

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

## Impact of renal dysfunction on the management and outcome of acute heart failure: results from the French prospective, multicenter, DeFSSICA survey

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022776
Article Type:	Research
Date Submitted by the Author:	03-Apr-2018
Complete List of Authors:	<p>dos Reis, Dominique; Val de Grâce Medical School, Ministère de la Défense</p> <p>Fratlicelli, Laurie; Centre Hospitalier de Vienne Lucien Hussenel, RESCUE Network</p> <p>Bassand, Adrien; CHRU Nancy, Emergency Department; CHRU Nancy, CIC-P</p> <p>Manzo-Silberman, Stéphane; Hopital Lariboisiere, Department of Cardiology; INSERM UMR-S-942</p> <p>Peschanski, Nicolas; Centre Hospitalier Eure-Seine, Emergency Department</p> <p>Charpentier, Sandrine; Hopital de Rangueil, Emergency Department; Universite Toulouse III Paul Sabatier</p> <p>Elbaz, Meyer; Hopital de Rangueil, Department of Cardiology</p> <p>Savary, Dominique; Annecy-Genevois, Emergency Department and Intensive Care Unit</p> <p>Bonnefoy-Cudraz, Eric; Hôpital Cardiologique de Lyon, Department of Cardiology</p> <p>Laribi, Said; Centre Hospitalier Regional Universitaire de Tours, Emergency Department; INSERM UMR-S-942, Université Paris-Diderot, Sorbonne</p> <p>Henry, Patrick; Hopital Lariboisiere, Department of Cardiology; INSERM UMR-S-942, Université Paris-Diderot, Sorbonne</p> <p>Guerraoui, Abdallah; Groupement Hospitalier Edouard Herriot, Emergency Department; Universite Claude Bernard Lyon 1</p> <p>Tazarourte, Karim; University Hospital, Hospices Civils, Lyon, Emergency Medicine; University Lyon 1, Health Services and Performance Research Laboratory, EA 7425</p> <p>Chouihed, Tahar; CHRU Nancy, SAMU-SMUR-SAU; Institut Lorrain du Coeur et des Vaisseaux</p> <p>El Khoury, Carlos; Centre Hospitalier de Vienne Lucien Hussenel, Emergency Department and RESCUE Network</p>
Keywords:	acute heart failure, AHF, cardio-renal syndrome, CRS, real-life, renal dysfunction

SCHOLARONE™  
Manuscripts

1 Impact of renal dysfunction on the management and outcome of acute heart failure: results  
2 from the French prospective, multicenter, DeFSSICA survey

3 Dominique dos Reis, MD<sup>1</sup>, Laurie Fraticelli PhD<sup>2</sup>, Adrien Bassand, MD<sup>3</sup>, Stéphane Manzo-  
4 Silberman, MD, PhD<sup>4</sup>, Nicolas Peschanski, MD, PhD<sup>5</sup>, Sandrine Charpentier, MD, PhD<sup>6</sup>,  
5 Meyer Elbaz, MD, PhD<sup>7</sup>, Dominique Savary, MD<sup>8</sup>, Eric Bonnefoy-Cudraz, MD, PhD<sup>9</sup>, Said  
6 Laribi, MD, PhD<sup>10</sup>, Patrick Henry, MD, PhD<sup>11</sup>, Abdallah Guerraoui, MD<sup>12</sup>, Karim Tazarourte,  
7 MD, PhD<sup>13</sup>, Tahar Chouihed, MD<sup>14</sup>, Carlos El Khoury, MD, PhD<sup>15</sup>

8 <sup>1</sup>Val de Grâce Medical School, Ministère de la Défense, Paris, France ([d.dosreis@live.fr](mailto:d.dosreis@live.fr));

9 <sup>2</sup>RESCUe Network, Lucien Hussel Hospital, Vienne, France ([l.fraticelli@resuval.fr](mailto:l.fraticelli@resuval.fr));

10 <sup>3</sup>SAMU-SMUR-SAU Nancy, Hôpital Central, CHRU Nancy, France

11 ([adrienbassand@gmail.com](mailto:adrienbassand@gmail.com)); <sup>4</sup>Lariboisière Hospital, Department of Cardiology, Paris, France

12 and INSERM UMR-S 942, Université Paris-Diderot, Sorbonne Paris Cité, Paris, France

13 ([stephane.manzosilberman@aphp.fr](mailto:stephane.manzosilberman@aphp.fr)); <sup>5</sup>Emergency Department, SAMU 27, Eure Seine

14 Evreux Hospital, France ([bansbari@gmail.com](mailto:bansbari@gmail.com)); <sup>6</sup>Emergency Department, Rangueil

15 University Hospital, Toulouse, France; INSERM, U1027, Toulouse, France; Université

16 Toulouse III – Paul Sabatier, Toulouse, France ([charpentier.s@chu-toulouse.fr](mailto:charpentier.s@chu-toulouse.fr)); <sup>7</sup>Department

17 of Cardiology, Rangueil Hospital, Toulouse, France ([elbaz.m@chu-toulouse.fr](mailto:elbaz.m@chu-toulouse.fr)); <sup>8</sup>Emergency

18 Department and Intensive Care Unit, Annecy-Genevois, Metz-Tessy, France

19 ([savaryd@wanadoo.fr](mailto:savaryd@wanadoo.fr)); <sup>9</sup>Department of Cardiology, Hôpital Cardiologique de Lyon, Lyon,

20 France ([eric.bonnefoy-cudraz@chu-lyon.fr](mailto:eric.bonnefoy-cudraz@chu-lyon.fr)); <sup>10</sup>Emergency Medicine Department, University

21 Hospital of Tours; INSERM UMR-S 942, Université Paris-Diderot, Sorbonne Paris Cité,

22 Paris, France ([s.laribi@chu-tours.fr](mailto:s.laribi@chu-tours.fr)); <sup>11</sup>Lariboisière Hospital, Department of Cardiology,

23 Paris, France; INSERM UMR-S 942, Université Paris-Diderot, Sorbonne Paris Cité, Paris,

24 France ([patrick.henry@aphp.fr](mailto:patrick.henry@aphp.fr)); <sup>12</sup>Calydial Dialysis Department, Lucien Hussel Hospital,

25 Vienne, France ([abdallah.guerraoui@calyodial.org](mailto:abdallah.guerraoui@calyodial.org)); <sup>13</sup>Emergency Department, Edouard

