International Journal of Cardiology 344 (2021) 127–134

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Early intravenous nitroglycerin use in prehospital setting and in the emergency department to treat patients with acute heart failure: Insights from the EAHFE Spanish registry

Òscar Miró [a,b,*], Pere Llorens [c], Yonathan Freund [d], Beth Davison [e,f], Koji Takagi [e,f], Pablo Herrero-Puente [g], Javier Jacob [h], Francisco Javier Martín-Sánchez [i], Víctor Gil [a], Xavier Rosselló [j,k], Aitor Alquézar-Arbé [l], Francesc X. Jiménez-Fábrega [m], Josep Masip [n], Alexandre Mebazaa [b,f,o], Gad Cotter [e,f], on behalf of the EAHFE Research Group [1]

[a] Emergency Department, Hospital Clinic, Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Catalonia, Spain
[b] The GREAT (Global Research in Acute Contditions Team) Network, Via Antonio Serra 54, 00191, Roma, Italy
[c] Emergency Department, Short-Stay Unit and Home Hospitalization, Hospital General de Alicante, Spain
[d] Emergency Department, Hôpital Pitié-Salpêtrière, Assistance Publique - Hôpitaux 18 de Paris (APHP), Sorbonne Université, Paris, France
[e] Momentum Research, Inc., Durham, NC, USA
[f] INSERM U-942 (Biotherapy in the critically ill), Paris, France
[g] Emergency Department, Hospital Universitario Central de Asturias, Oviedo, Spain
[h] Emergency Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Catalonia, Spain
[i] Emergency Department, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC), Universidad Complutense de Madrid, Madrid, Spain
[j] Cardiology Department, Health Research Institute of the Balearic Islands (IdISBa), Hospital Universitari Son Espases, Palma, Spain
[k] Centro Nacional de Investigaciones Cardiovasculares (CNIC), Spain
[l] Emergency Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Catalonia, Spain
[m] Emergency Medical Services, SEM-Catalunya, Barcelona, Catalonia, Spain
[n] Consultant Research Direction, University of Barcelona, Catalonia, Spain
[o] Department of Anaesthesiology and Critical Care Medicine, AP-HP, Saint Louis and Lariboisière University Hospitals, Paris, France.

* Corresponding author at: Emergency Department, Hospital Clínic, Villarroel 170, 08036 Barcelona, Catalonia, Spain.
E-mail address: omiro@clinic.cat (Ò. Miró).

[1] **Investigators of the ICA-SEMES (Research group on Acute Heart Failure of the Spanish Society of Emergency Medicine):** Marta Fuentes, Cristina Gil (Hospital Universitario de Salamanca), Héctor Alonso, Enrique Pérez-Llantada (Hospital Marqués de Valdecilla de Santander), Francisco Javier Martín-Sánchez, Guillermo Llopis García, Mar Suárez Cadenas (Hospital Clínico San Carlos de Madrid), Òscar Miró, Víctor Gil, Rosa Escoda, Carolina Xipell, Carolina Sánchez, Alba Jerez, Joan Padrosa (Hospital Clínic de Barcelona), María José Pérez-Durá, Eva Salvo (Hospital Politècnic La Fe de Valencia), José Pavón (Hospital Dr. Negrín de Las Palmas de Gran Canaria), Antonio Noval (Hospital Insular de Las Palmas de Gran Canaria), José Manuel Torres (Hospital Reina Sofía de Córdoba), María Luisa López-Grima, Amparo Valero, María Ángeles Juan (Hospital Dr. Peset de Valencia), Alfons Aguirre, Maria Àngels Pedragosa, Silvia Mínguez Masó (Hospital del Mar de Barcelona), María Isabel Alonso, Francisco Ruiz (Hospital de Valme de Sevilla), José Miguel Franco (Hospital Miguel Servet de Zaragoza), Ana Belén Mecina (Hospital de Alcorcón de Madrid), Josep Tost, Marta Berenguer, Ruxandra Donea (Consorci Sanitari de Terrassa), Susana Sánchez Ramón, Virginia Carbajosa Rodríguez (Hospital Universitario Rio Hortega de Valladolid), Pascual Piñera, José Andrés Sánchez Nicolás (Hospital Reina Sofía de Murcia), Raquel Torres Garate (Hospital Severo Ochoa de Madrid), Aitor Alquézar-Arbé, Miguel Alberto Rizzi, Sergio Herrera (Hospital de la Santa Creu y Sant Pau de Barcelona), Javier Jacob, Alex Roset, Irene Cabello, Antonio Haro (Hospital Universitari de Bellvitge de Barcelona), Fernando Richard, José María Álvarez Pérez, María Pilar López Diez (Hospital Universitario de Burgos), Pablo Herrero Puente, Joaquín Vázquez Álvarez, Belén Prieto García, María García García, Marta Sánchez González (Hospital Universitario Central de Asturias de Oviedo), Pere Llorens, Patricia Javaloyes, Víctor Marquina, Inmaculada Jiménez, Néstor Hernández, Benjamín Brouzet, Begoña Espinosa (Hospital General de Alicante), Juan Antonio Andueza (Hospital General Universitario Gregorio Marañón de Madrid), Rodolfo Romero (Hospital Universitario de Getafe de Madrid), Martín Ruíz, Roberto Calvache (Hospital de Henares de Madrid), María Teresa Lorca Serralta, Luis Ernesto Calderón Jave (Hospital del Tajo de Madrid), Beatriz Amores Arriaga, Beatriz Sierra Bergua (Hospital Clínico Lozano Blesa de Zaragoza), Enrique Martín Mojarro, Brigitte Silvana Alarcón Jiménez (Hospital Sant Pau i Santa Tecla de Tarragona), Lisette Travería Bécquer, Guillermo Burillo (Hospital Universitario de Canarias de Tenerife), Lluís Llauger García, Gerard Corominas La Salle. (Hospital Universitari de Vic de Barcelona), Carmen Agüera Urbano, Ana Belén García Soto, Elisa Delgado Padial (Hospital Costa del Sol de Marbella de Málaga), Ester Soy Ferrer (Hospital Josep Trueta de Girona), José Manuel Garrido (Hospital Virgen Macarena de Sevilla), Francisco Javier Lucas-Imbernón (Hospital General Universitario de Albacete), Rut Gaya (Hospital Juan XXIII de Tarragona), Carlos Bibiano, María Mir, Beatriz Rodríguez (Hospital Infanta Leonor de Madrid), José Luis Carballo (Complejo Hospitalario Universitario de Ourense), Esther Rodríguez-Adrada, Belén Rodríguez Miranda (Hospital Rey Juan Carlos de Móstoles de Madrid).

