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Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods

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Abstract *Purpose:* To date, treatment with intravenous (IV) agents such as vasodilators, diuretics, and inotropes has shown marginal or mixed benefits in acute heart failure (AHF) trials. The aim of this study was to identify the risks and benefits of IV drugs in patients hospitalized with acute decompensated heart failure. *Methods:* The AHF global survey of standard treatment (ALARM-HF) reviewed in-hospital treatments in eight countries. The present study was a post hoc analysis of ALARM-HF data in which propensity scoring was used to identify groups of patients who differed by treatment but had the same multivariate distribution of covariates. Such propensity matching allowed estimations of the effect of specific treatments on the outcome of in-hospital mortality. *Results:* Unadjusted analysis showed a lower in-hospital mortality rate in AHF patients receiving "diuretics + vasodilators" ($n = 1{,}805$) compared to those receiving "diuretics alone" ($n = 2{,}362$) (7.6 vs. 14.2%, $p < 0.0001$). Propensity-based matching ($n = 1{,}007$ matched pairs) confirmed the lower mortality of AHF patients receiving diuretics + vasodilators: 7.8 versus 11.0% ($p = 0.016$). Unadjusted analysis showed a much greater in-hospital mortality rate in patients receiving IV inotropes (25.9%) compared to those who did not (5.2%) ($p < 0.0001$). Propensity-based matching ($n = 954$ pairs) confirmed that IV catecholamine use was associated with 1.5-fold increase for dopamine or dobutamine use and a >2.5-fold increase for norepinephrine or epinephrine use. *Conclusions:* In terms of in-hospital survival, a vasodilator in combination with a diuretic fared better than treatment with only a diuretic. Catecholamine inotropes should be used cautiously as it has been seen that they actually increase the risk for in-hospital mortality.

Keywords Acute heart failure · ALARM-HF data · Intravenous agents · In-hospital survival

Abbreviations

AHF	Acute heart failure
SBP	Systolic blood pressure

Introduction

Hospitalization for acute decompensation of heart failure marks a significant turning point in the disease course. No single or simple treatment protocol can be recommended for acute heart failure (AHF) because of the large number of available drugs that can be given in various combinations, including inotropes, vasodilators, and diuretics [1–3]. The question remains as to what are the best treatment options in acute worsening heart failure. The AHF global survey of standard treatment (ALARM-HF) was developed to closely explore the safety and efficacy of currently used intravenous (IV) drugs in various populations. This study is an international, observational study of close to 5,000 patients that provides the unique opportunity to evaluate how patients admitted with AHF are managed in the "real-hospital world" setting.

Based on previous observations, we postulated that the most frequently administered IV inotropic and vasoactive (vasodilators or vasopressors) agents might influence short-term outcome. Specifically, we hypothesized, based on preliminary studies carried out in ALARM-HF, that patients who received early IV vasodilators would be associated with lower in-hospital mortality rates than those who received no vasodilators [4–6]. As initial systolic blood pressure (SBP) at admission is a major independent determinant of short-term outcome and influences the use of IV vasodilators, we further explored whether the levels of initial SBP might impact the beneficial effect of early administration of IV vasodilators [7].

In addition, we hypothesized that, in the ALARM-HF study, IV inotropic and/or IV vasopressor agents might be able to influence short-term outcome. It is becoming increasingly recognized that inotropes and vasopressors have detrimental effects on short-term outcome, but this recognition is almost solely based on expert opinion as data on the subject are scarce [1, 8–11]. More importantly, the paucity of controlled clinical trials led us to consider all inotropes and vasopressors as being equally harmful regardless of their hemodynamic effect or the pharmacological class (c-AMP-dependent catecholamines or calcium-sensitizing agent) they belong to.

Accordingly, we assessed the impact of early administration of IV vasodilators, IV inotropes, and/or IV vasopressors on the short-term outcome of AHF patients included in the ALARM- HF cohort. The methods used included multivariable model risk adjustment and propensity-based matching that controls for overt bias by balancing patient characteristics across treatment groups.

Methods

ALARM-HF data collection and study

The ALARM-HF global survey collected anonymized data from 4,953 patients collected from nine countries, namely, France, Germany, Italy, Spain, the United Kingdom, Greece, Turkey, Australia, and Mexico; 65% of these patients were hospitalized in teaching hospital and 75% in intensive care units (ICUs) or coronary care units (CCUs) [12]. The study was conducted as a retrospective in-hospital observational survey, via a questionnaire, from 666 hospitals. The hospital sample was recruited to be representative according to geographic region, hospital size (by number of beds), sector (public vs. private), and type (university vs. non-teaching status). The paper-based data collection was conducted over the period from October 2006–March 2007. At each hospital, patient case report forms (CRF) were completed based on medical records and other source documents promptly after approximately five to eight consecutive patients were discharged with the final diagnosis of AHF. Overall in-hospital mortality was 12%, and median hospital length of stay (LOS) was 6 days [inter-quartile range (IQR) 4–10 days].

Unadjusted analysis was first applied on the entire cohort of 4,953 patients to assess the effects of the three main classes of IV drugs, namely, diuretics, vasodilators or inotropes, and/or vasopressors, when administered during the first 48 h, on in-hospital mortality. Second, due to the fact that the large majority of the patients were treated with IV diuretics, the effects of IV vasodilators were assessed on the 4,167 (84% of the entire cohort) patients who received IV diuretics by comparing the 1,805 patients who received IV diuretics and IV vasodilator (the "vasodilators + diuretics" group) and the 2,362 patients who received only IV diuretics and no IV vasodilators (the "diuretics only" group). Third, the effects of IV inotropes were tested in the entire cohort of ALARM-HF. The group of patients receiving IV inotropes and/or IV vasopressors in the first 48 h ($n = 1{,}617$) was compared to the group of patients not receiving any inotropes and/or vasopressors in the first 48 h ($n = 3{,}256$). Of note, the latter group included a few patients ($n = 213$) who received IV inotropes and/or IV vasopressors later than the first 48 h of treatment initiation.

