman PH, Tijssen JG, Hillege HL, van Veldhuisen DJ; Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH) Investigators. Effect of moderate or intensive disease management program on outcome in patients with heart failure: Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH). *Arch Intern Med*. 2008;168:316–324.
9. van Veldhuisen DJ, Linssen GC, Jaarsma T, van Gilst WH, Hoes AW, Tijssen JG, Paulus WJ, Voors AA, Hillege HL. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. *J Am Coll Cardiol*. 2013;61:1498–1506.
10. Kleijn L, Belonje AM, Voors AA, De Boer RA, Jaarsma T, Ghosh S, Kim J, Hillege HL, Van Gilst WH, van Veldhuisen DJ, van der Meer P. Inflammation and anaemia in a broad spectrum of patients with heart failure. *Heart*. 2012;98:1237–1241.
11. de Boer RA, Lok DJ, Jaarsma T, van der Meer P, Voors AA, Hillege HL, van Veldhuisen DJ. Predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction. *Ann Med*. 2011;43:60–68.
12. Smilde TD, van Veldhuisen DJ, Navis G, Voors AA, Hillege HL. Drawbacks and prognostic value of formulas estimating renal function in patients with chronic heart failure and systolic dysfunction. *Circulation*. 2006;114:1572–1580.
13. Postmus D, van Veldhuisen DJ, Jaarsma T, Luttik ML, Lassus J, Mebazaa A, Nieminen MS, Harjola VP, Lewsey J, Buskens E, Hillege HL. The COACH risk engine: a multistate model for predicting survival and hospitalization in patients with heart failure. *Eur J Heart Fail*. 2012;14:168–175.
14. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med*. 2011;30:11–21.
15. Tkachenko E, Rhodes JM, Simons M. Syndecans: new kids on the signaling block. *Circ Res*. 2005;96:488–500.
16. Alexopoulou AN, Multhaupt HA, Couchman JR. Syndecans in wound healing, inflammation and vascular biology. *Int J Biochem Cell Biol*. 2007;39:505–528.
17. Endo K, Takino T, Miyamori H, Kinsen H, Yoshizaki T, Furukawa M, Sato H. Cleavage of syndecan-1 by membrane type matrix metalloproteinase-1 stimulates cell migration. *J Biol Chem*. 2003;278:40764–40770.
18. Kandalam V, Basu R, Moore L, Fan D, Wang X, Jaworski DM, Oudit GY, Kassiri Z. Lack of tissue inhibitor of metalloproteinases 2 leads to exacerbated left ventricular dysfunction and adverse extracellular matrix remodeling in response to biomechanical stress. *Circulation*. 2011;124:2094–2105.
19. Spinale FG. Matrix metalloproteinases: regulation and dysregulation in the failing heart. *Circ Res*. 2002;90:520–530.
20. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J*. 2011;32:670–679.

CLINICAL PERSPECTIVE

Syndecan-1 is a member of the heparan-sulfate proteoglycan family. It has been suggested to hold biological activity in the extracellular matrix as a transmembrane receptor and mediator of fibrosis. Syndecan-1 plasma levels were measured in 567 patients with chronic heart failure. Levels of syndecan-1 were found to be associated with fibrosis markers ST-2, galectin-3, and periostin. Furthermore, strong predictive value was found for syndecan-1 for patients with heart failure with a preserved ejection fraction, whereas no such observation was made for patients with heart failure with a reduced ejection fraction. Syndecan-1 might be a useful target in patients with heart failure, especially heart failure with a preserved ejection fraction.

Circulation
Heart Failure

Fibrosis Marker Syndecan-1 and Outcome in Patients With Heart Failure With Reduced and Preserved Ejection Fraction

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SUPPLEMENTAL MATERIAL

Supplemental Table. Baseline characteristics of the total population and syndecan-1 substudy

Variable	Total population (n = 1023)	Syndecan-1 substudy (n = 567)
Treatment allocation		
Control group	33.0	32.6
Basic support	33.3	33.3
Intensive support	33.6	34.0
Demographics and clinical signs		
Age (years)	70.8 ± 11.4	71.0 ± 11.0
Female sex (%)	37.5	38.1
BMI (kg/m^2)	26.2 (23.5 - 29.5)	26.1 (23.5 - 29.5)
Systolic BP (mmHg)	118.3 ± 21.0	118.2 ± 21.2
Heart rate (bpm)	74.6 ± 13.4	74.3 ± 13.1
LVEF (%)	33.7 ± 14.4	32.4 ± 14.0
Previous HF hospitalization	32.7	34.4
NYHA class, II/III/IV (%)	50.9/45.7/3.4	46.6/49.8/3.6
Medical history (%)		
Myocardial infarction	42.6	40.9
Stroke	16.0	15.3
Hypertension	42.9	42.3
Atrial fibrillation of flutter	44.0	46.0
Diabetes	29.3	30.5
COPD	26.2	28.0
Laboratory		
Hemoglobin (g/dL)	13.1 ± 2.0	13.1 ± 2.0
Sodium (mmol/L)	139 ± 4	139 ± 4
Creatinine (µmol/L)	125.0 ± 53	127.4 ± 54
eGFR (mL/min/1.73m^2)	55.2 ± 21.1	53.9 ± 20.2
< 60 (%)	59.6	61.4
BUN (mmol/L)	10.7 (8.1 - 15.2)	11.1 (8.3 - 15.8)
Treatment at discharge (%)		
ACE inhibitor or ARB	82.8	82.0
Beta blocker	66.2	66.7
Diuretic	95.8	95.6
MRA	54.1	54.8
Statin	37.9	38.8
Digoxin	30.2	32.6

For abbreviations, see *Table 1.*