1  
2  
3 26 Herriot Hospital, Lyon, France; Univ. Lyon, Claude Bernard Lyon 1 University, HESPER EA  
4  
5 27 7425, Lyon, France ([karim.tazarourte@chu-lyon.fr](mailto:karim.tazarourte@chu-lyon.fr)); <sup>14</sup>SAMU-SMUR-SAU Nancy, Hôpital  
6  
7 28 Central, CHRU Nancy, France; Centre d'Investigation Clinique Plurithématique 1433, Institut  
8  
9 29 Lorrain du Cœur et des Vaisseaux, Vandoeuvre-les-Nancy France; INSERM U1116,  
10  
11 30 Université de Lorraine, Nancy, France ([t.chouihed@gmail.com](mailto:t.chouihed@gmail.com)); <sup>15</sup>Emergency Department  
12  
13 31 and RESCUE Network, Lucien Hessel Hospital, Vienne, France; Univ. Lyon, Claude Bernard  
14  
15 32 Lyon 1 University, HESPER EA 7425, Lyon, France ([c.elkhoury@vienne.fr](mailto:c.elkhoury@vienne.fr))  
16  
17  
18

19 **Corresponding author:**

20  
21  
22 34 Carlos El Khoury, MD, PhD  
23  
24 35 Emergency Department and RESCUE Network, Lucien Hessel Hospital, Vienne, France;  
25  
26 36 Univ. Lyon, Claude Bernard Lyon 1 University, HESPER EA 7425, Lyon, France  
27  
28  
29 37 Tél. +33 (0) 4 7431 3257; Mob. +33 (0) 6 2410 4024; email [c.elkhoury@resuval.fr](mailto:c.elkhoury@resuval.fr)  
30  
31

32 **Target journal & format:** BMJ Open - Research Articles format (counts: abstract 300 words  
33  
34 [max 300]; 6 keywords; body 3513 words (max 4000); 74 references; 1 figure, 5 tables)  
35  
36  
37  
38  
39  
40

1  
2  
3 41 **Abstract (300 words [max 300])**  
4

5  
6 42 **Objectives:** Cardio-renal syndrome (CRS) is the combination of acute heart failure syndrome  
7  
8 43 (AHF) and renal dysfunction (creatinine clearance [CrCl]  $\leq 60$  mL/min). Real-life data were  
9  
10 44 used to compare the management and outcome of AHF with and without renal dysfunction.  
11

12  
13 45 **Design:** Prospective, multi-center.  
14

15  
16 46 **Setting:** Twenty-six academic, community, and regional hospitals in France.  
17

18  
19 47 **Participants:** 507 patients with AHF were assessed in two groups according to renal  
20  
21 48 function: Group 1 (CRS patients [CrCl  $\leq 60$  mL/min]: N=335) and Group 2 (AHF patients  
22  
23 49 with normal renal function [CrCl  $> 60$  mL/min]: N=172).  
24

25  
26  
27 50 **Results:** Differences were observed (Group 1 versus Group 2) at admission for the incidence  
28  
29 51 of chronic heart failure (56.42% versus 47.67%), use of furosemide (60.9% versus 52.91%),  
30  
31 52 insulin (15.52% versus 9.3%), and amiodarone (14.33% versus 4.65%); additionally, more  
32  
33 53 patients in Group 1 carried a defibrillator (4.78% versus 0%), had  $\geq 2$  hospitalizations in the  
34  
35 54 last year (15.52% versus 5.81%), and were under the care of a cardiologist (72.24% versus  
36  
37 55 61.63%). Clinical signs were broadly similar in each group. Brain-type natriuretic peptide  
38  
39 56 (BNP) and BNP prohormone were higher in Group 1 than Group 2 (1157.5 versus 534 ng/L  
40  
41 57 and 5120 versus 2513 ng/mL), and more patients in Group 1 were positive for troponin  
42  
43 58 (58.2% versus 44.19%), had cardiomegaly (51.04% versus 37.21%), and interstitial opacities  
44  
45 59 (60.3% versus 47.67%). The only difference in emergency treatment was the use of nitrates,  
46  
47 60 (higher in Group 1 [21.9% versus 12.21%]). In-hospital mortality and the percentage of  
48  
49 61 patients still hospitalized after 30 days was similar between groups, but median stay was  
50  
51 62 longer in Group 1 (8 days versus 6 days).  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 63 **Conclusions:** Renal impairment in AHF should not limit the use of loop diuretics and/or  
4  
5 64 vasodilators, but early assessment of pulmonary congestion and close monitoring of the  
6  
7 65 efficacy of conventional therapies is encouraged to allow rapid and appropriate  
8  
9 66 implementation of alternative therapies if necessary.  
10  
11  
12 67  
13  
14  
15 68  
16  
17  
18 69  
19  
20  
21 70 **Keywords:** acute heart failure, AHF, cardio-renal syndrome, CRS, real-life, renal dysfunction  
22  
23  
24  
25 71  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

1  
2  
3 72 **Strengths and limitations of this study**  
4  
5

- 6 73 • Few large-scale, prospective, real-life data exist for the real-life management and  
7  
8 74 outcome of patients with cardio-renal syndrome compared to acute heart failure patients  
9  
10 75 without renal dysfunction.  
11  
12 76 • Cardio-renal syndrome is of prognostic importance.  
13  
14 77 • Only two groups were included (i.e. patients with or without kidney dysfunction), rather  
15  
16 78 than for each stage of chronic kidney disease although the creatinine clearance cut-off (60  
17  
18 79 mL/min) is commonly used.  
19  
20 80 • Glomerular filtration rate estimations were performed by local laboratories for each  
21  
22 81 center (i.e. a real-life situation), rather than standardized at a single center, although this  
23  
24 82 reflects the real-life situation.  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 84 **Background**

85 Heart failure (HF) has an incidence of approximately 2% in adults in developed countries [1]  
86 and mainly affects elderly patients, who may have multiple comorbidities. One such  
87 comorbidity, impaired renal function, has been shown to be a stronger predictor of mortality  
88 than impaired cardiac function [2 3] and can be present in 50% of patients treated for acute  
89 HF (AHF) [4]. The prognostic importance of the association of renal dysfunction and AHF  
90 has only been demonstrated recently, and cardio-renal syndrome (CRS), a complex  
91 pathophysiological condition [5 6], is a combination of AHF syndrome and creatinine  
92 clearance (CrCl)  $\leq 60$  mL/min.

93 Even moderate degrees of renal insufficiency are independently associated with an increased  
94 risk of mortality from any cause in patients with HF [7] and CRS can lead to hesitancy among  
95 some clinicians to implement appropriate treatments for HF, such as diuretics, due to the  
96 effect that these may have to worsen the renal insufficiency. However, additional prospective  
97 research is needed and current recommendations are to maintain such treatments in CRS  
98 patients [8 9].

99 In this context, a sub-analysis was conducted using real-life data from the DeFSSICA study  
100 (Description de la Filière de Soins dans les Syndromes d'Insuffisance Cardiaque Aigue), a  
101 large-scale, prospective study that was conducted in patients with suspected dyspnea of  
102 cardiac origin in emergency departments (EDs) throughout France [10]. The aim of this sub-  
103 analysis was to compare the management and outcome of CRS patients to AHF patients  
104 without renal dysfunction in France using novel real-life data, based on the hypothesis that  
105 CRS and AHF patients would have the same outcome if the management of CRS was based  
106 on that for AHF patients without renal dysfunction.

