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International variations in the clinical, diagnostic, and treatment characteristics of emergency department patients with acute heart failure syndromes

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Aims Results from investigations in one area of the world may not translate to another if patient characteristics and practices differ. We examine differences in the presentation and management of emergency department (ED) patients with dyspnoea from acute heart failure syndromes (AHFS) between the USA, Western Europe, and Eastern Europe.

Methods and results The URGENT Dyspnoea study was a multinational prospective observational study of dyspnoeic ED patients with AHFS from 18 countries. Acute heart failure syndrome patients from the USA and Western and Eastern Europe underwent dyspnoea assessments within 1 h of the first physician evaluation. Patient characteristics, evaluation, and treatments were compared between geographical regions using analysis of variance and χ^2 tests. Four hundred and ninety-three patients with AHFS met the inclusion criteria. Participants in the USA were more frequently non-white, younger, on chronic beta-blocker therapy, and with an ejection fraction $\leq$40% when compared with Eastern and Western Europe. Patients from Eastern Europe were more likely to present with *de novo* heart failure and have ischaemic electrocardiogram changes. Pulmonary oedema was more common on chest radiograph in Western Europe, but natriuretic peptide levels were elevated in all three regions. Diuretic use was similar across all the regions. Intravenous nitroglycerin was used more frequently in Eastern (32.8%) and Western Europe (24.4%) compared with the USA (2.5%).

Conclusion International differences in AHFS presentations and management between regions suggest results from clinical trials in one region may not translate directly to another. These differences should be considered when designing trials and interpreting the results from clinical investigations.

Keywords Heart failure • Emergency • Geographical differences

Introduction

Differences between countries and regions in demographics, clinical characteristics, treatment patterns, and outcomes have been described for hospitalized patients with AHFS.[1–5] However, one commonality across patients with acute heart failure syndromes (AHFS) is frequent presentation to the emergency department (ED) for initial evaluation and treatment. This initial phase of

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management has typically been overlooked in prior AHFS study design, resulting in limited understanding of early therapeutic management and its downstream effects. Whether geography further highlights variation during the ED phase of management has not been well-delineated. Although clinical trials often recruit patients globally, there is a paucity of information to help caregivers generalize results of clinical investigations conducted outside their region in order to improve the emergent evaluation and treatment of AHFS.

Recent clinical trials have suggested that standard therapy rapidly improves dyspnoea in a majority of patients.[6–8] However, the speed and magnitude of improvement as a result of standard therapy has not been prospectively studied, and how findings from one trial can be extrapolated to the care of individual patients' remains unclear. The goal of the Ularitide Global Evaluation in Acute Decompensated Heart Failure (URGENT) Dyspnoea Study was to better understand how acute standard therapy impacts dyspnoea in AHFS.[9] Owing to its multinational nature, information from this study may provide an opportunity to determine differences in AHFS presentation and management between various regions of the world. We conducted this secondary analysis to describe the international variations in the presentation and management of ED patients with dyspnoea secondary to AHFS.

Methods

Study design and setting

URGENT Dyspnoea has been described previously.[9,10] Briefly, this was a multinational, observational, prospective cohort study, conducted at tertiary care, and community hospitals in 18 countries, which evaluated the effect of conventional AHFS therapy on self-assessed dyspnoea during the earliest hospital phase of AHFS care. The majority of the North American hospitals were tertiary care, urban, and academic medical centres. All of the hospitals in North America were associated with residency training programmes and all of the EDs in these hospitals had emergency medicine residents participating in patient care as well as enrolling subjects in the study. The majority of enrolling hospitals in Western Europe and Eastern Europe were university-affiliated institutions. The entire list of hospitals and investigators has been previously acknowledged.[9] The study was originally designed to precede the phase 3 programme with ularitide. This investigational agent was not used at any time during this study. Agents used to treat AHFS were at the discretion of the treating physician, however, investigational therapeutic agents were not allowed. Patients were enrolled by either attending physicians or physicians in training within 1 h of physician evaluation in an ED or equivalent acute care setting.

