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ORIGINAL ARTICLE

Prognostic impact of systolic blood pressure in acute heart failure with preserved ejection fraction in older patients

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Abstract

Aims Recent guidelines recommend a systolic blood pressure (SBP) target below 130 mmHg in heart failure patients with preserved ejection fraction (HFpEF), whatever their age. We investigated whether this intensive SBP control was associated with better survival in very old adults hospitalized for acute HFpEF.

Methods and results We conducted an observational study in an acute geriatric unit: all consecutive patients discharged from hospital for acute heart failure from 1 March 2019 to 29 February 2020 with a diagnosis of HFpEF were included. Re-hospitalization and all-cause mortality at 1 year were compared according to the mean SBP at discharge (patients with a mean SBP $<$ 130 mmHg vs. those with SBP $\geq$ 130 mmHg). We included 81 patients with a mean age of 89 years. Among them, 47 (58%) were re-hospitalized and 37 (46%) died at 1 year. All-cause mortality (hazard ratio [HR] [95% confidence interval]: 1.50 [0.75–2.98], P = 0.2) and re-hospitalization rate (HR: 1.04 [0.58–1.86], P = 0.90) at 1 year did not significantly differ between patients with SBP $\geq$ 130 mmHg and those with SBP $<$ 130 mmHg at discharge. However, a prescription for antihypertensive drugs at discharge was associated with a better long-term prognosis (all-cause mortality: HR: 0.42 [0.20–0.88], P = 0.02; re-hospitalization rate: HR: 0.56 [0.28–1.10], P = 0.09).

Conclusions Although SBP $<$ 130 mmHg at discharge was not associated with a better prognosis among very old patients hospitalized for acute HFpEF, the prescription of antihypertensive drugs was associated with mortality and re-hospitalization rates that were reduced by half. Future prospective studies are needed to assess target blood pressure in very elderly patients with HFpEF.

Keywords Heart failure; Preserved ejection fraction; Systolic blood pressure; Elderly; Re-hospitalization; Mortality

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Introduction

Heart failure (HF) is the leading cause of hospitalization in the elderly.[1] More than half of all patients with HF have a preserved left ventricular ejection fraction (LVEF), and this proportion rises to more than 70% in the elderly population.[2] HF with preserved LEVF (HFpEF) is defined by symptoms of HF often associated with physical signs, elevated natriuretic peptides, structural or functional cardiac abnormalities seen on transthoracic echocardiography (TTE), and an LVEF $\geq$ 50%.[3,4]

The morbidity and mortality of HFpEF is similar to HF with reduced ejection fraction, but its pathophysiology remains poorly understood.[5] In contrast to HF with reduced ejection fraction, no therapeutic strategy has convincingly reduced morbidity and mortality in HFpEF,[6–10] probably due to the heterogeneity of the mechanisms involved.[11] The majority of deaths and re-hospitalizations do not appear to be due to HF but rather to cardiovascular or non-cardiovascular causes.[12] It is therefore recommended to treat comorbidities such as high blood pressure, atrial

fibrillation, coronary artery disease, diabetes, chronic kidney failure, chronic obstructive pulmonary disease, and anaemia along with the congestive signs.[3]

Almost all patients with HFpEF have a history of hypertension.[7] Even though antihypertensive drugs have widely proven their prognostic interest in the whole population, observational studies have highlighted a higher risk of mortality in frail older patients with low systolic blood pressure (SBP) receiving multiple antihypertensive drugs.[13] While controlled SBP reduces the risk of developing HFpEF, once HFpEF is established, SBP $<$ 120 mmHg[14,15] and even $<$130 mmHg[16] have been associated with a higher risk of cardiovascular morbidity and mortality. However, the American College of Cardiology and the American Heart Association recommend a target of SBP $<$ 130 mmHg[15] in patients of all ages with HFpEF. There is an embarrassing paucity of data regarding this frequent question in the frail older population. We thus investigated whether the strict control of SBP also has a prognostic impact in very old patients hospitalized for acute HFpEF.

Methods

Design of the study

We conducted a retrospective, observational, single-centre study in the department of acute geriatric medicine at the Dijon Bourgogne University Hospital. All consecutive patients hospitalized for acute HF from 1 March 2019 to 29 February 2020 with a diagnosis of HFpEF were included. There were no exclusion criteria.