Statistical analysis

For the ALARM-HF observational study, 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 [13–17].

More specifically, two separate analyses were conducted in AHF patients: one to compare IV diuretic + IV vasodilator treatment versus IV diuretic alone treatment, and one to assess inotrope treatment versus no inotrope treatment. Details on propensity score development and propensity score matching are given in the Electronic Supplementary Material (ESM; Appendix).

The main endpoint of the study was all-cause in-hospital mortality. The LOS was computed from the date of treatment initiation until the date of death, discharge, or transfer. Patients transferred to the ICU or another hospital were censored at that date. Cumulative incidence of all-cause in-hospital mortality over time was estimated, considering alive at discharge as a competing event. Treatment effects were estimated using Cox proportional cause-specific hazards models. Analyses were first performed using the original samples, unadjusted or adjusted for characteristics associated with the outcome and other treatments. Methods appropriate to analyses of censored data were therefore used. Details on endpoint analysis are given in the ESM.

All analyses were performed using R 2.6.2 statistical software (The R Foundation for Statistical Computing, Vienna, Austria).

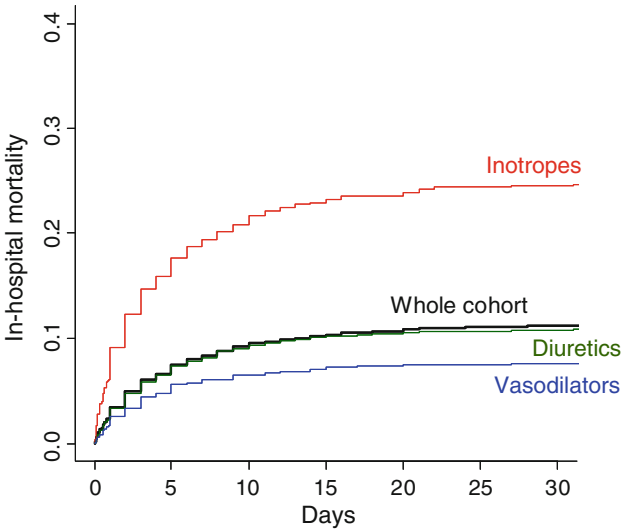

Fig. 1 Effect of the main intravenous (IV) drugs administered during first 48 h in acute heart failure (AHF) patients on in-hospital mortality. Whole cohort ($n = 4{,}953$), IV diuretics ($n = 4{,}167$), IV vasodilators (mostly nitrates, $n = 1{,}930$), IV inotropes and/or IV vasopressors ($n = 1{,}617$)

Results

Figure 1 shows the results of the unadjusted analysis which details the effect of the three main classes of IV drugs, namely, diuretics, vasodilators, and inotropes, on in-hospital mortality. In terms of in-hospital mortality, among the 4,953 patients studied in the ALARM-HF cohort, the use of IV diuretics had no effect, that of IV vasodilators had a beneficial effect, and that of IV inotropes and/or vasopressors had a detrimental effect.

Effects of IV vasodilators on in-hospital mortality

Characteristics of the patients who received treatment with IV diuretics + vasodilators ($n = 1{,}805$) were compared to those that received IV diuretics and no vasodilators (diuretics alone; $n = 2362$) (Table 1). IV diuretics and IV vasodilators were started at a median of 0.5 (IQR 0.0–1.0) and 0.5 (IQR 0.0–2) h, respectively, after admission. IV vasodilators were quasi-exclusively nitrates, with 76% of patients receiving nitroglycerine and 19% receiving isosorbite dinitrate.

Unadjusted analysis showed a lower in-hospital mortality rate in patients receiving diuretics + vasodilators compared to those receiving diuretics alone (7.6 vs. 14.2%, $p < 0.0001$) (Table 1). However, several parameters, including the level of SBP at admission, the existence of comorbidities (hypertension, diabetes, dyslipidemia), or the incidence of cardiogenic shock or acute myocardial infarction were different between two groups of patients (see Table 1 and Fig. S1a in the ESM). The dose of diuretics in the first 24 h of hospitalization was also similar in patients receiving diuretics + vasodilators and those receiving diuretics alone [50 (IQR 40–80) vs. 40 (IQR 40–80) mg, respectively.

Propensity-based matching produced 1,007 matched pairs with standardized differences in patient characteristics of less than 10%, indicating a successful balance between prognostic variables (Table 1). This confirms that the addition of IV vasodilators to the treatment regimen was associated with an approximate 20% reduction of in-hospital mortality: 7.8% with vasodilators versus 11.0% with no vasodilators ($p = 0.016$). Consistent results were found using a multivariable model adjusted for other treatments (such as beta-blockers, IV inotropic agents) on both the whole sample and on the paired-matched sample (Table 2).