Patients

Inclusion and exclusion criteria were sufficiently broad to include patients in whom AHFS was initially suspected. AHFS was then confirmed or refuted by the investigator 6 h after enrolment, utilizing all available data. Eligible patients were 18 years or older, able to give written informed consent, with signs and symptoms of AHFS and able to self-assess dyspnoea within 1 h of initial physician evaluation. Patients were included in this secondary analysis if they were enrolled in one of 18 countries in Western Europe or Eastern Europe, or in the USA, and had a final diagnosis of AHFS as determined by the investigator at 6 h after enrolment. The study complied with the Declaration of Helsinki, and institutional review board and/or ethics committee approval was obtained from each centre.

Study protocol and data collection

Dyspnoea was assessed with three instruments:

(i) a 5-point Likert scale done at the time of enrolment (baseline) and 6 h later: (a) not short of breath, (b) mildly short of breath, (c) moderately short of breath, (d) severely short of breath, (e) very severely short of breath;
(ii) a 7-point Likert scale administered at 6 h after baseline to determine the change from baseline: (a) markedly worse, (b) moderately worse, c) minimally worse, (d) no change, (e) minimally improved, (f) moderately improved, (g) markedly improved;
(iii) a 10 cm visual analogue scale (VAS) score done at baseline and 6 h later. *A priori*, this line was divided into 10 equal 1 cm increments, 0–10. If patients marked anywhere within a centimetre increment, it was counted as that centimetre (i.e. 26 mm = 3 cm, 21 mm = 3 cm).

Scales were translated into local languages as needed. If the subject was intubated at the time of the second dyspnoea test, this was indicated on the data collection form and the second dyspnoea test was not administered. It was recommended that the same physician make the assessment at baseline and 6 h.

Other data collected prospectively included demographics, medical history, patient reported signs and symptoms, physical examination, and electrocardiogram (ECG) findings as documented by the treating physician. Vital signs were obtained within 1 h of each dyspnoea test. Medications administered and use of non-invasive ventilation in the ED and prior to arrival were recorded. Laboratory tests and chest radiography (CXR) findings were obtained by medical record review. The radiology reading of the CXR was taken as the criterion standard. All patient evaluation and treatment was at the treating physician's discretion. There were no pre-specified criteria required to make an AHFS diagnosis; the final diagnosis of AHFS was determined by the care provider based on all available data present at the 6 h assessment. Available data included, for example, physical examination, CXR, B-type natriuretic peptide (BNP) or NT-proBNP, troponin, medications administered, and medical records. The physician's impression as to factors precipitating AHFS as well as patient disposition at the end of their acute presentation was also prospectively documented.

Statistical analysis

Data are described using medians and ranges or means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Variables from different geographical regions were compared between the three different regions: USA, Western Europe, and Eastern Europe. Analysis of variance (ANOVA) was used to analyse variables with continuous outcome measures, and χ^2 tests were used to analyse variables with proportional outcome measures. The critical *P*-value was set to 0.05; *post hoc* two-group comparisons used a Bonferroni adjusted *P*-value. Owing to the multiple comparisons, a highly conservative critical *P*-value of 0.008 can be used to maintain the overall type 1 error rate at 5%. Analyses were done with SPSS version 17 (SPSS Inc., Chicago, IL, USA).

Results

International origin of study subjects

From 1 January 2007 to 31 Aug 2007, 776 patients with suspected AHFS from 18 countries were enrolled. Of these, 524 (68%) had AHFS diagnosed at 6 h and 79 (10%) did not. For the remaining 173 (22%) patients, the diagnosis was indeterminate or was left

unmarked on the case report form at the 6 h time-point. There were 31 of 524 AHFS patients from South America excluded from this analysis, leaving 493 patients with AHFS from 28 sites eligible for inclusion: 122 (24.7%) from the USA, 293 (59.4%) from Eastern Europe, and 78 (15.8%) from Western Europe (*Table 1*).

Similarities and differences in patient characteristics, precipitating factors, signs, and symptoms

Patients from all regions were similar with respect to gender, and outpatient use of ACE inhibitors, diuretics, angiotensin II receptor blockers, and statins. Emergency department patients with AHFS from the USA were significantly more likely to be non-white, younger, prescribed chronic beta-blocker therapy as outpatients, and have an ejection fraction $\leq$40%; they were less likely to have valvular disease (*Table 2*). Patients from the USA were less likely to present with an arrhythmia, but more likely to have non-adherence as the precipitating factor of their AHFS. Patients from Eastern Europe were more likely to present with *de novo* heart failure. Those from Western Europe were less likely to have uncontrolled hypertension as a precipitating factor of their AHFS.

