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**Title:** Door-to-furosemide time and clinical outcomes in acute heart failure

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PM and MTB, the main authors, contributed equally to gather the data, statistical analysis and writing of the manuscript.

FV-N and JPF helped in the statistical analysis, reviewed the first version of the manuscript and added important input to its final version.

The remainder authors reviewed and helped with the final version of the manuscript.

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The reminder authors, including the main authors, declare no conflicts of interests.

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### **Abstract**

**Background and importance:** Acute heart failure (AHF) is one of the main causes of unplanned hospitalisation in patients with >65 years of age and is associated with adverse outcomes in this population. Observational studies suggest that intravenous (IV) diuretic therapy given in the first hour of presentation for AHF was associated with favourable outcomes.

**Objectives:** To study the short-term prognostic associations of the timing of IV diuretic therapy in patients admitted in the emergency department (ED) for acute AHF.

**Design, settings and participants:** Patients treated in the ED with IV diuretics were selected from the EDIFICA registry, a prospective study including AHF hospitalized patients. Early and non-early furosemide treatment groups were considered using the 1-hour cut-off: Door to furosemide  $\leq 1$ h and  $> 1$ h.

**Outcomes measure and analysis:** Primary outcomes were a composite of heart failure re-hospitalizations or cardiovascular death at 30- and 90-days.

**Main results:** 493 patients were included in the analysis. The median (interquartile range) Door to furosemide time was 85 (41-220) minutes, and 210 (43%) patients had diuretics in the first hour. Patients in the  $\leq 1$ h group had higher evaluation priority according to the Manchester Triage System, presented more often with acute pulmonary oedema, warm-wet clinical profile, higher blood pressure and signs of left-side HF, while  $> 1$ h group had higher Get With the Guidelines-HF risk score, more frequent signs of right-side HF, higher circulating B-type natriuretic peptides and lower albumin. Door to furosemide  $\leq 1$ h was independently associated with lower 30-day heart failure hospitalizations and composite of heart failure hospitalizations or cardiovascular death (adjusted analysis Heart Failure Hospitalizations: OR 3.65, 95%CI 1.22-10.9,  $p=0.020$ ;

Heart Failure Hospitalizations or Cardiovascular Death: OR 3.15, 95%CI 1.49-6.64;  $p < 0.001$ ). These independent associations lost significance at 90-days.

**Conclusion:** Door to furosemide  $\leq 1$ h was associated with a lower short-term risk of heart failure hospitalizations or cardiovascular death in acute heart failure patients. Our findings add to the existing evidence that an early identification and IV diuretic therapy of acute heart failure patients may improve outcomes.

**Key Words**

Acute Heart Failure; Diuretic therapy; Door-to-furosemide.

## **Background**

Acute heart failure (AHF) is characterized by the onset of symptoms and/or signs of heart failure (HF) leading to an emergency department (ED) visit or hospital admission [1]. AHF represents the main cause of unplanned hospitalisation in patients with >65 years of age, and is associated with high morbimortality [2].

Previous studies suggested that intravenous (IV) diuretic therapy given within the first hour of presentation for AHF was associated with lower in-hospital mortality.[3] Further replication of these results in different populations and hospital settings is needed, since such associations may be influenced by patient population and health care system's organization. In this regard, factors contributing for the rapid identification of an AHF episode and treatment administration remain poorly understood.

## **Aims**

We aim to study the short-term prognostic associations of the timing of IV diuretic therapy i.e., door-to-furosemide time (D2F), and the factors associated with a rapid IV diuretic therapy (i.e., within 1h after presentation) in patients admitted in the ED for AHF.

## Methods

The EDIFICA registry was a prospective registry of patients presenting and admitted to the hospital due to acute heart failure between January 2009 and December 2010 at the Internal Medicine Department of Centro Hospitalar Universitário São João, Porto, Portugal. We conducted a retrospective analysis of this prospectively collected data. Patients admitted with the primary diagnosis of AHF were eligible. Patients with acute coronary syndromes and whose symptoms were explained by conditions other than HF were excluded. All patients underwent detailed clinical history, physical examination, and venous blood sample analysis at admission and discharge. An echocardiogram was performed within 72h after admission. Renal function was estimated using the CKD-EPI creatinine–cystatin C equation [4]. The investigation conforms with the principles outlined in the Declaration of Helsinki and was approved by the local ethics committee.