We further investigated the effect of adding IV vasodilator to the therapy according to the level of initial SBP. Of note, in patients with low SBP, there was, before matching, a higher incidence of acute coronary syndrome in patients receiving IV vasodilators (see Table S1 of the ESM). In the propensity-matched sample (1,007 matched pairs), the effect of IV vasodilators was found to be different ($p = 0.045$) in AHF patients admitted with a SBP <120 mmHg [adjusted hazard ratio (HR) 0.57, 95% confidence interval (CI) 0.39–0.83)] compared to patients admitted with a SBP ≥120 mmHg (HR 1.00, 95% CI 0.54–1.85). Separate propensity scores in each subgroup

Table 1 Baseline characteristics before and after matching for patients who received intravenous (IV) vasodilators and diuretics versus those receiving IV diuretics alone

Baseline characteristics	Before propensity score match			After propensity score match		
	Vasodilators + diuretics (n = 1,805)	Diuretics alone (n = 2,362)	Standardized difference (%)	Vasodilators + diuretics (n = 1,007)	Diuretics alone (n = 1,007)	Standardized difference (%)
Age (years)						
16–45	49 (2.7)	130 (5.6)	14.6	34 (3.4)	37 (3.7)	1.6
46–60	383 (21.2)	439 (19)	5.6	194 (19.3)	187 (18.6)	1.8
61–70	569 (31.5)	643 (27.8)	8.1	298 (29.6)	298 (29.6)	0.0
71–80	562 (31.2)	694 (30)	2.4	323 (32.1)	327 (32.5)	0.8
>80	241 (13.4)	404 (17.5)	11.5	158 (15.7)	158 (15.7)	0.0
Women	629 (35.5)	898 (38.9)	7.1	374 (37.1)	376 (37.3)	0.4
Weight (kg)	80 (71–89)	78 (69–90)	12.3	80 (71–89)	80 (70–90)	2.2
De novo AHF	681 (37.7)	807 (34.2)	7.4	365 (36.2)	358 (35.6)	1.4
Secondary AHF	366 (20.3)	534 (22.6)	5.7	206 (20.5)	216 (21.4)	2.4
Cardiogenic shock	136 (7.5)	311 (13.2)	18.6	93 (9.2)	83 (8.2)	3.5
Atrial fibrillation/flutter						
No	979 (54.3)	1,301 (55.2)	1.8	569 (56.5)	569 (56.5)	0.0
Acute	370 (20.5)	456 (19.4)	2.9	198 (19.7)	200 (19.9)	0.5
Chronic	52 (2.9)	75 (3.2)	1.7	26 (2.6)	29 (2.9)	1.8
Acute and chronic	401 (22.3)	524 (22.2)	0.0	214 (21.3)	209 (20.8)	1.2
Acute myocardial infarction	846 (46.9)	660 (27.9)	40.0	377 (37.4)	374 (37.1)	0.6
Cardiovascular comorbidities						
Coronary artery disease	572 (31.8)	692 (29.5)	5.1	334 (33.2)	317 (31.5)	3.6
Chronic heart failure	625 (34.8)	881 (37.5)	5.7	379 (37.6)	377 (37.4)	0.4
Cardiomyopathy	188 (10.5)	355 (15.1)	14.0	109 (10.8)	118 (11.7)	2.8
Peripheral vascular disease	159 (8.9)	217 (9.2)	1.4	89 (8.8)	85 (8.4)	1.4
Heart valve disease	221 (12.3)	382 (16.3)	11.4	138 (13.7)	154 (15.3)	4.5
Obesity	538 (30)	558 (23.8)	14.0	290 (28.8)	301 (29.9)	2.4
Diabetes	942 (52.4)	946 (40.3)	24.5	502 (49.9)	512 (50.8)	2.0
Dyslipidemia	889 (49.5)	900 (38.3)	22.6	475 (47.2)	466 (46.3)	1.8
Hypertension	1,445 (80.5)	1,545 (65.8)	33.5	776 (77.1)	770 (76.5)	1.4
Symptoms and signs						
Cold extremities	490 (27.4)	583 (24.8)	5.9	252 (25)	253 (25.1)	0.2
Dyspnoea at rest	1,391 (77.8)	1,730 (73.7)	9.6	762 (75.7)	781 (77.6)	4.5
Fatigue	755 (42.2)	1,088 (46.3)	8.3	437 (43.4)	448 (44.5)	2.2
Orthopnoea	1,172 (65.5)	1,305 (55.6)	20.5	629 (62.5)	630 (62.6)	0.2
Peripheral edema	722 (40.4)	1,117 (47.6)	14.5	450 (44.7)	469 (46.6)	3.8
Jugular venous distension	732 (40.9)	1,008 (42.9)	4.0	429 (42.6)	421 (41.8)	1.6
Rales	1,252 (70)	1,430 (60.9)	19.3	711 (70.6)	683 (67.8)	6.0
Weight gain	396 (22.1)	694 (29.6)	17	281 (27.9)	278 (27.6)	0.7
NYHA functional class						
I	21 (1.2)	35 (1.5)	2.8	12 (1.2)	12 (1.2)	0.0
II	106 (5.9)	233 (9.9)	14.9	69 (6.9)	62 (6.2)	2.8
III	657 (36.4)	830 (35.1)	2.6	351 (34.9)	364 (36.1)	2.7
IV	705 (39.1)	856 (36.2)	5.8	407 (40.4)	399 (39.6)	1.6
Not specified or developed						
AHF in hospital	316 (17.5)	408 (17.3)	0.6	168 (16.7)	170 (16.9)	0.5
SBP (mmHg)	150 (118–179)	120 (96.2–150)	59.0	140 (110–170)	140 (108.5–165)	2.8
SBP >150 mmHg	896 (50.0)	657 (28.0)	46.3	429 (42.6)	427 (42.4)	0.4
Heart rate (bpm)	110 (96–120)	108 (90–120)	11.7	110 (92–120)	110 (90–120)	0.6
Serum concentrations						
Sodium (mmol/l)[a]	138 (133–140)	137 (132–140)	5.3	137 (132–140)	138 (133–141)	3.8
Creatinine (mg/dl)[a]	1.3 (1–1.7)	1.2 (0.9–1.7)	3.2	1.2 (0.9–1.7)	1.2 (1–1.7)	3.3
Uric acid (mg/dl)[a]	5.8 (1.2–7.8)	6.2 (1.5–8)	4.8	6.1 (1.4–7.8)	6.3 (3–8)	8.1
Oxygen saturation (%)[a]	89 (84–92)	90 (85–93)	15.7	90 (85–92)	90 (85–92)	0.6
LVEF (%) mean (SD)[a]	38.9 (13.1)	37.4 (15)	10.8	38.8 (13.4)	38.8 (14.3)	0.3
Beta-blockers pre-admission	617 (34.2)	780 (33)	2.5	363 (36)	352 (35)	2.3
ACEI pre-admission	571 (32)	768 (32.8)	1.8	349 (34.7)	339 (33.7)	2.1
IV inotropes						
Dopamine	171 (9.5)	294 (12.4)	9.5	95 (9.4)	96 (9.5)	0.3
Dobutamine	308 (17.1)	495 (21)	9.9	174 (17.3)	180 (17.9)	1.6
Epinephrine	27 (1.5)	73 (3.1)	10.7	20 (2)	21 (2.1)	0.7