Vital signs tended to be similar between regions, although the respiratory rate was slightly higher in Western Europe. Physical signs of congestion were present in the majority of patients, but patients from Eastern Europe were more likely to have jugular venous distension and less likely to have peripheral oedema, while those from Western Europe were more likely to have rales. At the time of initial ED evaluation, patient self-perceived dyspnoea was higher in Eastern and Western Europe compared with the USA ($P < 0.001$; *Figure 1*). Although dyspnoea levels were not significantly different between the three cohorts at the 6 h evaluation, the magnitude of change was significantly greater in Eastern and Western Europe compared with the USA ($P < 0.001$).

Table 1 Distribution of study subjects by country

Country	ED study sites	Subjects, *n* (%)
Belgium	2	8 (1.6)
Bulgaria	1	52 (10.5)
Croatia	1	14 (2.8)
Czech Republic	1	98 (19.9)
Finland	1	1 (0.2)
France	6	30 (6.1)
Germany	3	17 (3.4)
Poland	1	6 (1.2)
Romania	1	55 (11.2)
Slovakia	1	59 (12.0)
Spain	1	22 (4.5)
USA	8	122 (24.7)
Ukraine	1	9 (1.8)
Total	28	493 (100)

International variations in diagnostic characteristics

Congestion on CXR was common across all three regions, but the proportion of CXRs interpreted as having pulmonary oedema was greater in patients from Western Europe than those in the USA and Eastern Europe (42.4% vs. 21.8% and 19.7%, respectively; *Table 3*) Ischaemic changes on ECG were seen more often in AHFS patients in Eastern Europe than those in the USA and Western Europe (29.6% vs. 9.2% and 9.1%, respectively). Similarly, atrial fibrillation or atrial flutter was more common in Eastern and Western Europe than in the USA (26.0% and 28.9% vs. 10.9%). Creatinine values were higher in the USA, blood urea nitrogen (BUN) values were higher in Western Europe, and there was a trend toward lower serum sodium values in Eastern and Western Europe. B-type natriuretic peptide was utilized in a greater proportion of patients in the USA, while NT-proBNP was utilized more in Eastern and Western Europe. Natriuretic peptides were significantly elevated in patients from all three regions.

International variations in acute therapy and disposition

Intravenous loop diuretics were administered to the majority of patients in all three international regions (*Table 4*). Although intravenous vasodilators were used significantly more often in Eastern and Western Europe, topical nitrates were used more commonly in the USA than Eastern and Western Europe. Inotropic agent and vasopressor use was infrequent in all regions but their use was proportionally greater in Eastern Europe. There was a significantly greater proportion of patients admitted to a monitored setting in the USA (56.7%) than in Western Europe (4.5%) or Eastern Europe (3.6%). Further, there was a significantly greater proportion of patients admitted to the intensive care unit (ICU) in Eastern Europe (60.6% vs. 23.3% and 22.3% for the USA and Western Europe, respectively). Unmonitored floor bed utilization was the greatest in Western Europe (64.2% vs. 14.2% and 30.5% for the USA and Eastern Europe, respectively; *Table 4*).

Discussion

Our study suggests there are differences in characteristics and management of AHFS patients presenting to EDs in the USA, Western Europe, and Eastern Europe. These findings are consistent with similarly highlighted geographical differences in other heart failure studies that have focused on inpatient and post-discharge characteristics.[1,11,12] In aggregate, these findings suggest that patient characteristics starting at ED presentation and continuing through post-discharge follow-up vary substantially based on the geographic region, and should be considered when designing clinical trials as well as interpreting their results. Since the aetiologies, precipitating factors, and co-morbidities of AHFS presentations are very heterogeneous across the three regions studied, interventions and treatments in one region might be more or less effective in the other regions. Patient-perceived dyspnoea at the initial evaluation was higher in Eastern and Western Europe than in the USA and the severity of illness at the acute presentation (dyspnoea magnitude, pulmonary oedema on CXR, ischaemic ECG