Patients were screened using the data obtained from the French medical information system (*Programme de Médicalisation des Systèmes d'Informations*), which collects discharge abstracts for all hospital stays in public and private care institutions in France. The medical record of each patient with a hospital stay coded for HF was then retrospectively reviewed for inclusion. Acute HF was defined as a rapid onset of new or worsening signs (elevated jugular venous pressure and pulmonary congestion) and symptoms (dyspnoea, orthopnoea, and lower limb swelling) of HF. HFpEF was retained in HF patients with structural or functional cardiac abnormalities on TTE and an LVEF $\geq$ 50%.[3,4] Data collected from the medical record included demographics, cardiovascular comorbidities, Cockcroft creatinine clearance, mean SBP, mean diastolic blood pressure, and pulse rate for the 48 h prior to discharge, antihypertensive treatment (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], beta-blockers, calcium-channel blockers, and thiazides) and loop diuretics at discharge, re-hospitalization, and all-cause death at 1 year. Vital status at 1 year was investigated through the open-access website of the French National Institute of Statistics and Economic Studies.

We divided the population into two groups: patients with a mean SBP $<$ 130 mmHg and those with SBP $\geq$ 130 mmHg for the 48 h prior to discharge. Mean SBP was assessed on at least three daily measures during the 48 h prior to discharge.

The primary outcome was all-cause mortality at 1 year. The secondary outcome was all-cause re-hospitalization at 1 year.

This study was conducted in accordance with the Declaration of Helsinki. Because this was a retrospective study on anonymized data, the approval of an ethics committee was waived according to national standards.

Statistical analysis

As the distribution of quantitative variables was non-Gaussian, the results were expressed as medians and interquartile ranges. Qualitative variables were expressed as numbers and percentages. The χ^2 test and Fisher's test were used for categorical variables. The non-parametric Mann–Whitney *U* test was used to compare the distribution of quantitative variables. Cox regression models were built to assess hazard ratios (HRs), and Kaplan–Meier curves and the log rank test were used to compare survival data. A *P* value of $<$0.05 was considered significant.

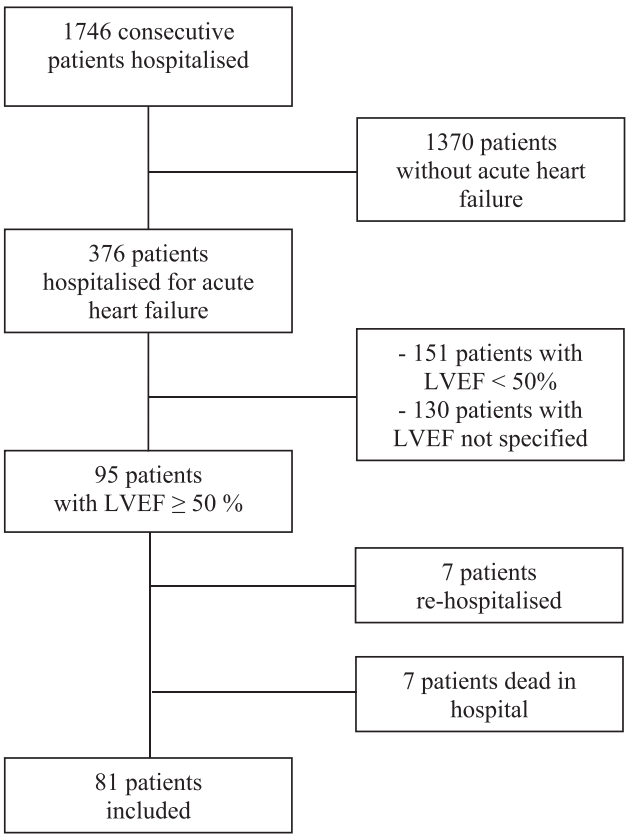
Results

A total of 1746 patients $\geq$ 75 years of age were admitted to the department of acute geriatric medicine between 1 March 2019 and 29 February 2020, of which 376 (22%) had a diagnosis of acute HF. Echocardiographic data were available for 246 (65%) acute HF patients in the year prior to hospital discharge, and 95 (39%) were found to have LVEF $\geq$ 50%. Seven patients were hospitalized twice during the period, and seven died during the hospital stay. Therefore, 81 patients with HFpEF hospitalized for the first time in the department during this period were included (*Figure 1*).