All patients considered in the analysis were firstly evaluated and treated at the ED. D2F time was calculated based on the time of ED arrival and time of IV furosemide administration recorded by the attending nurse. Patients were divided into early and non-early furosemide treatment groups based on previous studies [3,5]: D2F  $\leq$ 1 hour and D2F  $>$ 1 hour, respectively. Get With the Guidelines - Heart Failure (GWTG-HF) risk score was calculated as previously described [6].

Categorical variables are described as frequencies (proportions), and continuous variables are described as means $\pm$ standard deviation or median (25th and 75th percentiles), depending on their distributions. Comparisons of demographic, clinical, and biological parameters were analysed using analysis of Variance (ANOVA) for continuous normally distributed variables, the analogous non-

parametric Kruskal–Wallis test for continuous non-normally distributed variables, and Chi Squared Test ( $\chi^2$ ) for categorical variables.

The primary outcome a composite of heart failure re-hospitalizations (HFH) or cardiovascular death at 30- and 90-days. Logistic regression models were used to assess the relation between D2F groups and the clinical endpoints, adjusting for sex, atrial fibrillation, GWTG-HF score and B-type natriuretic peptide (BNP). Results are presented as Odds Ratio (OR) and respective 95% confidence interval (95%CI). All statistical analyses were performed with Stata® (StataCorp. 2021: Release 17.0.).

## Results

The median age was 80 years, and 203 (42%) patients were men. Median ejection fraction was 40%, and 38.3% of the patients had HF of ischemic aetiology. Median (IQR) D2F time was 85 (41-220) minutes, and 210 (42.6%) patients had a D2F $\leq$ 1h.

**Table 1** summarizes the patients characteristics according to the 1h D2F time cutoff. D2F $\leq$ 1h group were triaged more often as orange/red colour according to the Manchester Triage System (MTS)[7] (82.4 vs 53.3%;  $p<0.001$ ), and presented at the ED more often with acute pulmonary oedema, warm-wet clinical profile, higher blood pressure and signs of “left-side” HF (e.g., rales). In contrast, D2F $>$ 1h associated with higher GWTG-HF risk score, more frequent signs of “right-side” HF (e.g., jugular vein distension), higher circulating BNP, and lower albumin levels. Multivariate analysis identified MTS score, diastolic blood pressure, left ventricular mass index as positive, and BNP levels as negative, independent predictors of D2F $\leq$ 1h (**Supplemental Table 1**).

**Table 2** show the data regarding clinical outcomes. D2F was a significant predictor of 30-day heart failure hospitalizations and composite of heart failure hospitalizations or cardiovascular death: adjusted analysis for heart failure hospitalizations: OR 3.65, 95%CI 1.22-10.9,  $p=0.020$ ; and heart failure hospitalizations or cardiovascular death: OR 3.15, 95%CI 1.49-6.64;  $p<0.001$ . Regarding cardiovascular death, the association with D2F was lost after adjustment. These independent associations lost significance at 90 days. **Figure 1** illustrates the distribution of D2F time and its relationship with the composite outcome (heart failure hospitalizations or cardiovascular death).

## **Discussion**

Early IV diuretic therapy ( $D2F \leq 1h$ ) has been associated with lower short-term all-cause mortality in AHF [3,8]. However, patient, and organizational factors enabling an early treatment, and its association with HFH and cause-specific mortality, have not yet been reported. In this report, we show that  $D2F \leq 1h$  was an important predictor of short-term heart failure re-hospitalizations or cardiovascular death. By showing an association of  $D2F \leq 1h$  with heart failure hospitalizations or cardiovascular death (and in-hospital mortality), our findings expand previous reports that showed an association of  $D2F \leq 1h$  with in-hospital mortality only [3,9]. These findings are important because they suggest that strategies enabling an early IV diuretic therapy may improve the short-term outcomes in AHF. One exception was the KorAHF registry [5], which did not find any independent relation of  $D2F$  time with short-term mortality or heart failure re-hospitalization. Differences in the trial population and proportion of early treated patients (43% in EDIFICA vs 24% in the KorAHF registry), may underlie the different impact of early furosemide administration.

