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Decompensation of Heart Failure in "Fragile" Patients: Clinical Features and Approaches to Therapy

Aim To evaluate the impact of frailty syndrome (FS) on the course of acute decompensated heart failure (ADHF) and the quality of drug therapy before discharge from the hospital in patients with reduced and moderately reduced left ventricular ejection fraction (LVEF).

Material and methods This open prospective study included 101 patients older than 75 years with reduced and mid-range LVEF hospitalized for decompensated chronic heart failure (CHF). FS was detected during the outpatient follow-up and identified using the Age is Not a Hindrance questionnaire, the chair rise test, and the One Leg Test. The "fragile" group consisted of 54 patients and the group without FS included 47 patients. Clinical characteristics of patients were compared, and the prescribing rate of the main drugs for the treatment of CHF was assessed upon admission to the hospital. The sacubitril/valsartan or dapagliflozin therapy was initiated in the hospital; prescribing rate of the quadruple therapy was assessed upon discharge from the hospital. Patients with reduced LVEF were followed up for 30 days, and LVEF was re-evaluated to reveal possible improvement due to optimization of therapy during hospitalization. Statistical analysis was performed with the SPSS 23.0 software.

Results The main causes for decompensation did not differ in patients of the compared groups. According to the correlation analysis, FS was associated with anemia (r=0.154; p=0.035), heart rate ≥90 bpm (r=0.185; p=0.020), shortness of breath at rest (r =0.224; p=0.002), moist rales in the lungs (r=0.153; p=0.036), ascites (r=0.223; p=0.002), increased levels of the N-terminal pro-brain natriuretic peptide (NT-proBNP) (r= 0.316; p<0.001), hemoglobin concentration <120 g/l (r=0.183; p=0.012), and total protein <65 g/l (r=0.153; p=0.035) as measured by lab blood tests. Among patients with LVEF ≤40% in the FS group (n=33) and without FS (n=33), the quadruple therapy was a part of the treatment regimen at discharge from the hospital in 27.3 and 3.0% of patients, respectively (p=0.006). According to the 30-day follow-up data, improvement of LVEF was detected in 18.2% of patients with LVEF ≤40% in the FS group and 12.1% of patients with LVEF ≤40% in the FS-free group (p=0.020). In patients with LVEF 41–49% in the FS (n=21) and FS-free (n=14) groups, the prescribing rate of the optimal therapy, including sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors, beta-blockers, and mineralocorticoid receptor antagonists, no statistically significant differences were detected (14.3 and 7.1%, respectively; p=0.515) at discharge from the hospital.

Conclusion Patients with ADHF and FS showed more pronounced clinical manifestations of decompensation, anemia, heart rate ≥90 beats/min, and higher levels of NT-proBNP upon admission. The inpatient therapy with sacubitril/valsartan or dapagliflozin was more intensively initiated in FS patients with reduced LVEF. An individualized approach contributed to achieving a prescribing rate of sacubitril/valsartan of 39.4%, dapagliflozin of 39.4%, and quadruple therapy of 27.3% upon discharge from the hospital.

Keywords Acute decompensated heart failure; fragile syndrome; quadruple therapy; in-hospital initiation