The characteristics of the population are detailed in *Table 1*. The median age was 89 [84–93] years. Body mass index was significantly lower in the deceased patients (24 vs. 26 kg/m^2, *P* = 0.03). The majority of patients had a history of high blood pressure (59%), atrial fibrillation (60%), and chronic kidney failure (77%). The median blood pressure at discharge was 124/69 mmHg. Seventy-five per cent of patients were discharged on loop diuretics, 69% on beta-blockers, and 39% on ACE inhibitor or ARBs. Eighty-one (92%) patients were alive at discharge. Of these, more than half (55%) were re-hospitalized and half had died at 1 year.

All-cause mortality (HR [95% confidence interval]: 1.50 [0.75–2.98], *P* = 0.2) and the re-hospitalization rate (HR:

Figure 1 Study flow chart. LVEF, left ventricular ejection fraction.



1.04 [0.58–1.86], $P = 0.90$) at 1 year were not significantly different between patients whose SBP was ≥130 or <130 mmHg (*Figure 2*). *Figure 3* illustrates the J-curve phenomenon characterizing the relationship between extreme SBP and increased mortality.

A prescription of antihypertensive drugs at patient discharge was associated with a better long-term prognosis (all-cause mortality: HR: 0.42 [0.20–0.88], $P = 0.02$; re-hospitalization rate: HR: 0.56 [0.28–1.10], $P = 0.09$). In the subgroup of patients without a history of hypertension, antihypertensive drugs remain associated with improved prognosis (all-cause mortality: HR: 0.28 [0.10–0.76], $P = 0.01$).

However, as shown in *Figure 4*, this association depended on the therapeutic class: only beta-blockers use appeared to be significantly associated with an improved prognosis. Moreover, beta-blockers were associated with a better prognosis only in patients with a history of atrial fibrillation (all-cause mortality: HR: 0.33 [0.14–0.76], $P = 0.007$, vs. HR: 1.11 [0.37–3.33], $P = 0.9$, for patients without atrial fibrillation; re-hospitalization rate: HR: 0.47 [0.21–1.03], $P = 0.06$, vs. HR: 0.57 [0.22–1.44], $P = 0.2$, for patients without atrial fibrillation).

Discussion

While few studies have investigated the association between blood pressure and outcome in patients with HFpEF, all have

Table 1 Population characteristics (*n* (%) or median [interquartile range])

	Total population $n = 81$	Patients dead at 1 year $n = 37$	Patients alive at 1 year $n = 44$	*P*
Demographics				
Age (years)	89 [84–93]	88 [84–92]	89 [83–93]	0.42
Women	51 (63)	22 (60)	29 (66)	0.55
BMI (kg/m^2)	26 [22–30]	24 [20–30]	26 [24–31]	0.03
Medical history				
Hypertension	47 (58)	21 (57)	26 (60)	0.83
CAD	25 (31)	9 (24)	16 (36)	0.24
Atrial fibrillation	49 (60)	23 (62)	26 (60)	0.78
Diabetes	19 (23)	7(19)	12 (27)	0.38
Stroke	3 (4)	2 (5)	1 (2)	0.46
Creatinine clearance (mL/min/1.73 m^2)	39 [29–57]	38 [33–51]	47 [29–70]	0.14
Vital signs at discharge				
SBP (mmHg)	124 [115–137]	122 [111–137]	127 [117–137]	0.33
DBP (mmHg)	69 [61–77]	69 [61–80]	70 [62–78]	0.59
Heart rate (beats/min)	76 [66–86]	80 [69–87]	74 [65–83]	0.27
Medication at discharge				
ACE-I or ARB	32 (40)	15 (41)	17 (39)	0.86
Beta-blocker	57 (70)	23 (62)	34 (77)	0.14
Loop diuretics	59 (73)	24 (65)	35 (80)	0.22
CCBs	17 (21)	6 (16)	11 (25)	0.33
Thiazides	3 (4)	2 (2)	1 (1)	0.59
Outcomes				
1 year readmission	47 (58)	23 (62)	24 (55)	0.51
1 year mortality	37 (46)			

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCBs, calcium channel blockers; DBP, diastolic blood pressure; SBP, systolic blood pressure.

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Figure 2 One-year survival and re-hospitalization curves according to systolic blood pressure. HR, hazard ratio [95% confidence interval]; SBP, systolic blood pressure.

