ORIGINAL ARTICLE

Heart failure in elderly patients: differences in clinical characteristics and predictors of 1-year outcome in the Polish ESC-HF Long-Term Registry

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KEY WORDS

elderly patients, heart failure, hospitalization, prognosis, registry

ABSTRACT

INTRODUCTION Heart failure (HF) is the leading cause of hospitalization in elderly patients.
OBJECTIVES The aim of the study was to examine the clinical profile and 1-year outcomes of elderly patients (aged ≥65 years) compared with younger patients (aged <65 years) hospitalized for HF decompensation, as well as clinical differences among elderly patients aged 65–74 years and those aged ≥75 years.
PATIENTS AND METHODS The primary endpoint (PE; all-cause death) and the secondary endpoint (SE; all-cause death or rehospitalization for HF worsening) were assessed at 1 year in a group of 765 hospitalized Polish participants of the ESC-HF Long-Term Registry.
RESULTS The PE was observed in 9.1% of patients aged <65 years; 18.5% of those aged ≥65 years ($P = 0.0001$); 14.5% of those aged 65–74 years; and 21.6% of those aged ≥75 years ($P = 0.07$). The SE occurred in 28.0% of patients aged <65 years; 36.1% of those aged ≥65 years ($P = 0.04$); 29.2% of those aged 65–74 years; and 41.2% of those aged ≥75 years ($P = 0.01$). Independent predictors of the PE in patients aged ≥65 years were as follows: chronic obstructive pulmonary disease (COPD), systolic blood pressure (SBP), New York Heart Association (NYHA) class, β-blocker use; in patients aged 65–74 years: coronary revascularization, NYHA class, sodium, and creatinine; in patients aged ≥75 years: NYHA class and SBP. Independent predictors of the SE in patients aged ≥65 years were as follows: COPD, NYHA class, potassium, SBP, and physical activity; in patients aged <65 years: chronic kidney disease (CKD), NYHA, and SBP; in patients aged 65–74 years: NYHA and creatinine; and in patients aged ≥75 years, previous HF hospitalization, coronary artery disease, CKD, COPD, alcohol consumption, smoking, NYHA, and SBP.
CONCLUSIONS Elderly patients with HF differed from younger patients in terms of long-term outcome and prognostic factors. There were also important differences within the elderly group itself.

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INTRODUCTION Improvements in the treatment of cardiovascular diseases have resulted in a steady increase in the prevalence of chronic heart failure (HF) in seniors.[1] Approximately 50% to 80% of patients hospitalized for HF are aged 65 years or older, and more than half of them, 75 years or older.[1-3] As industrialized populations age, this becomes a more pressing issue. HF is a leading cause of hospitalization in the elderly and a great cost driver both for the health care system and for the patients themselves.[4,5] The amount of readmissions after HF hospitalization within 6 months of discharge exceeds 50%.[4,5] In Poland, HF is the most common cause of readmission for patients hospitalized for acute myocardial infarction (AMI-PL nationwide database).[6] Despite strict diagnostic criteria, the diagnosis of HF in the elderly may be difficult because of its unusual clinical manifestation and other comorbid conditions.[1,7] There is an ongoing discussion on optimal management of HF in older patients; however, there are no specific guidelines for HF treatment specific to seniors, recommended by the European Society of Cardiology (ESC).[2] Patients enrolled in randomized clinical trials are often young with a reduced left ventricular ejection fraction (LVEF) and do not represent the real-life population.[7,8] Clinical characteristics and pharmacodynamics in elderly patients with HF may differ from those in younger populations. It requires a closer look through properly designed studies. In the SENIORS study,[9] which included patients over 70 years of age with HF, the β-blocker nebivolol demonstrated efficacy and good tolerability.[9] Furthermore, the previously established definition of older age (≥65 years) seems to be no longer valid. Since the clinical conditions of people aged from 65 to 74 years have improved and there is an increasing number of HF patients aged 75 years or older, it is important to reevaluate the threshold of what we consider "older age".[1]

The aim of the study was to examine the clinical profile and 1-year outcomes of elderly Polish patients (aged ≥65 years) compared with younger patients (aged <65 years) hospitalized for HF decompensation. An additional subanalysis sought to determine clinical differences among elderly patients aged from 65 to 74 years and the very-elderly—aged 75 years or older.

PATIENTS AND METHODS

Study population The ESC-HF Long-Term Registry is an ongoing prospective, multicenter, observational survey of HF patients, involving 211 cardiology centers from 21 European countries. The registry includes outpatients with chronic HF, as well as patients admitted to the hospital for new-onset or worsening HF. The study enrolled patients who met diagnostic criteria for HF and were over 18 years of age. There were no specific exclusion criteria. All patients provided informed written consent. A local ethical review board approved the survey.

During phase I of the registry, lasting from May 2011 to April 2013, patients were enrolled on a single day per week for 12 consecutive months in each of the participating centers. In phase II of the registry (currently ongoing), patients are enrolled during 5 days each trimester. Detailed description of the registry construction can be found in the publication of Maggioni et al.[10]

The current analysis included Polish patients hospitalized for HF, enrolled during phase I of the ESC-HF Long-Term Registry. The study excluded outpatients seen in ambulatory care. The threshold of old age was assumed at 65 years. Patients aged 65 years or older were included in the elderly group, and those aged less thab 65 were included in the young group. Additional subanalysis concerned elderly patients aged from 65 to 74 years and very-elderly—aged 75 years or older.

In the main analysis (patients aged <65 years vs those aged ≥65 years) and in the subanalysis (patients aged ≥65–74 years and those aged ≥75 years), patients were compared with regards to their clinical status on admission, laboratory findings, management during index hospitalization, and discharge pharmacotherapy, as well as in-hospital (all-cause death during index hospitalization) and 1-year outcome (all-cause death and all-cause death or rehospitalization for decompensated HF).

Physical activity and alcohol consumption were predefined in the registry as "none, moderate, or intensive" and "never, former, sometimes, or daily", respectively. In that case, the choice of the appropriate intensity was at the discretion of the investigator.

Clinical endpoints at 1-year follow-up The primary endpoint was all-cause death at 1 year. The secondary endpoint was a composite of all-cause death and hospital readmission for HF worsening at 1 year. We assessed the frequency of the primary and secondary endpoints, and compared predictors of the primary and secondary endpoints between the main study groups and between the subgroups.