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Introduction

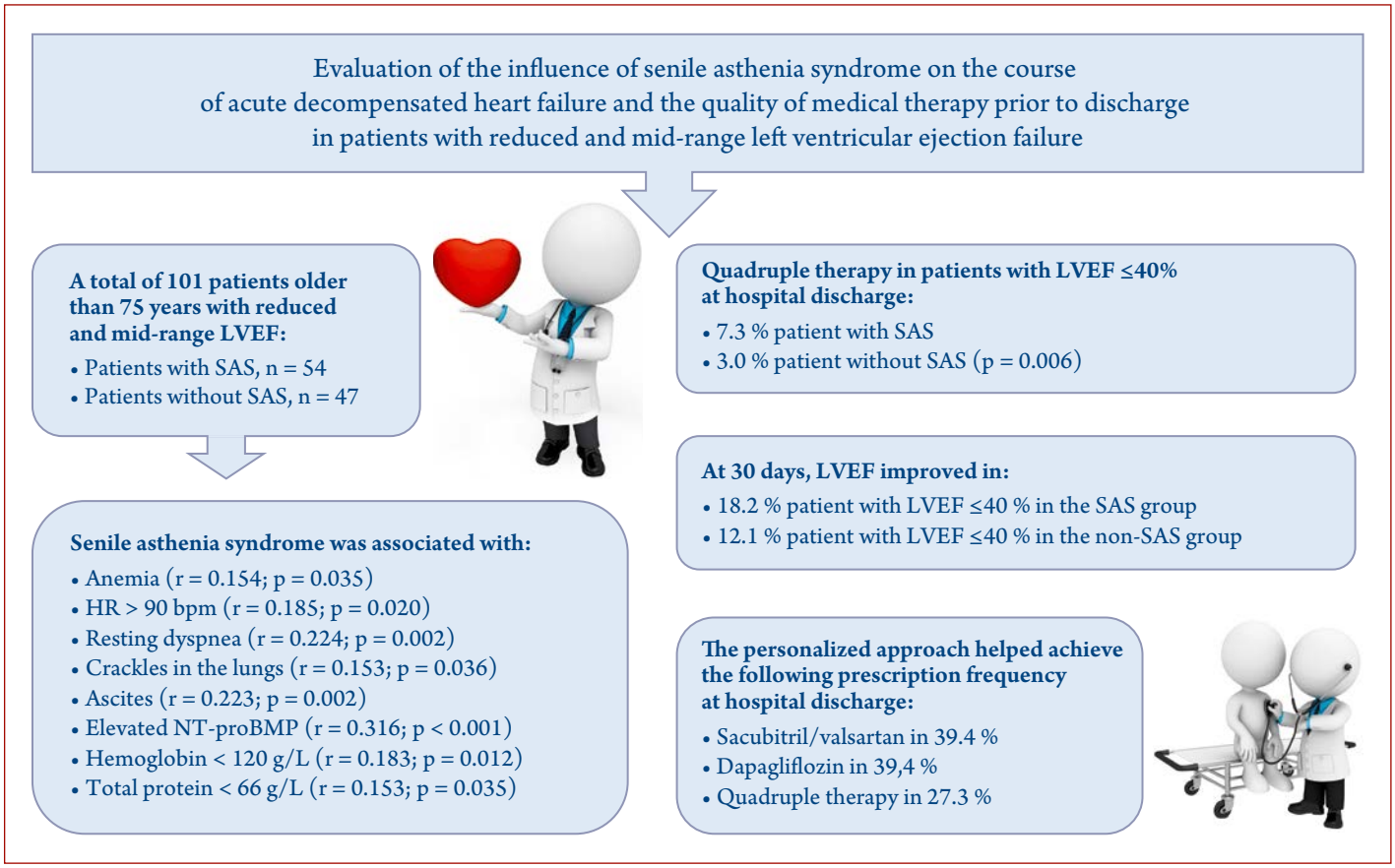
In recent decades, the number of elderly patients with chronic heart failure (CHF) has been rising in various countries around the world due to increased life expectancy of the population and improved methods of treatment of cardiovascular pathology [1, 2]. This trend has been accompanied by an increase in the number of patients with polymorbidity and geriatric syndromes [3]. Senile asthenia syndrome (SAS), or frailty syndrome, is one of the major diagnoses in modern geriatrics and is characterized by an age-related decline in physiological reserve and function of many body

systems, decreased physical activity, and the presence of sarcopenia [3–6].

In clinical practice, CHF and SAS are two conditions that frequently accompany each other in elderly patients. The prevalence of SAS in patients with CHF ranges from 15% to 74%, depending on the population and the methods used for its detection [7, 8]. The presence of frailty syndrome is an independent predictor of hospitalization for CHF, including emergency admissions, and adversely affects prognosis, leading to progression of CHF, increased morbidity and mortality [6–9]. The presence of SAS in patients with CHF was associated with a 2-fold increase in mortality during a 12-month follow-up period in the FRAIL-HF study [10]. Adverse factors in SAS patients include decreased mobility, falls, high comorbidity, polypragmasy, cognitive impairment, and low frequency of administration of drugs that may improve the prognosis [5, 7, 11].