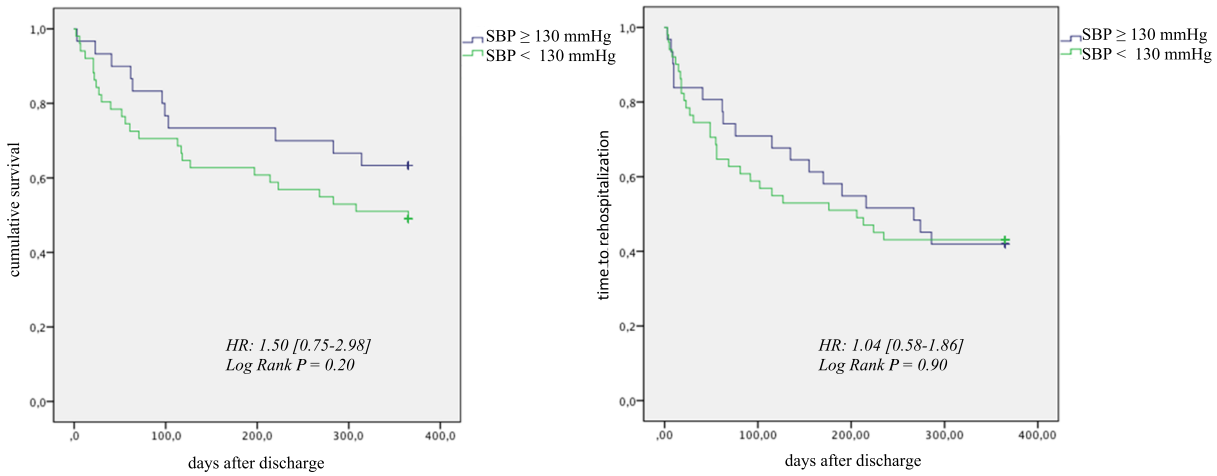
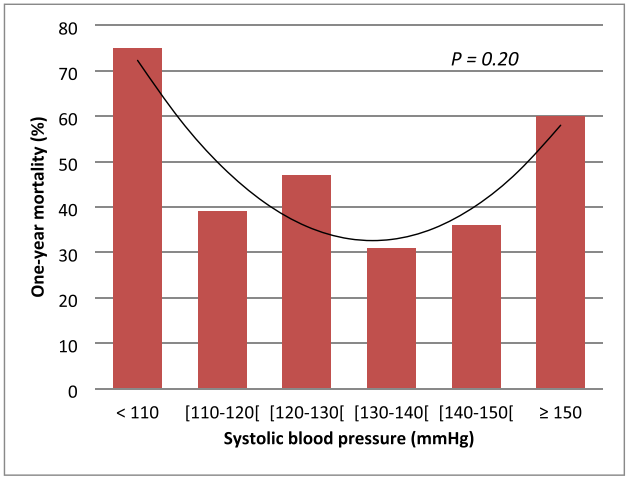


Figure 3 One-year mortality according to systolic blood pressure.