Table 2 Baseline clinical characteristics of emergency department patients with acute heart failure syndromes by international region

Clinical characteristic	USA, *n* = 122	Western Europe, *n* = 78	Eastern Europe, *n* = 293	*P*-value
Demographics				
Mean age (years, s.d.)	63 (16)	78 (11)	68.8 (12)	<0.001
Gender (male)	67 (54.9%)	38 (48.7%)	172 (58.7%)	0.272
Race (white)	45 (36.8%)	74 (94.9%)	293 (100%)	<0.001
Co-morbidities				
Prior HF history	96 (78.7%)	53 (68.0)	151 (51.4%)	<0.001
Prior myocardial infarction	32 (26.2%)	15 (19.2%)	79 (27.0%)	0.373
Valvular disease	12 (9.8%)	21 (26.9%)	45 (15.4%)	0.005
LVEF < 40%	51 (57.3%)	7 (24.1%)	56 (45.5%)	0.007
Asthma/COPD	37 (30.3%)	18 (23.1%)	32 (10.9%)	<0.001
Prior coronary bypass grafts	21 (17.2%)	10 (12.8%)	9 (3.0%)	<0.001
Diabetes (insulin dependent)	37 (30.3%)	21 (26.9%)	26 (8.9%)	0.032
Renal insufficiency*	38 (31.1%)	25 (32.1%)	70 (23.9%)	0.173
Current medications				
Beta-blocker	84 (68.9%)	39 (50.0%)	159 (54.3%)	<0.001
ACE inhibitor	57 (46.7%)	31 (39.7%)	144 (49.1%)	0.334
Diuretic	89 (73.0%)	47 (60.3%)	185 (63.1%)	0.1
Angiotensin II receptor blocker	14 (11.5%)	12 (15.4%)	35 (12.0%)	0.673
Statins	42 (34.4%)	23 (29.5%)	72 (24.6%)	0.116
Aldosterone antagonist	6 (4.92%)	6 (7.70%)	41 (14.0%)	0.016
Digoxin	11 (9.02%)	8 (10.3%)	77 (26.3%)	<0.001
Coumadin	23 (18.9%)	15 (19.2%)	43 (14.7%)	0.444
Pacemaker	19 (15.6%)	4 (5.1%)	10 (3.4%)	<0.001
Precipitating factors				
Acute coronary syndrome	22 (18.0%)	12 (15.4%)	46 (15.7%)	0.821
Arrythmia	10 (8.2%)	15 (19.2%)	58 (19.8%)	0.013
Medication non-adherence	22 (18.0%)	5 (6.4%)	40 (13.7%)	0.065
Dietary non-adherence	18 (14.8%)	3 (3.9%)	30 (10.2%)	0.047
Hypertension	32 (26.2%)	14 (18.0%)	97 (33.1%)	0.024
Physical examination findings				
Jugular Venous distension	35 (28.7%)	33 (42.3%)	140 (47.8%)	0.002
Rales	61 (50.0%)	69 (88.4%)	197 (67.2%)	<0.001
Peripheral oedema	79 (64.7%)	50 (64.1%)	136 (46.4%)	<0.001
Vital signs				
Heart rate (per minute, s.d.)	85 (19)	92 (24)	92 (26)	0.021
Respiratory rate (per minute, s.d.)	22 (6)	26 (8)	21 (6)	<0.0001
Systolic blood pressure (mm Hg, s.d.)	143 (36)	149 (30)	143 (34)	0.3
Temperature (°F, s.d.)	97.6 (0.9)	97.9 (1.3)	97.9 (0.6)	0.002

Data are presented as medians and ranges or proportions and percentages unless otherwise indicated.
*Renal insufficiency as documented in the medical record or per patient report.
HF, heart failure; LVEF, left ventricular ejection; COPD, chronic obstructive pulmonary disease.

changes) was significantly different across the three regions. Whereas in-hospital and near-term events were not recorded as part of this study, the significantly higher use of intravenous vasodilators and intensive care admissions in Eastern and Western Europe perhaps suggest that either disease severity, resource availability, or the approach to treatment and risk-stratification of patients with AHFS is widely divergent across regions.