Table 1 continued

Baseline characteristics	Before propensity score match			After propensity score match		
	Vasodilators + diuretics (n = 1,805)	Diuretics alone (n = 2,362)	Standardized difference (%)	Vasodilators + diuretics (n = 1,007)	Diuretics alone (n = 1,007)	Standardized difference (%)
Norepinephrine	26 (1.4)	113 (4.8)	19.3	21 (2.1)	22 (2.2)	0.7
PDEI	12 (0.7)	32 (1.4)	6.9	9 (0.9)	5 (0.5)	4.8
Levosimendan	121 (6.7)	89 (3.8)	13.2	39 (3.9)	46 (4.6)	3.5
CPAP[a]	177 (7.5)	215 (9.1)	–	136 (13.5)	66 (6.6)	–
Outcome[a]						
Discharge	1,391 (77.1)	1,734 (73.4)		793 (78.7)	779 (77.4)	
Death	125 (6.9)	303 (12.8)		73 (7.2)	104 (10.3)	
Transfer (ICU or other hospital)	289 (16)	325 (13.8)		141 (14.0)	124 (12.3)	
In-hospital mortality rate (95% CI)	7.6 (6.3–8.9)	14.2 (12.7–15.7)		7.8 (6.1–9.5)	11.0 (9.0–13.1)	

Data are presented as a number (n) with the percentage in parenthesis, or as the median with the inter-quartile range (IQR, Q1–Q3) in parenthesis, unless specified otherwise

AHF Acute heart failure, *NYHA* New York Heart Association, *LVEF* left ventricular ejection fraction, *SBP* systolic blood pressure, *ACE* angiotensin converting enzyme inhibitors, *PDE* phosphodiesterase inhibitors, *CPAP* continuous positive airway pressure, *ICU* intensive care unit, *CI* confidence interval

[a] Not used for propensity score development

(SBP <120 mmHg or ≥120 mmHg) were then developed and separate matched samples obtained, resulting in 300 matched pairs with SBP <120 mmHg and 653 matched pairs with a SBP ≥120 mmHg, which confirmed that a beneficial effect of IV vasodilators could be limited to patients with a low SBP at admission (Table 2). Figure 2 shows that the beneficial effect of IV vasodilators on survival rate was striking in patients with a low SBP at admission (<100 mmHg; additional data are presented in Table S1 and S2 of the ESM).

Effects of IV inotropes and/or IV vasopressors on in-hospital mortality

The characteristics of patients receiving IV inotropes and/or IV vasopressors (n = 1,617) and those who did not (n = 3,256) in the first 48 h are summarized in Table 3. The median dose of IV inotropes and/or IV vasopressors and the median delay between admission and drug initiation are presented in Table 4.

Unadjusted analysis showed a much greater in-hospital mortality rate in patients receiving IV inotropes and/or IV vasopressors (25.9%) compared to those who did not receive inotropes and/or vasopressors (5.2%) in the first 48 h ($p < 0.0001$). This relationship held true regardless of the initial SBP (data not shown). Table 3 shows that all IV inotropes and/or IV vasopressors did not equally affect in-hospital mortality rates. Indeed, the risk of in-hospital mortality was greater in patients receiving IV catecholamines (dobutamine, dopamine, norepinephrine and epinephrine) and lower in patients receiving levosimendan, both compared to patients not receiving any inotrope and/or any vasopressor (Table 5).

Table 2 Outcome analysis for in-hospital mortality in patients who received IV vasodilators and diuretics versus IV diuretics alone

Outcome analysis	Whole cohort	SBP (mmHg)	
		<120 mmHg	≥120 mmHg
Analysis			
Unadjusted	0.55 (0.47–0.71)	0.63 (0.47–0.84)	1.23 (0.86–1.78)
Adjusted[a]	0.73 (0.58–0.92)	0.64 (0.47–0.86)	0.94 (0.64–1.37)
Propensity analysis			
Unadjusted	0.70 (0.52–0.93)	0.69 (0.47–0.99)	1.09 (0.63–1.89)
Adjusted[a]	0.71 (0.51–0.98)	0.70 (0.47–1.04)	0.90 (0.49–1.66)

Data are presented as the hazard ratio (HR) with the 95%CI given in parenthesis

[a] Adjusted for other treatments and covariates related to the outcome. Of note, propensity analyses were performed on 1,007 matched pairs for the whole cohort, 300 matched pairs for SBP <120 mmHg, and 653 for SBP ≥120 mmHg

