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Abstract

Aims Biomarkers are not recommended until now to guide the management of patients with heart failure (HF). Soluble suppression of tumorigenicity 2 (sST2) appears as a promising biomarker. The current study considered pre-discharged sST2 values as a guide for medical management in patients admitted for acute HF decompensation, in an attempt to reduce hospital readmission.
Methods and results STADE-HF was a blinded prospective randomized controlled trial and included 123 patients admitted for acute HF. They were randomized into the usual treatment group (unknown sST2 level) or the interventional treatment group, for whom sST2 level was known and used on Day 4 of hospitalization to guide the treatment. The primary endpoint was the readmission rate for any cause at 1 month. It occurred in 10 patients (19%) in the usual group and 18 (32%) in the sST2 group without statistical difference ($P = 0.11$). Post hoc analysis in the whole group shows that the mean duration of hospitalization was lower in patients with low sST2 (<37 ng/mL) at admission vs. high sST2 (8.5 ± 9.5 vs. 14.8 ± 14.9 days, respectively, $P = 0.003$). In addition, a decrease in sST2 greater than 18% is significantly associated with a lower readmission rate.
Conclusions Soluble suppression of tumorigenicity 2-guided therapy over a short period of time does not reduce readmissions. However, sST2 was clearly associated with duration of hospitalization, and the decrease in sST2 was associated with decreased rehospitalizations. Long-term outcome using sST2-guided therapy deserves further investigations.

Keywords Heart failure; Biomarkers; sST2; Readmission; Natriuretic peptide; Therapeutic

Background

Acute heart failure (HF) exacerbations leading to hospital (re) admissions remain very frequent. Medication titration until maximum tolerated doses is recommended, but this strategy is not adequate for all patients, exposing them to adverse effects.[1] Therefore, strategies to better discriminate patients who may benefit most from titration are needed to improve the benefit–risk balance. Suppression of tumorigenicity 2 was identified as a new promising prognostic biomarker in HF. Its reduction might be related to a reduction in readmission.[2] High soluble suppression of tumorigenicity 2 (sST2) levels seem to be correlated to a high risk of readmission and therefore the need of medication improvement. On the contrary, low sST2 is correlated to a good prognosis.

Aims

The current study considered sST2 values as a guide for medical management in patients admitted for acute HF, in an attempt to decrease hospital readmission. Moreover, it is

interesting to evaluate whereas the reduction in sST2 levels after initial medical care could be related to better outcome.

Methods

STADE-HF (sST2 As a help for management of Diagnosis, Evaluation and management of HF) was a blinded prospective randomized controlled trial conducted at University Hospital of Montpellier. All patients admitted for acute HF [with preserved or altered left ventricular ejection fraction (LVEF)] between January 2017 and August 2018 were included in this study. Patients were randomized into two groups: usual treatment group, in which patient's sST2 level was unknown, and interventional treatment group, for whom sST2 level was known and used on Day 4 to guide

Figure 1 Study flowchart. sST2, soluble suppression of tumorigenicity 2.