When comparing our data to recent registry and survey data from the USA and Western Europe, there are a number of similarities. Compared with other data, our patients from the USA were slightly younger and had a greater proportion of black patients.[13] However, male sex, medical co-morbidities, and outpatient medications were similar, with the exception of digoxin, which was used much less in our cohort. In comparison with a survey conducted in England, Wales, and Northern Ireland, our patients from Western Europe had similar proportions of males, outpatient medication use, with the exception of beta-blockers, and a similar number of patients in atrial fibrillation on their

electrocardiogram.[14] The rate of admission to unmonitored floor beds was also similar. Despite extensive variability in the methods for assessing dyspnoea, our data are consistent with others in demonstrating significant improvement in the first 24 h in a majority of patients. In the PROTECT pilot trial, age and elevated systolic blood pressure were associated with an increased likelihood of dyspnoea improvement.[15] This is consistent with a body of evidence suggesting vasodilators may be more efficacious in patients with elevated systolic blood pressure as compared with those with relatively normal systolic blood pressure.[16–19] Dyspnoea improvement has been the target of therapeutic trials using intravenous vasodilators and a proposal to standardize dyspnoea assessments in clinical trials has been suggested.[15,20,21] This would afford investigators the opportunity to compare changes in dyspnoea across both study design and the pharmacologic agent used.

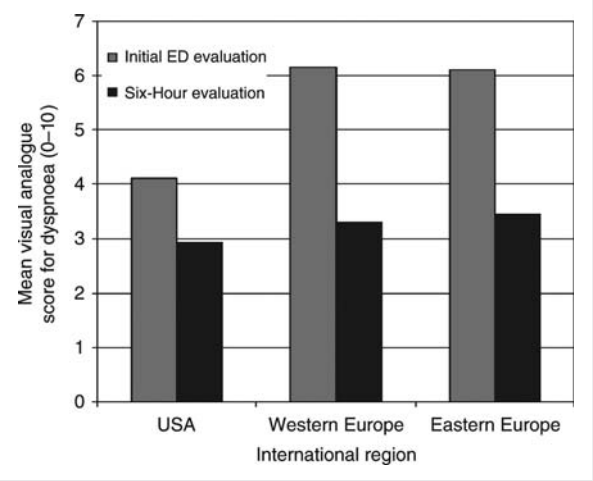

Figure 1 Visual analogue scale scores for dyspnoea at time of initial ED presentation and 6 h by international region.

Therapeutic trials must consider the impact of AHFS characteristics on their inclusion and exclusion criteria and ability to recruit patients. Moreover, when studying a novel therapeutic agent targeting dyspnoea improvement, investigators should consider that patients in Eastern and Western Europe may differ from those in the USA with regard to the severity of their dyspnoea and the magnitude of its improvement in response to standard therapy in the first 6–24 h.[10] Similar treatment and intervention strategies will likely result in different success rates between regions depending on the severity of underlying disease.

Table 3 Diagnostic characteristics of emergency department patients with acute heart failure syndromes by international region

Diagnostic Characteristic	USA (%)	Western Europe (%)	Eastern Europe (%)	*P*-value
Chest radiograph	$n = 119$	$n = 66$	$n = 147$	
Normal	10 (8.2%)	3 (3.85%)	0 (0.0%)	0.002
Cardiomegaly	18 (14.8%)	22 (28.2%)	71 (48.2%)	0.046
Cephalization	27 (22.2%)	1 (18.2%)	37 (25.2%)	0.039
Interstitial oedema	72 (60.5%)	42 (63.6%)	103 (70.1%)	<0.001
Pulmonary oedema	26 (21.8%)	28 (42.4%)	29 (19.7%)	<0.001
Pleural effusion	21 (17.6%)	22 (33.3%)	56 (38.1%)	0.135
Electrocardiogram	$n = 119$	$n = 77$	$n = 294$	
Normal	11 (9.2%)	16 (20.8%)	12 (4.1%)	<0.001
Sinus rhythm	54 (45.4%)	36 (46.8%)	182 (61.9%)	0.001
LBBB	10 (8.4%)	15 (19.5%)	42 (14.3%)	0.072
RBBB	8 (6.7%)	4 (5.2%)	24 (8.2%)	0.852
Paced rhythm	20 (16.8%)	4 (5.2%)	12 (4.1%)	<0.001
Atrial fibrillation or flutter	13 (10.9%)	20 (26.0%)	85 (28.9%)	<0.001
Ischaemic changes	11 (9.2%)	7 (9.1%)	87 (29.6%)	<0.001
Laboratory findings				
BNP done	117 (95.9%)	17 (21.8%)	4 (1.4%)	
NT-proBNP done	0	26 (33.3%)	64 (21.8%)	
BNP (pg/mL)	1258 (1263)	1126 (1031)	2850 (1215)	0.037
NT-proBNP (pg/mL)	0 (0)	7832 (7090)	11,274 (10,192)	0.120
Sodium (mmol/L)	138 (3)	133 (27)	133 (26)	0.937
BUN (mg/dL)	27.9 (20.6)	40.5 (43.7)	30.3 (30.6)	<0.001
Creatinine (mg/dL)	1.8 (2.1)	1.4 (0.8)	1.5 (1.1)	0.041