https://doi.org/10.1016/j.ijcard.2021.09.031
Received 28 June 2021; Received in revised form 13 September 2021; Accepted 15 September 2021
Available online 20 September 2021

ARTICLE INFO

Keywords:
Acute heart failure
Nitrates
Nitroglycerine
Outcome
Mortality

ABSTRACT

Background and objective: Although recommended for the treatment of acute heart failure (AHF), the use of intravenous (IV) nitroglycerin (NTG) is supported by scarce and contradicting evidence. In the current analysis, we have assessed the impact of IV NTG administration by EMS or in emergency department (ED) on outcomes of AHF patients.

Methods: We analyze AHF patients included by 45 hospitals that were delivered to ED by EMS. Patients were grouped according to whether treatment with IV NTG was started by EMS before ED admission (preED-NTG), during the ED stay (ED-NTG) or were untreated with IV NTG (no-NTG, control group). In-hospital, 30-day and 365-day all-cause mortality, prolonged hospitalization (>7 days) and 90-day post-discharge combined adverse events (ED revisit, hospitalization or death) were compared in EMS-NTG and ED-NTG respect to control group.

Results: We included 8424 patients: preED-NTG = 292 (3.5%), ED-NTG = 1159 (13.8%) and no-NTG = 6973 (82.7%). preED-NTG group had the most severely decompensated cases of AHF ($p < 0.001$) but it had lower in-hospital (OR = 0.724, 95%CI = 0.459–1.114), 30-day (HR = 0.818, 0.576–1.163) and 365-day mortality (HR = 0.692, 0.551-0.869) and 90-day post-discharge events (HR = 0.795, 0.643–0.984) than control group. ED-NTG group had mortalities similar to control group (in-hospital: OR = 1.164, 0.936–1.448; 30-day: HR = 0.980, 0.819–1.174; 365-day: HR = 0.929, 0.830–1.039) but significantly decreased 90-day post-discharge events (HR = 0.870, 0.780–0.970). Prolonged hospitalization rate did not differ among groups. Five different analyses confirmed these findings.

Conclusions: Early prehospital IV NTG administration was associated with lower mortality and post-discharge events, while IV NTG initiated in ED only improved post-discharge event rate. Further studies are needed to assess the role of early prehospital administration of IV NTG to patients with AHF.

1. Introduction

The use of intravenous (IV) nitrates (nitroglycerine, NTG) for the treatment of acute heart failure (AHF) has been debated. Initially, a small study reported improved oxygenation, and reduced need for mechanical ventilation and other adverse events in patients with AHF and significant desaturation when high doses of IV nitrates were administered in the prehospital setting [1]. This was followed by a more generalized recommendation in the guidelines for the treatment of AHF for the use of IV nitrates for longer periods of time in the in-hospital setting during the first days of admission for AHF [2,3]. As pointed, this recommendation was made without significant supporting data [4]. Of recent, a prospective study (GALACTIC) has found no benefit in the administration of IV nitrates during the first few days of an AHF admission [5]. However, in the GALACTIC study, nitrates were not administered intravenously and did not result in reduction of blood pressure during the first day of administration, hence their dosing may have been insufficient to affect in significant benefits. In the current analysis, we have attempted to explore the effects of prehospital administration of nitrates on mortality and adverse events in the EAHFE (Epidemiology of AHF in Emergency departments) Spanish registry that includes patients diagnosed with AHF in emergency department (ED) consecutively included in sets of 1–2 months cohorts during last 15 years. In addition, we have also explored the effects of IV NTG when this is started in the ED.

2. Methods

2.1. Setting

The present study is a subanalysis of the EAHFE Registry [6–9]. The AHF diagnosis was based on the Framingham clinical criteria [10]. The initial patient inclusion and data recording was made by the attending emergency physician, and the principal investigator of every center retrospectively reviewed medical reports and was the responsibly for the final diagnostic adjudication at local level. They revised every case to check the compliance criteria of AHF and to confirm diagnosis by measurement of plasma natriuretic peptide and/or echocardiography during ED or hospital stay when possible following the current recommendations of the ESC Guidelines [2] and this was available in about 92% of cases. The EAHFE Registry does not include any planned intervention, and the management of patients is entirely based on the attending ED physician decisions.

2.2. Ethics

The EAHFE Registry protocol was approved by a central Ethics Committee at the Hospital Universitario Central de Asturias (Oviedo, Spain) with the reference numbers 49/2010, 69/2011, 166/13, 160/15 and 205/17. The present study was carried out in strict compliance with the Declaration of Helsinki principles.