The course of CHF is often complicated by the acute or gradual development of acute decompensated heart failure (ADHF), and after each such episode, the severity of the course of CHF increases, and the patient's cardiac function and quality of life deteriorate [1, 2, 12]. According to the Russian EPOCH-D–CHF program [13], the progression of edema syndrome and the appearance of pulmonary congestion with hemodynamic instability led to hospitalization in 58.5% of patients. Further research is needed to answer many key questions regarding the management of patients with ADHF. These include the management of elderly patients with SAS, such as the detection of associated diseases and conditions, the set of characteristics that determine the CHF phenotype and their impact on the course of ADHF in this clinical patient population, approaches to therapy with drugs with proven ability to improve the prognosis. Difficulties in the medical management of elderly patients with CHF and SAS are associated with multiple comorbidities and polypragmasy, as well as a high incidence of adverse events [5, 14–16]. As a result, these patients often do not receive adequate therapy for CHF, and the prescribed drug doses are usually lower than those recommended [14, 15]. According to current guidelines [1, 17, 18], a quadruple therapy, including angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor neprilysin inhibitors (ARNIs), or angiotensin II receptor blockers (ARBs) if ARNIs/ACE inhibitors are not available, mineralocorticoid receptor antagonists (MRAs), beta-blockers and sodium-glucose cotransporter type 2 (SGLT2) inhibitors, is considered the best available therapy for CHF patients with reduced

Central Illustration. Decompensation of Heart Failure in "Fragile" Patients: Clinical Features and Approaches to Therapy



SAS, senile asthenia syndrome; LVEF, left ventricular ejection fraction; HR, heart rate; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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left ventricular ejection fraction (LVEF) [1, 17–19]. Current guidelines also indicate the need to optimize therapy aimed at improving prognosis in patients with reduced LVEF or to start it as early as possible [1, 17, 18]. According to Miller et al. [20] and Bhagat et al. [21], initiation of background drug therapy for CHF in the hospital is safe and associated with higher patient survival and better adherence to therapy during post-discharge follow-up [20, 21]. Assessing the frequency of prescribing and compliance of drug therapy in elderly ADHF and SAS patients with the current guidelines remains a priority, as do the issues of in-hospital initiation of sacubitril/valsartan and SGLT2 inhibitors and optimization of drug therapy in general.

Objective

Evaluate the effect of SAS on the course of ADHF and the quality of drug therapy prior to hospital discharge in patients with reduced and mid-range LVEF.

Material and Methods

The open-label, prospective study included 101 patients with ADHF older than 75 years with reduced and mid-range LVEF who were hospitalized at the Cardiology Department of the Central Clinical Hospital and Polyclinic of the Presidential Administration of Russia. Patients were included sequentially from June 1, 2021, to December 31, 2022. This study is part of the research investigating the characteristics of the course of ADHF in patients from different clinical populations. The study was approved by the local ethics committee (Minutes No. 11 dated 20.06.2018).

Inclusion criteria: age >75 years; hospitalization for decompensated CHF; reduced (≤40%) or mid-range (41–49%) LVEF shown by echocardiography; signed informed consent to take part in the study.

Exclusion criteria: acute myocardial infarction (MI), acute myocarditis, infective endocarditis, chemotherapy in cancer patients.

CHF was diagnosed and the presence of decompensation was determined according to current guidelines for the diagnosis and treatment of CHF [1]. The functional status of the patients was determined according to the New York Heart Association (NYHA) functional classification and the Symptomatic Hospital and Outpatient Clinical Score (SHOCS modified by Mareev V. Y., 2000) [1].

SAS was established during the outpatient follow-up of patients with CHF prior to hospitalization for ADHF and was determined using the "Age is not a barrier" questionnaire with a total score of 3 or more [3], the chair lift test, and the one leg test [22–25].

