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Long-term safety of intravenous cardiovascular agents in acute heart failure: results from the European Society of Cardiology Heart Failure Long-Term Registry

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Abstract
Aims. The aim of this study was to assess long-term safety of intravenous cardiovascular agents—vasodilators, inotropes and/or vasopressors—in acute heart failure (AHF).
Methods and results .The European Society of Cardiology Heart Failure Long-Term (ESC-HF-LT) registry was a prospective, observational registry conducted in 21 countries. Patients with unscheduled hospitalizations for AHF ($n = 6926$) were included: 1304 (18.8%) patients received a combination of intravenous (i.v.) vasodilators and diuretics, 833 (12%) patients received i.v. inotropes and/or vasopressors. Primary endpoint was long-term all-cause mortality. Main secondary endpoints were in-hospital and post-discharge mortality. Adjusted hazard ratio (HR) showed no association between the use of i.v. vasodilator and diuretic and long-term mortality [HR 0.784, 95% confidence interval (CI) 0.596–1.032] nor in-hospital mortality (HR 1.049, 95% CI 0.592–1.857) in the matched cohort ($n = 976$ paired patients). By contrast, adjusted HR demonstrated a detrimental association between the use of i.v. inotrope and/or vasopressor and long-term all-cause mortality (HR 1.434, 95% CI 1.128–1.823), as well as in-hospital mortality (HR 1.873, 95% CI 1.151–3.048) in the matched cohort ($n = 606$ paired patients). No association was found between the use of i.v. inotropes and/or vasopressors and long-term mortality in patients discharged alive (HR 1.078, 95% CI 0.769–1.512). A detrimental association with inotropes and/or vasopressors was seen in all geographic regions and, among catecholamines, dopamine was associated with the highest risk of death (HR 1.628, 95% CI 1.031–2.572 vs. no inotropes).
Conclusions. Vasodilators did not demonstrate any association with long-term clinical outcomes, while inotropes and/or vasopressors were associated with increased risk of all-cause death, mostly related to excess of in-hospital mortality in AHF.

Keywords
Acute heart failure; Inotrope; Vasopressor; Vasodilator; Prognosis; Long-term outcome

Introduction

Acute heart failure (AHF) represents a gradual or rapid change in heart failure (HF) signs and symptoms, requiring urgent medical therapies.1, 2 It is the most common cause of emergency department admission.3 The initial intravenous (i.v.) therapies of AHF have remained practically unchanged in the last decades. Most AHF patients are treated with diuretics and vasodilators, while others may also receive positive inotropes and/or vasopressors (mostly catecholamines). Several of these therapies have been shown to alleviate symptoms, though this did not translate in benefits on outcome.4 Furthermore, inappropriate use as well as increasing short-term safety concerns have been reported regarding the use of inotropes and/or vasopressors in AHF.5, 6 Data, often on small samples, have suggested neutral (levosimendan in SURVIVE7) or even increased short-term mortality with the use of catecholamines with positive inotropic effects (ALARM-HF[8] or milrinone in OPTIME-CHF9, 10). Data on long-term safety of these agents, especially in hospital survivors, are scarce. Therefore, the aim of our study was to assess safety, namely long-term mortality, of i.v. cardiovascular agents, including vasodilators, inotropes, and/or vasopressors in AHF.

Methods

The European Society of Cardiology Heart Failure Long-Term (ESC-HF-LT) registry was a prospective, observational registry that involved 211 cardiology centres from 21 European and Mediterranean countries. The study design and results have been previously described.11 Briefly, the ESC-HF-LT registry collected data on 12 440 patients on a one-day-per-week basis between May 2011 and April 2013. Patients were followed up in accordance with the usual practice of the participating centres and had a mandatory follow-up visit at 12 months to collect information on morbidity and mortality. Participation in the ESC-HF-LT registry had been approved by each local institutional review board in accordance with its country's legislation. All participants provided written informed consent.

Patients with unscheduled hospitalizations for AHF were included in this study. Intravenous cardiovascular agents, namely vasodilators, inotropes and/or vasopressors, that were administered during the first 24 hours after admission, were assessed in the present analysis. We retrospectively analysed long-term safety, especially mortality, of these agents. Primary endpoint was long-term all-cause mortality. Secondary endpoints were (i) in-hospital mortality, (ii) post-discharge all-cause mortality, (iii) post-discharge all-cause rehospitalization, and (iv) long-term cardiovascular mortality.

Statistical analysis

Categorical variables are presented as counts and percentages, and quantitative variables as mean ± standard deviation or median and interquartile range (IQR), as appropriate.

A propensity-based matching approach was used to create a sample of patients receiving a specific treatment and a sample of control patients with similar characteristics, thus allowing comparisons of treatment with reduced bias. More specifically, two separate matched samples were created in AHF patients: one to compare i.v. vasodilators + i.v. diuretics vs. i.v. diuretics alone (see Supplementary material online, *Figure* S1), and one to assess i.v. inotropes and/or vasopressors vs. no i.v. inotropes and/or vasopressors treatment (see Supplementary material online, *Figure* S2).

The propensity score is the probability that a patient with specific baseline characteristics would receive the treatment evaluated conditionally on individual characteristics. We estimated the propensity score using logistic regression, where the dependent variable was the treatment under study.

The independent variables were patient and centre characteristics. All variables with a potential association with the treatment assignment and/or the outcome were used in these models, except if there were more than 10% missing values in the original database. More precisely, patient baseline characteristics used for propensity score development were age, gender, body mass index, primary diagnosis, clinical presentation, previous atrial fibrillation, obesity, diabetes, treatment of hypertension, peripheral vascular disease, chronic obstructive pulmonary disease, chronic kidney disease, liver dysfunction, depression, current malignant (cancer) disease, peripheral hypoperfusion/cold, peripheral oedema, pulmonary rales, New York Heart Association functional class, systolic blood pressure, diastolic blood pressure, heart rate, sodium, beta-blockers and angiotensin-converting enzyme inhibitors (ACEi) pre-admission. Centre characteristics were country.