2.3. Design and variables recorded

The present analysis included all patients in whom the form of arrival to ED was registered (this variable was recorded from the EAHFE-3 registry onwards). Of them, we selected those that were delivered to the ED by an ambulance provided by emergency medical services (EMS). Patients were classified into three groups: 1) patients receiving IV NTG which was started by prehospital EMS, before ED arrival (preED-NTG Group); 2) patients receiving IV NTG started in ED, after assessment by the attending physician (ED-NTG Group); and 3) patients that did not receive IV NTG during the urgent management, neither during prehospital phase by the EMS nor during their stay in the ED (no-NTG Group, controls). Sublingual or oral NTG administration was not considered. Doses and time duration of IV NTG used by EMS and in the ED were not recorded.

Independent variables consisted on baseline and current episode data prospectively recorded during patients ED stay. Data regarding clinical characteristics of the current AHF episode consisted on phenotype classification according congestion (wet or dry) and perfusion (cold or warm) [2,8], vitals at ED arrival, laboratory findings and lung congestion in chest X-ray. In addition, the severity of the current episode of decompensation was assessed through the MEESSI score, a clinical score that has demonstrated a very good prediction of the 30-day mortality in patients with AHF using clinical data recorded in the ED [5,6]. The MEESSI score is calculated recorded during the first patient assessment in the ED.

2.4. Outcomes

Five outcomes were assessed in the present study. Three outcomes referred to all-cause mortality (in-hospital and at 30 and 365 days). Vital status of patients was ascertained by consultation of medical records,

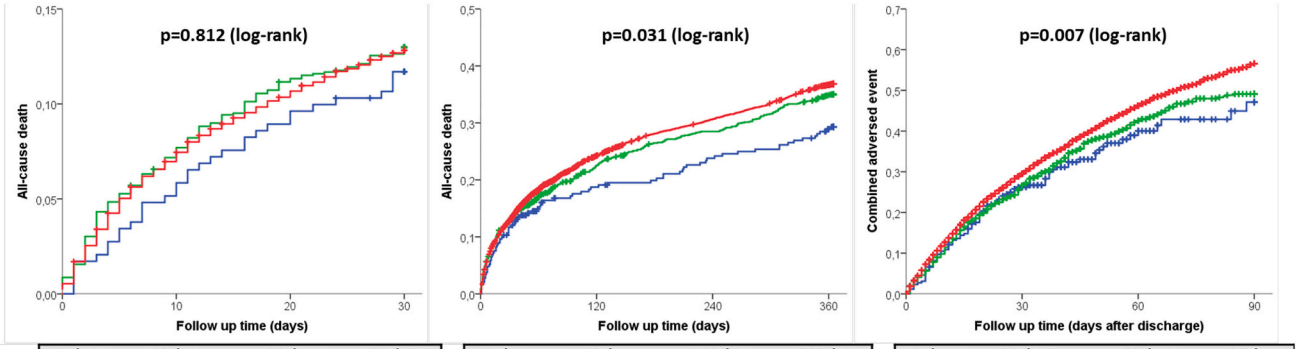
Table 1
Patients characteristics and comparison among the three groups according to intravenous nitroglycerine was provided by emergency medical services (preED-NTG Group), by emergency physicians in the emergency department (ED-NTG) or not provided at all (No-NTG Group).