In AHF, the rapid identification of clinical severity is critical, but challenging in the ED environment. In our registry, 95% of patients were triaged as yellow to red (MTS), indicating the need for a medical evaluation within the first hour. Still, despite a higher risk profile, patients in  $D2F > 1h$  group received lower priority and delayed medical evaluation and treatment. Distinct clinical presentations may explain this difference in treatment priority, with patients in the  $D2F \leq 1h$  group presenting with higher blood pressure and “left-sided” HF symptoms, which contrast with the lower blood pressure and “right-sided” HF symptoms present in the  $D2F > 1h$  group. This fact highlights an important limitation of the MTS system

in the evaluation of patients with heart failure in the Emergency Department, overlooking patients with “right sided” AHF.

## **Limitations**

Several limitations should be acknowledged in this study. The retrospective nature of our analysis does not make it possible to draw causality. Moreover, the smaller sample size comparing to the other registries and the lack of data on diuretic dosage prevents further investigation on the mechanisms involved and generalization to other AHF populations.

## **Conclusion**

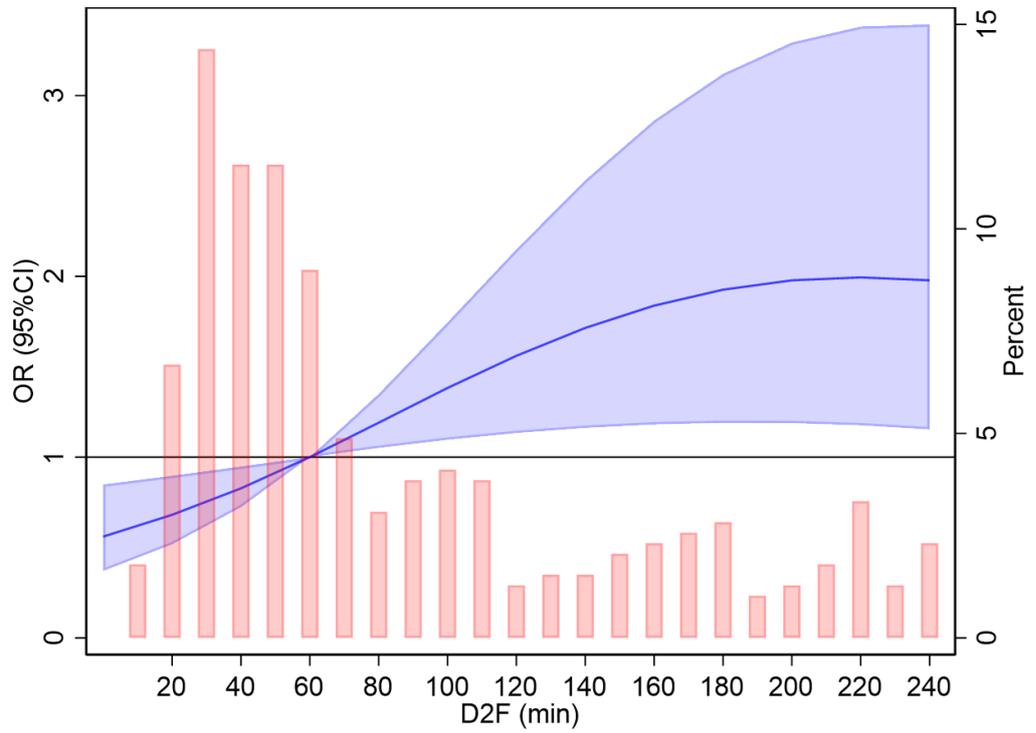
In conclusion,  $D2F \leq 1h$  was associated with a lower short-term risk of heart failure hospitalizations or cardiovascular death. Our findings, expanding on prior reports, suggest that an early identification and IV diuretic therapy of AHF patients may improve outcomes. An emergency department protocolled care, similar to that used in acute coronary syndromes or acute stroke, could potentially avoid the delays in the care of this population and improve patient care.