Propensity-based matching was used to create samples of patients treated by the therapy under study and not treated who were similar in terms of propensity score, i.e. in terms of probability of receiving the therapy. Unmatched observations were discarded, thus leading to possibly non-representative samples of the original database.

A 1:1 matching optimal algorithm without replacement was used, where all treated patients were matched to the closest control within an appropriate range. The success of the propensity score matching was assessed by checking standardized differences between the groups before and after matching, expressed as a percentage. Balancing was considered as successful, if the standardized differences were less than 10% for variables used for propensity score development.

The main endpoint of the study was long-term all-cause mortality. In addition, the secondary endpoints were all-cause in-hospital mortality, all-cause post-discharge death, and post-discharge rehospitalization. Treatment effects were estimated using Cox proportional cause-specific hazards models. Analyses were first performed using the original samples unadjusted and adjusted for characteristics associated with the outcome and other treatments (age, gender, history of HF, coronary artery disease, atrial fibrillation, diabetes, systolic blood pressure at admission, diastolic blood pressure, heart rate, renal function, hyperglycaemia, hyponatraemia) and secondly using the matching sample. Treatment effects were also estimated in different clinically relevant subgroups using Cox model with interaction between treatment and subgroup.

Plots of Kaplan–Meier for time to long-term all-cause mortality in the whole cohort and propensity-score matched cohorts, as well as in-hospital mortality and post-discharge mortality in the matched cohorts were performed. These plots were divided by treatment.

All analyses were performed using SAS statistical software version 9.4 (SAS institute, Inc., Cary, NC, USA).

Results

A total of 6926 AHF patients were included in the study. Median duration of follow-up was 389.0 (366.0–491.0) days. Among hospitalized AHF patients, 1304 received a combination of i.v. vasodilators (mostly nitrates) and i.v. diuretics during the initial AHF management. They were compared to 4083 patients receiving i.v. diuretics alone. Furthermore, a separate analysis was performed with 833 patients who received one or more i.v. inotropes and/or vasopressors. They were compared to 6067 patients who received neither i.v. inotropes, nor vasopressors (*Figure* 1).

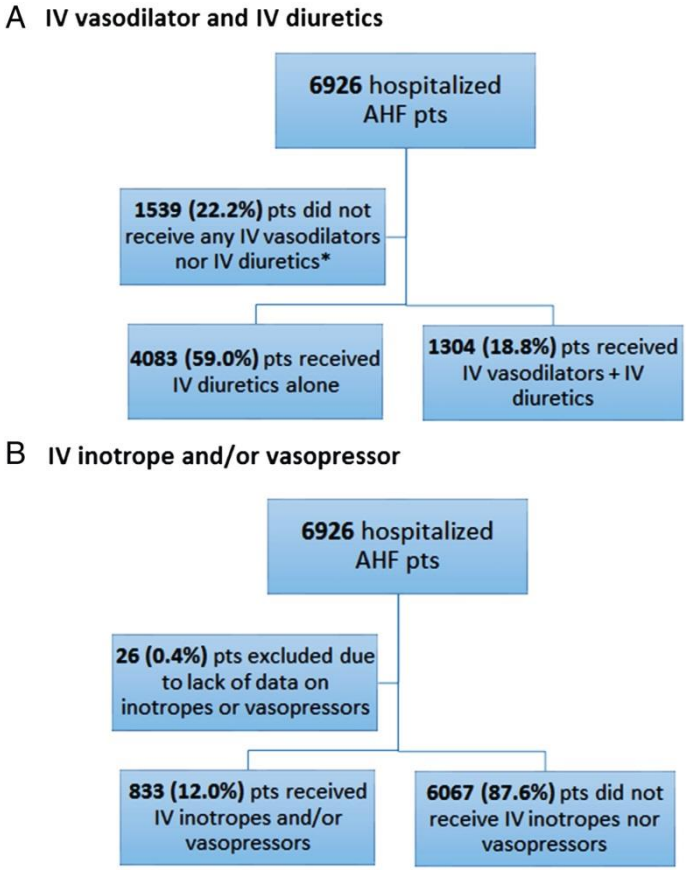

Figure 1. Hospitalized acute heart failure (AHF) patients flowchart through the study of the European Society of Cardiology Heart Failure Long-Term (ESC-HF-LT) registry. (*A*) Analysis of the combination of intravenous (IV) vasodilator and IV diuretics. (*B*) Analysis of IV inotrope and (or) vasopressor treatment. *This includes patients receiving oral diuretics and no vasodilators ($n = 809$); or no IV vasodilators and no diuretics (IV or oral) ($n = 304$).

Combination of i.v. vasodilators and diuretics and outcome

Table 1 shows baseline characteristics of patients who received the combination of i.v. vasodilator + i.v. diuretic and those receiving i.v. diuretics alone, before and after propensity score matching ($n = 976$ paired-matched patients). Duration of i.v. administration of vasodilators was greater than 12 hours for 45% of AHF patients.