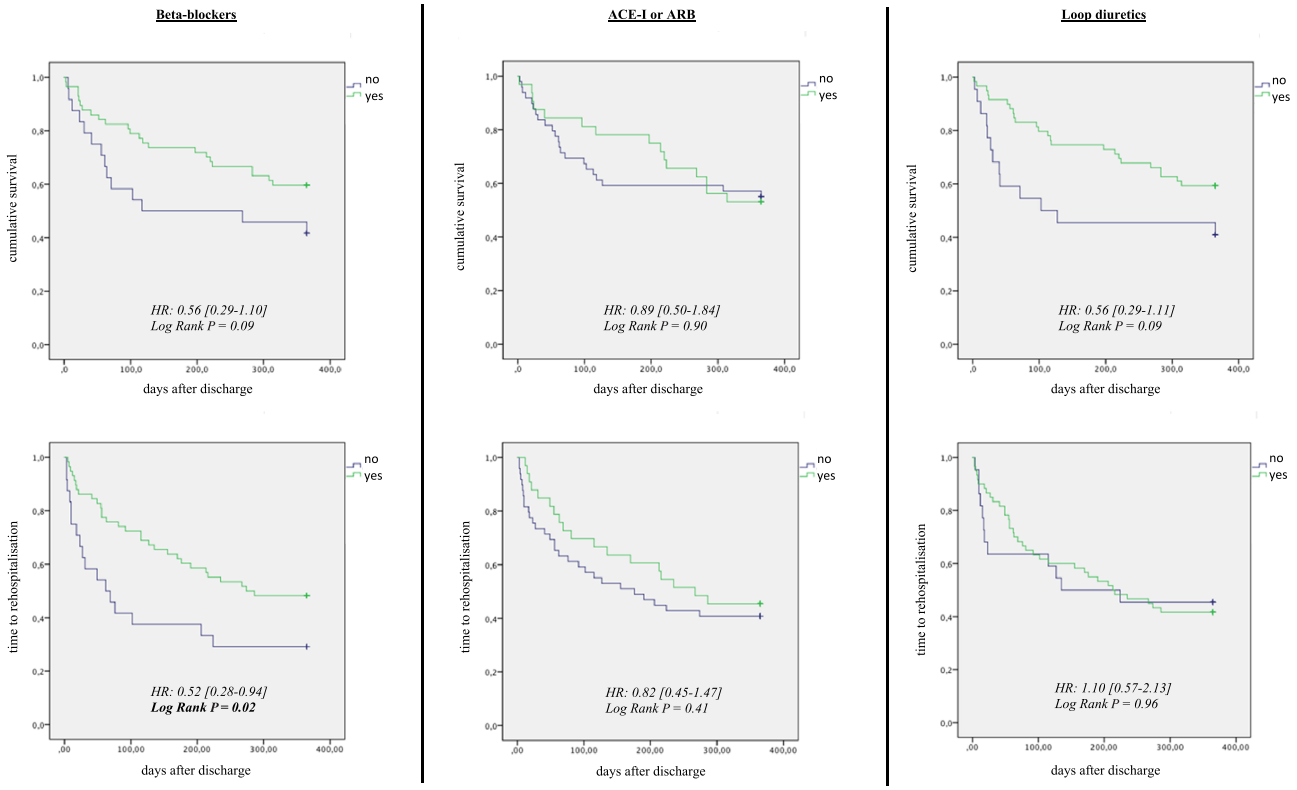


shown an association between low SBP and adverse outcomes.[16–18] The aim of our study was to investigate this link in a very elderly population hospitalized for acute HF. The first main result is the severe prognosis of HFpEF in this population: nearly half of patients died within the year after hospital stay. Second, mean SBP at discharge was only slightly associated with long-term prognosis (J-curve phenomenon), and strict blood pressure control (i.e. mean SBP $<$ 130 mmHg) was not associated with an improved prognosis. Third, patients under antihypertensive treatment at discharge were less likely to be readmitted to hospital and had better 1 year survival.

In our report, only 65% of patients with acute HF had access to a TTE. The low prevalence of TTE in the older population, which has been reported throughout the world,[19–21] raises questions. Advanced age has been independently related to the decision not to perform echocardiography,[19] yet we know that chronic HF cannot be diagnosed without TTE.[3,4] This may lead to questions about how diagnoses are made and the under-treatment of patients for whom valve disease, impaired LVEF, or ischaemic heart disease would have been discovered on TTE. There are several reasons for the low rate of TTE examinations. First of all, altered functional status, which is predominant in a very elderly population, results in lower access to cardiology consultations during hospitalization or even after the patient has been discharged.[22] Disability has been widely associated with a restricted access to health care in various settings.[23] Older disabled patients are thus especially affected by the lack of cardiologist availability. Finally, in older patients, doctors are quicker to propose palliative symptomatic treatment (i.e. diuretics) rather than an aetiologically based long-term therapy. Access to TTE and therefore to optimal treatment could be improved by training dedicated cardio-geriatricians to use this diagnostic tool. Such specialists bring added value to usual care by combining geriatric and cardiologic expertise, both of which are essential for this specific population.[24]

Interestingly, we identified a J-curve phenomenon characterizing the relationship between extreme SBP and increased mortality, which has already been shown in HFpEF.[25] An SBP target of 130–139 mmHg, as recommended by the European Society of Cardiology (ESC),[26] appeared to be associated with a better prognosis. It is likely that lower blood pressure is a marker of advanced HFpEF,[16] lower cardiac functional reserve, and lower cardiac output.[27] It may also be of extracardiac origin, leading to coronary hypoperfusion that will worsen HF.[25] This is in contrast to the American College of Cardiology/American Heart Association who recommend[15]

Figure 4 One-year survival and re-hospitalization curves according to discharge treatment. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HR, hazard ratio [95% confidence interval].



