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Effect of an emergency department care bundle on 30-day hospital discharge and survival among elderly patients with acute heart failure: the ELISABETH randomized trial

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KEY POINTS

Question: Does an intervention aimed at improving guideline adherence for the treatment of acute heart failure, including intensive IV nitrate therapy and treatment of precipitating factors, improve hospital discharge and survival at 30 days?

Findings: In this stepped-wedge cluster-randomized trial that included 503 patients aged 75 and older presenting to the emergency department with acute heart failure, implementation of an early and comprehensive care bundle compared with usual care improved guideline adherence, but had no significant effect on number of days alive and out of hospital at 30 days (median 19 in both groups).

Meanings: This emergency department care bundle did not improve 30-day outcomes among older patients with acute heart failure.

Abstract (word count 484)

Importance: Clinical guidelines for the early management of acute heart failure in the emergency department setting are based on only moderate levels of evidence with subsequent low adherence to these guidelines.

Objective: To test the effect on an early guideline-recommended care bundle on short-term prognosis in older patients with acute heart failure in the ED.

Design, Settings and Patients: Stepped-wedge cluster randomized trial in 15 EDs in France recruiting 503 patients aged ≥75 years with a diagnosis of acute heart failure in the ED from December 2018 to September 2019 and followed up for 30 days until October 2019.

Intervention: A care bundle that included early IV nitrate boluses, treatment of precipitating factors such as acute coronary syndrome, infection or atrial fibrillation and moderate dose of IV diuretics (n=200). In the control group, patients' care was left to the discretion of the treating emergency physician (n=303). Each center was randomized to the order in which they switched to the "intervention period." After the initial 4-week control period for all centers, one center entered in the intervention period every 2 weeks.

Main outcomes and measures: The primary endpoint was the number of days alive and out of hospital at 30 days. Secondary outcomes included 30-day all-cause mortality, 30-day cardiovascular mortality, unscheduled readmission, length of hospital stay, and renal impairment.

Results: Among 503 patients who were randomized (median age 87 years, 59% women), 502 were analysed. In the intervention group, patients received a median of 27 mg (IQR 9 – 54) of IV nitrates in the first four hours vs 4 mg (IQR 2 – 6) in the control group (adjusted difference 24 [95% CI 13.5 to 34.1]). They were also significantly more often treated for their precipitating factors than in the control group (59% vs 32% overall, adjusted difference 31% [95%CI 14% to 48%]). There was no statistically significant difference in the primary endpoint of number of days alive and out of hospital at 30 days (median 19 [0 - 24] in both groups, adjusted difference -1.9 [95%CI -6.6 to 2.8] and adjusted ratio 0.88 [95%CI 0.64 to 1.21]). At 30 days, there was no significant difference between groups in mortality (8% intervention vs 9.7%

control, adjusted difference 4.1% [95%CI -17.2% to 25.3%]), cardiovascular mortality (5% intervention vs 7% control, adjusted difference 2.1% [95%CI -15.5% to 19.8%]), unscheduled readmission (14% intervention vs 16% control, adjusted difference -1.3% [95%CI -26.3% to 23.7%]), median length of hospital stay (8 days in both groups, adjusted difference 2.5 [95%CI -0.9 to 5.8]) and renal impairment (1% in both groups).

Conclusions and Relevance: Among older patients with acute heart failure, use of a guideline-based comprehensive care bundle in the emergency department compared with usual care did not result in a statistically significant difference in the number of days alive and out of the hospital at 30 days. Further research is needed to identify effective treatments for acute heart failure in older patient.