107



1  
2  
3 108 **Methods**

4  
5  
6 109 *Study design*

7  
8  
9 110 This was a prospective, multi-center study in patients presenting with suspected heart failure  
10  
11 111 dyspnea in 26 EDs in academic, community, and regional hospitals (the DeFSSICA study) for  
12  
13 112 which the rationale and design are reported elsewhere [10]. The study received approval from  
14  
15 113 the National Commission for Liberties and Data Protection (Commission Nationale de  
16  
17 114 l'Informatique et des Libertés) (number DR-2014-543) and the Advisory Committee on the  
18  
19 115 Treatment of Information in the field of Health Research (Comité Consultatif sur le  
20  
21 116 Traitement de l'Information en matière de Recherche dans le Domaine de la Santé) (number  
22  
23 117 14-291). The study did not affect the patient-physician relationship or the patient's care and  
24  
25 118 follow-up.

26  
27  
28  
29 119 *Patient involvement*

30  
31  
32 120 Written information regarding the objectives of the survey was provided to all patients prior  
33  
34 121 to their inclusion. The research question was based on the prognostic importance of CRS and  
35  
36 122 a need for real-life data on the management and outcome of CRS patients. Patients were not  
37  
38 123 involved in the design, recruitment, and conduct of the study, and there is no plan to  
39  
40 124 disseminate the results specifically to the patients who provided data used in this analysis.

41  
42  
43  
44 125 *Selection of participants*

45  
46  
47 126 In the DeFSSICA survey, patients >18 years of age with dyspnea compatible with acute HF,  
48  
49 127 defined as dyspnea associated with peripheral edema and/or pulmonary crackles and/or  
50  
51 128 excessive weight gain and/or use of furosemide, were eligible for inclusion after ED  
52  
53 129 admission and prior to chest X-ray and laboratory tests. Patient enrollment occurred between  
54  
55 130 16 June 2014 and 7 July 2014.

1  
2  
3 131 In this analysis, only patients with known CrCl were included and were divided into those  
4  
5 132 with CrCl  $\leq$ 60 mL/min, i.e. renal dysfunction (Group 1) and those with CrCl >60 mL/min, i.e.  
6  
7 133 normal renal function (Group 2). Glomerular filtration rate (GFR) was calculated using either  
8  
9 134 the Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD) Study, or Chronic  
10  
11 135 Kidney Disease Epidemiology Collaboration (CKD-EPI) equations [11 12].  
12  
13

#### 14 136 *Study assessments*

15  
16  
17 137 Patients' baseline characteristics, medical history, social factors, in-hospital diagnostic tests  
18  
19 138 and treatment, destination after ED discharge, in-hospital mortality and length of stay were  
20  
21 139 recorded by emergency physicians in a case report form, which was structured according to  
22  
23 140 the progress of care. Cardiac sonographic evaluations were performed at the discretion of  
24  
25 141 emergency physician. Abnormal chest X-ray was defined by the presence of cardiomegaly,  
26  
27 142 and/or alveolar edema, and/or interstitial opacity, and/or pleural effusion. The choice of  
28  
29 143 treatment was at the emergency physician's sole discretion, according to their usual practice.  
30  
31 144 Final diagnosis of AHF was made by the emergency physician using a combination of a  
32  
33 145 clinical history, abnormal chest X-ray, elevated brain-type natriuretic peptide (BNP) or BNP  
34  
35 146 prohormone (proBNP), and echocardiographic signs.  
36  
37  
38  
39

40 147 Although it was not possible to impose any randomization or blinding since this was an  
41  
42 148 observational study, any potential bias in the study assessments was minimized by the  
43  
44 149 provision of standard instructions to all participating physicians.  
45  
46

47 150 Data were entered into a secure database located at the Réseau Cardiologie Urgence  
48  
49 151 (RESCUe) (Cardiovascular Emergency Network) Coordination Center.  
50  
51

#### 52 152 *Statistical analysis*

53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 153 Medians and interquartile ranges (IQR) are provided for continuous variables, and numbers  
4  
5 154 and percentages for qualitative variables. Comparative analyses were performed using the  $\chi^2$   
6  
7 155 or Fisher's test for binary variables and the Wilcoxon test for analysis of variance for  
8  
9 156 continuous variables [13]. The 5% level was used to identify differences between groups that  
10  
11 157 were of statistical significance ( $p < 0.05$ ). Statistical evaluations were performed using R  
12  
13 158 Statistical Software (Version 3.4.1).

15  
16  
17 159

## 160 **Results**

### 161 *Patient disposition and prevalence of CRS*

162 A total of 64,281 ED consultations took place during the survey period and 699 patients with  
163 dyspnea of cardiac origin were included in DEFSSICA study. Of these, 537 patients were  
164 identified as having AHF, of whom only those with known CrCl (N=507) were included in  
165 this analysis.

166 Patients in Group 1 (N=335 [66.1%]) had renal dysfunction (CrCl  $\leq$ 60 mL/min) and  
167 comprised the population with CRS. In this group, 99 patients (29.6%) had severe renal  
168 dysfunction (Stage 4 or 5: CrCl:  $<$ 30 mL/min) and 120 (35.8%) had a known history of  
169 chronic renal failure. All patients in Group 2 (N=172 [33.9%]) had normal renal function  
170 (CrCl  $>$ 60 mL/min).

171 Patient disposition is presented in Figure 1.

### 172 *Baseline characteristics*

173 The baseline characteristics of patients in Group 1 and Group 2 are shown in Table 1. There  
174 was no difference between Group 1 and Group 2 in age (median [IQR]: 84 [88-79] years and  
175 82 [75-88] years;  $p=0.0864$ ) or sex distribution (42.99% male in Group 1 and 44.19% male in  
176 Group 2;  $p=0.8699$ ).

177 As well as the higher incidence of chronic renal failure in Group 1, patients with CRS were  
178 more likely to have chronic HF (56.42% in Group 1 versus 47.67% in Group 2;  $p=0.0490$ ).

179 There was no difference in the incidence of any other comorbidity between groups. Patients in  
180 Group 1 were more likely than patients in Group 2 to receive furosemide (60.9% versus  
181 52.91%;  $p=0.0498$ ), insulin (15.52% versus 9.3%;  $p=0.0272$ ) and amiodarone (14.33% versus

1  
2  
3 182 4.65%;  $p=0.0004$ ) but there were no other differences between groups for medications.  
4  
5 183 Additionally, patients in Group 1 were more likely to carry a defibrillator (4.48% versus 0%;  
6  
7 184  $p=0.0018$ ), to have been hospitalized for HF at least twice during the last year (15.52% versus  
8  
9 185 8.81%;  $p=0.0031$ ), and to be under the care of a cardiologist (72.24% versus 61.63%;  
10  
11 186  $p=0.0198$ ), although there were no differences in the incidence of pacemakers between  
12  
13 187 groups.