The patients included in the study were divided into 2 groups: the SAS group consisted of 54 patients and the non-SAS group consisted of 47 patients. For all patients, a comparative analysis of clinical characteristics was performed, the frequency of prescription of the main treatments for CHF was evaluated at hospital admission, and therapy with sacubitril/valsartan or the SGLT2 inhibitor dapagliflozin was initiated in hospital after the patient's condition had stabilized. At hospital discharge, the frequency of quadruple therapy was evaluated, which included as the neurohumoral component the renin-angiotensin-aldosterone system blocker sacubitril/valsartan, which had been shown to improve prognosis in CHF patients, an SGLT2 inhibitor, a beta-blocker, and an MRA [1, 2, 17–19, 26, 27].

Patients with reduced LVEF were followed for 30 days, and LVEF was re-evaluated by echocardiography to determine possible improvement with optimization of therapy during hospitalization. LVEF was defined as improved if it increased by 10% or more from baseline, which was less than 40% [1, 17, 18], and re-evaluated values of LVEF should be greater than 40%.

All patients underwent clinical examinations and laboratory tests (electrocardiography, transthoracic electrocardiography, chest X-ray, clinical and biochemical blood tests). Echocardiography was conducted using a VIVID E9 device (GE HealhCare, USA). LVEF was assessed by the Simpson's method.

Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured in an electrochemiluminescence analyzer Cobas E 411 Roche HITACHI (Japan) using the proBNP II kit (Cobas Roche Diagnostics, Germany). NT-proBNP range: 5–35,000 pg/mL. Reference values for patients ≥75 years of age are 0–450 pg/mL.

Laboratory tests were performed using the Beckman Coulter AU 480 equipment (Japan). Glomerular filtration rate (GFR) was calculated using the CKD-EPI formula (mL/min/1.73 m^2).

The data obtained were processed using SPSS version 23.0 (USA). The distribution of the analyzed variables was estimated using the Kolmogorov-Smirnov test. The quantitative data were expressed as the means and standard deviations (M ± SD). The categorical signs were presented as the absolute (n) and relative (%) values. Pearson's chi-squared test and Fisher's exact test were used for frequency comparisons. Univariate analysis of variance (ANOVA) was used to compare means. Depending on the type and distribution of the variables, the relationship between the indicators was determined using correlation analysis. Differences were considered statistically significant at $p < 0.05$.

Results

The comparison showed no sex-related differences (p=0.664) and no difference in mean age (p=0.072) between frail patients and patients without SAS. Body mass index was 23.13±3.31 kg/m² in the frail patient group and 26.92 ± 6.97 kg/m² in the comparison group (p=0.001). The length of hospital stay for patients with and without SAS was 15.48 ± 7.45 days and 15.52±7.20 days, respectively (p = 0.968).

The underlying causes of decompensation, including a history of COVID-19, did not differ between the groups. In frail patients, ADHF was most commonly attributed to nonadherence to the recommended medication regimen or dosing in the outpatient setting (27.2%; p = 0.081).

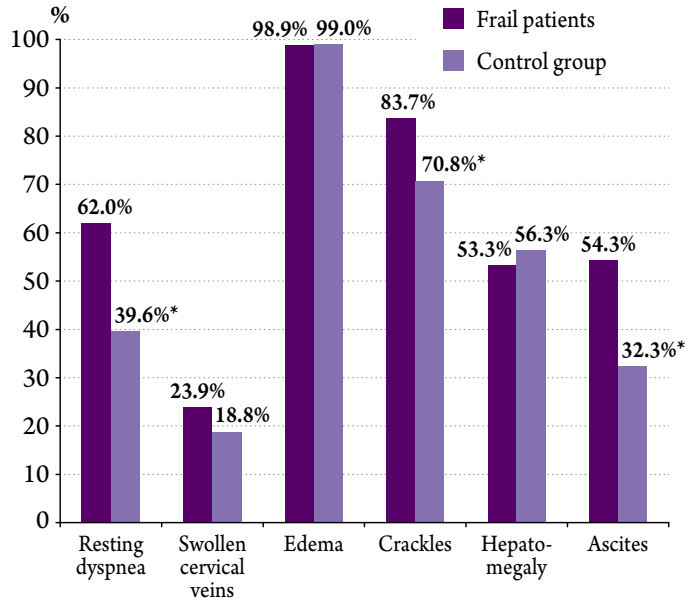
No statistically significant differences were found in the prevalence of coronary artery disease and history of MI (p = 0.996 and p = 0.970, respectively). Frail patients had a high incidence of hypertension (97.8%; p = 0.035) and anemia (65.2%; p = 0.035), and type 2 diabetes mellitus was significantly less common (25.0% versus 46.9%; p=0.002).