Table 1. Baseline characteristics before and after propensity score matching for patients who received intravenous vasodilators and diuretics vs. those receiving intravenous diuretics alone

Baseline characteristics	Before propensity score matching					After propensity score matching				
	Vasodilators + diuretics (n = 1304)		Diuretics alone (n = 4083)		Standardized difference	Vasodilators + diuretics (n = 976)		Diuretics alone (n = 976)		Standardized difference
	n	Stat	n	Stat	(%)	n	Stat	n	Stat	(%)
Age, years	1304	68.1 ± 12.0	4083	69.7 ± 13.2	12.8	976	68.9 ± 12.2	976	69.1 ± 12.7	1.7
Female gender	1304	505 (38.7)	4083	1535 (37.6)	2.3	976	368 (37.7)	976	382 (39.1)	2.9
BMI, kg/m^2	1299	29.7 ± 5.3	4058	28.3 ± 5.5	25.1	976	29.0 ± 5.2	976	28.8 ± 5.4	4.2
Primary diagnosis	1304		4083			976		976		
Ischaemic heart disease		935 (71.7)		2076 (50.8)	43.8		670 (68.6)		705 (72.2)	7.9
Non-ischaemic heart disease		369 (28.3)		2007 (49.2)	43.8		306 (31.4)		271 (27.8)	7.9
Clinical presentation	1304		4082			976		975		
ACS/HF		348 (26.7)		348 (8.5)	49.1		235 (24.1)		260 (26.6)	5.9
Cardiogenic shock		24 (1.8)		125 (3.1)	7.9		24 (2.5)		22 (2.3)	1.4
Decompensated HF		412 (31.6)		2869 (70.3)	83.9		406 (41.6)		375 (38.4)	6.5
Hypertensive HF		114 (8.7)		120 (2.9)	24.9		67 (6.9)		70 (7.2)	1.2
Pulmonary oedema		397 (30.4)		443 (10.8)	49.9		235 (24.1)		231 (23.7)	1.0
Right HF		9 (0.7)		177 (4.3)	23.4		9 (0.9)		17 (1.7)	7.2
Previous atrial fibrillation	1304	423 (32.4)	4083	1980 (48.5)	33.2	976	354 (36.3)	976	336 (34.4)	3.9
Cardiovascular co-morbidities										
Obesity	1299	566 (43.4)	4058	1277 (31.3)	25.3	976	356 (36.5)	976	347 (35.6)	1.9
Diabetes	1304	595 (45.6)	4083	1587 (38.9)	13.7	976	429 (44.0)	976	441 (45.2)	2.5
Hypertension	1304	953 (73.1)	4079	2563 (62.8)	22.0	976	665 (68.1)	972	687 (70.4)	4.9
Peripheral vascular disease	1304	190 (14.6)	4080	580 (14.2)	1.0	976	156 (16.0)	973	147 (15.1)	2.5
Non-cardiovascular co-morbidities										
COPD	1304	237 (18.2)	4081	828 (20.3)	5.3	976	191 (19.6)	975	204 (20.9)	3.3
Chronic kidney disease	1304	344 (26.4)	4083	1213 (29.7)	7.4	976	249 (25.5)	976	270 (27.7)	4.9
Sleep apnoea	1289	34 (2.6)	3987	116 (2.8)	1.4	965	32 (3.3)	956	19 (1.9)	8.3
Liver dysfunction	1304	69 (5.3)	4082	398 (9.7)	17.0	976	58 (5.9)	975	73 (7.5)	6.1
Depression	1303	100 (7.7)	4076	303 (7.4)	0.9	975	75 (7.7)	974	91 (9.3)	5.9
Current malignant (cancer) disease	1304	47 (3.6)	4078	229 (5.6)	9.6	976	37 (3.8)	971	32 (3.3)	2.8
Symptoms and signs										
Peripheral hypoperfusion/cold	1300	274 (21.0)	4061	728 (17.8)	8.1	972	215 (22.0)	971	212 (21.7)	0.7
Peripheral oedema	1303	636 (48.8)	4078	2701 (66.2)	35.7	975	541 (55.4)	975	535 (54.8)	1.2
JVP >6	1242	475 (36.4)	3840	1559 (38.2)	3.6	921	372 (38.1)	905	349 (35.8)	4.9
Pulmonary rales	1300	1180 (90.5)	4068	3222 (78.9)	32.6	972	860 (88.1)	970	855 (87.6)	1.6
NYHA functional class	1303		4075			975		975		
II		87 (6.7)		421 (10.3)	13.1		82 (8.4)		97 (9.9)	5.3
III		584 (44.8)		2336 (57.2)	25.1		464 (47.5)		439 (45.0)	5.1
IV		632 (48.5)		1318 (32.3)	33.4		429 (44.0)		439 (45.0)	2.1
SBP, mmHg	1304	148.0 ± 33.1	4083	128.4 ± 26.0	65.8	976	139.2 ± 29.1	976	139.3 ± 30.2	0.3
DBP, mmHg	1304	86.2 ± 18.2	4074	76.7 ± 14.6	57.5	976	82.0 ± 16.4	976	81.7 ± 16.1	1.4
Heart rate, b.p.m.	1304	98.1 ± 25.3	4083	91.5 ± 25.3	26.3	976	95.7 ± 25.3	976	94.3 ± 25.9	5.1
Serum concentrations										
Sodium, mmol/L	1204	138.1 ± 5.6	3817	137.6 ± 5.5	8.3	901	137.7 ± 5.5	893	137.6 ± 5.7	1.8

Table 1. Baseline characteristics before and after propensity score matching for patients who received intravenous vasodilators and diuretics vs. those receiving intravenous diuretics alone