14  
15  
16 188 Patients in Group 1 were more likely to have a housekeeper (31.13% versus 23.26%;  
17  
18 189  $p=0.0170$ ) and nurse (29.25% versus 20.93%;  $p=0.0359$ ) but there was no difference between  
19  
20 190 groups regarding family support, known cognitive impairment, or the incidence of being  
21  
22 191 bedridden.

#### 23 24 25 26 192 *Hospitalization and clinical status*

27  
28  
29 193 The only difference in clinical signs between the groups was a higher incidence of inspiratory  
30  
31 194 retraction in Group 1 than Group 2 (31.94% versus 22.67%;  $p=0.0229$ ) (Table 2).

32  
33  
34 195 Vital signs were generally similar in Group 1 and Group 2, and there were no significant  
35  
36 196 differences between groups in their means of transport to the ED (most commonly by  
37  
38 197 personal means [45.76% overall]), Killip status (most patients in each group had a Killip  
39  
40 198 status of 2 [53.06% overall]), and signs of cardiogenic shock (2.96% overall).

#### 41 42 43 44 199 *Early management and diagnosis*

45  
46  
47 200 At admission, blood samples from all patients underwent biological analysis (Table 3). As  
48  
49 201 well as the differences between groups for CrCl, significant differences were observed for  
50  
51 202 BNP, which was 2.2-fold higher in Group 1 than Group 2 (1157.5 ng/L versus 534 ng/L;  
52  
53 203  $p=0.0048$ ), and proBNP, which was 2.0-fold higher in Group 1 than Group 2 (5120 ng/L  
54  
55 204 versus 2513 ng/L;  $p<0.0001$ ). Additionally, troponin was more likely to be positive in patients

1  
2  
3 205 in Group 1 than Group 2 (58.21% versus 44.19%;  $p=0.0011$ ). There were no differences  
4  
5 206 between groups for sodium, potassium, or hemoglobin.

6  
7  
8 207 Most patients underwent under an electrocardiogram (98.61% overall) chest X-ray (94.87%  
9  
10 208 overall). Patients in Group 1 were more likely than those in Group 2 to have left bundle  
11  
12 209 branch block (19.1% versus 12.79%;  $p=0.0461$ ), cardiomegaly (51.04% versus 37.21%;  
13  
14 210  $p=0.0144$ ), and interstitial opacities (60.3% versus 47.67%;  $p=0.0199$ ).

15  
16  
17 211 Echography was performed for 16.17% patients overall, more often by a cardiologist (57.32%  
18  
19 212 overall) than by an emergency physician (42.68% overall). There was no significant  
20  
21 213 difference between groups in left ventricular ejection fraction.

#### 22 23 24 25 214 *Emergency treatments*

26  
27  
28 215 Patients in Group 1 were more likely than Group 2 to receive emergency treatment of nitrates  
29  
30 216 (21.19% versus 12.21%;  $p=0.0057$ ), but there were no group differences in other emergency  
31  
32 217 measures (furosemide, oxygen, anticoagulant, continuous positive airway pressure, non-  
33  
34 218 invasive ventilation, anti-arrhythmics, inotropic agents, tracheal intubation) (Table 4). Overall  
35  
36 219 6.31% of patients received no emergency treatment, with no difference between groups.

#### 37 38 39 40 220 *Outcomes*

41  
42  
43 221 Precipitating factors were not determined in 42.21% of cases overall, with no overall  
44  
45 222 difference between groups (Table 5). The most common determined precipitating factors were  
46  
47 223 infection (25.25% overall), arrhythmia (15.19% overall), and hypertension (10.65% overall).  
48  
49 224 Diabetes decompensation was considered to be the precipitating factor for AHF in 2.99% of  
50  
51 225 patients in Group 1 but none in Group 2 ( $p=0.0110$ ). There were no other group differences in  
52  
53 226 precipitating factors.

1  
2  
3 227 There was no difference between groups in discharge destination (which was most often  
4  
5 228 cardiology [28.01% overall]), and the discharge destination was deemed appropriate for a  
6  
7 229 similar number of patients in each group (75.35% overall).  
8  
9

10 230 Neither in-hospital mortality (5.92% overall) nor the percentage of patients still hospitalized  
11  
12 231 at 30 days (6.31% overall) were significantly different between Group 1 and Group 2.  
13

14 232 However, the median length of stay was 2 days longer in Group 1 than in Group 2 (8 days  
15  
16 233 versus 6 days;  $p=0.0327$ ) (Table 5).  
17  
18

19  
20 234  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 235 Discussion

236 The DeFSSICA study was a large-scale, prospective, real-life study conducted following  
237 admission of AHF patients to EDs throughout France. As such, the data are primarily  
238 applicable to the French population, although wider extrapolation is possible due to  
239 coherences with similar studies in other geographical regions. The overall DeFSSICA study  
240 data are presented elsewhere [10] and the present sub-analysis reports novel real-life data  
241 from sub-groups of AHF patients from the DeFSSICA study with or without concomitant  
242 renal dysfunction, based on a CrCl threshold of 60 mL/min. The results show that AHF  
243 admissions to EDs are often associated with renal impairment, with almost two-thirds of AHF  
244 admissions having CrCl  $\leq$ 60 mL/min. This prevalence is comparable to published data from  
245 France [14], Italy [15 16], Poland [17], Spain [18 19], Taiwan [20], and the USA [21-23], as  
246 well as from pan-European [24 25] and wider international studies [26]. In these studies [14-  
247 26], the prevalence of renal impairment on admission of AHF patients ranged from 54.5% to  
248 64%, including 12.4 to 27.4% of patients with severe renal insufficiency. Patients with a  
249 history of chronic renal failure ranged from 21.4% to 32.5%, which is also comparable to the  
250 findings of the DeFSSICA survey. However, it should be noted that impaired cardiac function  
251 leads to reduced renal perfusion, which could be in addition to an underlying chronic renal  
252 insufficiency or not, and so the proportion of CRS patients is likely to be over-estimated due  
253 to a possible associated transient increase in serum creatinine at admission (GFR was  
254 calculated using the Cockcroft-Gault, MDRD, or CKD-EPI equations). Additionally, increased  
255 abdominal pressure at admission that can result from ascites can lead to a renal vein  
256 compression and reduced GFR at admission, which could also result in elevated serum  
257 creatinine. It is likely, therefore, that a proportion of acute kidney injury diagnosed at  
258 admission based on serum creatinine could be due to temporary changes in perfusion  
259 pressures rather than kidney damage *per se*; these functional reductions in GFR would be



1  
2  
3 260 expected to recover once normal hemodynamic function is restored. It is therefore important  
4  
5 261 to use biomarkers to provide a more precise assessment of kidney function than serum  
6  
7 262 creatinine [27 28]. Equations to estimate GFR have replaced 24-hour creatinine clearance  
8  
9 263 measurement in EDs because of the difficulty of urine collection. Creatinine clearance, urea  
10  
11 264 clearance, net sodium excretion, and fractional excretion of sodium calculated over 6 hours  
12  
13 265 can be used to evaluate kidney function and to define the natriuretic response precisely [29].  
14  
15 266 Conversely, the proportion of patients with a history of chronic renal injury is likely to be  
16  
17 267 under-estimated due to memory bias.