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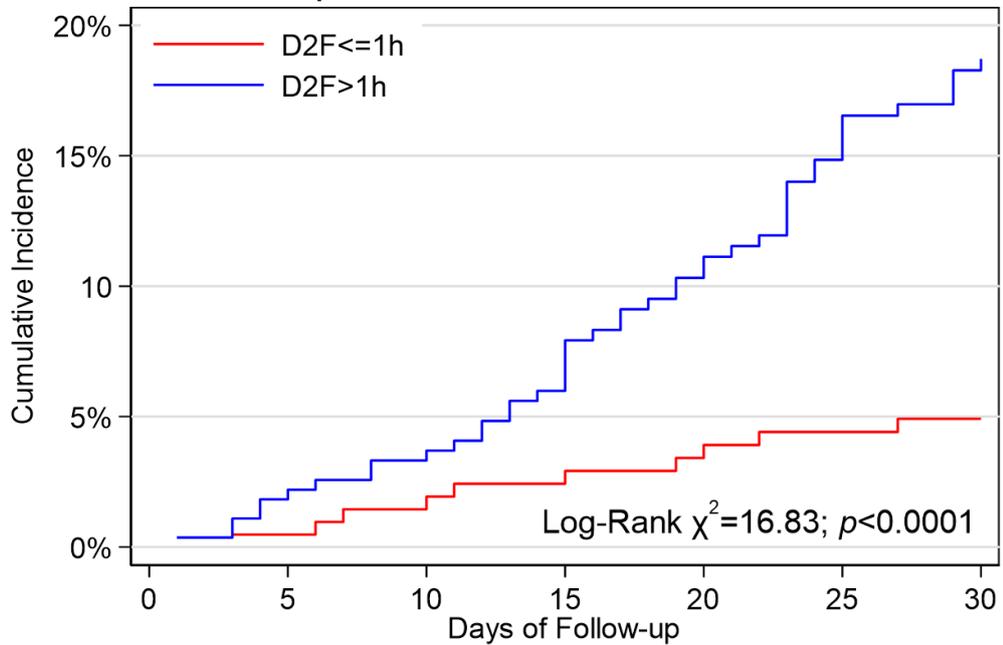
Figure 1