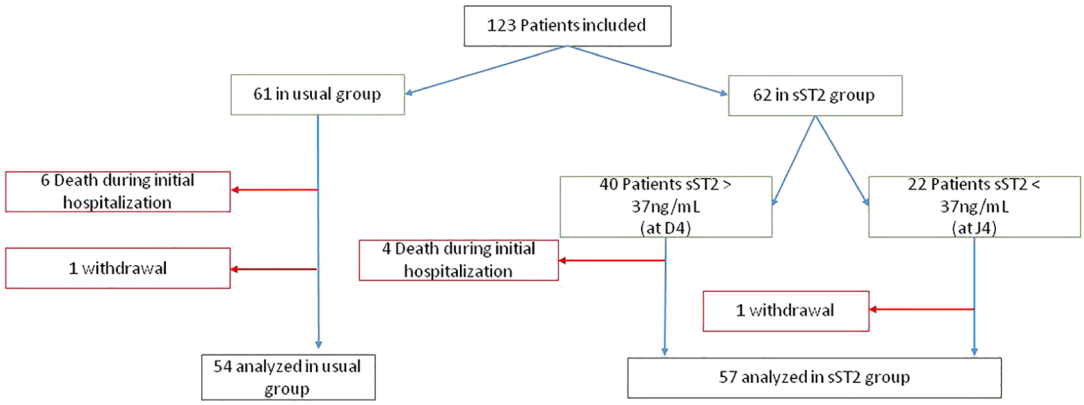


Table 1 Baseline characteristics

Variable		Total (N = 123)	Usual group (N = 61)	sST2 group (N = 62)	P
Clinical and echographic data					
Female sex, *n* (%)		51 (41.5)	25 (41)	26 (42)	0.9
Age (years), mean ± SD		73.7 ± 13.6	73.6 ± 13.7	73.7 ± 13.6	0.9
BMI (kg/m^2), mean ± SD		30.3 ± 19.7	31.0 ± 21.7	29.7 ± 17.8	0.9
Hypertension, *n* (%)		66 (53.7)	29 (48)	37 (60)	0.2
Smoker, *n* (%)		18 (14.6)	13 (21)	5 (8)	0.03
Diabetes mellitus, *n* (%)		47 (38.2)	26 (43)	21 (34)	0.3
Dyslipidaemia, *n* (%)		31 (25.2)	15 (25)	16 (26)	0.8
NYHA, *n* (%)	1	1 (0.8)	0 (0)	1(2)	0.4
	2	11 (8.9)	7 (11)	4 (6)	
	3	69 (56.1)	36 (59)	33 (53)	
	4	42 (34.2)	18 (30)	24 (39)	
Ischaemic cardiomyopathy, *n* (%)		44 (35.8)	20 (33)	24 (39)	0.4
Hypertensive cardiomyopathy, *n* (%)		16 (13)	6 (10)	10 (16)	0.3
Valvular cardiomyopathy, *n* (%)		41 (33.3)	22 (36)	19 (30)	0.5
Rhythmic cardiomyopathy, *n* (%)		64 (52)	29 (48)	35 (56)	0.3
LVEF (%), mean ± SD		41.4 ± 14.5	40.5 ± 14.6	42.3 ± 14.4	0.3
Biological data					
eGFR (mL/min/1.73 m^2), mean ± SD		53.8 ± 22.5	51.8 ± 22.3	55.9 ± 22.7	0.2
NT-proBNP (pg/mL), mean ± SD		7534 ± 10 730	8471 ± 11 706	6612 ± 10 426	0.3
sST2 (ng/mL), mean ± SD		123.8 ± 84.5	135.6 ± 87.8	112.2 ± 80.0	0.2
Heart failure treatment					
Beta-blockers, *n* (%)		78 (63)	39 (64)	39 (63)	0.9
ACE-I, *n* (%)		33 (29)	19 (31)	14 (23)	0.3
ARB, *n* (%)		18 (15)	7 (11)	11 (18)	0.3
MRA, *n* (%)		25 (20)	14 (23)	11 (18)	0.5
ARNI, *n* (%)		0 (0)	0 (0)	0 (0)	—
Ivabradine, *n* (%)		0 (0)	0 (0)	0 (0)	—
Diuretics, *n* (%)		114 (93)	57 (93)	57 (92)	1
Digoxin, *n* (%)		3 (2)	2 (3)	1 (2)	0.6

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; sST2, soluble suppression of tumorigenicity 2.

the treatment. High sST2 levels (above 37 ng/mL) indicated both insufficient treatment and an 'active' disease, urging to optimize medical treatments to the maximally tolerated doses (*Figure 1*). In case of low sST2 levels (below 37 ng/mL), the treatment was considered to be sufficient, and no medication changes were needed. Medical care for the usual treatment group was performed at physicians' discretion.

The main clinical endpoint was the readmission rate for any cause at 1 month according to the treatment received.

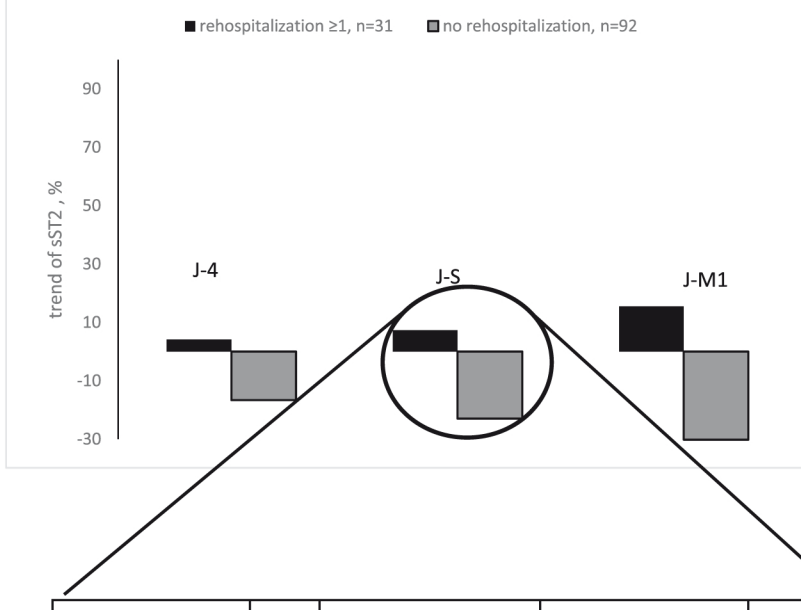
Secondary clinical endpoints included the rehospitalization rate for acute HF decompensation at 1 month, the duration of initial hospitalization, and tolerance criteria based on the evaluation of kidney function at 1 month after discharge.