that SBP targets be below 130 mmHg, in the absence of evidence in favour of blood pressure control in patients with existing HF. Similarly, this reinforces the idea that the lowest possible blood pressure is not an optimal target in very elderly with HFpEF.[25] An ongoing national clinical trial evaluating the prognostic impact of intensive versus less-intensive blood pressure control in the very elderly population will be of particular interest for the subgroup of HFpEF patients.[28]

Our results highlight the poor long-term prognosis of older HFpEF patients, whose 1 year mortality was found to be nearly 50%. A large English study[29] reported a mortality of 40% in patients aged 80 years with HF, regardless of LVEF. While cardiovascular mortality is decreasing due to therapeutic advances in HF, all-cause mortality in these patients is stagnating. Particularly in HFpEF, the majority of deaths and re-hospitalizations are due to causes other than HF: infection, trauma, or respiratory and neurocognitive causes.[8,30,31] This justifies screening for comorbidities and frailty in all HF patients[32] and providing multidisciplinary care for polypathological HF patients; evaluation by a geriatrician is therefore essential.

To date, no treatment has shown any real benefit in the heterogeneous population of HF patients with preserved LVEF.[6–10] It is therefore recommended to control cardiovascular or other comorbidities. Blood pressure control is considered one of the most important preventive measures for HFpEF.[33] In our study, antihypertensive drugs, irrespective of the class, were associated with a trend towards an improved prognosis. To note, 42% of patients who received antihypertensive drugs had no history of hypertension. Indeed, most of antihypertensive drugs are also indicated in other pathologies, including HF, coronary artery disease, arrhythmia, or chronic kidney disease. However, in the subgroup of patients without a history of hypertension, antihypertensive drugs remain associated with improved prognosis, suggesting a benefit of antihypertensive irrespective of hypertensive status. It is thus likely that the association of antihypertensive drugs with survival is related, at least in part, to a cardioprotective effect independent of their antihypertensive effect. Whether loop diuretics at discharge are associated with a lower mortality remains a matter of debate.[33,34] There is also no evidence of benefit for ACE inhibitors, ARBs, or beta-blockers[33] in patients with HFpEF, but they do play an important role in the management of associated comorbidities like hypertension, atrial fibrillation, and coronary artery disease. The improved long-term prognosis in patients on beta-blockers is probably due to the large number of patients with atrial fibrillation in our study. Indeed, our results suggest a benefit of beta-blockers only in the subgroup of patients with atrial fibrillation. Beta-blockers have previously been

shown to improve prognosis in patients with HFpEF in atrial fibrillation.[35] They could prolong the diastolic period and increase ventricular volumes, therefore increasing the ventricular load.[36] Despite this evidence, very elderly subjects are often under-treated.[37] The following reasons can be hypothesized: short life expectancy, fear of side effects, lack of familiarity with the current guidelines by the prescriber,[38] uncertain diagnoses, reluctance to modify the background treatment, and focus on the acute phase without considering the long term.[39] Drug efficacy/safety studies in the very elderly and continuing education for clinicians could help to limit under-prescription.

Limits

First, the small size and monocentric design makes it impossible to draw any definite conclusions, so we can only put forward trends and hypotheses. Second, this study includes patients hospitalized for acute HF in an acute geriatric unit, so the results may differ in other settings, especially in cardiology units that tend to have fewer comorbid patients. Third, the causes of mortality at 1 year were not known, which did not allow us to deduce the cardiovascular burden. Fourth, a recent study[40] showed a significant improvement in prognosis with anti-aldosterone in the subgroup of American patients with HFpEF, but unfortunately none of the patients in our study were taking this drug. Finally, given the observational design, we cannot establish a causal link between blood pressure control and survival.

Nevertheless, to our knowledge, this is the first study to examine the prognostic impact of SBP in the very elderly population of HF patients with preserved LVEF, despite its high frequency in geriatric settings.

Heart failure with preserved ejection fraction is the main form of HF in the very elderly but remains a diagnostic and therapeutic challenge for clinicians, particularly because of the heterogeneity of the population and the associated mortality that is essentially non-cardiovascular. In this pilot study of very elderly patients with HFpEF, extreme SBP levels appeared to be associated with increased 1 year mortality, further reinforcing the SBP target of 130–139 mmHg recommended by the ESC in this specific population.[26] Our results suggest that antihypertensive treatment could be associated with lower rates of re-hospitalization and mortality at 1 year. These results need to be confirmed by larger-scale observational studies and interventional data.

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Conflict of interest

None declared.

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