Statistical analysis Normally distributed continuous variables were presented as mean values and standard deviations. For ordinal variables and nonnormally distributed continuous variables, median values and interquartile ranges were used. Categorical data were presented as the number of patients and percentages. The main groups and the subgroups were compared using the Fisher exact test (for categorical variables) and the Mann–Whitney test (for continuous variables). Cox proportional hazards regression model was used to identify predictors of the primary and secondary endpoints. Variables found to be statistically significant in univariate analyses were included into multivariate analyses. In the univariate analyses, in order to maintain adequate events per predictor variable (EPV) value, due to the relatively small size of the groups, variables with more than 5% of incompleteness of data were not included in the Cox proportional hazards regression model. Kaplan–Meier curves were developed for the primary and secondary endpoints for all groups (FIGURES 1 and 2). For all tests, a P value of less than 0.05 was considered statistically significant. All tests were 2-tailed. Statistical analyses were performed using the SPSS software, version 22 (IBM SPSS Statistics 22, New York, United States).

RESULTS

Study group selection A total of 12 440 patients were enrolled in the ESC-HF Long-Term Registry (Phase 1) across Europe. The final analysis included a total of 765 Polish inpatients. The mean age of the overall population was 69.1 ±12.3 years. In the study group, 266 patients were aged less than 65 years (34.8%), and 499 patients—65

FIGURE 1
Kaplan–Meier curves for the primary endpoint in patients with heart failure

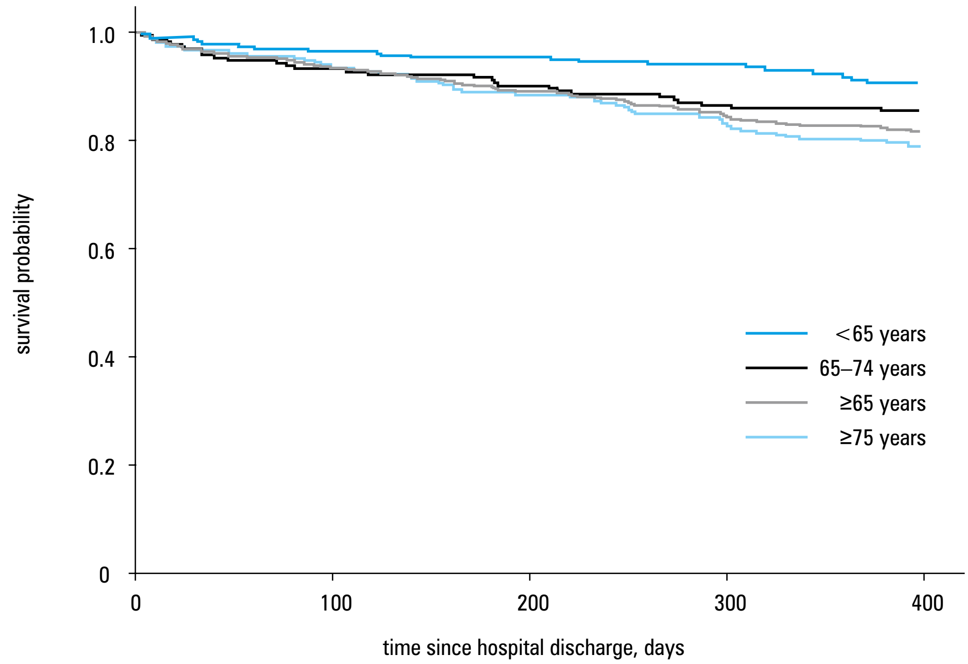
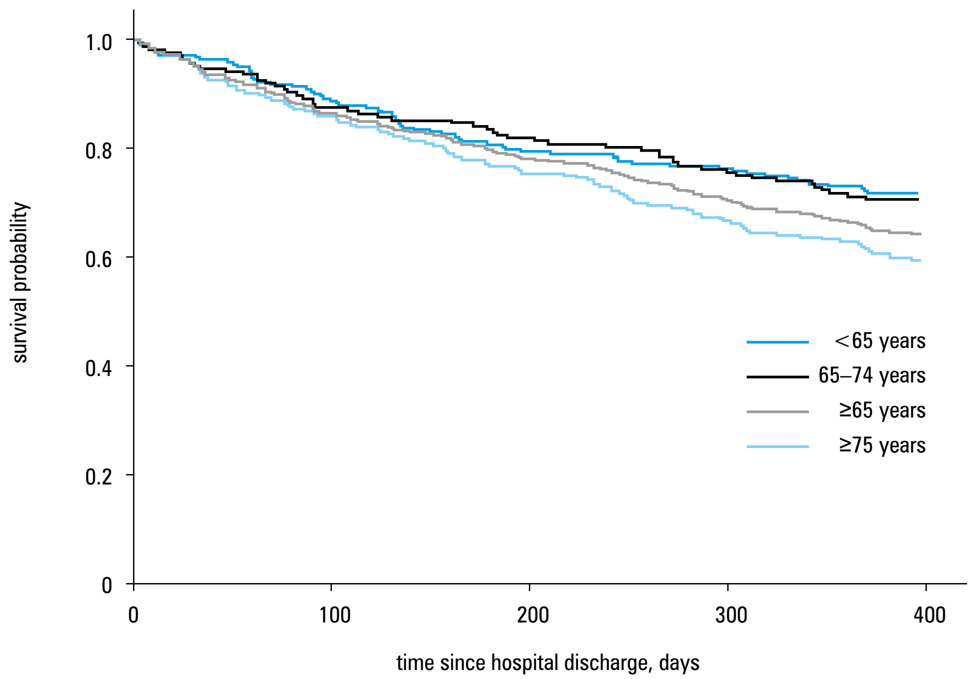


FIGURE 2
Kaplan–Meier curves for the secondary endpoint in patients with heart failure