Registration: NCT03683212

Introduction

Acute heart failure is one of the most common syndromes in older patients visiting the emergency department (ED).[1] In an international observational study, which included patients aged 75 years and older from 2010 to 2013, acute heart failure was associated with a 10% mortality risk and up to 30% risk of hospital readmission at 30 days.[2]

International recommendations and clinical guidelines on acute heart failure include the use of moderate doses of diuretics, early initiation of nitrates, and non-invasive ventilation when indicated, along with the early detection and treatment of precipitating factors such as acute coronary syndrome, infection or atrial fibrillation.[3–5] However, these recommendations are based on low levels of evidence. The cornerstone trials on small samples of patients with acute heart failure reported a clinical benefit with early high dose IV nitrates.[6,7] Subsequent large scale trials testing novel agents with vasodilator properties failed to confirm improved outcomes, possibly because of effects besides vasodilation that might affect mortality risk.[8,9] As a potential consequence, previous reports confirmed low adherence to these recommendations, leading to under-utilization of nitrates in the ED.[10,11]

The failure of recent acute heart failure studies to report clinical benefits with specific treatments may be attributable to both the delay from presentation to treatment because recent studies suggest that an early therapy is associated with better prognosis. and the lack of management of precipitating factors, because acute heart failure prognosis has been reported to be associated with the underlying precipitant of worsening heart failure.[12,13] Whether early ED management of congestion and precipitating factors improves outcomes is unknown.

The aim of this trial was to test the efficacy on clinical outcomes of an early, comprehensive and guideline-recommended care bundle on older patients with acute heart failure in the ED.[14]

Methods

Study design

The protocol and statistical analysis plan of the ELISABETH trial is available in the Supplement 1, and has been previously published in detail.[14]

This was an unblinded superiority, stepped-wedge, cluster randomized clinical trial in France aimed at testing the effect of an early comprehensive care bundle for acute heart failure in older patients in the ED. Fifteen EDs in France participated in the study. The trial recruited from December 2018 to September 2019 and follow up ended in October 2019. The study was approved by an institutional review board (Comité de Protection des Personnes SOOM 2, Toulouse academic hospital, France). Written informed consent was sought for all patients before inclusion. If the patient lacked capacity to give consent, the emergency physician sought consent from a patient's relative. If no such relative was available, research staff were able to proceed to an emergency inclusion. For the latter, as soon as the patient's clinical condition allowed it, a clinical research technician or a physician informed him or her about the trial and sought written informed consent. The reporting of this trial followed the Consolidated Standards of Reporting Trials (CONSORT) statement extended to stepped-wedge cluster randomized trials.[15,16]

Patients

Consecutive patients aged 75 and older with a clinical diagnosis of acute heart failure in the ED were eligible for inclusion in the trial. Acute heart failure diagnosis was made on the basis of at least one of acute or worsening dyspnea, or orthopnea and at least one of the following: bilateral pulmonary rales or peripheral edema, signs of

pulmonary congestion on chest radiography or cardiac echography, or elevation in level of natriuretic peptides (BNP or NT pro BNP)

As a pragmatic study, whether the diagnosis of acute heart failure was confirmed was left to the discretion of the physician and echocardiography was not mandatory.

Patients were not included if they presented with another obvious cause of acute illness (e.g. ST elevation myocardial infarction or severe sepsis), a systolic blood pressure less than 100 mmHg, any contra-indication for nitrate therapy (severe mitral or aortic stenosis, or severe aortic regurgitation), or a known chronic kidney impairment that required dialysis. Since this trial focused on early treatment of acute heart failure, patients in whom time from ED presentation to inclusion was > 6h were also not included. Patients with no social security, who were incarcerated or under guardianship were also excluded.

All patients were followed up at 30 days, either by hospital visit or by phone interview if already discharged. They were instructed to return to the same ED or hospital in the event of recurrent or worsening symptoms. A local clinical research assistant checked for return visits to the ED or admission to the hospital during the follow up period. The phone interview was performed using a structured questionnaire that recorded length of initial hospital stay, any return visit to the ED or admission to the hospital. When patients could not be contacted by phone, the patient's general practitioner was contacted. When it was not possible to contact the patient or their physician, death records were sought from the patient's birth town administrative record.