	All patients N=8,424 n (%)	Missing values n (%)	preED-NTG Group N=292 n (%)	ED-NTG Group N=1,159 n (%)	No-NTG Group N=6,973 n (%)	P value
PATIENT BASELINE CHARACTERISTICS						
Demographic data						
Age (in years) (median (IQR))	84 (78-89)	3 (0.0)	80 (72-86)	82 (76-87)	84 (79-89)	**<0.001**
Sex: Male	3,481 (41.3)	18 (0.2)	138 (47.6)	466 (40.2)	2,877 (41.3)	0.07
Comorbidities						
Hypertension	7,127 (84.8)	15 (0.2)	252 (86.6)	1,010 (87.3)	5,865 (84.3)	**0.02**
Diabetes mellitus	3,495 (41.6)	17 (0.2)	146 (50.2)	565 (48.9)	2,784 (40.0)	**<0.001**
Coronary artery disease	2,417 (28.7)	15 (0.2)	137 (47.1)	375 (32.4)	1,905 (27.4)	**<0.001**
Chronic kidney failure (creatinine >2 mg/mL)	2,446 (28.7)	15 (0.2)	84 (28.9)	362 (31.3)	2,000 (28.7)	0.20
Cerebrovascular disease	1,175 (14.0)	15 (0.2)	41 (14.1)	165 (14.3)	969 (13.9)	0.95
Atrial fibrillation	4,176 (49.7)	14 (0.2)	104 (35.)	513 (44.3)	3,559 (51.1)	**<0.001**
Peripheral artery disease	820 (9.8)	15 (0.2)	48 (16.5)	162 (14.0)	610 (8.8)	**<0.001**
Heart valve disease	2,141 (25.5)	15 (0.2)	71 (24.4)	310 (26.8)	1,760 (25.3)	0.49
Chronic obstructive pulmonary disease	2,158 (25.7)	17 (0.2)	60 (20.6)	254 (22.0)	1,844 (26.5)	**0.001**
Dementia	1,304 (15.5)	15 (0.2)	32 (11.0)	137 (11.8)	1,135 (16.3)	**<0.001**
Active neoplasia	1,242 (14.8)	18 (0.2)	40 (13.7)	159 (13.8)	1,043 (15.0)	0.48
Previous episodes of acute heart failure	5,221 (63.8)	244 (2.9)	172 (59.7)	685 (60.3)	4,364 (64.6)	**0.007**
Baseline status						
NYHA class III/IV	2,224 (27.6)	380 (4.5)	61 (22.3)	282 (25.1)	1,881 (28.3)	**0.01**
Left ventricular ejection fraction (LVEF, %) (median (IQR))	55 (45-64)	3,606 (42.8)	50 (38-60)	55 (42-63)	55 (45-65)	**<0.001**
-LVEF <40%	838 (17.4)		47 (19.3)	131 (19.3)	660 (16.7)	
-LVEF 40-49%	645 (13.4)		35 (19.3)	96 (14.2)	514 (13.0)	
-LVEF ≥50%	3,335 (69.2)		99 (54.7)	451 (66.6)	2,785 (70.3)	
Barthel Index (points)* (median (IQR))	80 (60-100)	674 (8.0)	90 (65-100)	90 (60-100)	80 (60-100)	**<0.001**
Chronic treatments with disease-modifying drugs at home						
Beta-blockers	3,563 (43.2)	169 (2.0)	161 (55.7)	516 (44.9)	2,886 (42.3)	**<0.001**
Renin-angiotensin system inhibitors	4,599 (55.7)	164 (1.9)	183 (63.3)	678 (59.0)	3,738 (54.8)	**0.001**
Mineralcorticosteroid-receptor blockers	1,245 (15.1)	164 (1.9)	39 (13.5)	145 (12.6)	1,061 (15.6)	**0.03**
CLINCAL CHARACTERISTICS OF THE ACUTE HEART FAILURE EPISODE						
Clinical phenotype		0 (0)				**<0.001**
Warm & wet	6,572 (78.0)		189 (64.7)	833 (71.9)	5,550 (79.6)	
Cold & wet	942 (13.5)		83 (28.4)	282 (24.3)	942 (13.5)	
Warm & dry	465 (5.5)		14 (4.8)	35 (3.0)	416 (6.0)	
Cold & dry	80 (0.9)		6 (2.1)	9 (0.8)	65 (0.9)	
Vitals at ED arrival (median (IQR))						
Systolic blood pressure	139 (121-158)	76 (0.9)	159 (134-185)	153 (134-175)	137 (120-154)	**<0.001**
Heart rate	86 (72-103)	170 (2.0)	93 (76-110)	88 (75-108)	85 (71-101)	**<0.001**
Pulse-oxymetry	93 (89-96)	164 (1.9)	93 (87-97)	93 (88-96)	94 (90-96)	**0.002**
Laboratory findings						
Hemoglobin (g/L) (median (IQR))	119 (106-133)	72 (0.9)	121 (109-137)	119 (105-134)	119 (106-132)	**0.009**
Creatinine (mg/dL) (median (IQR))	1.15 (0.88-1.59)	105 (1.2)	1.18 (0.92-1.54)	1.17 (0.90-1.60)	1.15 (0.87-1.59)	0.13
Sodium (mmol/L)	139 (136-141)	200 (2.4)	138 (136-141)	139 (136-141)	139 (136-141)	0.28
Potassium (mmol/L)	4.4 (4.0-4.8)	525 (6.2)	4.3 (3.9-4.8)	4.4 (4.0-4.8)	4.4 (4.0-4.8)	0.88
NT-proBNP (pg/L) (median (IQR))	4,444 (2,089-9,523)	4,196 (49.8)	4,050 (2,167-9,325)	4,405 (2,070-9,449)	4,456 (2,088-9,541)	0.93
Raised troponin (>99th percentile)	2,602 (56.6)	3,825 (45.4)	145 (60.9)	411 (58.6)	2,046 (55.7)	0.07
Lung congestion in chest X-ray						
Interstitial and/or alveolar edema	1,371 (30.2)	3,890 (46.2)	89 (57.4)	231 (52.0)	1,051 (26.7)	**<0.001**
SEVERITY OF THE ACUTE HEART FAILURE EPISODE						
MEESSI-AHF risk score						**0.004**
Predicted 30-day mortality (in %, 95% CI)	8.7 (8.4-9.0)	2,935 (34.8)	11.1 (9.4-13.1)	9.1 (8.4-10.2)	8.5 (8.2-8.9)	
Low risk category	1,654 (30.2)		51 (24.4)	257 (29.5)	1,349 (30.6)	
Intermediate risk category	2,325 (42,4)		82 (39.2)	364 (41.8)	1,876 (42.5)	
High risk category	745 (13.6)		38 (18.2)	132 (15.2)	577 (13.1)	
Very high risk category	761 (13.9)		38 (18.2)	117 (13.4)	608 (13.8)	

Bold p values denote statistical significance ($p < 0.05$).

* *The higher the score, the better the patient functional status (range of the score: 0 to 100 points).*

which is electronically accessible in nearly all Spanish communities. In addition, we contacted with patients when no clear data was present in the clinical history or access was not possible, as at the time of patient inclusion into the EAHFE Registry they provide phone numbers and permission to be called. Death was also ascertained through the Spanish database of public health insurance, that covers >99% of Spanish population, as every patient dying is immediately retired of such a database at the exact time point that death occurs. The forth outcome consisted on prolonged hospitalization. This outcome was adjudicated when patient had been hospitalized, discharged alive and length of hospitalization was longer than 7 days, according to previous studies [7,11]. Patients directly discharged from the ED and those dying during the index event were not considered for this outcome. Finally, the fifth outcome referred to adverse event during the 90 days after discharge from the index event. We considered as 90-day post-discharge adverse events a combined variable that included ED revisit due to AHF (with or without