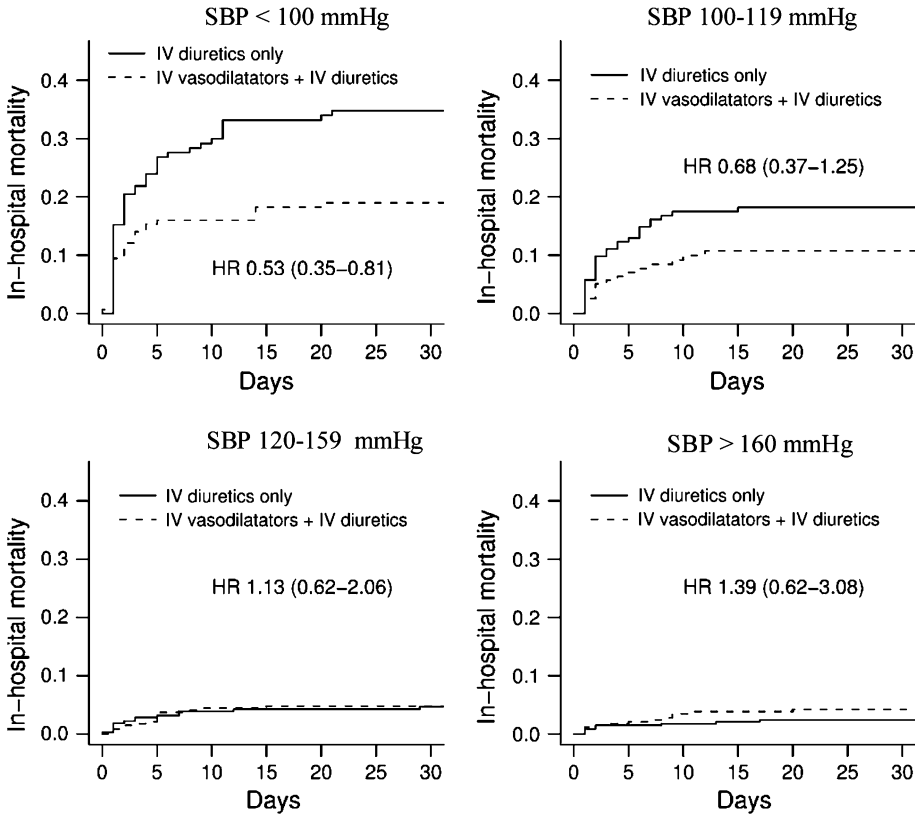

Fig. 2 Effects of IV vasodilators on in-hospital mortality of patients with various levels of systolic blood pressure (*SBP*). SBP ranged from <100 to ≥160 mmHg. The number of patients is 318, 334, 668 and 694 for SBP <100, 100–119, 120–159 and ≥160 mmHg respectively. *HR* Hazard ratio. Value *in parenthesis* is the 95% confidence interval

Table 3 Baseline characteristics before and after matching for patients who received any IV inotropes and/or IV vasopressors in the first 48 h versus other treatments and no inotropes in the first 48 h

Baseline characteristics	Before propensity score match Inotropes/vasopressors			After propensity score match Inotropes/vasopressors		
	Yes (n = 1,617)	No (n = 3,256)	Standardized difference (%)	Yes (n = 954)	No (n = 954)	Standardized difference (%)
Age (years)						
16–45	103 (6.5)	125 (3.9)	12.0	52 (5.5)	62 (6.5)	4.4
46–60	401 (25.4)	575 (17.8)	18.6	237 (24.8)	234 (24.5)	0.7
61–70	485 (30.7)	931 (28.8)	4.2	296 (31.0)	305 (32.0)	2.0
71–80	426 (27)	1,030 (31.9)	10.7	257 (26.9)	257 (26.9)	0.0
>80	163 (10.3)	569 (17.6)	21.1	112 (11.7)	96 (10.1)	5.4
Women	551 (34.9)	1,246 (39)	8.7	328 (34.4)	333 (34.9)	1.1
Weight (kg)	78 (70–88)	79 (70–90)	11.8	78 (70–88)	78 (70–88)	0.5
De novo AHF	640 (39.6)	1,145 (35.2)	9.1	326 (34.2)	323 (33.9)	0.7
Secondary AHF	495 (30.6)	681 (20.9)	22.3	253 (26.5)	249 (26.1)	1.0
Cardiogenic shock	425 (26.3)	149 (4.6)	63.0	133 (13.9)	111 (11.6)	6.9
Atrial fibrillation/flutter						
No	920 (57)	1,815 (55.8)	2.4	503 (52.7)	508 (53.2)	1.0
Acute	320 (19.8)	635 (19.5)	0.8	211 (22.1)	211 (22.1)	0.0
Chronic	55 (3.4)	99 (3.0)	2.1	31 (3.2)	31 (3.2)	0.0
Acute and chronic	318 (19.7)	701 (21.6)	4.6	209 (21.9)	204 (21.4)	1.3
Cardiovascular comorbidities						
Coronary artery disease	504 (31.4)	983 (30.4)	2.2	287 (30.1)	295 (30.9)	1.8
Chronic heart failure	546 (34)	1,178 (36.4)	5.0	375 (39.3)	368 (38.6)	1.5
Cardiomyopathy	242 (15.1)	374 (11.6)	10.3	135 (14.2)	141 (14.8)	1.8
Peripheral vascular disease	161 (10)	276 (8.5)	5.2	83 (8.7)	96 (10.1)	4.7