Baseline characteristics	Before propensity score matching					After propensity score matching				
	Vasodilators + diuretics (n = 1304)		Diuretics alone (n = 4083)		Standardized difference	Vasodilators + diuretics (n = 976)		Diuretics alone (n = 976)		Standardized difference
	n	Stat	n	Stat	(%)	n	Stat	n	Stat	(%)
Potassium, mmol/L	1201	4.3 ± 0.6	3807	4.4 ± 0.7	9.5	898	4.3 ± 0.6	896	4.4 ± 0.7	4.5
Creatinine, mg/dL	1281	1.5 ± 2.4	4030	1.5 ± 4.1	1.5	955	1.5 ± 2.7	954	1.7 ± 8.3	2.0
Uric acid, mg/dL	783	7.3 ± 8.4	2149	7.8 ± 8.4	6.2	526	7.5 ± 10.1	508	7.6 ± 2.7	0.5
Fasting glucose, mg/dL	1155	152.2 ± 75.2	3523	132.3 ± 64.5	28.3	850	144.9 ± 69.3	830	145.7 ± 71.5	1.1
BNP, pg/mL	117	1628.1 ± 2510.7	436	1378.6 ± 1708.4	11.6	98	1669.3 ± 2603.7	95	1061.2 ± 1401.4	29.1
LVEF, %	876	40.3 ± 13.4	2650	40.5 ± 15.4	1.0	620	39.6 ± 13.2	556	40.7 ± 15.4	7.9
Beta-blockers pre-admission	1304	604 (46.3)	4078	2199 (53.9)	15.1	976	495 (50.7)	971	498 (51.0)	0.6
ACEi pre-admission	1304	724 (55.5)	4078	1930 (47.3)	16.6	976	511 (52.4)	971	515 (52.8)	0.8
Intravenous inotropes	181		546			160		140		
Dobutamine		84 (6.4)		231 (5.7)	3.3		71 (7.3)		62 (6.4)	3.7
Dopamine		54 (4.1)		135 (3.3)	4.4		50 (5.1)		29 (3.0)	10.9
Enoximone		1 (0.1)		1 (0.0)	2.3		1 (0.1)		0 (0.0)	4.5
Epinephrine		3 (0.2)		7 (0.2)	1.3		3 (0.3)		3 (0.3)	0.0
Levosimendan		25 (1.9)		59 (1.4)	3.7		21 (2.2)		21 (2.2)	0.0
Norepinephrine		3 (0.2)		33 (0.8)	8.1		3 (0.3)		8 (0.8)	6.8
Other		11 (0.8)		80 (2.0)	9.5		11 (1.1)		17 (1.7)	5.2
Outcome										
In-hospital death	1304	67 (5.1)	4083	254 (6.2)	4.7	976	59 (6.0)	976	58 (5.9)	0.4
Long-term mortality	1243	299 (22.9)	3787	1167 (28.6)	13.0	932	227 (23.3)	916	247 (25.3)	4.8

Data are presented as mean ± standard deviation, or number (%).
ACEi, angiotensin-converting-enzyme inhibitor; ACS, acute coronary syndrome; BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HF, heart failure; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

When studying the primary endpoint, long-term all-cause mortality was lower in AHF patients receiving i.v. vasodilator + i.v. diuretic than those receiving i.v. diuretics alone in both the whole (22.9% vs. 28.6%) and the matched cohorts (23.3% vs. 25.3%) (*Table* 1). When using multivariate Cox regression analysis, the hazard ratio (HR) for the association between the use of i.v. vasodilator and diuretic and long-term all-cause mortality was not statistically significant [HR 0.784, 95% confidence interval (CI) 0.569–1.032] (see Supplementary material online, *Figure* S3).

Concerning the secondary endpoints, no association was seen neither in the whole nor in the matched cohort between the use of i.v. vasodilator and diuretic and all-cause in-hospital mortality, all-cause post-discharge death or post-discharge readmission. Kaplan–Meier analysis confirmed those results (*Figure* 2). Long-term cardiovascular mortality was not significantly different between the two treatment groups in the matched cohort (adjusted HR 0.823, 95% CI 0.607–1.116).

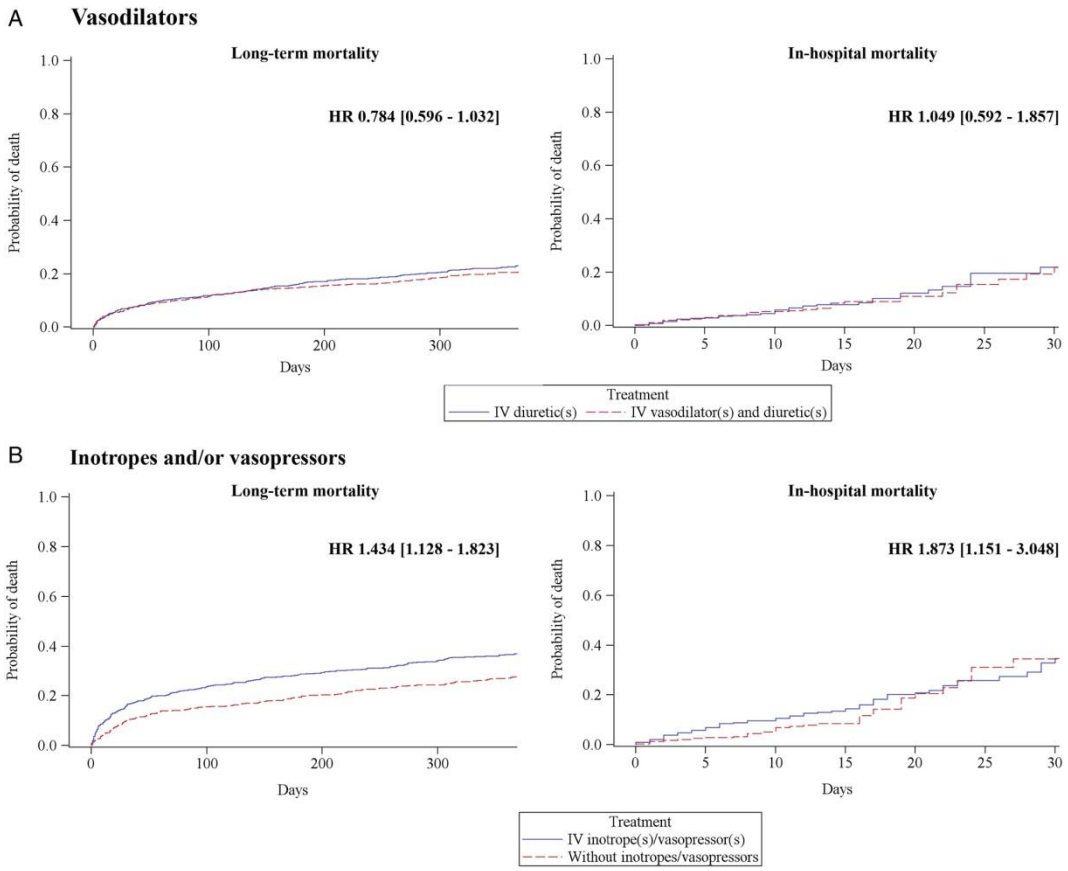

Figure 2. Risk of all-cause death in acute heart failure patients receiving intravenous (IV) vasodilators and diuretics (*A*), or IV inotropes and/or vasopressors (*B*). Kaplan–Meier analysis for all-cause mortality and the hazard ratios (HR) and 95% confidence intervals in the propensity-score matched cohort for 1-year and in-hospital mortality in patients receiving IV vasodilators (*A*) and IV inotropes and/or vasopressors (*B*).