**A**



**B**

Cumulative HF Rehospitalizations or Cardiovascular Death



Number at risk

D2F<=1h	208	207	205	203	201	199	198
D2F>1h	275	270	265	258	247	236	227

**Table 1. Baseline Characteristics**

Characteristic	D2F≤1h (n=210)	D2F>1h (n=283)	P-value
Age (years)	79 (72-85)	80 (72-84)	0.9
Male sex	89 (42.8)	114 (41.5)	0.8
BMI (Kg/m <sup>2</sup> )	25.4 (22.9-28.7)	24.9 (22.6-27.7)	0.1
<b>Previous Medical History</b>			
Hypertension	165 (81.7)	194 (74.9)	0.08
Diabetes Mellitus	85 (41.1)	112 (40.7)	0.9
Atrial Fibrillation	86 (42)	129 (47.6)	0.2
Coronary artery disease	85 (31.4)	75 (27.4)	0.3
Chronic kidney disease	46 (23)	65 (24.6)	0.7
COPD	43 (25.0)	46 (21.1)	0.4
Anaemia	91 (44.8)	116 (43.3)	0.7
<b>Previous Medication</b>			
Beta-blocker	98 (46.7)	123 (43.5)	0.5
ACEi or ARB	131 (62.4)	169 (59.7)	0.6
MRA	25 (11.9)	40 (14.1)	0.5
Loop diuretics	139 (66.2)	191 (67.5)	0.8
Thiazide diuretics	39 (18.6)	55 (19.4)	0.8
<b>ED Clinical Presentation</b>			
Manchester Triage colour (red/orange)	173 (82.4)	148 (53.3)	<b>&lt;0.001</b>
Systolic blood pressure (mmHg)	140 (120-157)	129 (113-149)	<b>&lt;0.001</b>
Diastolic blood pressure (mmHg)	78 (69-92)	73 (60-85)	<b>&lt;0.001</b>
Heart rate (bpm)	89 (74-110)	85 (73-100)	<b>0.038</b>
Respiratory rate (cpm)	25 (21-31)	24 (20-32)	0.4
Jugular venous distension	62 (36.0)	107 (47.6)	<b>0.022</b>
Peripheral oedema	143 (76.9)	191 (81.6)	0.2
Rales	183 (94.3)	214 (88.4)	<b>0.032</b>
Acute pulmonary oedema	48 (23.1)	27 (9.8)	<b>&lt;0.001</b>
New York Heart Association (III/IV)	207 (98.6)	279 (98.6)	0.99
Clinical Profile			<b>0.012</b>
<i>Warm-wet</i>	199 (97.5)	242 (90.0)	
<i>Cold-wet</i>	3 (1.5)	14 (5.2)	
<i>Cold-dry</i>	0 (0.0)	3 (1.1)	
GWTC-HF score	43 (38-48)	45 (39-51)	<b>0.014</b>
<b>Admission Analytical Evaluation</b>			
Hemoglobin (g/dL)	11.6 (10.4-13.3)	11.7 (10.3-13.2)	0.8
Albumin (g/L)	36.4 (33.1-39.0)	35.1 (32.0-37.9)	<b>0.003</b>
AST (IU/L)	28 (21-38)	27 (20-40)	0.6
ALT (IU/L)	23 (15-36)	20 (15-35)	0.4

Characteristic	D2F≤1h (n=210)	D2F>1h (n=283)	P-value
Creatinine (mg/dL)	1.4 (1.1-1.8)	1.4 (1.1-1.8)	0.9
Cystatin C (mg/L)	1.3 (1.0-1.9)	1.5 (1.1-2.0)	0.07
Urea (mg/dL)	62 (47-92)	70 (48-105)	0.2
eGFR <sup>1</sup> (mL/min/1.73m <sup>2</sup> )	42.1 (28.7-56.1)	41.7 (27.8-55.1)	0.5
Sodium (mmol/L)	139 (135-141)	139 (135-142)	0.9
Potassium (mmol/L)	4.1 (3.7-4.4)	4.1 (3.7-4.6)	0.4
Iron (mg/mL)	36 (23-55)	37 (24-51)	0.9
C-reactive protein (mg/L)	18.3 (8.3-51.1)	22.2 (10.2-54.0)	0.2
Troponin I (ng/mL)	0.1 (0.0-0.2)	0.1 (0.0-0.1)	0.2
BNP (pg/mL)	1293 (852-2536)	1922 (1016-3028)	<b>0.003</b>
<b>Echocardiographic Evaluation</b>			
Ejection Fraction (%)	40 (27-56)	41 (26-57)	0.8
LAVI (mL/m <sup>2</sup> )	48 (39-58)	51 (39-41)	0.1
LVMI (g/m <sup>2</sup> )	161 (129-189)	144 (121-176)	<b>0.024</b>
PASP (mmHg)	47 (38-56)	47 (38-57)	0.7
Cardiac output (L/min)	4.5 (3.5-5.6)	4.1 (3.4-5.1)	<b>0.021</b>
E/e'	16.8 (12.7-24.2)	18.0 (13.0-22.9)	0.8
<b>Admission to Discharge variations</b>			
Length of stay (days)	8 (5-12)	8 (6-12)	0.4
Δ Weight (Kg)	-1.3 (-3.0, 0.0)	-1.0 (-3.0, 0.0)	0.5
Δ BNP (pg/mL)	-477 (-933, -95)	-501 (-1229, -65)	0.6
Δ eGFR <sup>1</sup> (mL/min/1.73m <sup>2</sup> )	-1.1 (-1.2, 8.0)	2.7 (-6.1, 15.0)	<b>0.002</b>

<sup>1</sup>CKD-EPI Cr-Cystatin C formula

ACEi – Angiotensin converting enzyme inhibitor; ARB – Angiotensin receptor blocker; AST - aspartate aminotransferase; BNP – B-type natriuretic peptide; BMI – Body Mass Index; COPD – Chronic obstructive pulmonary disease; D2F – Door to furosemide; ED – Emergency department; eGFR – estimated Glomerular filtration rate; GWTG-HF – Get With the Guidelines – Heart Failure; LAVI – Left atrial volume indexed; LVMI – Left ventricular mass indexed; MRA – Mineralocorticoid receptor antagonist; PASP – Pulmonary artery systolic pressure.