Randomization

After an initial control period (first step) of four weeks in all centers, one ED switched to the “intervention period” every two weeks. The order in which they switched was randomized. The first two weeks of the intervention period in each center was also a training period, in which a clinical research technician presented and detailed the care bundle and assisted emergency physicians in implementing it. After 32 weeks, all EDs were in the “intervention period” for the eight remaining weeks of inclusion (eFigure 1 in Supplement 2). Randomization of the order of the switch was performed by an independent statistician. At study commencement, EDs were classified on size based on their annual census. Randomization was stratified on cluster size (small, medium, large). Each set of 3 consecutive time periods would contain one small, one medium-sized, and one large site, in random order.

Intervention

This was an unblinded design, which was chosen because the intervention could not be performed in a blinded fashion for either physicians or patients.

In participating EDs and in most French EDs, patients are first seen by a triage nurse, then managed by a senior emergency physician, with or without the help of a trainee. Only senior emergency physicians could include patients, and consequently the entirety of the ED medical management was completed by a senior emergency physician. In France, regular emergency medical services (EMS) cannot administer treatments, therefore no patients conveyed by regular EMS received any treatment before inclusion in the ED. However, some patients may have been transported by a physician-staffed EMS (Service mobile d’urgence-réanimation) where treatment could have been given. These patients are usually directly admitted to an intensive

care unit. If that was not the case, patients in whom treatment was already started before inclusion were excluded.

The intervention of this trial consisted of a guideline-recommended care bundle for the early management of acute heart failure in the ED.

In the control period, patients' care was left to the discretion of the treating emergency physician (usual care). At the beginning of the trial, the recommendations for acute heart failure management were described to all emergency physicians, including moderate dose diuretics, high dose IV nitrates, search for and early treatment of most frequent precipitating factors, and non-invasive ventilation (NIV) when indicated.

In the intervention period, after a patient's inclusion, emergency physicians were instructed to follow the early care bundle for acute heart failure, with the help of a handover check-list. This care bundle mandates treatment initiation within one hour and completion within four hours of early treatment of pulmonary oedema with 40 mg (if naïve) or daily dose (if already on oral diuretics) of intravenous furosemide, IV nitrates in titration (given in 3 mg boluses every 5 minutes for one hour, titrated to a systolic blood pressure (BP) above 100 mmHg), detection and treatment of precipitating factors (specifically acute coronary syndrome, rapid atrial fibrillation and suspected infection). Suspicion of cardiac injury (based on troponin level measurement, echocardiography and electrocardiogram analysis) required introduction of antiplatelet therapy and referral to cardiologic intensive care unit for potential admission and coronary angiogram if indicated. Suspicion of respiratory tract infection (based on chest X-ray, C-reactive protein, procalcitonin and leucocytes level) required early introduction of antibiotics. Atrial fibrillation with a heart rate above 100 beats per minute required introduction of antiarythmic therapy

(amiodarone, digoxin or beta-blockers as indicated). NIV was administered in the event of respiratory distress or hypercarbia with pH<7.35.

All treatments were to be initiated in the ED within the first hour of medical management, and for at least 4 hours. Their discontinuation was left to the discretion of the admitting physician.

Outcomes

The primary objective of the trial was to test the effect of an early comprehensive guideline-recommended care bundle on morbidity and mortality at 30 days in older patients. The primary endpoint was the number of days alive and out of hospital during the 30-day period after the ED visit. The choice of this endpoint allowed capturing the burden of acute heart failure in terms of mortality, hospital length of stay, and early readmission to the hospital, as recommended by the European Society of Cardiology consensus paper.[17] Patients that died before day 30 were counted as having zero days alive and out of hospital. A return visit to the ED was considered as one day in the hospital. Details on the calculation of this endpoint were previously detailed.[14]

The secondary endpoints included 30-day all-cause mortality, 30-day cardio-vascular mortality, hospital readmission within 30 days, length of in-hospital stay truncated at 30 days, and changes of more than 2-fold in creatinine level from inclusion to day 30 or to discharge (whichever comes first). Creatinine was measured at day zero in the ED, and at discharge or day 30.