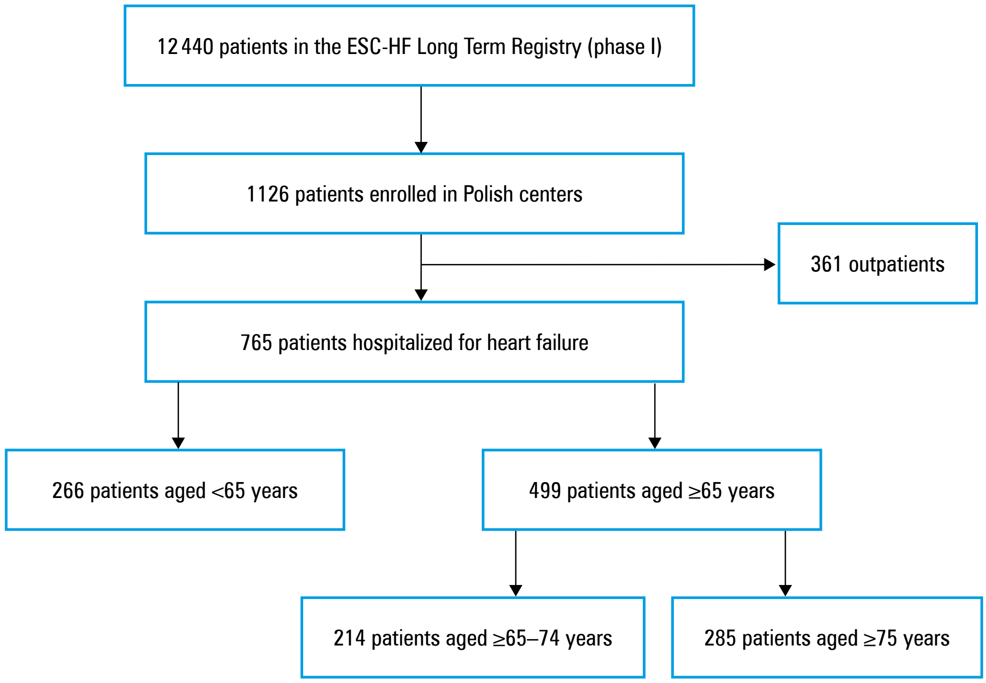
years or older (65.2%). Approximately 37% of the patients (n = 285) were in the very-elderly group (≥75 years). **FIGURE 3** shows the flow chart of patient enrollment in the study.

Comparative analysis of the patient subgroups according to age Comparative baseline characteristics, clinical course, and management during index hospitalization, as well as in-hospital and 1-year outcomes of patients aged less than 65 years and those aged 65 years or older, as well as patients aged 65 to 74 years and those aged 75 years or older are presented in **TABLES 1** and **2**.

In-hospital outcome During index hospitalization, death occurred in 22 of the 765 patients, including 6 of the 266 patients aged less than 65 years (2.3%), and 16 of the 499 patients aged 65 years or older (3.2%; $P = 0.51$). The subanalysis revealed that in-hospital death for the age group of 65 to 74 years occurred in 4 of the 216 patients (1.9%); however, most deaths were recorded in the very-elderly group (12 of the 285 patients [4.2%]; $P = 0.2$), as shown in **TABLE 2**.

Primary endpoint Data on 1-year survival were available for 689 patients (92.7%) of the 743 patients, who were discharged after index hospitalization. In the main analysis, the primary

FIGURE 3 Flow chart of patient enrollment in the study



endpoint was reached by 105 of the 689 patients, including 22 of the 241 patients aged less than 65 years (9.1%), and 83 of the 448 patients aged 65 years or older (18.5%; *P* = 0.0001). The subanalysis revealed that death occurred in 28 of the 193 patients (14.5%) aged from 65 to 74 years and 55 of the 255 patients aged 75 years or older (21.6%, *P* =0.07), as shown in **TABLE 2**. One-year survival probability of both the main patient groups and the subanalysis subgroups are presented by the Kaplan–Meier curves in **FIGURE 1**.

Univariate analyses of the primary endpoint predictors in patients aged less than 65 years and those aged 65 years or older, as well as those aged from 65 to 74 years and those aged 75 years or older, are shown in the Supplementary material online, *Table S1* and *S2*, respectively. All variables that were predictive of the primary endpoint in the univariate analyses in patients aged 65 years or older, 65 to 74 years, and 75 years or older were consequently included in the multivariate Cox proportional hazards regression models (**TABLES 3** and **4**). A multivariate analysis in patients aged less than 65 years was not performed due to a very small EPV number.

Secondary endpoint Data on 1-year survival and readmission were available for 641 patients (86.3% of the 743 patients discharged after index hospitalization). The secondary endpoint occurred in 213 of the 641 patients, including 63 of the 225 patients aged less than 65 years (28.0%), and in 150 of the 416 patients aged 65 years or older (36.1%; *P* = 0.04). In the subanalysis, the secondary endpoint was observed in 52 of the 178 patients (29.2%) aged from 65 to 74 years and in 98 of the 238 patients aged 75 years or older (41.2%, *P* = 0.01), as shown in **TABLE 2**. The Kaplan–Meier curves for all subgroups are shown in **FIGURE 2**.

Univariate analyses of the secondary endpoint predictors in patients aged less than 65 years and those aged 65 years or older, as well as those aged from 64 to 74 years and those aged 75 years or older, are shown in the Supplementary material online, *Table S1* and *S2*, respectively. All variables that were predictive of the secondary endpoint in the univariate analyses in patients aged less than 65 years or older, 65 to 74 years, and 75 years or older were consequently included in the multivariate Cox proportional hazards regression models (**TABLES 3** and **4**).

DISCUSSION Like previous reports, our analysis revealed that approximately 65% of patients hospitalized for HF were aged 65 years or older and more than a half of them—75 years or older.[1-3] The mean age of the overall population (69.1 ±12.3 years) in our study was lower than that in the OPTIMIZE-HF[1] (73.2 ±14 years) or ATTEND[11] (72.9 ±13.8) registries. This finding probably reflects a still lower life expectancy in Poland than in the United States or Japan, respectively. In the international version of the ESC-HF Long-Term Registry,[8] the mean age of hospitalized HF patients was the lowest in Eastern European countries (Poland, Romania). In the study population, a diminishing contribution of men was also observed (in patients aged <65 years, 83.1%; 65–74 years, 68.2%; and ≥75 years, 52.3%), which is consistent with the results of other studies.[1,11] Patients aged 65 years or older and the subpopulation of those aged 75 years or older also had a lower body mass index. There is a consensus that the risk of cardiovascular diseases is increased in obese patients. However, among patients with HF,

TABLE 1 Baseline characteristics of patients aged <65 years, ≥65years, 65–74 years, and ≥75 years