At the time of admission to the hospital, patients with SAS had more pronounced clinical manifestations of ADHF. For example, the comparative analysis showed (Figure 1) that 62.0% of frail patients had resting dyspnea (p=0.002), 83.7% had crackles in the lungs (p=0.036), and 54.3% had ascites (p=0.002).

The comparative assessment of blood pressure (BP) and heart rate (HR) showed that there was a high incidence of elevated systolic BP ≥ 140 mm Hg at hospital admission in both groups (42.4% and 41.7%, respectively; p = 0.920). Frail patients were 2 times more likely to have HR ≥90 bpm than those in the comparison group (27.2% versus 13.5%; p = 0.020). There were no statistically significant differences in functional classes between the groups compared. Frail patients had higher NT-proBNP levels (p<0.001) and lower levels of albumin (p=0.001), hemoglobin (63.0%; p=0.012), and total protein (79.3%; p=0.035). There were no differences in other blood biochemistry parameters (glucose, blood lipid profile, liver and kidney tests). GFR was <90 mL/min/1.73 m² in all patients older than 75 years. Patients in both groups most commonly had a significantly reduced GFR of 30–44 ml/min/1.73 m² (38.0% and 46.9%, respectively; p=0.221). Echocardiographic assessment of structural and functional cardiac parameters showed no differences between the groups in mean LVEF (p=0.118), the number of patients with reduced LVEF ≤ 40% (p=0.890) and the number of patients with mid-range LVEF 41–49% (p=0.147).

According to correlation analysis, the frailty syndrome in patients with ADHF was associated with anemia (r=0.154; p=0.035), HR ≥ 90 bpm (r = 0.185; p=0.020), resting dyspnea (r = 0.224; p = 0.002), crackles in the lungs (r=0.153; p=0.036), ascites (r = 0.223; p=0.002), elevated NT-proBNP (r = 0.316; p < 0.001), decreased hemoglobin < 120 g/L (r = 0.183; p=0.012) and total protein < 65 g/L (r = 0.153; p = 0.035).

Figure 1. Clinical manifestations of ADHF in patients with SAS (n = 54) and without SAS (n = 47) at hospital admission



* p < 0.05. ADHF, acute decompensated heart failure; SAS, senile asthenia syndrome.

Oxygen therapy and vasodilator/inotrope therapy were administered according to the clinical profile of hospitalized patients with ADHF, assessment of hemodynamic abnormalities, severity of pulmonary congestion, and peripheral hypoperfusion. Agents with positive inotropic effects were administered during hospital stay in 31.5% and 17.7% of patients with and without SAS, respectively (p=0.033). Diuretic therapy was ordered in 100% of cases in both groups. In the hospital, most patients in both groups required intravenous furosemide and/or ultrafiltration and increased doses of oral diuretics. There were no statistically significant differences in the frequency of IV furosemide administration (p = 0.072). However, ultrafiltration was performed 2 times more frequently in the frail patients than in the control group (42.4% and 21.9%, respectively; p = 0.003).

At hospital admission, the frequency of ACE inhibitors/ARBs (83.3% and 85.1%, respectively; p=0.635), beta-blockers (92.6% and 93.6%, respectively; p = 0.855), and MRAs (90.7% and 85.1%, respectively; p = 0.169) was high in both groups of patients with pre-existing CHF.

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In our study, therapy with sacubitril/valsartan or the SGLT2 inhibitor dapagliflozin was initiated during the hospital stay in patients with reduced and mid-range LVEF. The combined initiation of these drugs was not performed. Hemodynamic stabilization, withdrawal of intravenous diuretics, vasodilators, and inotropic agents were the prerequisites for starting in-hospital therapy. The possibilities to initiate in-hospital therapy with sacubitril/valsartan or dapagliflozin were in some cases limited by the clinical status of the patients (hypotension, hyperkalemia, renal dysfunction) or by the duration of the hospital stay. We recognized the limited experience with initiating in-hospital therapy with sacubitril/valsartan and dapagliflozin in elderly patients with ADHF. Indicated in-hospital therapy was not initiated in patients with severe renal impairment (GFR < 30 mL/min/1.73 m^2).