	0 days	10 days	20 days	30 days
At risk0	291	276	265	255
Events	0	15	26	34
Survival (%)	100	94.8	91.1	89.3
At risk	1157	1072	1025	1007
Events	0	83	129	146
Survival (%)	100	92.8	88.8	87.4
At risk	6966	6476	6230	6050
Event	0	485	721	882
Survival (%)	100	93.0	89.6	87.3

0 days	120 days	240 days	365 days
291	210	195	173
0	53	66	80
100	81.3	76.2	70.7
1157	813	741	659
0	253	316	382
100	77.6	71.5	65.1
6966	4463	4041	3593
0	1610	1986	2348
100	75.8	69.4	63.2

0 days	30 days	60 days	90 days
240	154	52	23
0	63	81	86
100	73.1	60.4	51.9
929	608	267	166
0	231	337	365
100	74.5	57.6	50.9
5179	3234	838	313
0	1418	1937	2047
100	71.9	55.1	44.3

preED-NTG Group (iv NITRATES started at PREHOSPITAL by EMS)
ED-NTG Group (iv NITRATES started at HOSPITAL in the ED)
No-NTG Group (iv NITRATES not provided at PREHOSPITAL nor at ED)

Fig. 1. Survival curves for 30-day (left) and 365-day (middle) all-cause mortality and 90-day post-discharge combined adverse event (right) according to intravenous nitroglycerine was provided by emergency medical services (preED-NTG Group), by emergency physicians in the emergency department (ED-NTG) or not provided at all (No-NTG Group).

hospitalization), hospitalization due to AHF or death or all-cause death (whichever happening first). Every event adjudication was performed at local level by the principal investigator of each hospital.

2.5. Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD) or median and interquartile range (IQR) if not normally distributed, and categorical variables as absolute values and percentages. Comparison among the three groups was carried out using one-way ANOVA for continuous variables (or by Kruskal Wallis non-parametrical test if not normally distributed) and the chi square test for categorical variables.

For comparison of in-hospital mortality and prolonged hospitalization, we used odds ratio (OR) with 95% confidence interval (CI) while for 30-day and 365-day mortality and 90-day post-discharge combined adverse event we used survival tables and curves using the Kaplan-Meier method and compared by log-rank test, and we calculated hazard ratios (HR) with 95%CI using the Cox regression. In all cases, the no-NTG was used as control group. We adjusted OR and HR by baseline differences (by adding age, sex and variables that were unequally distributed among groups, $p < 0.05$, with the exception that those variables that are already included in the MEESSI score) and by the severity of the current AHF decompensation (using the MEESSI score). Missing values in the variables included in the adjusted models were replaced using the multiple imputation technique, generating 5 datasets in which there were no missing values among all the variables included in the adjustment.

We performed five different sensitivity analyses for every outcome in the fully adjusted model. In the first one (sensitivity analysis A), we removed from the group of patients receiving IV NTG started by EMS those in whom, after assessment by the emergency physician in the ED, IV NTG was discontinued. In the second and third ones, we eliminated from the three groups all patients with a first systolic blood pressure below 100 mmHg (sensitivity analysis B) and 100 mmHg (sensitivity analysis C), respectively, because they could include, in some extend, patients in whom IV NTG was incorrectly initiated (in the two groups of IV NTG treatment) or patients with more advanced forms of cardiomyopathy and poorer prognosis (in the group that not received IV NTG). In the fourth analysis (sensitivity analysis D), we only included patients with wet and warm phenotype, as they are those that could potentially have higher benefit to be treated with IV NTG. Finally, the last one (sensitivity analysis E) compared groups of patients paired using a propensity score (PS) matching approach. A PS to be treated with IV NTG was separately calculated for patients of the preED and ED groups respect to patients of the No-NTG group. With this purpose, we constructed a multivariable model including age, sex, baseline patient characteristics that significantly differed between groups (except those variables included in the MEESSI score), as well as the severity of current AHF episode estimated by the MEESSI score. Finally, patients were paired (1:1) based on a maximum standardized difference of 0.1% in the PS.

In the other hand, we carried out a stratified analysis for outcomes in which statistically significant differences had been detected in the analysis of the whole cohort of patients. Stratification was performed in the fully adjusted model according to age ($<$ or $\geq$ 80 years), sex, coronary artery disease and chronic heart failure as previous comorbidity, and first systolic blood pressure record ($<$ or $\geq$ 120 mmHg), and interaction was assessed.

Statistical significance was accepted if the p value was less than 0.05. Since this was an exploratory study, a pre-hoc sample size calculation was not made. All calculations were made using SPSS v24.0 software (IBM, New Castle, NY, USA).

3. Results

Between EAHFE cohort 3 and cohort 6, 8424 patients who were delivered to the hospital by the emergency medical services (EMS) were prospectively enrolled into a registry. Among them, 292 (3.5%) were treated with IV NTG by EMS before admission to the ED (preED-NTG Group), 1159 (13.8%) were started treated by IV NTG in the ED (ED-NTG Group) and 6973 (82,8%) were not treated by nitrates in either the EMS or during the ED stay (no-NTG Group, controls) (Supplementary Figure). The baseline characteristics of the patients enrolled in by those 3 groups are presented in Table 1. Patients treated by IV NTG, and especially preED-NTG Group, were younger, they had more diabetes

Table 2
Unadjusted and adjusted outcomes.