Parameter	Total of 765 patients			Patients aged ≥65 years (n = 499)		
	<65 years (34.8%; n = 266)	≥65 years (65.2%; n = 499)	*P* value	65–74 years (42.9%; n = 214)	≥75 years (57.1%; n = 285)	*P* value
demographic characteristics						
male, %; n/N	83.1; 221/266	59.1; 295/499	<0.0001	68.2; 146/214	52.3; 149/285	0.0003
BMI, kg/m^2, median (range)	28.7 (25.4–32.0) n = 266	27.1 (24.8–30.4) n = 496	<0.0001	27.7 (25.3–31.2) n = 213	26.4 (24.2–29.8) n = 283	0.001
heart failure						
LVEF, %, median (range)	30 (21–40); n = 232	40 (26–54) n = 429	<0.0001	35 (23–50); n = 178	45 (30–55) n = 251	<0.0001
HF-PEF, %; n/N	13.4; 31/232	36.4; 156/429	<0.0001	25.3; 45/178	44.2; 111/251	<0.0001
previous HF hospitalization	50.2; 133/265	53.0; 264/498	0.49	56.3; 120/213	50.5; 144/285	0.2
ischemic etiology, %; n/N	48.5; 129/266	58.9; 294/499	0.01	64.5; 138/214	54.7; 156/285	0.03
valve disease, %; n/N	7.9; 21/266	16.2; 81/499	0.001	12.6; 27/214	18.9; 54/285	0.07
dilated cardiomyopathy, %; n/N	27.1; 72/266	8.8; 44/499	<0.0001	11.2; 24/214	7.0; 20/285	0.11
medical history, %; n/N						
hypertension	59.52; 157/265	77.7; 387/498	<0.0001	72.8; 155/213	81.4; 232/285	0.03
atrial fibrillation	39.1; 104/266	52.1; 260/499	0.001	48.1; 103/214	55.1; 157/285	0.13
coronary artery disease	47.4; 126/266	57.3; 286/499	0.01	60.3; 129/214	55.1; 157/285	0.27
prior PCI or CABG	34.2; 91/266	35.5; 177/499	0.75	44.4; 95/214	28.8; 82/285	0.0003
peripheral artery disease	8.3; 22/265	20.1; 100/498	<0.0001	23.8; 51/214	17.3; 49/284	0.07
diabetes	30.5; 81/266	37.7; 188/499	0.047	43.0; 92/214	33.7; 96/285	0.04
chronic kidney disease	15.0; 40/266	35.3; 176/499	<0.0001	30.8; 66/214	38.6; 110/285	0.09
COPD	12.8; 34/265	16.0; 80/499	0.29	15.9; 34/214	16.1; 46/285	1.00
stroke	9.8; 26/266	11.6; 58/499	0.47	7.0; 15/214	15.1 43/285	0.01
mitral regurgitation[a]	60.9; 148/243	60.8; 274/451	1.00	59.4; 111/187	61.7; 163/264	0.63
aortic stenosis[a]	5.5; 13/238	14.1; 62/440	0.0004	12.1; 22/182	15.5; 40/258	0.33
current smoking	74.1; 197/266	46.5; 232/499	<0.0001	58.4; 125/214	37.5; 107/285	<0.0001
alcohol[b]	74.1; 192/256	55.2; 270/489	<0.0001	64.6; 135/209	48.2; 135/280	0.0003
physical activity[c]	61.5; 155/252	47.9; 233/486	<0.0001	52.9; 109/206	44.3; 124/280	0.07
previous pharmacotherapy, %; n/N						
diuretics	73.7; 196/266	69.5; 347/499	0.24	73.8; 158/214	66.3; 189/285	0.08
AA	54.9; 146/266	43.5; 217/499	0.003	50.5; 108/214	38.2; 109/285	0.01
ACEI	67.3; 179/266	61.7; 308/499	0.13	65.4; 140/214	58.9; 168/285	0.16
ARB	8.3; 22/266	9.2; 46/499	0.69	11.2; 24/214	7.7; 22/285	0.21
β-blocker	78.9; 210/266	75.4; 376/499	0.28	79.0; 169/214	72.6; 207/285	0.12
CCB	9.4; 25/266	17.6; 88/499	0.002	15.9; 34/214	18.9; 54/285	0.42
statins	51.9; 138/266	59.1; 295/499	0.056	63.1; 135/214	56.1; 160/285	0.14
anticoagulants	31.6; 84/266	36.3; 181/499	0.2	42.5; 91/214	31.6; 90/285	0.01
antiplatelets	51.5; 137/266	55.3; 276/499	0.32	58.9; 126/214	52.6; 150/285	0.17
digoxin	24.4; 65/266	14.6; 73/499	0.001	17.8; 38/214	12.3; 35/285	0.1

P values of less than 0.05 are statistically significant.

a moderate or severe; b former or sometimes; c moderate or intensive

Abbreviations: AA, aldosterone antagonist; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; HF, heart failure; HF-PEF, heart failure with persistent ejection fraction; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention

outcomes seem to be better in obese individuals.[12] This phenomenon is known as the obesity paradox, the mechanisms of which remain unclear.[12] One of its possible interpretations is that HF is a catabolic state and obese patients may have more metabolic reserve, which is especially important in elderly patients.[12]

As a person ages, the heart undergoes structural and physiological changes.[9] The incidence of concomitant diseases, especially hypertension,

TABLE 2 Clinical course of index hospitalization, in-hospital and long-term outcomes of patients aged <65 years, ≥65 years, 65–74 years, and ≥75 years