Table 3 continued

Baseline characteristics	Before propensity score match Inotropes/vasopressors			After propensity score match Inotropes/vasopressors		
	Yes (n = 1,617)	No (n = 3,256)	Standardized difference (%)	Yes (n = 954)	No (n = 954)	Standardized difference (%)
Heart valve disease	210 (13.1)	481 (14.9)	5.2	138 (14.5)	126 (13.2)	3.6
Obesity	424 (26.4)	856 (26.4)	0.1	260 (27.3)	257 (26.9)	0.7
Diabetes	768 (47.8)	1,424 (44.0)	7.7	473 (49.6)	490 (51.4)	3.6
Dyslipidemia	692 (43.1)	1,361 (42.0)	2.1	408 (42.8)	399 (41.8)	1.9
Hypertension	1,084 (67.5)	2,317 (71.6)	8.9	668 (70)	664 (69.6)	0.9
Symptoms and signs						
Cold extremities	685 (42.8)	580 (18.0)	56.0	304 (31.9)	318 (33.3)	3.1
Dyspnoea at rest	1,152 (71.9)	2,397 (74.2)	5.1	704 (73.8)	684 (71.7)	4.7
Fatigue	668 (41.7)	1,469 (45.5)	7.6	435 (45.6)	413 (43.3)	4.6
Orthopnoea	889 (55.5)	1,856 (57.4)	3.9	558 (58.5)	553 (58.0)	1.1
Peripheral edema	634 (39.6)	1,461 (45.2)	11.4	411 (43.1)	411 (43.1)	0.0
Jugular venous distension	714 (44.6)	1,270 (39.3)	10.7	425 (44.5)	422 (44.2)	0.6
Rales	1,025 (64)	1,970 (61)	6.2	615 (64.5)	604 (63.3)	2.4
Weight gain	318 (19.9)	900 (27.9)	18.9	225 (23.6)	218 (22.9)	1.7
NYHA functional class						
I	31 (1.9)	41 (1.3)	5.3	16 (1.7)	15 (1.6)	0.8
II	110 (6.8)	340 (10.4)	13.0	66 (6.9)	75 (7.9)	3.6
III	437 (27)	1,288 (39.6)	26.8	303 (31.8)	293 (30.7)	2.3
IV	655 (40.5)	1,063 (32.6)	16.4	370 (38.8)	361 (37.8)	1.9
Not specified or developed						
AHF in hospital	384 (23.7)	524 (16.1)	19.2	199 (20.9)	210 (22.0)	2.8
Systolic blood pressure (mmHg)	100 (85–140)	140 (110–170)	78.3	120 (100–150)	120 (100–155)	2.8
Heart rate (bpm)	110 (93–125)	105 (90–120)	12.3	110 (90–120)	110 (90–120)	2.5
Serum concentrations						
Sodium (mmol/l)[a]	136 (132–140)	138 (134–140)	8.9	136 (132–140)	137 (132–140)	4.0
Creatinine (mg/dl)[a]	1.4 (1–1.9)	1.2 (0.9–1.6)	8.1	1.4 (1–1.8)	1.3 (1–1.8)	2.2
Uric acid (mg/dl)[a]	6 (1.3–7.9)	6 (1.3–8)	5.5	6 (1.3–7.5)	6 (1.4–7.9)	7.7
Oxygen saturation (%)[a]	89 (83–92)	90 (85–93)	19.4	90 (85–92)	90 (85–92)	0.7
LVEF (%) mean (SD)[a]	33.9 (14.2)	40.4 (13.9)	46.0	35.1 (14.0)	37.5 (13.9)	17.0
Beta-blockers pre-admission	487 (30.1)	1,149 (35.3)	11.0	318 (33.3)	335 (35.1)	3.8
ACEI pre-admission	372 (23.2)	1,125 (34.9)	26.1	259 (27.1)	252 (26.4)	1.7
IV inotrope[a]						
Dopamine	541 (33.5)	0 (0)		319 (33.4)	0 (0)	
Dobutamine	926 (57.3)	0 (0)		518 (54.3)	0 (0)	
Epinephrine	142 (8.8)	0 (0)		63 (6.6)	0 (0)	
Norepinephrine	164 (10.1)	0 (0)		89 (9.3)	0 (0)	
PDEI	48 (3.0)	0 (0)		23 (2.4)	0 (0)	
Levosimendan	234 (14.5)	0 (0)		156 (16.4)	0 (0)	
CPAP	234 (23.4)	242 (7.3)	–	145 (15.1)	107 (11.2)	–
Outcome[a]						
Discharge	964 (59.6)	2,642 (81.1)		632 (66.2)	760 (79.7)	
Death	375 (23.2)	148 (4.5)		177 (18.6)	76 (8.0)	
Transfer (ICU or other hospital)	278 (17.2)	466 (14.3)		145 (15.2)	118 (12.4)	
In-hospital mortality rate (95% CI)	25.9 (23.5–28.2)	5.2 (4.4–6.1)		20.6 (17.8–23.4)	9.0 (7.0–11.0)	

Data are presented as a number (n) with the percentage in parenthesis, or as the median with the inter-quartile range (IQR, Q1–Q3) in parenthesis, unless specified otherwise

[a] Not used for propensity score development

However, several parameters, including the SBP at admission, the severity of AHF, or the incidence of cardiogenic shock, were different between patients receiving inotropes and/or vasopressors and those who did not receive them. Propensity-based matching produced 954 matched pairs with standardized differences in patient characteristics of less than 10%, indicating a successful balance between prognostic variables, with the exception of left ventricular ejection fraction (LVEF) drugs (Table 3 and Figure S1b of the ESM). LVEF data were missing for approximately 30% of patients and therefore not used for propensity score development. However, we did perform a sensitivity analysis in the subgroup of patients for whom the LVEF was recorded, as summarized below. Analysis on the matched pairs confirmed that IV catecholamines (dobutamine, dopamine, norepinephrine, or epinephrine)

Table 4 Characteristics of continuous infusion of IV inotropes and/or vasopressors administered in the first 48 h

IV inotropes and/or vasopressors	Dose (μg/kg/min)	Delay between admission and drug initiation (h)
Dopamine	3 (2–7)	1.5 (0.5–7.5)
Dobutamine	10 (5–14)	2 (0.5–6)
Epinephrine	0.5 (0.3–7.0)	2 (0.5–11.5)
Norepinephrine	0.8 (0.6–0.9)	3.5 (1–14)
Levosimendan	0.1 (0.1–0.2)	4 (1–22)