All participants signed a written consent form and were aware of their right to withdraw from the study at any time. The study protocol was approved by the French institutional review board (Sud Méditerranée IV, Montpellier) on 21 September 2016.

Results

- A total of 123 participants were randomly assigned to the usual treatment group (61 patients) or to the interventional treatment group (62 patients). The study groups were well balanced with respect to baseline characteristics (*Table 1*) as well as LVEF (Supporting Information, *Table S1*). The mean LVEF was 41.4%.
- The primary endpoint of readmission during the first month of follow-up was observed in 28 patients (25%): 10 patients (19%) in the usual group and 18 (32%) in the sST2 group without statistical difference ($P = 0.11$).
- Readmissions for acute HF at 1 month were not statistically different between the two groups ($P = 0.14$).
- No safety issues were noted in the interventional group concerning the patient renal function ($P = 0.89$).
- Interestingly, further sub-analysis showed that low baseline sST2 level predicts initial hospitalization duration. Indeed, the mean duration of hospitalization was lower in patients with sST2 <37 ng/mL at admission vs. >37 ng/mL (8.5 ± 9.5 vs. 14.8 ± 14.9 days, respectively, $P = 0.003$).

Figure 2 Kinetic study of sST2 levels according to patients with or without rehospitalization. Lower panel: Analysis of rehospitalization rate according to the cut-off of 18% sST2 decrease. sST2, soluble suppression of tumorigenicity 2.



		Decrease in ST2 > 18%	Decrease in ST2 < 18%	P (Chi2)
Rehospitalization	No	16 (57.1%)	37 (78.7%)	0.047
	Yes	12 (42.9%)	10 (21.3%)	

- Moreover, a clear relationship between sST2 decrease and rehospitalization is observed (*Figure 2*). Kinetic analysis demonstrates a decrease cut-off at 18%. Indeed, a decrease in sST2 between admission and discharge greater than 18% is associated with a low rate (21.3%) of readmissions at 1 month. On the opposite, in case of low sST2 decrease (less than 18%) or in the presence of an increase in sST2 levels, the risk of hospitalization was significantly higher, rising to 42.9% ($P = 0.04$) (*Figure 2*).
- Beta-blocker titration increased by 15.9% when sST2 was above 37 ng/mL and by 8.3% when sST2 was below 37 ng/mL and decreased by 3.3% in the usual group with statistical difference between the three groups ($P = 0.01$). However, there was no significant modification in other treatment doses (Supporting Information, *Table S2*).
- Even in patients with preserved LVEF, some actions have been taken (Supporting Information, *Tables S2* and *S3*).

Conclusions

STADE-HF is the first prospective randomized controlled trial evaluating a sST2-guided treatment dose titration in patients hospitalized for acute HF. Although safety was established, including in patients with renal failure, this approach failed to decrease both all-cause and acute HF decompensation rehospitalization rates at 1 month. One important result was the positive correlation between sST2 levels upon admission and duration of hospitalization, suggesting that sST2 baseline levels appeal for better stratification of patients' risk and management (e.g. ambulatory management vs. close follow-up in hospital).

Soluble suppression of tumorigenicity 2 levels are related to the chronic inflammatory process, remodelling, and fibrosis. It is interesting to underline that treatments recognized to reduce ventricular remodelling and fibrotic processes in HF are also known to decrease sST2 values in chronic heart failure patients.[2–5]

This study acknowledges some limitations:

- The population is small, and sub-analysis could not be performed.
- The hypotheses used for the calculation of the size of the effect have not been observed, especially in terms of adaptations of treatments. This could be corrected in a larger trial with more directive recommendations for the investigators as well as the multicentric design.
- The potential beneficial effect of personalizing treatment could also be not evidenced because the follow-up period is limited to 1 month.
- Our study included patients with a mean age of 73 years old, while benefit was found only on the oldest patients included in the BATTLESCARED study.[6]
- Patients with both altered and preserved LVEFs were included, while long-term treatments systematically failed to improve prognosis in this population of HF patients.
- Above all, the optimization of long-term treatments is difficult during the first few days after admission, hence here a little rate of changes despite of clear protocols.

Following this pilot study, a large multicentric, long-term follow-up, with a personalized treatment according to the regular determination, is now conducted to evaluate the effect on cardiovascular hospitalization and mortality at 2 years after the index hospitalization. Because of the preliminary results presented here, we will pay special attention to this new trial to what could hamper it. This pilot study will enable us to take these difficulties into account to build a more accurately designed more extensive study, especially by (i) changing deeply the inclusion criteria allowing a better homogeneity of the population (as regards the various clinical forms or stages of HF, for instance) and (ii) defining more precise and more aggressive strategies for adaptations of the treatments following the groups of the patients.

Finally, it will insist on the long-term effect of sST2-guided therapy on the long-term prognosis in those patients.

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Conflict of interest

None declared.

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