Parameter	Total of 765 patients			Patients aged ≥65 years (n = 499)		
	age <65 years (34.8%; n = 266)	age ≥65 years (65.2%; n = 499)	*P* value	age 65–74 years (42.9%; n = 214)	age ≥75 years (57.1%; n = 285)	*P* value
clinical status on admission						
NYHA class	3 (2–4); n = 265	3 (3–4); n = 497	0.13	3 (3–4); n = 214	3 (3–4); n = 283	0.56
SBP, mmHg	120 (110–138); n = 266	130 (110–145) n = 499	0.002	127 (110–140) n = 214	130 (115–150) n = 285	0.06
heart rate, bpm	80 (70–100); n = 266	80 (70–100); n = 499	0.48	80 (70–95); n = 214	80 (70–100); n = 285	0.34
AF as a cause of admission	23.7; 63/266	36.3; 181/499	0.003	34.1; 73/214	37.9; 108/285	0.4
laboratory findings at admission						
serum sodium, mmol/l	140 (137–142); n = 263	139 (136–141) n = 496	<0.0001	140 (13141) n = 214	140 (137–142) n = 282	0.44
serum potassium, mmol/l	4.4 (4.1–4.8); n = 263	4.5 (4.1–4.8); n = 497	0.43	4.5 (4.2–4.8); n = 214	4.5 (4.1–4.9); n = 283	0.97
serum creatinine, mg/dl	1.02 (0.88–1.28); n = 264	1.15 (0.91–1.45) n = 497	<0.0001	1.15 (0.92–1.47) n = 214	1.15 (0.9–1.45) n = 283	0.97
hemoglobin, g/dl	14.1 (12.6–15.2) n = 264	13.1 (11.9–14.2) n = 494	<0.0001	13.4 (12.0–14.4) n = 212	13.0 (11.7–14.0) n = 282	0.02
cholesterol, mg/dl	165.0 (134.0–205.8) n = 202	157.0 (127.0–188.0) n = 391	0.01	154.0 (127.1–189.0) n = 168	157.4 (126.0–188.0); n = 223	0.74
major management during index hospitalization, clinical status at discharge						
NYHA class	2 (2–3); n = 260	2 (2–3); n = 483	0.45	2 (2–3); n = 210	2 (2–3); n = 273	0.64
SBP, mmHg	120 (105–130) n = 260	120 (110–130) n = 483	0.16	120 (105–130) n = 210	120 (110–130) n = 273	0.04
heart rate, bpm	70 (65–80); n = 260	70 (65–80); n = 483	0.43	70 (65–80); n = 210	70 (65–80); n = 273	0.42
hemoglobin, g/dl	13.4 (12.1–14.8) n = 148	12.0 (11.4–13.9) n = 309	0.001	13.0 (11.8–14.2) n = 140	12.7 (11.1–13.6) n = 169	0.04
serum creatinine, mg/dl	1.05 (0.9–1.25) n = 184	1.17 (0.91–1.48) n = 370	0.004	1.14 (0.90–1.45) n = 162	1.18 (0.94–1.50) n = 208	0.23
serum sodium, mmol/l	139 (137–142) n = 194	139 (136–141) n = 397	0.01	140 (137–142) n = 174	139 (137–141) n = 223	0.02
serum potassium, mmol/l	4.4 (4.1–4.8); n = 263	4.5 (4.1–4.8); n = 497	0.43	4.4 (4.1–4.7); n = 174	4.4 (4.1–4.7); n = 224	0.14
PCI or CABG	12.8%; 34/265	11.7%; 58/496	0.64	16.1%; 34/211	8.4%; 24/285	0.01
pacemaker	1.1%; 3/266	8.6%; 43/499	<0.0001	3.7%; 8/214	12.3%; 35/285	0.001
CRT	5.6%; 15/266	6.0%; 30/499	0.87	9.8%; 21/214	3.2%; 9/285	0.004
ICD	25.2%; 67/266	16.6%; 83/499	0.01	22.0%; 47/214	12.6%; 36/285	0.01
pharmacotherapy at discharge						
diuretics	85.7%; 228/266	85.2%; 425/499	0.92	86.9%; 186/214	83.9%; 239/285	0.38
AA	71.4%; 190/266	63.5%; 316/499	0.03	69.2%; 141/214	59.3%; 169/285	0.02
ACEI	73.7%; 196/266	73.3%; 366/499	0.93	76.2%; 163/214	71.2%; 203/285	0.22
ARB	9.0%; 24/266	10.6%; 53/499	0.53	10.7%; 23/14	10.5%; 30/285	1.00
β-blocker	89.5%; 236/266	87.8%; 438/499	0.55	90.2%; 193/214	86.0%; 245/285	0.17
CCB	9.0%; 24/266	18.6%; 93/499	0.0003	16.8%; 36/214	20.0%; 57/285	0.42
statins	61.7%; 164/266	69.1%; 345/499	0.04	72.4%; 155/214	66.7%; 190/285	0.17
anticoagulants	42.1%; 112/266	47.3%; 236/499	0.2	52.8%; 113/214	43.2%; 123/285	0.04
antiplatelets	58.3%; 155/266	60.1%; 300/499	0.64	63.1%; 135/214	57.9%; 165/285	0.27
digoxin	28.2%; 75/266	19.8%; 99/499	0.01	23.4%; 50/214	17.2%; 49/285	0.09
in-hospital and 1-year outcomes						
hospitalization length, days	7 (4–11); n = 266	7 (4–10); n = 499	0.52	7 (4–11); n = 214	7 (4–10); n = 285	0.31
death during hospitalization	2.3; 6/266	3.2; 16/499	0.51	1.9; 4/214	4.2; 12/285	0.2
PE	9.1; 22/241	18.5; 83/448	0.0001	14.5; 28/193	21.6; 55/255	0.07
SE	28.0; 63/225	36.1; 150/416	0.04	29.2; 52/178	41.2; 98/238	0.01

Data are presented as median (interquartile range) or percantage and number of patients/total number of patients.

P values of less than 0.05 are statistically significant.

Abbreviations: AF, atrial fibrillation; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; PE, primary endpoint (death at 1 year) SBP, systolic blood pressure; SE, secondary endpoint (death or rehospitalization at 1 year); others, see TABLE 1

TABLE 3 Multivariate analyses of predictors of the primary and secondary endpoints in patients with heart failure, aged <65 years and ≥65 years

Parameter	Primary endpoint		Secondary endpoint	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
patients aged <65 years				
chronic kidney disease	–	–	2.44 (1.17–5.12)	0.02
NYHA class on admission, per 1 class	–	–	1.73 (1.11–2.70)	0.02
serum sodium on admission, per 1 mmol/l	–	–	1.00 (0.94–1.07)	0.95
NYHA class at discharge, per 1 class	–	–	0.73 (0.43–1.23)	0.23
SBP at discharge, per 10 mm/Hg	–	–	0.96 (0.94–0.98)	0.0002
ACEI at discharge	–	–	0.99 (0.53–1.86)	0.97
anticoagulants at discharge	–	–	0.97 (0.52–1.81)	0.92
digitalis at discharge	–	–	1.61 (0.90–2.88)	0.11
patients aged ≥65 years				
previous heart failure hospitalization	–	–	1.23 (0.85–1.91)	0.25
coronary artery disease	–	–	1.49 (0.98–2.27)	0.06
atrial fibrillation	–	–	1.28 (0.88–1.86)	0.21
chronic kidney disease	1.60 (0.97–2.64)	0.07	1.29 (0.87–1.92)	0.2
chronic obstructive pulmonary disease	1.71 (1.02.–2.88)	0.04	1.69 (1.11–2.27)	0.02
prior PCI or CABG	0.56 (0.31–1.00)	0.05	–	–
alcohol (former or sometimes)	–	–	0.79 (–.53–1.16)	0.22
physical activity (moderate or intensive)	0.82 (0.49–1.36)	0.44	0.66 (0.44–0.99)	0.04
NYHA class on admission, per 1 class	2.03 (1.31–3.13)	0.002	1.76 (1.25–2.46)	0.001
SBP on admission, per 10 mmHg	–	–	1.00 (0.99–1.01)	0.71
serum sodium on admission, per 1 mmol/l	0.97 (0.92–1.02)	0.23	0.97 (0.94–1.01)	0.19
serum creatinine on admission, per 1 mg/dl	1.04 (0.81–1.33)	0.75	–	–
serum potassium on admission, per 0.5 mmol/l	–	–	0.69 (0.49–0.95)	0.03
hemoglobin on admission, per 1 g/dl	0.90 (0.80–1.03)	0.11	0.94 (0.85–1.03)	0.18
NYHA class at discharge, per 1 class	0.96 (0.62–1.49)	0.87	1.10 (0.74–1.61)	0.65
SBP at discharge, per 10 mmHg	0.98 (0.96–0.996)	0.01	0.99 (0.97–0.998)	0.03
diuretics at discharge	–	–	1.33 (0.62–2.84)	0.46
β-blocker at discharge	0.51 (0.28–0.91)	0.02	–	–

P values of less than 0.05 are statistically significant.