Power analysis

The full statistical plan and sample size calculation are available in Supplement 1. Sample size was calculated under the superiority hypothesis. Based on previous cohort analysis, the mean number of days alive and out of hospital at 30 days was estimated at 14 (standard deviation [SD] 9).[10,12,18] To be clinically relevant and consistent with previous literature, it was estimated that the intervention should improve this endpoint by 20% (i.e. three days at least).[8,9] For a power of 80% and alpha at 5%, 283 patients needed to be included. Adding the cluster effect for this stepped-wedge design and assuming an intra-cluster correlation at 0.001, the required sample size was 454 patients. Taking into account a rate of lost to follow up of 10%, the necessary sample size was 500 patients – two per cluster for each two-week period (step). Due to acute heart failure seasonality and fewer cases in the summer period, we had to increase the length of the last inclusion step from four weeks to eight weeks in order to reach the target.[19,20]

Statistical analysis

The primary analysis included all patients who were randomized, with missing outcome data replaced using worst-case imputation (zero days alive and out of the hospital). Baseline characteristics were expressed as number (percentage) for categorical variables, and mean (standard deviation) or median (interquartile range, [IQR]) for continuous variables depending on their distribution. Unadjusted differences and 95% CIs were calculated using using Wald method with continuity correction for binary variables and using Brookmeyer and Crowley method for continuous variables. Adjusted differences were calculated using a generalized linear regression mixed model with Bernoulli (binary) distribution and an identity link function, with intervention, time period and cluster size (categorical) as fixed effects and cluster as a random effect for binary variables and using quantile regression

model for continuous variables.[21] The 2-week training period for each site was analyzed as part of the intervention period. Primary and secondary outcomes were analyzed in all randomized patients with a primary outcome available. The number of days alive and out of hospital was analyzed using a generalized linear regression mixed model with negative binomial distribution with intervention, time period and cluster size as fixed effects and cluster as a random effect.[22] A sensitivity analysis was performed on all patients that completed the trial. All-cause mortality at 30 days, cardiovascular mortality at 30 days and hospital readmission were compared between groups by using generalized linear regression mixed model with Poisson distribution. The logarithm of the number of patients was included as an offset term in the model. In surviving patients, the length of stay in hospital in days was compared between the two strategies by using a generalized linear regression mixed model with negative binomial distribution. For secondary outcome, fixed and random effects were defined as described previously. For non-hospitalized patients, length of hospital stay was counted as zero day. Percentage of patients with a change of more than 2-fold in creatinine between inclusion and 30 days were not analyzed because of the presence of a small number of cases and no or negligible differences between the two groups. Because of the potential for type 1 error due to multiple comparisons, the findings of analyses of secondary endpoints should be interpreted as exploratory. The original analysis plan was intended to study different extensions of the models as sensitivity analyses, including both a time x cluster interaction as a fixed effect, and also as random effects. However, due to the structure of the data (low proportion of events by cluster by period), these sensitivity analyses could not be performed. All superiority tests were two-sided and P values <0.05 were considered significant. SAS

V.9.4 software (SAS Institute Inc., Cary, NC) and Stata version 16 (Stata Corp), were used for statistical analyses.

Results

Study population

Fifteen EDs participated in the trial and 503 patients were recruited. Among them, one patient was under guardianship and was excluded, five patients withdrew their consent, three were lost to follow-up and the primary endpoint was missing for one patient. Therefore, 502 patients were included in the primary analysis: 303 in the control group and 199 in the intervention group. A total of 493 patients completed the trial and were included in the sensitivity analysis (Figure 1, eFigure 1 and eTable 1). The mean number of patients recruited by center and by step was respectively 34 (12) and 31 (20). The median age was 87 (IQR 81 - 91) years, 298 (59%) were women, and 269 (54%) had known chronic cardiac failure. Patients' baseline characteristics were similar between the two groups and are reported in table 1. Pulmonary congestion was similar between the two groups: mean oxygen saturation was 90.6% (6.7) versus 91.1% (6.9), mean respiratory rate 26.2 (6.7) versus 25.9 (7.3) per min in intervention and control groups respectively, and mean systolic blood pressure was 155 (29) mmHg in the intervention group and 149 (28) mmHg in the control group.