**Table 2.** Door-to-furosemide time and cardiovascular outcomes

Outcomes <sup>a</sup>	N (%)	Unadjusted		Adjusted <sup>b</sup>	
			<i>P</i> -value		<i>P</i> -value
<b>HF Hospitalization</b>					
<b>30-Day</b>					
<i>D2F</i> ≤ 1h	4 (1.9)	Reference	-	Reference	-
<i>D2F</i> > 1h	21 (7.6)	4.21 (1.42-12.5)	<b>0.009</b>	3.65 (1.22-10.9)	<b>0.020</b>
<b>90-Day</b>					
<i>D2F</i> ≤ 1h	36 (17.3)	Reference	-	Reference	-
<i>D2F</i> > 1h	52 (18.9)	1.11 (0.70-1.67)	0.7	1.02 (0.63-1.68)	0.9
<b>Cardiovascular Death</b>					
<b>30-Day</b>					
<i>D2F</i> ≤ 1h	9 (4.3)	Reference	-	Reference	-
<i>D2F</i> > 1h	27 (9.5)	2.31 (1.06-5.04)	<b>0.036</b>	1.51 (0.64-3.57)	0.3
<b>90-Day</b>					
<i>D2F</i> ≤ 1h	19 (9.1)	Reference	-	Reference	-
<i>D2F</i> > 1h	48 (17.5)	2.10 (1.19-3.70)	<b>0.010</b>	1.47 (0.77-2.82)	0.2
<b>HF Hospitalization or Cardiovascular Death</b>					
<b>30-Day</b>					
<i>D2F</i> ≤ 1h	10 (4.8)	Reference	-	Reference	-
<i>D2F</i> > 1h	46 (17.2)	4.10 (2.02-8.33)	<b>&lt;0.001</b>	3.15 (1.49-6.64)	<b>0.003</b>
<b>90-Day</b>					
<i>D2F</i> ≤ 1h	49 (23.6)	Reference	-	Reference	-
<i>D2F</i> > 1h	88 (32.1)	1.53 (1.02-2.31)	<b>0.040</b>	1.17 (0.75-1.85)	0.5

<sup>a</sup> Odds ratios (OR) are presented with their 95% confidence interval.

<sup>b</sup> Adjusted for sex, atrial fibrillation, GWTG-HF score (systolic blood pressure, BUN, sodium, age, heart rate, COPD and black race), ejection fraction,  $BNP_{log}$   
 BNP – B-type natriuretic peptide; BUN – Blood urea nitrogen; COPD – Chronic obstructive pulmonary disease; D2F – Door to furosemide; HF – Heart failure; GWTG-HF – Get With the Guidelines – Heart Failure;

**Table 1 (Supplemental).** Multivariate analysis identifying independent associations with D2F≤1h.

<b>Characteristic</b>	<b>OR<sup>1</sup></b>	<b>Z</b>	<b>95% CI<sup>2</sup></b>	<b>p-value</b>
<b>Manchester Triage colour</b> (red or orange)	4.65	6.66	2.96, 7.31	<b>&lt;0.001</b>
<b>Diastolic Blood Pressure</b> (per 10 mmHg)	1.24	3.68	1.10, 1.37	<b>&lt;0.001</b>
<b>Left Ventricular Mass Index</b> (per 5 g/m <sup>2</sup> )	1.07	2.84	1.02, 1.12	<b>0.005</b>
<b>BNP</b> (per log2)	0.83	-2.19	0.70, 0.98	<b>0.029</b>

<sup>1</sup>OR = Odds Ratio, <sup>2</sup>CI = Confidence Interval