Abbreviations: CI, confidence interval; HR, hazard ratio; others, see **TABLES 1** and **2**

diabetes, and chronic kidney disease (CKD) increased with age and was more frequently observed in patients aged 65 years or older and those aged 75 years or older, compared with patients aged less than 65 years and those aged 65 to 74 years, respectively. These pathological conditions propel the stiffening of the myocardium, which may cause diastolic dysfunction, especially in women.[11,13] In our analysis, HF with preserved ejection fraction (HF-PEF), with a threshold of 50% or higher, was significantly more frequent in patients aged 65 years or older and those aged 75 years or older than in younger groups. Also, we observed a higher LVEF in patients aged 75 years or older, compared to those aged 65 to 74 years who more frequently had an ischemic etiology of HF and required percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) before and during index hospitalization. In the entire Polish population, HF-PEF was observed in 28% and evidently increased with age, reaching 44% in the group aged 75 years or older. The prevalence of HF-PEF has risen over the last decades due to the growing incidence of obesity, diabetes, and arterial hypertension, and a further increase may be expected due to population aging.[14]

In older patients, the presence of valvular heart disease (VHD) plays a central role in the pathogenic process leading to HF. Our observations confirm that HF etiology in the elderly is more likely to be ischemic or related to VHD.[1,15] The most frequent VHD in HF patients is aortic stenosis (in the present analysis, 14.1% of patients aged ≥65 years), which currently can be treated with classic surgery or transcatheter aortic valve implantation in symptomatic elderly patients.[16] In comparison, for younger patients aged less than 65 years, a more frequent reason of HF was dilated cardiomyopathy (27.1%), which in the majority of patients is diagnosed before the age of 50 years, based on the European Cardiomyopathy Pilot Registry.[17]

TABLE 4 Multivariate analyses of predictors of the primary and the secondary endpoint in patients aged 65–74 years and ≥75 years

	Primary endpoint		Secondary endpoint	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
heart failure patients 65–74 yrs				
prior PCI or CABG	0.33 (0.13–0.87)	0.03	–	–
chronic kidney disease	1.13 (0.42–3.04)	0.8	1.00 (0.48–2.06)	0.99
diabetes	–	–	1.43 (0.81–2.51)	0.22
physical activity	0,55 (0.22–1.40)	0.21	0.49 (0.26–0.91)	0.24
NYHA class at admission, per 1 class	2.70 (1.18–6.19)	0.02	1.70 (1.03–2.80)	0.04
serum sodium at admission, per 1 mmol/l	0.89 (0.81–0.99)	0.03	–	–
serum creatinine at admission, per 1 mg/dl	3.71 (1.89–7.26)	0.0001	1.95 (1.06–3.59)	0.03
NYHA class at discharge, per 1 class	0.87 (0.40–1.92)	0.73	1.25 (0.72–2.18)	0.41
SBP at discharge, per 10 mm/Hg	0.99 (0.97–1.02)	0.61	–	–
digitalis at discharge	–	–	1.58 (0.75–2.01)	0.39
heart failure patients ≥75 yrs				
previous HF hospitalization	–	–	1.57 (1.00–2.45)	0.048
coronary artery disease	–	–	1.88 (1.20–2.94)	0.006
chronic kidney disease	1.52 (0.89–2.62)	0.13	1.61 (1.04–2.48)	0.03
chronic obstructive pulmonary disease	–	–	1.98 (1.23–3.20)	0.03
alcohol (former or sometimes)	–	–	0.48 (0.28–0.81)	0.006
physical activity (moderate or intensive)	–	–	0.92 (0.57–1.48)	0.73
current smoking	–	–	2.25 (1.35–3.75)	0.002
NYHA class at admission, per 1 class	1.90 (1.23–2.92)	0.004	2.02 (1.33–3.06)	0.001
SBP at admission, per 10 mmHg	–	–	1.00 (0.99–1.01)	0.95
serum potassium at admission, per 0.5 mmol/l	–	–	0.70 (0.47–1.04)	0.08
NYHA class at discharge, per 1 class	–	–	1.07 (0.72–1.59)	0.75
SBP at discharge, per 10 mmHg	0.98 (0.96–998)	0.03	0.98 (0.97–0.99)	0.049
hospitalization length	–	–	1.03 (0.98–1.07)	0.22
diuretics at discharge	–	–	1.50 (0.67–3.40)	0.33
aldosterone antagonist at discharge	–	–	1.12 (0.68–1.84)	0.65
CCB at discharge	–	–	1.00 (0.53–1.89)	1.00
β-blocker at discharge	0.53 (0.27–1.03)	0.06	–	–

P values of less than 0.05 are statistically significant.

Abbreviations: CABG, coronary artery bypass grafting; CCB, calcium channel blocker; CI, confidence interval; HF, heart failure; HR, hazard ratio; SBP, systolic blood pressure; others, see **TABLE 1**

With aging, the occurrence of atherosclerosis and arterial stiffening is higher. This is closely associated with the progression of cardiovascular disease. In our study, patients aged 65 years or older were more likely to have clinical manifestation of coronary artery disease (CAD), peripheral artery disease, and also a higher systolic blood pressure (SBP) on admission. These pathologies limit the ability to perform physical activity and contribute to a worse general physical condition, which was observed in our analysis of patients aged 65 years or older and 75 years or older, compared to those aged less than 65 years and 65 to 74 years, respectively. Furthermore, clinically apparent atherosclerosis often resulted in longer hospital stays, more complications, and rhythm disturbances.[18] An older heart also becomes less responsive to neurological and catecholamine stimulation, rendering it unable to increase the strength and rate of its contractions. This frequently results in the need for pacemaker implantation, especially when comparing patients aged 65 years or older with those younger than 65 years, as well as patients aged 75 years or older with those aged between 65 and 74 years. Due to a lower LVEF, patients aged less than 65 years and those aged from 65 to 74 years are more likely to require an implantable cardioverter defibrillator.[2]

Atrial fibrillation (AF) is a very frequent condition, with the prevalence of up to 50% in HF patients.[19] In our analysis, there was also a higher incidence of AF history, and AF as a cause of index hospitalization in patients aged 65 years or older. It is also likely that it had a contribution to the incidence of a previous stroke in the group aged 75 years or older, who were also less frequently treated with anticoagulants, when compared with patients aged from 65 to 74 years. Anticoagulation therapy in the elderly is a serious problem and requires individual assessment of the risk for thromboembolic and bleeding events.[19,20]

Our findings show significant differences in laboratory results on hospital admission and at discharge between patients aged less than 65 years and those aged 65 years or older. Older patients had lower serum concentrations of sodium, creatinine, and hemoglobin on admission and at discharge, and lower total cholesterol levels on admission. We also observed lower hemoglobin concentrations on admission and at discharge and serum sodium concentrations at discharge in the subpopulation aged 75 years or older, compared with patients aged from 65 to 74 years.