Use of i.v. inotropes and/or vasopressors and outcome

Table 2 shows baseline characteristics of patients who received i.v. inotropes and/or vasopressors ($n = 833$) or not ($n = 6067$), before and after propensity score matching ($n = 606$ paired-matched patients). Dobutamine was the most used agent (43%) followed by dopamine (25%) and levosimendan (13%). Median duration of i.v. inotrope and/or vasopressor use was 24.0 (IQR 24.0–60.0) hours (*Table* 3).

Table 2. Baseline characteristics before and after propensity score matching for patients who received intravenous inotropes and/or vasopressors vs. other treatments and no inotropes

Baseline characteristics	Before propensity score matchingInotropes/vasopressors					After propensity score matchingInotropes/vasopressors				
	Yes ($n = 833$)		No ($n = 6067$)		Standardized difference	Yes ($n = 606$)		No ($n = 606$)		Standardized difference
	n	Stat	*n*	Stat	(%)	*n*	Stat	*n*	Stat	(%)
Age, years	833	67.2 ± 13.3	6067	69.2 ± 13.0	15.7	606	67.7 ± 13.3	606	67.2 ± 13.0	3.6
Female gender	833	278 (33.4)	6067	2278 (37.5)	8.7	606	202 (33.3)	606	212 (35.0)	3.5
BMI, kg/m^2	808	27.7 ± 5.1	5763	28.6 ± 5.5	17.0	606	27.7 ± 5.0	606	27.8 ± 5.1	0.6
Primary diagnosis	832		6024			606		606		
Ischaemic heart disease		498 (59.8)		3363 (55.4)	8.8		344 (56.8)		349 (57.6)	1.7
Non-ischaemic heart disease		334 (40.1)		2661 (43.9)	7.6		262 (43.2)		257 (42.4)	1.7
Clinical presentation	812		5792			606		605		
ACS/HF		107 (12.8)		843 (13.9)	3.1		94 (15.5)		95 (15.7)	0.5
Cardiogenic shock		158 (19.0)		37 (0.6)	65.0		23 (3.8)		27 (4.5)	3.3
Decompensated HF		395 (47.4)		3641 (60.0)	25.5		355 (58.6)		342 (56.4)	4.3
Hypertensive HF		5 (0.6)		314 (5.2)	27.6		5 (0.8)		12 (2.0)	9.8
Pulmonary oedema		124 (14.9)		747 (12.3)	7.5		108 (17.8)		113 (18.6)	2.1
Right HF		23 (2.8)		210 (3.5)	4.0		21 (3.5)		16 (2.6)	4.8
Previous atrial fibrillation	833	386 (46.3)	6067	2622 (43.2)	6.3	606	298 (49.2)	606	308 (50.8)	3.3
Cardiovascular co-morbidities										
Obesity	808	217 (26.1)	5763	1951 (32.2)	13.4	606	161 (26.6)	606	160 (26.4)	0.4
Diabetes	833	318 (38.2)	6067	2360 (38.9)	1.5	606	229 (37.8)	606	237 (39.1)	2.7
Hypertension	832	455 (54.6)	6060	3994 (65.8)	23.1	606	346 (57.1)	604	334 (55.1)	4.0
Peripheral vascular disease	812	151 (18.1)	5788	768 (12.7)	15.2	606	114 (18.8)	605	114 (18.8)	0.0
Non-cardiovascular co-morbidities										
COPD	832	184 (22.1)	6063	1147 (18.9)	7.9	606	140 (23.1)	604	159 (26.2)	7.3
Chronic kidney disease	833	317 (38.1)	6065	1480 (24.4)	29.8	606	226 (37.3)	606	232 (38.3)	2.0
Sleep apnoea	795	17 (2.0)	5680	175 (2.9)	5.4	594	14 (2.3)	593	23 (3.8)	8.6
Liver dysfunction	812	127 (15.2)	5792	391 (6.4)	28.6	606	85 (14.0)	605	74 (12.2)	5.4
Depression	830	112 (13.4)	6060	391 (6.4)	23.6	605	70 (11.6)	605	78 (12.9)	4.0
Current malignant (cancer) disease	830	47 (5.6)	6062	275 (4.5)	5.1	605	35 (5.8)	605	42 (6.9)	4.7

Table 2. Baseline characteristics before and after propensity score matching for patients who received intravenous inotropes and/or vasopressors vs. other treatments and no inotropes