Data are presented as medians and ranges or proportions and percentages.
ECG, electrocardiogram; A fib/flutter, atrial fibrillation or atrial flutter; LBBB, left bundle branch block; RBBB, right bundle branch block; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen.

Table 4 Treatment and disposition characteristics of emergency department patients with acute heart failure syndromes by international region

Treatment	USA, $n = 122$	Western Europe, $n = 78$	Eastern Europe, $n = 293$	*P*-value
CPAP/BiPAP	7 (5.7%)	8 (10.3%)	5 (1.71%)	0.006
Intravenous diuretics				
Furosemide	94 (77.1%)	62 (79.5%)	237 (80.9%)	0.674
Bumetanide	0 (0.0%)	6 (7.7%)	0 (0.0%)	<0.001
Torasemide	0 (0.0%)	1 (1.3%)	1 (0.3%)	0.366
Intravenous vasodilators				
Nitroglycerin	3 (2.5%)	19 (24.4%)	96 (32.8%)	<0.001
Nitroprusside	1 (0.8%)	1 (1.3%)	0 (0.0%)	0.203
Nesiritide	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
Others				
Nitroglycerin SL	26 (21.3%)	1 (1.3%)	19 (6.5%)	<0.001
Nitroglycerin Topical	27 (22.1%)	6 (7.7%)	1 (0.3%)	<0.001
Sublingual ACEI	1 (0.8%)	1 (1.3%)	19 (6.5%)	0.012
Inotropes/Vasopressors				
Dobutamine	1 (0.8%)	1 (1.3%)	16 (5.5%)	0.034
Dopamine	0 (0.0%)	1 (1.3%)	16 (5.5%)	0.011
Disposition				<0.001
Home	7 (5.8%)	6 (9.0%)	5 (1.8%)	
Unmonitored floor	17 (14.2%)	43 (64.2%)	86 (30.5%)	
Monitored floor	68 (56.7%)	3 (4.5%)	10 (3.6)	
Intensive care unit	28 (23.3%)	15 (22.3%)	171 (60.6%)	
Died	0 (0%)	0 (0%)	10 (3.6%)	

Data are presented as proportions and percentages.
CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure; SL, sublingual; ACEI, angiotensin converting enzyme inhibitor.

These findings have important implications for comparisons of observational studies as well. Observational trials should consider differences in background therapy (beta-blockers), co-morbidities and AHFS aetiology (coronary artery disease, acute coronary syndromes, arrhythmias), and severity of initial presentation (pulmonary oedema and ischaemic ECG changes) when evaluating novel diagnostic and prognostic tools and their association with outcomes. In combination with previously published findings, these differences in AHFS presentations suggest that results from international diagnostic, prognostic, and therapeutic studies may only be applicable to specific subsets of patients.[1,11,12]

Although heterogeneity in AHFS presentations and aetiologies were apparent in this study, there are also many striking similarities. First and foremost, congestion (on physical exam and CXR) is commonly present at initial evaluation. Second, while patient-perceived dyspnoea was greater upon presentation in Eastern and Western Europe, patients in all three regions had similar levels of dyspnoea within 6 h of initial treatment, highlighting the perceived importance and congruity of early, sustained dyspnoea relief to both patients and physicians. Third, targeting congestion relief with intravenous diuretics is a cornerstone of therapy in all regions. Those patients in Eastern and Western Europe also received intravenous vasodilators significantly more often, possibly contributing to the similar dyspnoea scores at the 6 h assessment. Finally, inotropes and vasopressors are used in a minority of patients. These subtleties are important, especially when evaluating dyspnoea improvement or resolution as an endpoint in a therapeutic trial.