Data are given as the median dose with the IQR (Q1–Q3) in parenthesis
Data are recorded in more than 87% of the patients

use was associated with a several fold increase in the mortality rate and in the risk of in-hospital mortality (Table 5): a 1.5-fold increase for dopamine or dobutamine and a >2.5-fold increase for norepinephrine or epinephrine; both were compared to patients not receiving any inotrope and/or vasopressor. By contrast, levosimendan was associated with a reduced, although not statistically significant, risk of in-hospital mortality. Propensity-based results were further confirmed (1) on the 589 matched pairs obtained when adding LVEF for propensity score development, which produced well-balanced groups for LVEF (standardized difference 2.3%) and (2) when propensity scores were performed on levosimendan use. In the latter analysis, propensity score matching produced 105 matched pairs of patients treated with levosimendan (<48 h after initiation of therapy) or not receiving any inotrope and/or vasopressor; the HR was 0.64 (95% CI 0.18–2.34). Lastly, a propensity-based analysis was performed to compare in-hospital mortality of patients treated only with IV levosimendan versus those treated only with catecholamine within 24 h of therapy initiation. Propensity score matching produced 104 matched pairs and showed that the use of levosimendan resulted in a significant reduction in the risk of in-hospital mortality (HR 0.25, 95% CI 0.07–0.85).

Discussion

Our analyses used propensity matching to reveal new risk–benefit patterns for in-hospital IV treatments for patients with AHF. We found that a regimen with an IV vasodilator combined with a diuretic was more favorable than treatment with a diuretic alone. This finding is based on better in-hospital survival rates, particularly in patients with normal or low SBP at admission. In contrast, we found that AHF patients had an 1.5-fold increased risk of in-hospital death when treated with dopamine or dobutamine and a greater than 2.5-fold increased risk of in-hospital death when treated with norepinephrine or epinephrine. A decreased risk of in-hospital death was, however, found when patients were treated with levosimendan.

To date, a limited number of studies have been designed to directly test the efficacy and safety of specific drug regimens in patients with acute heart failure. Marginal benefits and mixed outcomes are common findings among the studies that have been performed [18–28].

IV vasodilators

Three IV vasodilators, namely, nitroglycerin, nitroprusside, and nesiritide, are recommended by all national and international cardiological societies in the early treatment of AHF in patients with SBP >110 mmHg [1, 3]. These recommendations are based on level B evidence (single randomized or large non-randomized studies), largely due to the fact that there are no large-scale randomized

Table 5 Outcome analysis for in-hospital mortality by use of IV inotropes and/or vasopressors during the first 48 h

Outcome analysis	Any inotrope/ vasopressor	Individual effect of inotropic and/or vasopressor agents				
		Dopamine	Dobutamine	Epinephrine	Norepinephrine	Levosimendan
Analysis on the whole cohort						
Unadjusted	5.34 (4.41–6.46)	2.48 (2.03–3.02)	2.78 (2.33–3.32)	4.16 (3.19–5.41)	2.88 (2.23–3.72)	0.71 (0.46–1.09)
Adjusted[a]	3.01 (2.39–3.78)	1.62 (1.30–2.02)	2.15 (1.76–2.61)	2.73 (2.04–3.65)	1.74 (1.31–2.29)	0.79 (0.50–1.24)
Propensity analysis I[b]						
Unadjusted	2.53 (1.98–3.22)	1.48 (1.05–2.07)	1.88 (1.43–2.46)	4.26 (2.61–6.94)	2.84 (1.93–4.16)	0.55 (0.30–1.02)
Adjusted[a]	2.43 (1.87–3.17)	1.30 (0.92–1.85)	1.84 (1.40–2.41)	3.98 (2.55–6.23)	1.77 (1.15–2.73)	0.86 (0.49–1.52)
Propensity analysis II[b]						
Unadjusted	2.62 (1.83–3.74)	1.44 (0.91–2.28)	1.79 (1.25–2.56)	3.39 (1.48–7.74)	3.68 (2.23–6.08)	0.61 (0.28–1.36)
Adjusted[a]	2.48 (1.70–3.60)	1.54 (0.94–2.53)	1.64 (1.09–2.47)	2.84 (1.35–5.98)	2.15 (1.21–3.84)	0.98 (0.43–2.19)

Data are presented as hazard ratios, with the (95% CI in parenthesis)
[a] Adjusted for other treatments and all other covariates related to the outcome
[b] Propensity analysis I: LVEF and other variables with too many missing data were not used to construct the propensity score; II: propensity score using LVEF, in the subset without missing values

clinical trials of IV vasodilator on short-term outcome in AHF patients. A few small studies have shown that IV vasodilators relieve dyspnea and improve arterial oxygen saturation by reducing both left ventricular preload and afterload, leading to reduced pulmonary congestion [4–6]. Despite the expected beneficial effects on dyspnea and oxygen saturation, all IV vasodilators may carry the risk of hypotension. Nesiritide has also been associated with a trend for an increased 30-day mortality [18]. However, propensity analyses of a database with more than 99,000 patients hospitalized patients for AHF showed that neither nesiritide nor nitroglycerin in sequential use with a diuretic increased mortality rates when compared to monotherapy with a diuretic agent (ADHERE National Registry) [8].