Baseline characteristics	Before propensity score matchingInotropes/vasopressors					After propensity score matchingInotropes/vasopressors				
	Yes ($n = 833$)		No ($n = 6067$)		Standardized difference	Yes ($n = 606$)		No ($n = 606$)		Standardized difference
	n	Stat	*n*	Stat	(%)	*n*	Stat	*n*	Stat	(%)
Symptoms and signs										
Peripheral hypoperfusion/cold	809	381 (45.7)	5764	795 (13.1)	76.7	604	233 (38.4)	602	249 (41.1)	5.4
Peripheral oedema	812	500 (60.0)	5787	3167 (52.2)	18.8	606	387 (63.9)	603	382 (63.0)	1.7
JVP >6	775	422 (50.7)	5441	1772 (29.2)	44.9	574	297 (49.0)	568	272 (44.9)	8.3
Pulmonary rales	807	663 (79.6)	5773	4187 (69.0)	24.4	603	491 (81.0)	602	482 (79.5)	3.7
NYHA functional class	810		5767			604		604		
II		34 (4.1)		959 (15.8)	40.0		32 (5.3)		25 (4.1)	5.5
III		237 (28.5)		3234 (53.3)	52.3		215 (35.5)		199 (32.8)	5.6
IV		539 (64.7)		1574 (25.9)	84.5		357 (58.9)		380 (62.7)	7.8
SBP, mmHg	812	112.1 ± 27.2	5793	135.4 ± 27.6	85.1	606	117.9 ± 26.6	606	119.7 ± 23.4	7.0
DBP, mmHg	804	69.4 ± 15.9	5789	79.9 ± 15.3	67.5	606	72.3 ± 15.3	606	73.4 ± 13.5	7.5
Heart rate, b.p.m.	812	95.5 ± 28.1	5793	90.7 ± 25.0	18.0	606	94.6 ± 27.9	606	94.2 ± 29.0	1.4
Serum concentrations										
Sodium, mmol/L	781	135.7 ± 6.3	5405	138.2 ± 5.0	45.0	606	136.2 ± 6.0	606	136.0 ± 5.6	4.6
Potassium, mmol/L	779	4.4 ± 0.8	5394	4.4 ± 0.6	2.9	602	4.3 ± 0.7	603	4.4 ± 0.7	11.2
Creatinine, mg/dL	804	1.6 ± 0.8	5704	1.4 ± 3.6	7.1	605	1.5 ± 0.7	602	1.5 ± 0.8	6.7
Uric acid, mg/dL	443	8.0 ± 2.7	3158	7.4 ± 8.1	10.0	346	7.9 ± 2.7	347	9.2 ± 23.5	7.5
Fasting glucose, mg/dL	692	139.7 ± 73.6	5019	133.1 ± 64.9	9.6	533	133.7 ± 63.5	541	134.1 ± 64.3	0.5
BNP, pg/mL	84	2480.4 ± 2917.7	614	1171.9 ± 1590.5	55.7	73	2544.0 ± 3099.2	80	1683.9 ± 2188.0	32.1
LVEF, %	555	34.8 ± 14.6	3754	40.8 ± 14.8	41.2	421	35.1 ± 14.7	424	38.3 ± 15.4	21.2
Beta-blockers pre-admission	809	441 (52.9)	5790	3206 (52.8)	0.2	605	346 (57.1)	606	344 (56.8)	0.7
ACEi pre-admission	809	353 (42.4)	5790	3001 (49.5)	14.3	605	276 (45.5)	606	268 (44.2)	2.7
Intravenous inotropes	833		0			606		0		
Dobutamine		354 (42.5)		0 (0.0)			256 (42.2)		0 (0.0)	
Dopamine		206 (24.7)		0 (0.0)			157 (25.9)		0 (0.0)	
Enoximone		2 (0.2)		0 (0.0)			2 (0.3)		0 (0.0)	
Epinephrine		14 (1.7)		0 (0.0)			8 (1.3)		0 (0.0)	
Levosimendan		109 (13.1)		0 (0.0)			84 (13.9)		0 (0.0)	
Norepinephrine		45 (5.4)		0 (0.0)			18 (3.0)		0 (0.0)	
Other		103 (12.4)		0 (0.0)			81 (13.4)		0 (0.0)	

Table 2. Baseline characteristics before and after propensity score matching for patients who received intravenous inotropes and/or vasopressors vs. other treatments and no inotropes

Baseline characteristics	Before propensity score matchingInotropes/vasopressors				Standardized difference	After propensity score matchingInotropes/vasopressors				Standardized difference
	Yes ($n = 833$)		No ($n = 6067$)			Yes ($n = 606$)		No ($n = 606$)		
	n	Stat	*n*	Stat	(%)	*n*	Stat	*n*	Stat	(%)
Outcome										
In-hospital death	832	170 (20.4)	6067	214 (3.5)	53.9	606	92 (15.2)	606	49 (8.1)	22.3
Long-term mortality	797	364 (43.7)	5684	1410 (23.2)	44.4	580	241 (39.8)	562	178 (29.4)	22.0

Data are presented as mean ± standard deviation, or number (%).
ACEi, angiotensin-converting-enzyme inhibitor; ACS, acute coronary syndrome; BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HF, heart failure; JVP, jugular venous pressure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

Table 3. Duration and dosage of treatment with intravenous inotropes and/or vasopressors and their association with long-term all-cause death

Inotrope/vasopressor	Dobutamine	Dopamine	Levosimendan	Norepinephrine	Epinephrine
(whole cohort, $n = 833$)	($n = 354$)	($n = 206$)	($n = 109$)	($n = 45$)	($n = 14$)
Hours of treatment					
Mean ± SD	42.5 ± 29.9	43.4 ± 32.3	24.8 ± 6.3	40.2 ± 28.3	37.6 ± 41.7
Median (IQR)	36.0 (23.0–72.0)	36.0 (20.0–72.0)	24.0 (24.0–24.0)	35.0 (17.0–60.0)	22.0 (1.0–72.0)
Long-term all-cause death, %	37.9	49.0	38.5	55.6	64.3
Inotrope/vasopressor	Dobutamine	Dopamine	Levosimendan	Norepinephrine	Epinephrine
(matched cohort, $n = 606$)	($n = 512$)	($n = 314$)	($n = 168$)	($n = 36$)	($n = 16$)
HR (95% CI) for long-term all-cause death	1.055 (0.727–1.531)	1.628 (1.031–2.572)	1.229 (0.618–2.445)	3.762 (0.903–15.663)	NA

Each of the 833 patients received at least one inotrope and/or vasopressor. Investigators indicated the main inotrope and/or vasopressor used in the initial management of acute heart failure. Of note, for 105 patients, investigators indicated inotropes and/or vasopressors other than those presented in the table.
CI, confidence interval; HR, hazard ratio; IQR, interquartile range; NA, not available; SD, standard deviation.