Treatment in the ED

In the intervention group, patients were significantly more frequently treated by IV nitrates (96% vs 25%, adjusted difference 71% [95%CI 62% to 80%]), with higher median dose (27 mg vs 4 mg at four hours of initial management; adjusted difference 24mg [95%CI 13.5 to 34.1]) and more frequently treated by diuretics (98% vs 90%, adjusted difference 6.8% [95%CI 0.5 to 13.0]), (table 2). A precipitating factor was

present in 45% of patients, and was significantly more frequently treated in the ED in the intervention group than in the control group (59% vs 32% overall, adjusted difference 31% [95%CI 14% - 48%]), (eTable 2).

Study endpoints

Among the 502 patients included in the primary analysis, the median number of days alive and out of hospital at 30 days was 19 (IQR 0 - 24) in the intervention group and 19 (IQR 0 - 24) in the control group (adjusted difference -1.9 [95%CI -6.6 to 2.8]), adjusted ratio = 0.88 [95% CI 0.64 to 1.21], p=0.44) (table 3). The intra-class correlation coefficient was 0.057. A sensitivity analysis of patients that completed the trial exhibited similar results (eTable 3 and eTable 4). There was no statistically significant difference in all-cause mortality at day 30 (8.0% in the intervention vs 9.7% in the control, adjusted difference 4.1% [95%CI -17.2 ; 25.3], adjusted risk ratio aRR 1.17 [95% CI 0.53 to 2.57]; reversal in direction due to the adjustement for covariates) (Figure 2), median length of initial hospital stay (8 days [IQR 5 – 21] vs 8 days [IQR 5 – 16] in the intervention and control groups respectively, adjusted difference 2.5 [95%CI -0.9 to 5.8] adjusted ratio=1.22 95%CI [0.94 to 1.59]), unscheduled readmission (14% vs 16% in the intervention and control groups respectively, adjusted difference -1.3% [95%CI -26.3% to 23.7%], adjusted risk ratio 0.96 [95%CI 0.48 to 1.95]) or acute kidney injury at 30 days (1.0% vs 1.4% in the intervention and control groups respectively) (table 3).

There was a similar rate of nitrate use in the control group (eFigure 2) and treatment of precipitating factors in the 5 centers randomized to later crossover than in the usual care period (17% vs 15% respectively).

Discussion

In this stepped-wedge, cluster randomized trial that included 502 older patients with acute heart failure, an early and comprehensive, guideline-recommended care

bundle resulted in a significantly increased use of IV nitrates and more frequent treatment of precipitating factors but did not significantly improve the number of days alive and out of hospital at 30 days, nor any other early outcome.

For the past few decades, IV nitrates have been recommended for the early management of patients with acute heart failure.[6,7] However, the failure of further trials to confirm any clinical benefit of IV nitrates in patients with acute heart failure resulted in subsequent moderate level of evidence for this recommendation, hence the reported low adherence in older patients.[11] Several studies suggested that a more comprehensive and early management of patients with acute heart failure in the ED could improve prognosis, because prognosis could be dependent on underlying conditions and precipitating factors.[18,27] The implementation of the tested care bundle resulted in a significantly higher compliance with guideline-recommended therapy both in the treatment of acute pulmonary congestion and of the precipitating factors. The control group in this study received similar treatments to those reported in a recent multicenter observational study.[23] In that study, only 34% of patients with acute heart failure received IV nitrates, and very few were treated for precipitating factors in the ED. In France, IV nitrates are the only nitrates used for patients with acute heart failure, and no other nitrates were used in this study, or in France in general.[24] More patients in the intervention group had to be admitted to an intensive care department. Whether this was the result of adverse effect of the intervention or of a more proactive approach in this group is unknown.

In the present trial, it is possible there could have beena Hawthorne effect in that control patients would receive similar treatments to intervention patients, because physicians would be aware that the patients were in the trial, and aware their management decisions were being recorded. That this was not the case could be

due to the stepped-wedge cluster-randomisation methodology.[10] There was also a low risk of contamination in sites randomized to later crossover, with a similar rate of nitrate use and treatment of precipitating factors. Furthermore, these results showed an intraclass correlation coefficient estimation of 0.05, higher than the one anticipated, which reduced statistical power. However, it seems unlikely that this would have change results on the primary outcome.