	Unadjusted ratio (95% CI)	Adjusted ratio* (95% CI)
In-hospital all-cause mortality (OR)		
No-NTG Group	1 (reference)	1 (reference)
ED-NTG Group	1.172 (0.536–1.254)	1.164 (0.936–1.448)
preED-NTG Group	0.820 (0.536–1.254)	0.724 (0.459–1.114)
Prolonged hospitalization (OR)**		
No-NTG Group	1 (reference)	1 (reference)
ED-NTG Group	0.927 (0.804–1.070)	0.908 (0.785–1.050)
preED-NTG Group	1.043 (0.804–1.354)	0.988 (0.758–1.288)
30-day all-cause mortality (HR)		
No-NTG Group	1 (reference)	1 (reference)
ED-NTG Group	1.016 (0.855–1.208)	0.980 (0.819–1.174)
preED-NTG Group	0.900 (0.639–1.268)	0.818 (0.576–1.163)
365-day all-cause mortality (HR)		
No-NTG Group	1 (reference)	1 (reference)
ED-NTG Group	0.938 (0.842–1.045)	0.929 (0.830–1.039)
preED-NTG Group	**0.759 (0.607–0.948)**	**0.692 (0.551–0.869)**
90-day post-discharge combined endpoint (HR)		
No-NTG Group	1 (reference)	1 (reference)
ED-NTG Group	**0.867 (0.779–0.966)**	**0.870 (0.780–0.970)**
preED-NTG Group	0.814 (0.659–1.004)	**0.795 (0.643–0.984)**

**Covariables included in the adjustment were sex, hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, peripheral artery disease, chronic obstructive pulmonary disease, dementia, previous episodes of acute heart failure, left ventricular ejection fraction, chronic treatment with renin-angiotensin system inhibitors and beta-blockers, and MEESSI-AHF risk score. Age, Barthel index and NYHA class at baseline were not included as covariates as they form part of the MEESS-AHFI risk score.
**Prolonged hospitalization (>7 days) was only calculated for hospitalized patients (i.e., patients directly discharged from the emergency department were not taken into account) who survived to hospitalization (i.e., patients experiencing in-hospital mortality were not taken into account).
EMS: emergency medical service; ED: emergency department; NTG: nitroglycerine; OR: odds ratio; HR: hazard ratio; CI: confidence interval.
Bold ORs/HRs denote statistical significance ($p < 0.05$).

mellitus and coronary artery disease, peripheral vascular disease, but less atrial fibrillation, lung disease, valvular heart disease and previous admission for HF. Less were in NYHA class III/IV but their ejection fraction as lower. Patients who received IV NTG were treated more with betablockers and RAS inhibitors but less by MRA. The majority of patients were congestive (wet), and hypoperfusion (cold) was more frequently observed in patients treated with IV NTG. Pulmonary congestion was also more severe in patients receiving IV NTG. Similarly, these patients had higher systolic blood pressure and lower pulse-oxymetry at ED arrival. Importantly, the MEESSI score, a well validated prognostic score for patients admitted to the ED with AHF [5,6], was worst in patients who received IV NTG, and especially worst in preED-NTG Group.

In-hospital mortality was observed in 845 patients (10.0%). In-hospital mortality in preED-NTG Group (24 deaths, 8.2%) was not statistically different from no-NTG Group (689 deaths, 9.9%; $p = 0.413$), and the same was observed for in-hospital mortality in ED-NTG group (132 deaths, 11.4%; $p = 0.127$). Among patients that were hospitalized and survived to the index AHF episode, prolonged hospitalization was observed in 48.1% of cases, with no differences between control group (48.3%) and preED-NTG group (49.4%, $p = 0.752$) and ED-NTG group (46.4%, $p = 0.301$). On the other hand, survival curves for 30-day mortality did not exhibit statistical difference among the three groups as well, with mortality rates of 10.7%, 12.6% and 12.7% for preED-NTG, ED-NTG and no-NTG groups, respectively (log-rank test $p = 0.812$) (Fig. 1). Conversely, we observed statistically significant differences in 365-day mortality (29.3%, 34.9% and 36.8%, respectively; log-rank test $p = 0.031$) and 90-day post-discharge combined event (48.1%, 49.1% and 55.7%, respectively; log-rank test $p = 0.007$) curves, with differences appearing early (by around 30 days from the starting point) and persisting throughout the follow up period (Fig. 1).

The unadjusted and adjusted associations with outcomes for preED-NTG and ED-NTG groups respect to no-NTG Group are presented in the Table 2. Remarkably, we observed that preED-NTG patients persisted with a lower risk of 365-day mortality than controls even after adjustment for differences in baseline characteristics and severity of AHF decompensation (HR = 0.692, 95%CI = 0.551–0.869), as well as with a lower risk for 90-day post-discharge combined events (HR = 0.795, 95% CI = 0.642–0.984). On the other hand, ED-NTG patients had a lower risk of 90-day post-discharge combined events (HR = 0.870, 95%CI = 0.780–0.970). The five sensitivity analyses showed very similar results for all these associations, although in a few cases statistical significance disappeared (Supplementary Table).

Finally, the subgroup analysis of outcomes for preED-NTG and ED-NTG groups (respect to controls) showed that associations were not affected by age (≥ or < 80 years), sex, presence of previous coronary artery disease or heart failure, or systolic blood pressure ≥ or < 120 mmHg (Fig. 2). The only exception was the 90-day post-discharge combined events for preED-NTG Group that was significantly lower if patients had no previous history of heart failure.

4. Discussion

We found that early starting of IV NTG treatment by EMS was associated with long-term survival of patients with AHF compared with patients in whom IV NTG was not used. In addition, post-discharge adverse events among patients who are discharged alive after decompensation are also lower in those administered IV NTG by EMS. For patients in whom IV NTG was started in the ED, similar association with post-discharge events was observed, although there was no association with survival.