Our analysis also revealed differences in pharmacotherapy between the age groups. It was surprising to find that patients aged less than 65 years were prescribed digoxin more frequently before the index hospitalization (24.4%) and at discharge (28.2%), although AF was more prevalent in older patients. Older patients are more susceptible to digoxin overdose; therefore, it should be prescribed with caution. This was reflected in our study, as digoxin was used less frequently in the elderly Polish population.

Most of calcium channel blockers, with the exception of amlodipine and felodipine, should not be used in HF patients.[2] In the study population, the use of calcium channel blockers did not exceed 20% and was most frequent in patients aged 65 years or older, most likely due to accompanying hypertension.

We also observed differences in the use of statins at discharge in favor of patients aged 65 years or older. It was related to more frequent CAD in seniors; however, it is necessary to emphasize that the evidence supporting the initiation of statins in HF patients is unclear, and some studies postulate that a reduced total cholesterol concentration is a risk factor for long-term mortality in HF patients.[21] However, other recently published trials have demonstrated decreased all-cause mortality and incidence of rehospitalization for HF,[22] probably due to improved cardiac sympathetic nerve activity and prevention of left ventricular remodelling.[23]

Recently published results by Teixeira et al[24] have revealed that proper treatment of HF decreases with age (from 14% adequately treated patients aged <65 years to only 2% of patients aged 85–94 years).[24] We also observed a decreased use of typical HF drugs with age, but only administration of aldosterone antagonists significantly differed between the groups. It should be mentioned that newly approved drug, sacubitril-valsartan, may become an interesting therapeutic option for the elderly.[3] There have been encouraging reports on its effectiveness from the PARADIGM-HF trial,[3] across all studied age groups, in contrast to enalapril.[3] Also, the ongoing PARAGON trial (clinicaltrial.gov, NCT01920711) is aimed to asses efficacy of sacubitril-valsartan in patients with HF-PEF, which is prevalent in the elderly. However, we need much more information about its effectiveness and safety, including data from international registries.

Use of ivabradine in elderly patients with HF still needs further investigation. However, there are some convincing reports that the effect of a reduction in heart rate with ivabradine is maintained in patients with several comorbidities, which is also the case for elderly patients.[25] However, in our study, administration of ivabradine did not exceed 1% in any of the groups. Based on the ESC guidelines, there are no specific age-related differences in recommendations for HF treatment, although relevant data specific to the elderly are lacking.[2]

In the CHARM study,[25] which included HF patients with and without left ventricular systolic dysfunction, and in the I-PRESERVE[13] trial on patients with HF-PEF, older age was a strong independent predictor of cardiovascular death/HF hospitalization and death.[13,26] Based on previous reports, compared to patients aged less than 65 years, those aged 65 years or older are characterized by higher short- and long-term mortality after hospital discharge, and they are at an increased risk of hospital readmissions.[1,3,9,26-28] In our analysis, there was no difference for in-hospital outcomes between patients aged less than 65 years and those aged 65 years or older, as well as in patients aged from 65 to 74 years and those aged 75 years or older. Those findings may be associated with the fact that there is still suboptimal ambulatory HF treatment in Poland (few outpatient HF clinics). In consequence, patients hospitalized in Polish hospitals may have less severe advancement of HF. In our study, there were no significant differences in a clinical condition on hospital admission either in younger or in older patients, as well as among the elderly subgroups.

In the 1-year follow-up, patients aged 65 years or older were at a higher risk of all-cause death, as well as death or rehospitalization, than patients aged less than 65 years. In the subanalysis, patients aged 75 years or older, compared with patients aged from 65 to 74 years, were at a higher risk of death or rehospitalization, with a trend for a more frequent death at 1 year.

The results of our analysis indicate that older patients differ from younger patients not only with regard to baseline characteristics and long-term outcome, but also in terms of prognostic factors. The presence of chronic obstructive pulmonary disease (COPD) was associated with a higher 1-year risk of the secondary endpoint in patients aged 65 years or older and those aged 75 years or older, and also the primary endpoint in patients aged ≥65 years. COPD in patients with HF is an independent predictor of death and hospitalization,[29,30] and it is suggested that the incidence of left ventricular dysfunction in COPD patients tends to increase the risk of mortality.[31] The prevalence of COPD in HF patients is very common, and it is reported in up to 40% of patients with HF.[32] Importantly, in patients with both conditions, only very low and very high concentrations of natriuretic peptides have highly negative and positive predictive values for diagnosing HF.[26] In the HF-ACTION trial,[33] HF patients with COPD were older, had more concomitant diseases, higher New York Heart Association (NYHA) class, and lower use of β-blockers. Because of intense adrenergic activation, cardioselective β-blockers (metoprolol, bisoprolol, or nebivolol) are recommended in HF patients with coexistent COPD.[2] Also oral corticosteroids, used in COPD treatment, due to sodium and water retention, may contribute to the worsening of HF,[2] but we did not have information about the route of administration of corticosteroids in our study.

Physical activity, higher serum potassium concentrations on admission, and β-blocker use at discharge had protective prognostic effects in patients aged 65 years or older. The evidence suggests that physical training is beneficial in HF; however, elderly patients were not enrolled in most trials.[2] The positive effect of higher serum potassium concentrations may be attributed to the use of potassium-sparing diuretics in HF treatment.[2] Use of β-blockers yielded a 50% reduction of the risk of death in the 1-year follow-up, as shown in **TABLE 3**. This finding is consistent with the SENIORS trial,[9] which showed that nebivolol is a well-tolerated drug. It resulted in the reduction of the composite endpoint of death or cardiovascular hospitalization ($P = 0.039$) and insignificantly reduced mortality ($P = 0.21$). Surprisingly, the use of β-blockers was beneficial in patients aged 65 years or older, but not in the subgroups of elderly patients (there was a trend in patients aged 75 years or older; $P = 0.06$). This might be due to a decreasing use of appropriate doses of β-blockers in elderly patients,[34] and a worse response to β-adrenergic blockade in elderly patients with reduced LVEF.[35]