18  
19  
20  
21 268 The overall baseline characteristics, clinical status, biological and diagnostic tests, emergency  
22  
23 269 treatment, and outcome of the patients included in this sub-analysis was similar to the overall  
24  
25 270 population in the DeFSSICA study; however, some differences were observed between AHF  
26  
27 271 patients with and without renal dysfunction. As would be expected due to reduced kidney  
28  
29 272 excretion [30], and as described elsewhere [31-34], BNP and pro-BNP levels were higher in  
30  
31 273 patients with CRS than in AHF patients with normal renal function and the percentage of  
32  
33 274 troponin positive patients was also higher in the CRS group. These biomarkers probably  
34  
35 275 reflect the congestion status and remain formally recommended for the management of AHF  
36  
37 276 patients, especially for their prognostic value. The appropriate use of loop diuretics and/or  
38  
39 277 vasodilators [35] in the CRS group, as well as in the AHF group without renal dysfunction,  
40  
41 278 may explain in part the similar intra-hospital mortality rate in each group and the similar  
42  
43 279 proportion of AHF patients with and without renal dysfunction who were still in hospital at 30  
44  
45 280 days after ED admission. Importantly, therefore, the prognosis of CRS patients was not  
46  
47 281 significantly different using loop diuretics and/or nitrates to those without renal dysfunction.  
48  
49 282 As such, it appears that the correct congestive assessment is vital in this complex clinical  
50  
51 283 situation with concomitant failures in two organs.  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 284 Worsening renal function (WRF), which leads to a progressive loss of kidney function [30], is  
4  
5 285 a factor for poor long-term prognosis [21 36 37] and Ferreira et al [2] showed that all  
6  
7 286 formulae used to estimate renal function showed a strong and independent association with  
8  
9 287 cardiovascular mortality, with eGFR or CrCl rates under 60 mL/min being associated with  
10  
11 288 increasing cardiovascular mortality. As such, the use of loop diuretics has been considered to  
12  
13 289 be deleterious to long-term renal function, probably since impaired renal function can have  
14  
15 290 etiologies other than those related to congestion. However, despite WRF, Testani et al have  
16  
17 291 recently shown an improvement in prognosis in AHF patients when loop diuretics are used  
18  
19 292 [9]. Moreover, for patients treated for AHF, kidney injury appears to be more common in  
20  
21 293 those with an altered ejection fraction than in those with a preserved ejection fraction [37].  
22  
23 294 However, despite these differences in pathophysiology and etiology between AHF patients  
24  
25 295 with and without renal dysfunction, patient outcome is similar [38 39] meaning that renal  
26  
27 296 dysfunction does not have an impact on outcome in AHF patients. Overall, the results of the  
28  
29 297 sub-analysis of the DeFSSICA survey data for AHF patients with and without renal  
30  
31 298 dysfunction support this conclusion. Although a small but statistically significant increase in  
32  
33 299 the length of hospital stay from 6 to 8 days was observed in CRS patients, who showed a  
34  
35 300 greater incidence of certain co-morbidities (inspiratory retraction, left bundle branch block,  
36  
37 301 cardiomegaly and interstitial opacities), there was no difference in in-hospital mortality or in  
38  
39 302 the number of patients still hospitalized at 30 days post-admission. Additionally, there was no  
40  
41 303 difference in ejection fraction in CRS patients compared to AHF patients with normal renal  
42  
43 304 function.

44  
45  
46  
47  
48  
49 305 Recent publications suggest that appropriate, fast-acting decongesting therapies, as  
50  
51 306 recommended by international guidelines, improve the prognosis for AHF patients as long as  
52  
53 307 such therapies are introduced early, even if renal impairment develops at the same time [8].

54  
55 308 Furthermore, it appears that renal impairment in AHF patients does not have an adverse

1  
2  
3 309 impact on patient prognosis provided that the congestion is improved. Renal function should  
4  
5 310 be assessed according to the level of patient congestion, and so tools for the assessment of  
6  
7 311 congestion, such as the BNP or proBNP biomarkers [40], lung ultrasound (LUS) B-lines (38),  
8  
9 312 or the assessment of the dimensions and compliance of the inferior vena cava are vital. Novel  
10  
11 313 biomarkers such as urinary angiotensinogen [41], neutrophil gelatinase-associated lipocalin  
12  
13 314 [42 43], kidney injury molecule-1 [44], interleukin-18 [45 46], N-acetyl- $\beta$ -d-glucosaminidase  
14  
15 315 [47], cystatine C [48 49] or a combination of some or all of these could also be used to  
16  
17 316 improve the diagnosis of acute kidney injury. Furthermore, the assessment of diuresis and  
18  
19 317 natriuresis, which reflect both glomerular and tubular function, could offer a more successful  
20  
21 318 strategy to achieve decongestion [47 50 51]. Ferreira et al [52] and Palazzuoli et al [53] have  
22  
23 319 recently demonstrated that the lack of a diuretic response is a more important prognostic  
24  
25 320 factor than the use of loop diuretics. This suggests a new diagnostic challenge, i.e. to assess  
26  
27 321 the patient's response to diuretics [54-57]. However, despite some proposals to define diuretic  
28  
29 322 resistance (e.g. persistent congestion despite adequate and escalating doses of diuretic with  
30  
31 323 >80 mg furosemide/day, amount of sodium excreted as a percentage of filtered load <0.2%,  
32  
33 324 failure to excrete  $\geq$ 90 mmol of sodium within 72 hours of a 160 mg oral furosemide dose  
34  
35 325 given twice daily) and the means of evaluation (e.g. weight loss per unit of 40 mg furosemide  
36  
37 326 [or equivalent], net fluid loss/mg of loop diuretic [40 mg of furosemide or equivalent] during  
38  
39 327 hospitalization, natriuretic response to furosemide as the ratio of urinary sodium to urinary  
40  
41 328 furosemide) [58], there is currently no consensus for commonly accepted standards.  
42  
43 329 Additionally, it is important that any alteration of GFR should be interpreted in the context of  
44  
45 330 the deterioration of the clinical situation.