Among the included patients with LVEF ≤ 40% before hospitalization, only 6 (18.8%) patients with SAS (n=33) and 2 (6.1%) patients without SAS (n = 33) were taking sacubitril/valsartan. ACE inhibitor was substituted with sacubitril/valsartan based on patient characteristics and the latter was started 36 hours after ACE inhibitor withdrawal at an initial dose of 100 mg twice daily. At hospital discharge after ACE inhibitor replacement in 7 patients with SAS and 5 patients without SAS, the rate of sacubitril/valsartan administration was 39.4% (n = 13) and 21.2% (n = 7), respectively (p = 0.108).

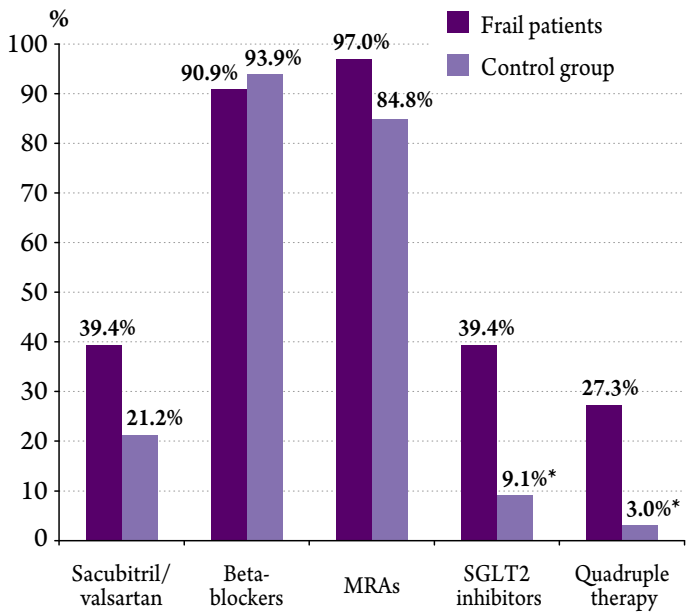
Statistically significant differences were observed regarding the frequency of prescribing SGLT2 inhibitors at discharge (Figure 2). Hospital treatment with dapagliflozin 10 mg once daily was initiated in 8 patients with SAS and 3 patients without SAS. At hospital discharge, SGLT2 inhibitors were prescribed to 13 (39.4%) patients with SAS compared to only 3 (9.1%) patients without SAS (p = 0.002).

In addition, we evaluated the frequency of prescription of quadruple therapy including sacubitril/valsartan, an SGLT2 inhibitor, a beta-blocker, and an MRA at hospital discharge. Quadruple therapy was part of the treatment regimen at hospital discharge in 9 (27.3%) patients with SAS and in 1 (3.0%) patient without SAS (p = 0.006).

In our study, LVEF was re-evaluated by echocardiography within 30 days in patients with a reduced LVEF. LVEF improvement was noted in 6 (18.2%) of 33 patients in the SAS group and 4 (12.1%) of 33 patients without SAS (p = 0.020).

In the included patients with LVEF 41–49%, there were no statistically significant differences between the SAS (n=21) and non-SAS (n=14) groups in the frequency of prescription of sacubitril/valsartan, SGLT2 inhibitors, and best available therapy with sacubitril/valsartan, an SGLT2 inhibitor, a beta-blocker, and an MRA at hospital discharge (Figure 3).

Figure 2. Frequency of prescription of therapy components and quadruple therapy in patients with LVEF ≤40 % in the SAS group (n = 33) and in the non-SAS group (n = 33) at hospital discharge



* p < 0.05. LVEF, left ventricular ejection fraction; SAS, senile asthenia syndrome; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium glucose cotransporter type 2.

At hospital admission, 3 (14.3%) patients with SAS and 2 (14.3%) patients without SAS were receiving sacubitril/valsartan. As a result of ACE inhibitor substitution in 1 patient with SAS, the rate of sacubitril/valsartan prescription at discharge 19.0% and 14.3%, respectively (p=0.714).