Regarding treatment of acute pulmonary congestion, these results are consistent with those from the GALACTIC trial in which early and sustained vasodilatation therapy was not significantly associated with improved outcomes. The present trial also tested a comprehensive approach, with earlier implementation of the intervention: patients were randomized within 6 hours of ED presentation and the care bundle was initiated during the first hour of medical management. With a significantly higher rate of treatment of precipitating factors, this trial is complementary to the GALACTIC trial and others that tested intervention during the first days of admission for acute heart failure.[8]

This trial focused on older patients, and it is likely that in these patients, who often present with comorbidities, the prognosis is not driven by pulmonary edema but rather by precipitating factors and underlying conditions[8,9,12,25].

Given the study findings, a more specific geriatric care pathway may need to be considered.

Limitations

This study has several limitations. First, only patients aged 75 and older were included, since this trial focused on a more homogeneous phenotype of patients.[26] However, this population may still include both patients with preserved and reduced

systolic cardiac function. This parameter was not assessed in included patients, and it is possible that the intervention may cause different outcomes in different phenotypes of patients. The present trial included mostly wet and warm patients, the most common phenotype of acute heart failure.[27]

Second, a selection bias may also have occurred since some patients may have refused to be included in the study, and some eligible patients may have not been screened by the emergency physicians. Since this number was not recorded, the extent of this bias cannot be ascertained.

Third, the intervention included high-intensity IV nitrates, with a median of 27 mg of isosorbide dinitrate in the intervention group vs 4mg in the control group in the first four hours. The optimal dose may lie somewhere between these two numbers.

Fourth, the rate of hypotension that may have been caused by this treatment was not recorded, since the objective was to evaluate the overall effect of the bundle. However, this risk is limited as the intervention included close monitoring of BP, and withholding nitrate therapy if the systolic BP dropped below 100 mmHg.

Fifth, the potential use in the ED of oral or topical nitrates, was not recorded in this study. However, in France, only IV nitrates are used for acute heart failure, and the proportion of patients previously treated with topical nitrates for chronic heart failure was similar in both groups (6%).

Sixth, a short term prognosis endpoint (30 days) was chosen to capture the overall effect of the tested care bundle and this endpoint may have been influenced by post-ED therapy in the ward that is not standardized.

Seventh the rate of treatment of acute coronary syndrome was low in both groups, suggesting a suboptimal treatment of this precipitating factor, which in turn may have limited the benefit of the intervention.

Conclusion

Among older patients with acute heart failure, use of a guideline-based comprehensive care bundle in the emergency department compared with usual care did not result in a statistically significant difference in the number of days alive and out of the hospital at 30 days. Further research is needed to identify effective treatments for acute heart failure in older patient.

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All other authors declare they have no conflict of interest with this study.

Data access

Yonathan Freund and Tabassome Simon had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All data of the study can be provided upon request to the corresponding author. Data sharing statement: See online supplement 2.

Authors' contribution

YF conceived the study. YF, AM, MC and TS contributed to the study protocol. QD, SD, YY, JG, TC, ALF, JT, TD, CO, XB, MK, OG, JB, FB, SB included patients. MC provided statistical analysis. YF, AM and BB interpreted the results. YF drafted the

manuscript. AM, BB, TS and MC provided substantial revisions. All authors agree to be accountable for all aspects of the work.

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Figure 1: Flow of patients and clusters in the ELISABETH trial. The order in which each of the 15 clusters (emergency department) switched to the intervention period was randomized.

Figure 2: Cumulative incidence of all-cause mortality**.** Shading for the 95% confidence intervals.

[a]All patients observed to date of death or 30 days.