These results have to be put in perspective with the currently available data respect to nitrates use in patients with AHF. In fact, the administration of IV nitrates to patients with AHF has been recommended by some authorities and in the guidelines for treatment of AHF [2,3] despite lack of significant evidence. A Cochrane review published in 2013 identified only four randomized controlled trials comparing nitrates with alternative interventions in the management of AHF [12] and there was no significant difference between nitrate vasodilator therapy and alternative interventions in the treatment of AHF, with regard to symptom relief and haemodynamic variables. None of them reported significant changes in mortality rates. A latter report that analyzed the impact of NTG administration in the ED to patients with AHF also did not observe any association with short-term survival [13]. Very recently, to assess the importance of vasodilator therapy in the management of AHF, the GALACTIC study has been conducted [4]. In this study 781 patients with AHF were randomized to early intensive and sustained vasodilatation versus standard of care during hospitalization. Both groups received loop diuretics, beta-blockers, aldosterone antagonists, cardiac devices, and routine follow-up. The primary outcome, death or AHF rehospitalization at 180 days, occurred at a similar frequency between groups (hazard ratio 1.07, $p = 0.59$). No benefits were seen in any of the other secondary study endpoints. However, in the GALACTIC study, nitrates were not administered IV and there was no substantial difference in blood pressure between the two arms in the first day suggesting that the doses of nitrates administered may have not induced the early desired vasodilation. As suggested in our original

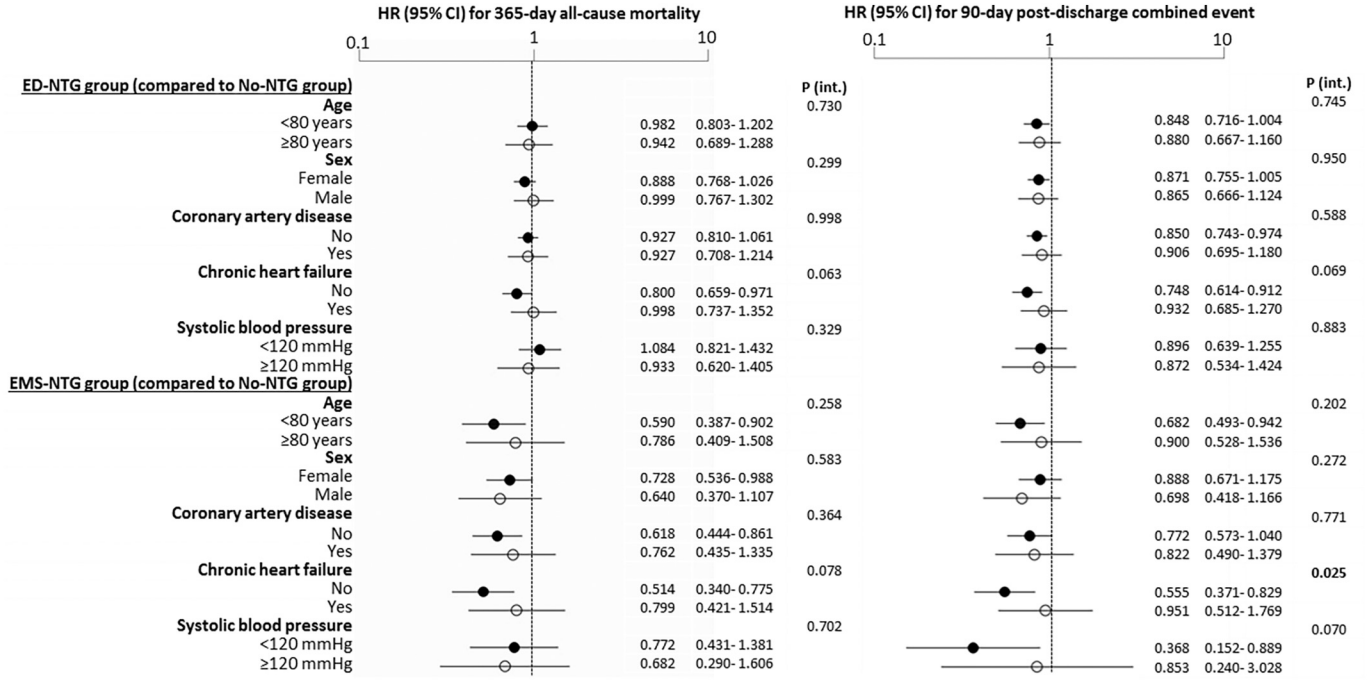


Fig. 2. Analysis of subgroups and interaction in the fully adjusted model (by baseline characteristics* and MEESSI score) for the association between the administration of intravenous nitroglycerin by emergency medical services (preED-NTG Group) and by emergency physicians at the emergency department (ED-NTG Group) and outcomes for which significant differences among groups had been found in the analysis of the whole cohort.
*Baseline covariables included in the adjustment were sex, hypertension, diabetes mellitus, ischemic cardiomyopathy, atrial fibrillation, peripheral artery disease, chronic obstructive pulmonary disease, dementia, previous episodes of acute heart failure, left ventricular ejection fraction, and chronic treatment with renin-angiotensin system inhibitors and beta-blockers. Age, Barthel index and NYHA class at baseline were not included as covariates as they form part of the MEESSI risk score.
Bold p values denote statistical significance ($p < 0.05$).

manuscript proposing nitrated of treatment in AHF [1], nitrates have different effects at high and low doses [14]. At low doses, nitrates induce only venodilatation, while at higher doses, they induce arterial dilatation. Therefore, early administration of high dose of nitrates is likely to induce significant afterload reduction, while lower doses administered over time would induce mostly preload reduction, very different effects. Furthermore, administration of IV nitrates for more than a few hours would likely result in tachyphylaxis [15,16]. Hence, the strategies utilized in our initial study [1] and that investigated in the GALACTIC trial [4] were very different. None of the above commented studies evaluated the role of early administration of NTG, during the prehospital management. Our results suggest that early administration of IV nitrates may be of value, and especially in the prehospital arena.