SGLT2 inhibitors were prescribed at discharge in 6 (28.6%) patients with SAS and 2 (14.3%) patients without SAS (p = 0.324). Dapagliflozin was initiated during hospital stay in 2 patients with SAS and 1 patient without SAS.

Quadruple therapy was part of the treatment regimen at discharge in 3 (14.3%) patients with SAS and in 1 (7.1%) patient without SAS (p = 0.515).

Thus, in SAS patients with reduced LVEF, more intensive therapy with sacubitril/valsartan or dapagliflozin was initiated. Significant discrepancy in approaches to initiation of treatment components and frequency of prescription of quadruple therapy during hospital stay is most likely due to clinical characteristics of frail patients: greater severity of congestion, higher levels of NT-proBNP (p<0.001), which allowed to consider and take measures to optimize drug therapy in this patient population in the first place.

Discussion

Our findings suggest a high prevalence of SAS in elderly patients with CHF. SAS was found in 53.4% of the patients who were hospitalized for decompensated CHF. The prevalence of SAS in patients with CHF ranges from 15% to 74% [7, 8] depending on age of the included patient and the methods used for SAS detection. According to Altimir et al [28], the incidence of SAS in patients with CHF younger than 70 years was 30% and increased significantly in patients older than 70 years, which was comparable to our data.

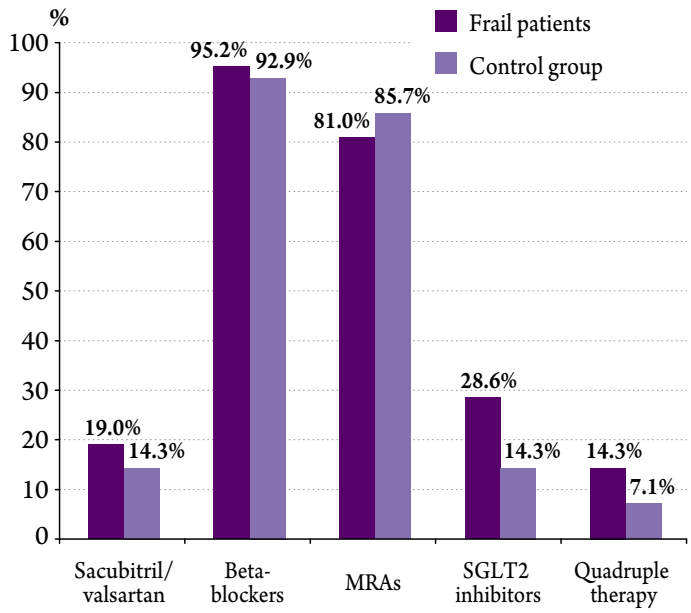
In the Russian EPOCH-D–CHF program (2016), persistent atrial fibrillation with a high heart rate and uncontrolled hypertension were the main reasons for hospitalization of patients with ADHF [13]. According to our data, a high frequency of systolic BP ≥ 140 mm Hg was observed at hospital admission in patients with and without SAS (42.4% and 41.7%, respectively; p = 0.920), HR ≥ 90 bpm was detected 2 times more frequently in frail patients (27.2% and 13.5%, respectively; p = 0.020).

Patients with SAS had a more severe course of CHF in the SICA-HF study [29]. In our study, the presence of SAS also influenced the course of CHF in patients older than 75 years. According to correlation analysis, anemia, HR ≥90 bpm, resting dyspnea, crackles in the lungs, and ascites were associated with frailty syndrome in patients with ADHF. Statistically significant correlations were found with elevated NT-proBNP levels, decreased hemoglobin < 120 g/L and total protein < 65 g/L according to laboratory blood tests.

We evaluated the impact of SAS on treatment approaches in patients with decompensated CHF. Evaluation of drug therapy in patients over 75 years of age with and without SAS at hospital admission showed that the frequency of outpatient prescription of ACE inhibitors/ARBs, beta-blockers and MRAs was generally in line with current guidelines for the treatment of CHF [1, 17, 18]. However, inadequate adherence to prescribed therapy should be noted, as one of the most common causes of ADHF in patients older than 75 years in our study was nonadherence to the regimen or recommended drug doses established at hospital admission.