[b] Mortality data were missing for 4 patients who are not included in this analysis

Variable	Intervention (n=199)		Usual Care (n=303)		Normal values
	n		n		
Age, median (IQR), y	199	87.0 [81.0 ; 90.0]	303	87.0 [81.0 ; 91.0]	
Sex	199		303		
Women, n (%)		112 (56.3)		186 (61.4)	
Men, n (%)		87 (43.7)		117 (38.6)	
Comorbidities, n (%) [a]	199		303		
Chronic pulmonary disease		39 (19.6)		46 (15.2)	
Chronic heart failure		111 (55.8)	302	158 (52.3)	
Chronic kidney disease		49 (24.6)		73 (24.1)	
Diabetes		54 (27.1)		92 (30.4)	
Myocardial infarction		80 (40.2)		91 (30.0)	
Vital signs at randomization, mean (SD)	199		303		
Heart rate, /min		86.3 (23.5)		86.6 (23.8)	
Oxygen saturation, (%)	185	90.6 (6.7)	286	91.1 (6.9)	

Respiratory rate, /min	187	26.2 (6.7)	273	25.9 (7.3)	
Systolic blood pressure, mmHg		155.3 (28.8)		148.8 (27.9)	
Temperature, °C	198	36.8 (0.6)		36.7 (0.7)	
Medication at randomization, n (%)	199		303		
ACE inhibitor		58 (29.1)		84 (27.7)	
ARB		41 (20.6)		79 (26.1)	
Antibiotic		18 (9.0)		25 (8.3)	
Anti-platelet		75 (37.7)		116 (38.3)	
Anticoagulant		96 (48.2)		147 (48.5)	
Beta-blocker		123 (61.8)		165 (54.5)	
Diuretic		129 (64.8)		222 (73.3)	
Nitrates		13 (6.5)		17 (5.6)	
Laboratory results, median (IQR) [b]	199		303		
Brain natriuretic peptide, ng/L	81	591.0 (251.5 ; 977.0)	151	620.0 (319.6 ; 1220.0)	< 450
Creatinine, mg/L		11.2 (8.7 ; 14.7)	301	11.5 (8.9 ; 16.0)	6-12
C-reactive protein, mg/L	155	13.7 (5.0 ; 47.1)	236	13.4 (5.0 ; 43.7)	< 5
Haemoglobin, mean (SD), g/dL		12.4 (2.0)	300	12.1 (1.8)	12 - 17
Leucocytes, G/L		9.0 (6.9 ; 11.9)	301	8.3 (6.6 ; 10.8)	4 - 10
NT pro-BNP, ng/L	116	$4.2x10^3$ ($1.8x10^3$; $7.9x10^3$)	144	$5.0x10^3$ ($2.3x10^3$; $9.3x10^3$)	$2x10^3$
Procalcitonin, µg/L	54	0.1 (0.1 ; 0.2)	45	0.1 (0.1 ; 0.3)	< 0.1
Troponin, µg/L	185	0.0 (0.0 ; 0.1)	243	0.0 (0.0 ; 0.1)	< 14

pH, mean (SD)	176	7.4 (0.1)	210	7.4 (0.1)	7.35 - 7.45
PaCO2, mmHg	176	40.0 (33.5 ; 47.0)	210	39.0 (34.0 ; 45.0)	35 - 45
PaO2, mmHg	176	74.0 (65.0 ; 91.5)	210	70.0 (60.0 ; 87.0)	80 - 100
Bicarbonate, mmol/L, mean (SD)	150	25.8 (5.2)	221	24.7 (4.4)	22 - 26

Table 1: baseline characteristics. SD: standard deviation. ARB: angiotensin receptor blockade.

[a] Comorbidities were recorded by the emergency physician during emergency department visit.

[b] Laboratory results were obtained as part of Emergency Department care.