50  
51 331 Another alternative therapy in this challenging clinical situation is the use of  
52  
53 332 mineralocorticoid antagonists, which have been associated with an improvement in both  
54  
55 333 congestion [59 60] and mortality in HF patients [61 62], although the ATHENA-HF trial

1  
2  
3 334 results appear to cast doubt on these favorable conclusions [63]. Combined therapies have  
4  
5 335 also been evaluated, including hypotonic saline serum in combination with diuretic therapy to  
6  
7 336 improve diuresis [64 65] and mannitol in combination with furosemide [58], although their  
8  
9 337 benefit in diuretic-resistant patients is not confirmed. The addition of metozalone to  
10  
11 338 furosemide could be of interest because of its capacity to produce diuresis even in patients  
12  
13 339 with low GFR [66 67], although metozalone is not yet marketed in France. In a recent meta-  
14  
15 340 analysis, Wang and al have shown that tolvaptan, an oral vasopressin V<sub>2</sub>-receptor antagonist,  
16  
17 341 may also represent an alternative therapy in WRF [68], and several studies have demonstrated  
18  
19 342 that it can decrease the rate of WRF in patients treated with furosemide [69 70]. Finally,  
20  
21 343 venous ultrafiltration allows a controlled hydrosodic depletion by subtracting isotonic fluid  
22  
23 344 while diuretics allow the subtraction of hypotonic fluid. Other studies also suggest that the  
24  
25 345 effectiveness of ultrafiltration is associated with a reduction in inflammatory cytokines [71].  
26  
27 346 These and other approaches in patients with cardiac insufficiency and resistance to diuretics  
28  
29 347 have recently been reviewed [58].  
30  
31  
32  
33

34 348 The CRS analysis using data from the DeFSSICA survey has some limitations. First, only two  
35  
36 349 groups have been analyzed (i.e. patients with or without kidney dysfunction), although  
37  
38 350 chronic kidney disease is characterized by 5 stages. However, the CrCl threshold of 60  
39  
40 351 mL/min is commonly used [2 34 72-74] and is considered to be satisfactory for this analysis,  
41  
42 352 especially since the small number of patients would not allow a thorough analysis for five  
43  
44 353 sub-categories. The choice of a CrCl threshold of 30 mL/min could have led to a greater  
45  
46 354 chance of obtaining a significant difference between groups in terms of outcome, but the 60  
47  
48 355 mL/min cut-off is more widely used. Second, since the data used are observational, it was not  
49  
50 356 possible to impose any randomization or blinding, and the number of patients in each group  
51  
52 357 was not balanced. Third, GFR assessments were performed by local laboratories for each  
53  
54 358 center, rather than standardized at a single center, and repeated measures of GFR could have  
55  
56  
57  
58  
59  
60

1  
2  
3 359 improved their accuracy and comparability. The use of different formulae to evaluate CrCl in  
4  
5 360 a chronic disease state but in an acute context without knowledge of the baseline value  
6  
7 361 reflects the real-life situation. While potentially problematic, with the possibility of some  
8  
9 362 incorrect classification of CKD, numerous previous studies of the impact of renal failure in  
10  
11 363 AHF have used a similar approach [2 34 72]. Finally, it was not possible to sub-classify  
12  
13 364 different types of CRS in this analysis since Kidney Disease Improving Global Outcomes  
14  
15 365 (KDIGO) data were not collected.

## 18 366 **Conclusion**

20  
21  
22 367 These real-life data suggested that CRS patients have the same outcome as AHF patients  
23  
24 368 without renal dysfunction when the treatment of the former group is modeled on that for the  
25  
26 369 latter group. This finding should not limit the use of loop diuretics and/or vasodilators as long  
27  
28 370 as the patient presents congestion as assessed using biomarkers and ultrasound. The use of  
29  
30 371 diuretic treatment should be based on a more rapid diagnosis of congestion and evaluation of  
31  
32 372 an inadequate response to diuretics, allowing the rapid and appropriate implementation of  
33  
34 373 alternative therapies if necessary.  
35  
36  
37  
38 374

1  
2  
3 375 **Funding**  
4

5  
6 376 This work was supported by Novartis France, but the Sponsor was not involved in the study  
7  
8 377 protocol, methods, or choice of centers.  
9

10  
11 378 **Competing interests**  
12

13  
14 379 CEK and has received grants from Novartis (other than this work), Daiichy Sankyo, and  
15  
16 380 Boehringer Ingleheim.  
17

18  
19 381 NP reports has acted as a paid consultant for Vygon SA.  
20

21  
22 382 SC reports personal fees from Novartis (other than this work).  
23

24  
25 383 LF is an employee of RESCUe Network.  
26

27  
28 384 DdR, AB, SMZ, ME, DS, EBC, SL, PH, AG, KT and TC have no competing interests.  
29

30  
31  
32 385 **Authors' contributions**  
33

34  
35 386 SMZ, NP, SC, ME, DS, EBC, SL, PH, TC, and CEK conceived the study, designed the trial,  
36

37 387 and obtained research funding. TC and CEK supervised the conduct of the trial and data  
38

39 388 collection. NP, SC, DS and TC undertook recruitment of participating centers and patients. LF  
40

41 389 managed the data, including quality control, provided statistical advice and analyzed the data.  
42

43 390 DdR, LF, AB, AG, KT, TC and CEK drafted the manuscript, and all authors contributed  
44

45 391 substantially to its revision. All authors reviewed and approved the final version of the  
46

47 392 manuscript and are accountable for its content.  
48  
49

50  
51 393 **Consent for publication**  
52

53  
54 394 Not applicable since no individual patient is identified.  
55  
56  
57  
58  
59  
60

1  
2  
3 395 **Availability of data and material**  
4

5  
6 396 No additional data available.  
7

8  
9 397 **Acknowledgements**  
10

11 398 The authors thank the emergency physicians and cardiologists and patients who participated  
12  
13 399 in this survey at the following centers: CHU Toulouse, CHU Rouen, CHU Clermont Ferrand,  
14  
15 400 CHU Nancy, CHR Metz-Thionville-Hôpital de Mercy, Hôpital Lariboisière-Paris, CHR  
16  
17 401 Annecy Genevois, CHU Lyon-Hôp, Edouard Herriot, CHRU de Lille, Chu De Caen, CHU  
18  
19 402 Nice-Hôpital Saint-Roch, CHU de Grenoble, Hôpital Bicêtre-Paris, Hôpital St Louis Paris,  
20  
21 403 CH I Meulan, CH d'Avignon, CH Jacques Lacarin-Vichy, CH d'Aix En Provence, CH  
22  
23 404 Fleyriat –Bourg En Bresse, CH Bourgoin Jallieu, CHU de Saint Etienne, CH du Forez  
24  
25 405 Montbrison-Feurs, CH de Firminy, CH Villefranche-Sur-Saône, CHU De Brest, CH Henri  
26  
27 406 Mondor, CH de Vienne.  
28  
29

30  
31  
32 407 The authors also thank the RESCUE Network for the practical implementation of this survey  
33  
34 408 and statistical analysis and Novartis France for its financial support.  
35