The results of recent studies have significantly influenced approaches to the management of patients with CHF, including episodes of decompensation [26, 30–36]. The need to optimize therapy in patients with reduced and mid-range LVEF has become apparent [17–19, 26]. The in-hospital initiation of sacubitril/valsartan and SGLT2 inhibitors, which are essential components of a quadruple therapy that can improve the prognosis of patients with CHF, is an important and widely discussed approach to the treatment of CHF and its decompensation. Such therapy can target all modifiable pathways of

Figure 3. Frequency of prescription of the best available therapy in patients with LVEF 41–49 % in the SAS group (n = 21) and in the non-SAS group (n = 14) at hospital discharge (p > 0.05)



LVEF, left ventricular ejection fraction; SAS, senile asthenia syndrome; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium glucose cotransporter type 2.

CHF progression [26] and prevent episodes of ADHF. Quadruple therapy, including ACE inhibitors or ARNIs, or ARBs when ARNIs or ACE inhibitors cannot be used, beta-blockers, MRAs and SGLT2 inhibitors, is currently recommended as the best available therapy in CHF patients with reduced LVEF [1, 17–19, 26]. Approaches to prescribing the components of the best available therapy for CHF during hospital stay allowed us to evaluate the results of the TRANSITION, PIONEER-HF, EMPULSE, EMPA-RESPONSE-AHF, and EMPAG-HF trials, which demonstrated the feasibility of initiating therapy with sacubitril/valsartan and empagliflozin prior to hospital discharge after hemodynamic stabilization, withdrawal of inotropic and vasopressor support, and withdrawal of intravenous loop diuretics [1, 17, 18, 26, 27, 31, 33, 37]. At present, an individualized approach to the initiation of such therapy in the hospital setting is recommended [26, 38], as current guidelines do not provide clear recommendations.

Sacubitril/valsartan and the SGLT2 inhibitor dapagliflozin were not initiated in combination in our study. An intensive approach with initiation of combined triple therapy (without SGLT2 inhibitors) prior to hospital discharge was evaluated in the STRONG-HF trial, the results of which were published in 2022. [34]. Measures evaluated in the study, such as the rate of achieving target drug doses, risk of all-cause mortality and rehospitalizations, showed benefits in the intensive

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management group at 90 and 180 days of follow-up compared to the conventional therapy group.

Promising directions include both further study of the phenotype characteristics of elderly patients with ADHF, many of whom have SAS with functional and cognitive impairment, and approaches to personalized therapy, including in-hospital initiation of therapy based on clinical characteristics and continuity of patient management to reduce emergency hospitalizations and mortality.

Limitations

The doses of sacubitril/valsartan and other components of the quadruple therapy were not evaluated in the study groups, except for the SGLT2 inhibitors, whose daily dose was 10 mg in all patients. The incidence of hospitalization for recurrent ADHF during the 30-day follow-up after in-hospital initiation of quadruple therapy and longer-term follow-up was not evaluated. These questions remain to be answered for further research on the therapeutic approaches used in clinical practice.

Conclusion

The results of the study revealed a number of features characteristic of frail patients with acute decompensated heart failure, including more severe clinical manifestations of decompensation, anemia, high heart rate at hospital admission, higher levels of N-terminal pro-brain natriuretic peptide, and a high need for ultrafiltration. In the hospital setting, more intensive initiation of therapy with sacubitril/valsartan or dapagliflozin was performed in patients with senile asthenia syndrome and heart failure with reduced left ventricular ejection fraction. The personalized approach contributed to a discharge prescription rate of 39.4% for sacubitril/valsartan, 39.4% for dapagliflozin, and 27.3% for quadruple therapy.

The peculiarities of the course of decompensated heart failure in patients with senile asthenia syndrome and the approaches to in-hospital initiation of quadruple therapy revealed in our study may contribute to the improvement of diagnostic and therapeutic approaches to the management strategy aimed at reducing the risk of recurrent episodes of decompensated heart failure.

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