Limitations

Our results suggest important differences in the presentation and management of patients with AHFS, but the results should be interpreted considering the limitations of our data collection. Patients were enrolled prospectively and the majority of data were collected prospectively, which avoids biases inherent in many registries and retrospective chart reviews. However, based on the availability of study staff, only a convenience sample of patients was enrolled, and only at participating EDs, which may not be representative of the entire health system within a geographic region. It is not possible to extrapolate beyond the sample to comment on population-level of health system differences, nor does the sampling method allow us to comment on the disease burden among the populations served by each ED. Nonetheless, crude comparisons of treatment rates and demographics between regions provide sufficient evidence to formulate hypotheses about likely differences between regions. Moreover, the comparisons demonstrate that treatment trials conducted in one geographic region are not necessarily generalizable to other regions since practice patterns, populations, and disease state

may all vary between regions. Indeed, the sampling methodology, both in selecting participating EDs and in enrolling patients, may partly explain some of the differences observed between the findings in this study and those from registries such as ADHERE, OPTIMIZE, and EuroHeart Failure.[3,5,22] Whether the advantages of prospective data collection in ED patients outweigh the disadvantages of retrospective data collection in only those patients admitted, is unclear.

If there was circadian variability in AHFS presentations at the participating centres, this may have introduced bias. Further, we enrolled patients who were able to give consent, perhaps eliminating the most acute presentations. However, the proportion of patients with pulmonary oedema on CXR, VAS scores, and number of ICU admissions suggest that the continuum of disease severity was well represented. There was an unclear or missing diagnosis at the 6 h mark in about 20% of our study population. This missing data may have impacted the overall results if these patients differed from the included patients in any way. However, given the clear trends in the data we consider this possibility unlikely, and similarities between included and excluded patients on baseline variables further suggest this is unlikely to have been a cause of significant bias; there were no clinically significant differences in age (64 vs. 69 years), male sex (55.5% vs. 56.2%), systolic blood pressure (135 vs. 144 mmHg), heart rate (92 vs. 90 beats per minute), or respiratory rate (23 vs. 22 breaths per minute).

Several comparisons are somewhat limited by the disproportionately small number of patients in one or more of the groups. Although comparisons such as use of inotropic agents, bumetanide, and sublingual ACE-I appear to be statistically different between the three regions, they were used in such a small proportion of patients that the clinical significance of this is unclear.

Treatment for AHFS was not protocolized in this study and was at the discretion of the treating physician. The use of intravenous vasodilators may suggest increased disease severity in Eastern and Western Europe, but this may also reflect different practice patterns, different types of hospitals (tertiary care vs. community), and different health-care resources available such as the ICU or telemetry beds and the means of non-invasive ventilation. Further, admission decisions may have been influenced by systematic differences in bed availability rather than geographic location. However, the type of hospital bed and bed availability were not documented in the current study. Further, disease severity may have been impacted if AHFS patients with chronic heart failure bypassed the ED and were admitted directly to the hospital. Direct admissions were not tracked in this study. Differences in physician diagnoses rather than actual patient characteristics may also account for some of the observed results. Because there was no central criterion standard for the diagnosis of AHFS, there may have been a systematic bias between sites and regions in how they defined AHFS, which has the potential to confound our results. Patients were diagnosed as AHFS by treating physicians at the various sites, and recent findings suggest that the acute care physician's accuracy is over 90% for predicting an AHFS diagnosis, using the cardiology chart review as the criterion standard.[23] This would suggest any confounding by misclassification is likely to be small.

Conclusion

The presentation and early management of patients with AHFS differs between the USA, Western Europe, and Eastern Europe. These differences should be considered when designing and interpreting clinical investigations, since standard therapy, co-morbidities, risk profile, and disease severity may influence outcomes and the generalizability of results from one geographic region to another.

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