36  
37 409 Dr Andrew Lane (Lane Medical Writing), funded by the RESCUE network, provided  
38  
39 410 professional medical writing assistance in the preparation and development of the manuscript  
40  
41 411 in accordance with the European Medical Writers Association guidelines and Good  
42  
43 412 Publication Practice.  
44  
45

46  
47 413  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

414 **References**

- 415 1. Sayago-Silva I, Garcia-Lopez F, Segovia-Cubero J. Epidemiology of heart failure in Spain  
416 over the last 20 years. *Rev Esp Cardiol (Engl Ed)* 2013;**66**(8):649-56 doi:  
417 10.1016/j.rec.2013.03.012.
- 418 2. Ferreira JP, Girerd N, Pellicori P, et al. Renal function estimation and Cockcroft-Gault  
419 formulas for predicting cardiovascular mortality in population-based, cardiovascular  
420 risk, heart failure and post-myocardial infarction cohorts: The Heart 'OMics' in  
421 AGEing (HOMAGE) and the high-risk myocardial infarction database initiatives.  
422 *BMC Med* 2016;**14**(1):181 doi: 10.1186/s12916-016-0731-2.
- 423 3. Hillege HL, Girbes AR, de Kam PJ, et al. Renal function, neurohormonal activation, and  
424 survival in patients with chronic heart failure. *Circulation* 2000;**102**(2):203-10
- 425 4. Damman K, Valente MA, Voors AA, et al. Renal impairment, worsening renal function,  
426 and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J*  
427 2014;**35**(7):455-69 doi: 10.1093/eurheartj/eh386.
- 428 5. Ronco C, Haapio M, House AA, et al. Cardiorenal syndrome. *J Am Coll Cardiol*  
429 2008;**52**(19):1527-39 doi: 10.1016/j.jacc.2008.07.051.
- 430 6. Ronco C, House AA, Haapio M. Cardiorenal syndrome: refining the definition of a  
431 complex symbiosis gone wrong. *Intensive Care Med* 2008;**34**(5):957-62 doi:  
432 10.1007/s00134-008-1017-8.
- 433 7. Dries DL, Exner DV, Domanski MJ, et al. The prognostic implications of renal  
434 insufficiency in asymptomatic and symptomatic patients with left ventricular systolic  
435 dysfunction. *J Am Coll Cardiol* 2000;**35**(3):681-9.



- 1  
2  
3 436 8. Hanberg JS, Tang WHW, Wilson FP, et al. An exploratory analysis of the competing  
4  
5 437 effects of aggressive decongestion and high-dose loop diuretic therapy in the DOSE  
6  
7 438 trial. *Int J Cardiol* 2017;**241**:277-82 doi: 10.1016/j.ijcard.2017.03.114.  
8  
9  
10 439 9. Testani JM, Ter Maaten JM. Decongestion in Acute Heart Failure: Does the end justify the  
11  
12 440 means? *JACC Heart Fail* 2016;**4**(7):589-90 doi: 10.1016/j.jchf.2016.03.024.  
13  
14  
15 441 10. Chouihed T, Manzo-Silberman S, Peschanski N, et al. Management of suspected acute  
16  
17 442 heart failure dyspnea in the emergency department: results from the French  
18  
19 443 prospective multicenter DeFSSICA survey. *Scand J Trauma Resusc Emerg Med*  
20  
21 444 2016;**24**(1):112 doi: 10.1186/s13049-016-0300-x.  
22  
23  
24  
25 445 11. National Institute of Diabetes and Digestive and Kidney Diseases. Estimating glomerular  
26  
27 446 filtration rate (GFR) 2015. [https://www.niddk.nih.gov/health-information/health-](https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr/estimating/Pages/estimating.aspx)  
28  
29 447 [communication-programs/nkdep/lab-evaluation/gfr/estimating/Pages/estimating.aspx](https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr/estimating/Pages/estimating.aspx).  
30  
31 448 Accessed 29 March 2018.  
32  
33  
34  
35 449 12. Botev R, Mallie JP, Couchoud C, et al. Estimating glomerular filtration rate: Cockcroft-  
36  
37 450 Gault and modification of diet in renal disease formulas compared to renal inulin  
38  
39 451 clearance. *Clin J Am Soc Nephrol* 2009;**4**(5):899-906 doi: 10.2215/CJN.05371008.  
40  
41  
42 452 13. Ancelle T. *Statistique Epidémiologique*. 3rd ed. Paris: Maloine, 2011.  
43  
44  
45 453 14. Logeart D, Isnard R, Resche-Rigon M, et al. Current aspects of the spectrum of acute  
46  
47 454 heart failure syndromes in a real-life setting: the OFICA study. *Eur J Heart Fail*  
48  
49 455 2013;**15**(4):465-76 doi: 10.1093/eurjhf/hfs189.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 456 15. Oliva F, Mortara A, Cacciatore G, et al. Acute heart failure patient profiles, management  
4  
5 457 and in-hospital outcome: results of the Italian Registry on Heart Failure Outcome. *Eur*  
6  
7 458 *J Heart Fail* 2012;**14**(11):1208-17 doi: 10.1093/eurjhf/hfs117.  
8  
9
- 10 459 16. Tavazzi L, Maggioni AP, Lucci D, et al. Nationwide survey on acute heart failure in  
11  
12 460 cardiology ward services in Italy. *Eur Heart J* 2006;**27**(10):1207-15 doi:  
13  
14 461 10.1093/eurheartj/ehi845.  
15  
16
- 17 462 17. Straburzynska-Migaj E, Kaluzna-Oleksy M, Maggioni AP, et al. Patients with heart  
18  
19 463 failure and concomitant chronic obstructive pulmonary disease participating in the  
20  
21 464 Heart Failure Pilot Survey (ESC-HF Pilot) - Polish population. *Arch Med Sci*  
22  
23 465 2015;**11**(4):743-50 doi: 10.5114/aoms.2014.47878.  
24  
25  
26
- 27 466 18. Conde-Martel A, Formiga F, Perez-Bocanegra C, et al. Clinical characteristics and one-  
28  
29 467 year survival in heart failure patients more than 85 years of age compared with  
30  
31 468 younger. *Eur J Intern Med* 2013;**24**(4):339-45 doi: 10.1016/j.ejim.2013.01.005.  
32  
33
- 34 469 19. Llorens P, Escoda R, Miró O, et al. Characteristics and clinical course of patients with  
35  
36 470 acute heart failure and the therapeutic measures applied in Spanish emergency  
37  
38 471 departments: based on the EAHFE registry (Epidemiology of Acute Heart Failure in  
39  
40 472 Emergency Departments). *Emergencias* 2015;**27**:11-22.  
41  
42  
43
- 44 473 20. Chang H-Y, Wang C-C, Wu Y-W, et al. One-Year Outcomes of Acute Decompensated  
45  
46 474 Systolic Heart Failure in Taiwan: Lessons from TSOC-HFrEF Registry *Acta*  
47  
48 475 *Cardiologica Sinica* 2017;**33**(2):127-38.  
49  
50
- 51 476 21. Abraham WT, Fonarow GC, Albert NM, et al. Predictors of in-hospital mortality in  
52  
53 477 patients hospitalized for heart failure: insights from the Organized Program to Initiate  
54  
55  
56  
57  
58  
59