In our study, we noted that the use of an intravenous vasodilator, mainly nitroglycerine, in a wide spectrum of propensity score-matched AHF patients was associated with a 30% decreased risk of in-hospital mortality. Interestingly, this beneficial effect of IV vasodilator is also seen in patients with a SBP <100 mmHg at admission. The latter result may seem contradictory to current guidelines. Indeed, based on the assumption that IV vasodilators should achieve the best benefit in AHF patients, even at the risk of hypotension, they have been recommended by the European Society of Cardiology/European Society of Intensive Care Medicine (ESC/ESICM) and the American College of Cardiology/American Heart Association (ACC/AHA) in AHF patients with SBP >110 mmHg (1, 3, 29). The paradoxical beneficial effect of IV vasodilators in patients with normal or low SBP may be related to a higher mortality rate in those patients compared patients with SBP ≥120 mmHg.

A negative impact of IV vasodilators cannot be excluded, especially in some patients with severe coronary artery disease [30]. However, our study shows that in the subgroup of patients with normal or even low SBP at presentation, the administration of IV vasodilators was associated with favorable in-hospital outcomes. The mechanism of the beneficial effect of IV vasodilators, mostly nitrates, on in-hospital mortality remains to be elucidated and may include a decrease in dyspnea leading to a decrease in body oxygen consumption and an improvement in arterial oxygenation.

Nitrates, as NO-donors, may also have direct beneficial effects on diastolic properties of the heart and on mitochrondial function by opening the K_{ATP} channel and reducing mitochondrial Ca^{2+} loading [31–33]. In our study group, all patients receiving IV vasodilators also received IV diuretics. Diuretics have been suspected to have unfavorable effects on renal function and outcome mediated through the activation of the neuroendocrine system or extensions of common clinical adverse events, such as worsening kidney function [35–37]. Another potential hypothesis in terms of the favorable effect of IV vasodilators on short-term outcome may therefore be that IV vasodilators prevent these unfavorable effects of diuretics, especially in patients with low SBP at admission.

Catecholamines

The ESC/ESICM and ACC/AHA recommend the use of inotropic agents in AHF patients presenting with signs of low cardiac output, hypoperfusion, or congestion [1, 3]. Inotropes, which are used for their short-term hemodynamic benefits, have been frequently shown to have little or no effect on clinical outcomes. Indeed, despite their expected beneficial effect on cardiac output and/or blood pressure, all inotropes and vasopressors may carry the risk for increased myocardial ischemia and arrythmias, leading to a detrimental effect on short-term outcome [1, 8–11]. However, data are limited, and the interpretation of findings are often skewed by the fact that positive inotropes are administered to the most severe cases of AHF patients who already carry a high risk of death. Using the propensity score technique in this study, which addressed selection and residual biases, we demonstrated that the use of an IV positive inotropic agent was associated with an increased risk of in-hospital death.

More importantly, our study is the first to compare the five most commonly used inotropic agents and vasopressors and to show important differences in their effect on short-term outcome. Based on our results, we have classified those agents and their effects into three categories: (1) epinephrine and norepinephrine markedly worsen the risk of in-hospital death; (2) dopamine and dobutamine moderately worsen the risk of in-hospital death; (3) levosimendan had no or a slight beneficial effect on the risk of in-hospital death, in line with recent publications [38, 39] and possibly due to the vasodilator properties of this agent.

Limitations

Our study has several limitations. Propensity score methodology allowed us to balance groups according to variables that were recorded in the ALARM-HF study. If factors associated with the administration of a specific treatment were unavailable, this could result in a bias in the estimates of treatment effectiveness. Nevertheless, our study included factors known to influence the decision to treat AHF with IV vasodilators, or IV inotropes, and/or IV vasopressors (SBP, signs of cardiogenic shock). Our data were retrospectively collected in ALARM-HF, leading to a potential bias. However, it should be noted that although this was a retrospective study, the CRF were filled out immediately after discharge of the patients by the attending physicians, which was advantageous to data

collection in terms of accuracy. On this note it cannot be overlooked that some centers recorded data differently than the majority of the other centers. However, the number of patients was limited to five to eight per center, and centers and countries were accounted for in the propensity score development. Thus, the impact of any one particular center should be limited in most cases. Furthermore, the associations were strong and consistent among the different analyses conducted (unadjusted, adjusted, and different propensity scores). The use of IV vasodilators was associated with a decreased risk in in-hospital mortality in patients with normal or low SBP at admission. We did not record SBP during the course of hospitalization and, therefore, no information was available on the time course of SBP during IV vasodilator therapy. Furthermore, the effect of IV vasodilator therapy was tested by comparing diuretic + vasodilator therapy versus diuretic alone therapy; it is likely that the results can be extended to the patients excluded because they did not receive any IV diuretics.

Conclusions

Our study, based on ALARM-HF data, revealed observable associations between the use of IV vasodilators, mostly nitrates, and beneficial effects on in-hospital outcome in a wide spectrum of AHF patients hospitalized in nine different countries. This effect was the most striking in AHF patients with a normal or low SBP. This finding is based on a non-randomized design, is largely hypothesis generating, and calls for similar analyses with larger, multinational databases. Most importantly, these finding need to be confirmed in the setting of a prospective randomized clinical trial. We also observed associations between four IV catecholamines, namely, epinephrine, norepinephrine, dopamine, and dobutamine, and poor in-hospital outcome in this large multinational AHF cohort. The use of levosimendan did not incur a higher risk of in-hospital mortality. This study therefore brings to light the fact that existing guidelines need to be revisited in order to bring safety to the treatment of AH patients. Based on our results, we advocate for a wider use of agents with vasodilator properties and a very limited use of catecholamines in AHF patients.

Conflict of interest AM, JP, FVB, JFD and FF received an honorarium from Abbott for lectures and/or consulting. Abbott funded the ALARM-HF survey; data were acquired by IMS. Analyses were performed by the Département de Biostatistique et Informatique Médicale, Hôpital Saint-Louis, APHP, Université Paris 7, INSERM—UMR-S 717, Paris France by RP and EG.

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