In both groups of patients aged 65 years or older and those aged less than 65 years, independent predictive factors of the secondary endpoint were higher NYHA class on admission and lower SBP at discharge. Additionally, in elderly patients, these factors were also predictive of the primary endpoint. Chronic kidney disease was predictive in both age groups, but it only reached statistical significance in the multivariate analysis for patients aged less than 65 years. These findings were confirmed in previously published studies.[9,11,22,26,36]

In the subanalysis, higher NYHA class on admission was an independent predictive factor of the primary and secondary endpoints in both groups. Lower SBP at discharge was predictive of both endpoints in patients aged 75 years or older, and higher serum creatinine concentrations had the same predictive value in patients aged 65 to 74 years on admission. In comparison with patients aged 75 years or older, CKD was a predictor of the secondary endpoint. Prior PCI or CABG and higher serum sodium concentrations had a positive effect on mortality in patients aged from 65 to 74 years. Elderly HF patients with severe CAD and ventricular dysfunction may derive the greatest clinical benefit from coronary revascularization; however, they are also at the highest operative risk.[18] Therefore, the decision to operate requires careful verification of the entire clinical profile for each individual patient.[18] Hyponatremia in our previous study was associated with more frequent death at 1-year follow-up, as well as death or HF readmission.[37] It is mostly a consequence of the enhanced secretion of arginine vasopressin, which is frequently aggravated by loop diuretics.[37]

Current smoking, CAD, and a previous hospitalization for HF in patients aged 75 years or older was associated with a higher risk of the secondary endpoint. Numerous observations suggest that patients with CAD and prior HF hospitalization, regardless of their LVEF, are at higher risk of future readmissions.[13,26] In our analysis, in individuals aged 75 years or older, alcohol consumption (former or sometimes) had a protective effect on the occurrence of the secondary endpoint. This finding suggests that despite the fact that alcohol is a known cardiac toxin and can lead to HF, it may have a positive influence when used in moderate proportions.[38] Modest alcohol consumption in middle-aged patients may be associated with a lower risk of HF development, but the impact on elderly HF patients remains unclear.[38]

Limitations of the study The main advantage of the registry is that it includes "real world" patients. However, it has also serious limitations, such as incomplete data and observational design. Thus, we had access only to the data that were available in the case report forms, predefined by the Coordinators of the Registry.

In our study, data on death at 1 year were available for 689 patients (92.7% of the 743 patients) and missing for 54 patients in the primary endpoint analysis. Data on hospital readmissions at 1 year were missing for 102 patients, and were available for 641 patients (86.3% of the 743 patients) for the secondary endpoint analysis. Consequently, because of the relatively small size of the study groups, the multivariate analysis for the primary endpoint in the age group of less than 65 years was not performed. In order to achieve adequate EPV value in the univariate and multivariate analyses, it was necessary to limit the number of variables included in the Cox proportional hazards regression model. The excluded variables with more than 5% of incomplete data were LVEF, mitral regurgitation, serum concentration of hemoglobin, as well as sodium and creatinine levels at discharge.

Conclusions We have identified the elderly as an important subpopulation of HF patients. They differed significantly from HF patients aged less than 65 years with regard to baseline characteristics, long-term outcome, and prognostic factors. It should also be stressed that there were important differences within the group of the elderly aged 65 years or older. Additionally, as the age increased, it was less likely that patients received the appropriate pharmacotherapy for HF, despite worse prognosis for these patients. These data motivates further investigation of the elderly population with HF.

Contribution statement KO conceived the idea for the study. KO and PB designed the analysis, conducted data interpretation, performed statistical analysis, and wrote the manuscript. KO, PB, AT, MP, AKC, ŁŁ, MG, MM, and KJF researched data. JD and GO designed the study. JD coordinated the study nationwide. All authors edited and approved the final version of the manuscript.

Supplementary material online Supplementary material online is available with the online version of the article at www.pamw.pl.

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Niewydolność serca u pacjentów w podeszłym wieku: różnice w charakterystyce klinicznej i czynniki rokownicze w rocznej obserwacji w polskim ESC-HF Long-Term Registry

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hospitalizacja, niewydolność serca, rejestr, rokowanie, wiek podeszły

STRESZCZENIE

WPROWADZENIE Niewydolność serca (NS) jest najczęstszą przyczyną hospitalizacji osób w podeszłym wieku.

CELE Celem badania była ocena profilu klinicznego i rocznego rokowania osób w podeszłym wieku (≥65 lat) w porównaniu z młodszymi pacjentami (<65 lat) hospitalizowanymi z powodu zdekompensowanej NS, a także różnic klinicznych wśród osób starszych w wieku 65–74 i ≥75 lat.

PACJENCI I METODY W rocznej obserwacji oceniono wystąpienie pierwszorzędowego punktu końcowego (PPK; zgon z jakiejkolwiek przyczyny) i wtórnego punktu końcowego (WPK; zgon z jakiejkolwiek przyczyny lub hospitalizacja z powodu zaostrzenia NS) w grupie 765 hospitalizowanych polskich uczestników rejestru ESC-HF Long-Term.

WYNIKI PPK osiągnęło 9,1% pacjentów w wieku <65 lat, 18,5% w wieku ≥65 lat (p = 0,0001), 14,5% w wieku 65–74 lat oraz 21,6% w wieku ≥75 lat (p = 0,07). Wtórny punkt końcowy wystąpił u 28,0% pacjentów w wieku <65 lat, 36,1% w wieku ≥65 lat (p = 0,04), 29,2% w wieku 65–74 lat oraz 41,2% w wieku ≥75 lat (p = 0,01). Niezależnymi PPK u pacjentów w wieku ≥65 lat były: przewlekła obturacyjna choroba płuc (POChP), skurczowe ciśnienie tętnicze (SCT), klasa New York Heart Association (NYHA), stosowanie β-blokera; w wieku 65–74 lat: rewaskularyzacja wieńcowa, klasa NYHA, sód oraz kreatynina; w wieku ≥75 lat: klasa NYHA oraz SCT. Niezależnymi predyktorami WPK u pacjentów w wieku ≥65 lat były: POChP, klasa NYHA, potas, SCT oraz aktywność fizyczna; w wieku ≤65 lat: przewlekła choroba nerek (PChN), klasa NYHA oraz SCT; w wieku 65–74 lat: klasa NYHA oraz kreatynina; w wieku ≥75 lat: poprzednia hospitalizacja z powodu NS, choroba wieńcowa, PChN, POChP, alkohol, palenie tytoniu, klasa NYHA oraz SCT.

WNIOSKI Osoby w podeszłym wieku z NS różniły się od młodszych pacjentów pod względem rokowania odległego i czynników predykcyjnych. Występowały także istotne różnice w grupie osób w podeszłym wieku.

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