Our results are in line with previous studies emphasizing the importance of the EMS in the very early treatment of AHF decompensations. A Japanese study reported that transportation time of AHF patients by EMS correlated with risk-adjusted mortality [17], and the SEMICA-2 study reported that AHF that have received high-intensity prehospital treatment by EMS teams have a better short-term outcome, especially during the first 7 days [18]. However, the use of EMS and the administration of prehospital medication by EMS are low in patients with AHF [19]. A recent international survey involving 104 EMS teams from 18 countries showed that difficulty of diagnosing AHF at scene could be an issue in starting specific medication, as it seems to be moderate compared with other pre-hospital conditions [20]. Additionally, although the prevalence of AHF protocols in EMS is rather high, the contents seem to vary from country to country; of note, among therapeutic actions included in the protocol, the use of IV NTG was the less frequent, only present in 57% of protocols, in front of the 93% of supplementary oxygen, 81% of non-invasive ventilation, or 69% of intravenous furosemide and opiates [20]. Our results suggest that although beneficial effects seem to be present from the beginning (OR for in-hospital mortality of 0.724; HR for 30-day mortality of 0.818), this benefits only achieved statistical significance in the long term (HR for 365-day mortality of 0.691; HR for 90-day post-discharge adverse events of 0.795). This could be due to lack of power for early events in this exploratory study, as the number of patients included in the preED-NTG Group was small (292). The question of why an early administration of therapy in the first few hours of presentation would affect decrease in events, especially mortality over the long run, has not be adequately answered. Some authors have indeed doubted whether such an outcome is even possible. However, the current analysis is in line with other studies showing longer term mortality benefit or potential benefits from early administration of IV interventions in AHF. Such example includes the mortality benefit seen with IV serelaxin [21,22] and a recent study examining a short term intervention relaying on higher doses of IV nitrates in which, despite showing no effect on the primary endpoint, has seen trends towards longer-term mortality benefit in the active arm [23]. The mechanism for such a benefit, if such a benefit indeed exists, are not known, although some authors suggested that early IV administration of some therapies in AHF may reduce the end organ damage caused during the first hours of an AHF event and by that affect longer term outcome, due to preservation of longer term organ function [24].

4.1. Limitations

First, as in every observational study, causal relationships cannot be inferred. Therefore, the results of the current analysis are limited by the retrospective design and therefore the potential bias by indication. Similarly, we some key data that could help to better understand the effects of early administration of IV NTG were not recorded, like response of systolic blood pressure to vasodilator initiation, sequential assessment of dyspnea or creatinine to identify patients with worsening heart failure or renal failure, or relevant outcomes as need of intensive

care. However, as seen in Table 1, patients administered IV nitrates in the prehospital phase were at higher risk of adverse outcome as measured by higher MEESSI score. Second, the preED-NTG Group was quite limited in size. This could influence the lack of statistical significance in some comparisons involving this group and we could have potentially committed a beta-error. Third, the patients came from a nationwide cohort with a universal public healthcare system, and external validation might be needed to confirm their generalizability. Roles of doctors and nurses in EMS can vary among countries [25]. As example, advance live support ambulances in Spain are staffed by doctors and nurses and they are allowed to provide IV drugs, but this is not the case in other countries and healthcare systems. Fourth, in our study we did not record the doses and duration of IV NTG provided by EMS or in the EDs, neither the elapsed time between ED arrival and starting of IV NTG. Fifth, our study included a high percentage of elderly AHF patients in whom frailty and dependence are frequent, two factors strongly related to mortality [26,27]. Although stratified analysis did not suggest differences depending on age, we believe that effects of IV NTG in other AHF populations should be explored. Sixth, this was real life cohort without any planned intervention, and differences in physician strategies of diuretic use could exist, not only in terms of route of administration, but also in the initial doses and in dose adjustment based on patient response. Seventh, the diagnosis of AHF was based on clinical criteria, and the final diagnosis of AHF was not supported in all cases by natriuretic peptide or echocardiographic results in a number of cases. Although these two latter limitations could impose caution in the interpretation of some of our conclusions, this approach makes our findings more generalizable to the real-world EMS and ED practice.

5. Conclusions

The results of the current analysis suggest that the use of IV nitrates in patients with AHF should be examined in two different time frames. In the prehospital setting administration of higher doses of IV nitrates by inducing arterial dilation may have a beneficial effect on some mid- and long-term outcomes. This should be reinvestigated in future prospective studies. On the other hand, administration of IV nitrates during the ED admission, probably in lower doses for prolonged periods of time, seems to have a more reduced beneficial effects [4] and should therefore be reserved for specific indications such as patients with uncontrolled high blood pressure or ischemic chest pain.

Acknowledgements and funding

This study was partially supported by grants from the Instituto de Salud Carlos III supported with funds from the Spanish Ministry of Health and FEDER (PI15/01019, PI15/00773, PI18/00393, PI18/00456) and Fundació La Marató de TV3 (2015/2510). The “Emergencies: Processes and Pathologies” research group of the IDIBAPS receives financial support from the Catalonian Government for Consolidated Groups of Investigation (GRC 2009/1385, 2014/0313, and 2017/1424). We thank Alícia Díaz for her professionalism in data management.

Declaration of Competing Interest

The authors state that they have no conflict of interests with the present work. The ICA-SEMES Research Group has received unrestricted support from Orion Pharma and Novartis. The present study has been designed, performed, analyzed and written exclusively by the authors independently of these pharmaceutical companies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.09.031.

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