The primary endpoint of long-term all-cause mortality was greater in patients receiving i.v. inotrope and/or vasopressor compared to those who did not, whether analyses were performed in the whole (43.7% vs. 23.2%) or in the matched cohort (39.8% vs. 29.4%). Unadjusted and adjusted HR on the whole or matched cohort are shown in *Figure* 3. Using the multivariate Cox regression analysis, adjusted HR for the association between the use of i.v. inotrope and/or vasopressor and long-term all-cause mortality was 1.720 (95% CI 1.498–1.975] in the whole cohort and 1.434 (95% CI 1.128–1.823) in the matched cohort. Adjusted HR for long-term all-cause mortality remained roughly between 1.5 and 2 in all clinically relevant subgroups of the matched cohort (see Supplementary materials online, *Figure* S4 and *Table* S1) with few positive interactions (age or peripheral hypoperfusion).

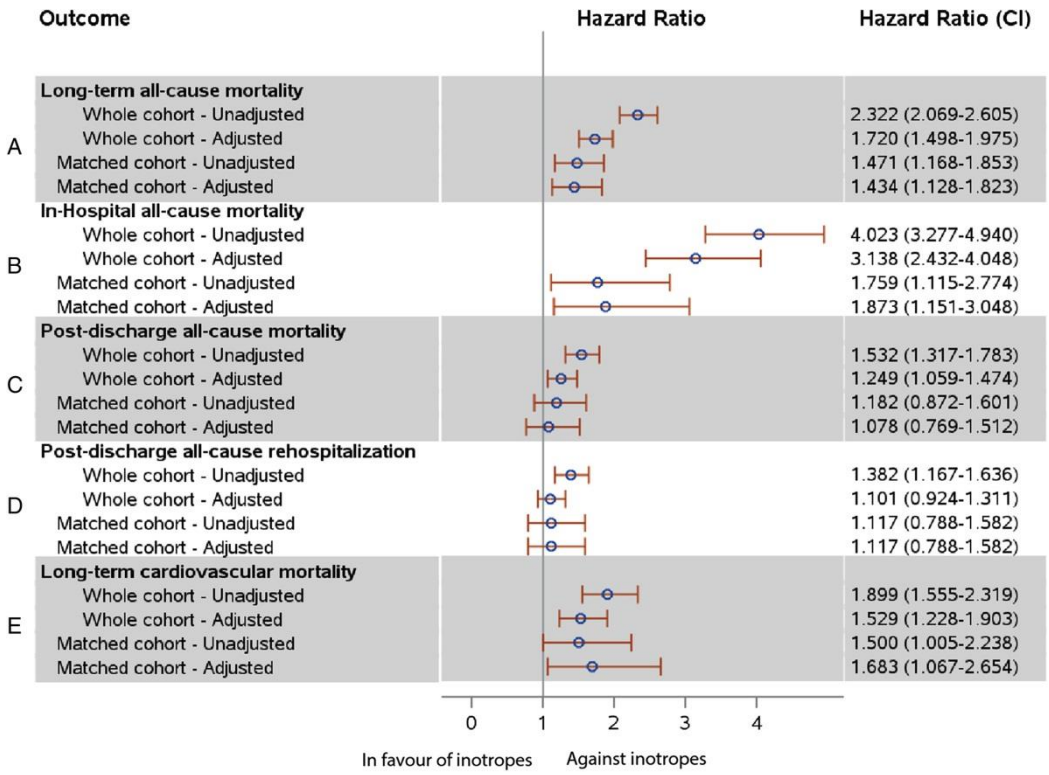

Figure 3. Hazard ratio for the association between the use of inotropes/vasopressors and (*A*) long-term all-cause mortality, (*B*) in-hospital mortality, (*C*) post-discharge all-cause mortality, (*D*) rehospitalization, (*E*) long-term cardiovascular mortality. CI, confidence interval.

Concerning the secondary endpoints, adjusted HR for associations between the use of i.v. inotrope and/or vasopressor and all-cause in-hospital mortality were 3.138 (95% CI 2.432–4.048) in the whole cohort and 1.873 (95% CI 1.151–3.048) in the matched cohort (*Figure* 3). Adjusted HR for all-cause post-discharge mortality were 1.249 (95% CI 1.059–1.474) in the whole cohort. However, this association became non-significant after propensity score matching (HR 1.078, 95% CI 0.769–1.512 in the matched cohort). No association was found between the use of i.v. inotrope and/or vasopressor and all-cause rehospitalization (HR 1.117, 95% CI 0.788–1.582 in the matched cohort). Adjusted HR for the association between i.v. inotrope and/or vasopressor use and long-term cardiovascular mortality was also significant in the whole as well as in the matched cohorts (HR 2.522, 95% CI 2.137–2.977, and HR 1.832, 95% CI 1.369–2.451, respectively).

Sensitivity analysis (presented in the Supplemental *Figure* S5) confirmed the associations between the use of i.v. inotropes and/or vasopressors and long-term all-cause mortality throughout geographic regions (see also Supplementary material online, *Table S2*). Moreover, adjusted HR showed a significant association between dopamine and all-cause long-term mortality (HR 1.628, 95% CI 1.031–2.572) but not with dobutamine or levosimendan (HR 1.055, 95% CI 0.727–1.531, and HR 1.229, 95% CI 0.618–2.445, respectively). This detrimental association of dopamine with long-term mortality is mostly seen in AHF patients with systolic blood pressure < 130 mmHg and signs of peripheral hypoperfusion (HR 3.34, 95% CI 1.01–11.11) rather than in patients with systolic blood pressure ≥ 130 mmHg and no clinical signs of hypoperfusion (HR 0.33, 95% CI 0.03–3.32).