Variable		Intervention		Usual Care	Adjusted difference [a]	95%CI
	n		n			
Treatment in the Emergency Department, n(%)						
Furosemide[b]	199	195 (98.0)	303	274 (90.4)	6.8	(0.5 to 13.0)
dose, mg, median (IQR)	195	40.0 (40.0 - 80.0)	273	60.0 (40.0 - 80.0)	-13.1	(-25.4 to -0.9)
iv nitrates [c]	199	191 (96.0)	302	74 (24.5)	71.0	(61.6 to 80.3)
Cumulative dosing at hour 1, mg, median (IQR)	187	18.0 (9.0 - 30.0)	54	3.0 (2.0 - 4.0)	14.9	(8.9 to 20.8)
Cumulative dosing at hour 4, mg, median (IQR)	188	27.0 (9.0 - 53.5)	73	4.0 (2.0 - 6.0)	23.8	(13.5 to 34.1)
Antibiotics	199	39 (19.6)	303	38 (12.5)	10.8	(1.6 to 19.9)
Antiplatelet agents	199	15 (7.5)	303	23 (7.6)	0.2	(-7.9 to 8.4)
Dual antiplatelet agents [d]	199	4 (2.0)	303	3 (1.0)		
Antiarrhythmics	199	22 (11.1)	303	23 (7.6)	2.6	(-5.7 to 10.8)
Non-invasive ventilation	199	29 (14.6)	303	29 (9.6)	6.0	(-4.6 to 16.6)
Emergency Department discharge disposition, n(%)	199		303			
Home		3 (1.5)		15 (5.0)	-3.1	(-9.4 to 3.2)
ED observation unit		96 (48.2)		137 (45.2)	-2.9	(-16.3 to 10.6)
Hospital ward		60 (30.2)		111 (36.6)	3.2	(-9.7 to 16.2)
Intensive care unit [e]		40 (20.1)		38 (12.5)	9.2	(-1.6 to 20.0)

Table 2: Management in the Emergency Department. IQR, interquartile range;

[a] Differences were adjusted for intervention, time period and cluster size (categorical) as fixed effects and cluster as a random effect.

[b] Furosemide was the only iv diuretic used in participating centers.

[c] Cumulative dose of nitrates over the period of time that includes boluses (first hour) and infusion (between first hour and 4th hour), among patients that were treated with nitrates.

[d] Given the small numbers, no analysis was performed for the dual antiplatelet agents variable.

[e] Including cardiac intensive care unit.

Endpoints	Intervention		Usual Care		Unadjusted difference	95%CI	Adjusted difference[a]	95%CI	Adjusted ratio	95% CI	Adjusted risk ratio	95% CI
	n		n									
Primary endpoint, median (IQR)												
Days alive and out of hospital at day 30	199	19.0 (0.0 - 24.0)	303	19.0 (0.0 - 24.0)	0.0	(-4.0 to 4.0)	-1.9	(-6.6 to 2.8)	0.88	(0.64 to 1.21)		
Secondary endpoints, N (%)												
30-day all-cause mortality	199	16 (8.0)	299[c]	29 (9.7)	-1.7%	(-7.1% to 3.8%)	4.1%	(-17.2% to 25.3%)			1.17	(0.53 to 2.57)
30-day cardiovascular mortality	199	10 (5.0)	299	22 (7.4)	-2.3%	(-7.0 to 2.3)	2.1%	(-15.5% to 19.8%)			1.12	(0.45 to 2.82)
30-day hospital re-admission	154	22 (14.3)	235	37 (15.7)	-1.5%	(-9.2% to 6.3%)	-1.3%	(-26.3 to 23.7%)			0.96	(0.48 to 1.95)
Length of hospital stay, days, median (IQR)	182	8.0 (5.0 - 21.0)	269	8.0 (5 - 16.0)	0.0	(-1.8 to 1.8)	2.5	(-0.9 to 5.8)	1.22	(0.94 to 1.59)		
2-fold rise in creatinine level[b]	192	2 (1.0)	287	4 (1.4)								

Table 3: Study endpoints in the primary analysis. IQR: interquartile range. RR: risk ratio

[a] Difference, ratios and risk ratios were adjusted for time period and cluster size (categorical) as fixed effects and cluster as a random effect. The difference is expressed as intervention minus control, and the ratio intervention/control.

[b] Given the small numbers, no analysis was performed for the 2-fold rise in creatinine level variable.