Discussion

This study describes the contemporary use of i.v. vasoactive medications and their association with long-term survival in an unselected global patient population with AHF. Our results showed that the use of vasodilators and diuretics in the initial management of AHF did not alter long-term clinical outcomes. Notably, this is the first analysis to demonstrate that the use of inotropes and/or vasopressors in AHF was associated with increased long-term risk of all-cause and cardiovascular death throughout different geographic regions.

The ESC-HF-LT registry indicated that only a minority of AHF patients received vasodilators during the initial hospital management. The combination of vasodilators and diuretics had a tendency to lower the risk of mortality compared to diuretics alone. However, statistical significance is diminished due to the smaller sample size. As a result, our study showed neither harmful, nor beneficial associations with clinical outcomes. These findings are consistent with the neutral effect of vasodilators on mortality described in previous studies,12, 13 in particular a post-hoc analysis of ESCAPE trial,14 as well as novel agents such as nesiritide in ASCEND-HF[15] and ularitide in TRUE-AHF.16, 17

Our study further showed that the prevalence of the use of inotropes and/or vasopressors in the ESC-HF-LT registry was still common (12%), though lower than in previous studies: the Italian IN-HF Outcome registry (20%, $n = 360$)18 and the global ALARM-HF registry (33%, $n = 1617$).8 Our study also suggests a rather inappropriate use of inotropes and/or vasopressors, as only a small proportion of patients treated with catecholamines presented with cardiogenic shock and less than half had signs of peripheral hypoperfusion. Despite the widespread use of inotropes, data from controlled trials have failed to demonstrate benefit with these agents.4, 7-9, 19 On the contrary, catecholamines have been associated with increased risk for adverse outcomes. The CardShock study recently demonstrated the association between the use of adrenaline in cardiogenic shock and a striking myocardial injury as well as increased 90-day mortality, thus raising questions about the safety of this treatment.20 The increasing safety concerns for the use of catecholamines are reflected in current clinical practice guidelines. The recent ESC guidelines for the diagnosis and treatment of acute and chronic HF further restrict the use of inotropic agents to AHF patients only with symptomatic hypotension and hypoperfusion.21, 22 Our results confirm that the use of inotropes and/or vasopressors in AHF was consistently associated with short-term death, in line with previous studies, including the global ALARM-HF registry.8 Our study further extended these findings by showing that detrimental effects of inotropes and/or vasopressors on long-term all-cause and cardiovascular mortality were still pronounced several months after AHF episodes and seen in all studied geographic regions. Our study, however, showed the lack of association between inotropes and/or vasopressors and long-term mortality in hospital survivors. This may suggest an immediate rather than prolonged detrimental effect of inotropes and/or vasopressors on clinical outcome. This needs further evaluation.

The present study also indicates that dopamine has an excess mortality compared to other studied inotropes (such as dobutamine and levosimendan). However, our study was not adequately powered to analyse the differences between individual inotropes and/or vasopressors, thus this finding remains to be confirmed in future studies.

Our study has important clinical implications as it reinforces safety concerns of inotropes and/or vasopressors in AHF. Our results suggest that the recommendation of careful use of i.v. catecholamines in AHF seems wise. Furthermore, it highlights the universal need for safe agents to stabilize and restore haemodynamics in AHF patients. What is more, our study draws attention to the use of dopamine, as it was associated with worse short- and long-term outcomes compared to other inotropes and/or vasopressors.

Limitations

Our study has several limitations. The observational design of our study is subject to selection bias and confounding. Propensity score methodology allowed balancing groups according to variables that were recorded in the ESC-HF-LT registry. This is an especially detailed registry notably with regard to AHF related variables. By matching patients by propensity scores generated from 25 baseline variables, we accounted for most conceivable confounders. Nevertheless, we cannot rule out inaccuracies in registry data or residual unmeasured confounding. Propensity score analysis strengthens our findings but still cannot replace a randomized study design. Since this was a multicentre registry, it should not be overlooked that some centres recorded data differently than others. There was no central committee for the establishment of AHF diagnosis, or to assure that the requirements of enrolment were equally respected in all countries. However, centres and countries were accounted for in the propensity score development. Furthermore, the associations were strong and consistent among the different analyses conducted (unadjusted, adjusted and propensity scoring). Thus, the impact of any one particular centre should be limited in most cases. There is also a certain amount of missing data that may have influenced the results, especially concerning certain markers that reflect disease severity (such as B-type natriuretic peptide and left ventricular ejection fraction). It should also be noted that propensity score does not allow to match patients who have an absolute indication for the use of vasoactive medications, such as cardiogenic shock. The number of patients presenting with cardiogenic shock was small and therefore not sufficient to analyse the impact of vasopressors and inotropes in this subgroup of patients. However, the detrimental association with the use of inotropes and/or vasopressors and mortality remained evident in the subgroup analysis of hypotensive patients as well as patients with a low ejection fraction. Another important limitation of our study is the lack of data on doses of different inotropes. This might be the source of bias as there might be disparities between low and high dose of certain catecholamines, such as dopamine. It should also be noted that there is a difference between levosimendan and other inotropes, because levosimendan can be administered with much less monitoring and does not require an intensive care unit setting. Therefore, this is a potential source of bias. Moreover, the study is also limited by the absence of data on the course of the disease during the first 24 hours of i.v. therapy administration. Post-baseline factors such as clinical worsening during the admission could affect outcomes, and further analyses adjusting for markers of clinical worsening could have strengthened the propensity score analysis.

Conclusions

Our study, based on the ESC-HF-LT registry data, did not confirm any harms or benefits of the use of vasodilators on long-term clinical outcomes. More importantly, observable associations were revealed between the use of inotropes and/or vasopressors and long-term all-cause and cardiovascular death in all geographic regions. We also observed that dopamine had the greatest negative association with mortality among studied inotropes. Because our study does not prove causality, these findings need to be confirmed in the setting of a prospective randomized clinical trial.

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