- 1  
2  
3 478 Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). J  
4  
5 479 Am Coll Cardiol 2008;**52**(5):347-56 doi: 10.1016/j.jacc.2008.04.028.  
6  
7  
8 480 22. Adams KF, Jr., Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients  
9  
10 481 hospitalized for heart failure in the United States: rationale, design, and preliminary  
11  
12 482 observations from the first 100,000 cases in the Acute Decompensated Heart Failure  
13  
14 483 National Registry (ADHERE). Am Heart J 2005;**149**(2):209-16 doi:  
15  
16 484 10.1016/j.ahj.2004.08.005.  
17  
18  
19  
20 485 23. Diercks DB, Fonarow GC, Kirk JD, et al. Risk stratification in women enrolled in the  
21  
22 486 Acute Decompensated Heart Failure National Registry Emergency Module  
23  
24 487 (ADHERE-EM). Acad Emerg Med 2008;**15**(2):151-8 doi: 10.1111/j.1553-  
25  
26 488 2712.2008.00030.x.  
27  
28  
29 489 24. Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme-- a  
30  
31 490 survey on the quality of care among patients with heart failure in Europe. Part 1:  
32  
33 491 patient characteristics and diagnosis. Eur Heart J 2003;**24**(5):442-63  
34  
35  
36  
37 492 25. Nieminen MS, Brutsaert D, Dickstein K, et al. EuroHeart Failure Survey II (EHFS II): a  
38  
39 493 survey on hospitalized acute heart failure patients: description of population. Eur  
40  
41 494 Heart J 2006;**27**(22):2725-36 doi: 10.1093/eurheartj/ehl193.  
42  
43  
44 495 26. Follath F, Yilmaz MB, Delgado JF, et al. Clinical presentation, management and  
45  
46 496 outcomes in the Acute Heart Failure Global Survey of Standard Treatment (ALARM-  
47  
48 497 HF). Intensive Care Med 2011;**37**(4):619-26 doi: 10.1007/s00134-010-2113-0.  
49  
50  
51  
52 498 27. Molitoris BA, Levin A, Warnock DG, et al. Improving outcomes of acute kidney injury:  
53  
54 499 report of an initiative. Nat Clin Pract Nephrol 2007;**3**(8):439-42 doi:  
55  
56 500 10.1038/ncpneph0551.  
57  
58  
59

- 1  
2  
3 501 28. Waikar SS, Bonventre JV. Creatinine kinetics and the definition of acute kidney injury. *J*  
4  
5 502 *Am Soc Nephrol* 2009;**20**(3):672-9 doi: 10.1681/ASN.2008070669.  
6  
7  
8 503 29. Testani JM, Hanberg JS, Cheng S, et al. Rapid and Highly Accurate Prediction of Poor  
9  
10 504 Loop Diuretic Natriuretic Response in Patients With Heart Failure. *Circ Heart Fail*  
11  
12 505 2016;**9**(1):e002370 doi: 10.1161/CIRCHEARTFAILURE.115.002370.  
13  
14  
15 506 30. Tuegel C, Bansal N. Heart failure in patients with kidney disease. *Heart* 2017 doi:  
16  
17 507 10.1136/heartjnl-2016-310794.  
18  
19  
20 508 31. Anwaruddin S, Lloyd-Jones DM, Baggish A, et al. Renal function, congestive heart  
21  
22 509 failure, and amino-terminal pro-brain natriuretic peptide measurement: results from  
23  
24 510 the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. *J*  
25  
26 511 *Am Coll Cardiol* 2006;**47**(1):91-7 doi: 10.1016/j.jacc.2005.08.051.  
27  
28  
29  
30 512 32. Group NW, Wu AH, Jaffe AS, et al. National Academy of Clinical Biochemistry  
31  
32 513 laboratory medicine practice guidelines: use of cardiac troponin and B-type natriuretic  
33  
34 514 peptide or N-terminal proB-type natriuretic peptide for etiologies other than acute  
35  
36 515 coronary syndromes and heart failure. *Clin Chem* 2007;**53**(12):2086-96 doi:  
37  
38 516 10.1373/clinchem.2007.095679.  
39  
40  
41  
42 517 33. Lamb EJ, Vickery S, Price CP. Amino-terminal pro-brain natriuretic peptide to diagnose  
43  
44 518 congestive heart failure in patients with impaired kidney function. *J Am Coll Cardiol*  
45  
46 519 2006;**48**(5):1060-1; author reply 61 doi: 10.1016/j.jacc.2006.06.019.  
47  
48  
49 520 34. Vickery S, Price CP, John RI, et al. B-type natriuretic peptide (BNP) and amino-terminal  
50  
51 521 proBNP in patients with CKD: relationship to renal function and left ventricular  
52  
53 522 hypertrophy. *Am J Kidney Dis* 2005;**46**(4):610-20 doi: 10.1053/j.ajkd.2005.06.017.  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 523 35. Peacock WF, Emerman C, Costanzo MR, Diercks DB, Lopatin M, Fonarow GC. Early  
4  
5 524 vasoactive drugs improve heart failure outcomes. *Congest Heart Fail* 2009;**15**(6):256-  
6  
7 525 64 doi: 10.1111/j.1751-7133.2009.00112.x.  
8  
9  
10 526 36. Damman K, Navis G, Voors AA, et al. Worsening renal function and prognosis in heart  
11  
12 527 failure: systematic review and meta-analysis. *J Card Fail* 2007;**13**(8):599-608 doi:  
13  
14 528 10.1016/j.cardfail.2007.04.008.  
15  
16  
17 529 37. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart  
18  
19 530 failure: prognostic and therapeutic implications from a prospective cohort study.  
20  
21 531 *Circulation* 2004;**109**(8):1004-9 doi: 10.1161/01.CIR.0000116764.53225.A9.  
22  
23  
24  
25 532 38. Abebe TB, Gebreyohannes EA, Tefera YG, et al. Patients with HFpEF and HFrEF have  
26  
27 533 different clinical characteristics but similar prognosis: a retrospective cohort study.  
28  
29 534 *BMC Cardiovasc Disord* 2016;**16**(1):232 doi: 10.1186/s12872-016-0418-9.  
30  
31  
32  
33 535 39. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes  
34  
35 536 within the heart failure spectrum. *Circulation* 2011;**123**(18):2006-13; discussion 14  
36  
37 537 doi: 10.1161/CIRCULATIONAHA.110.954388.  
38  
39  
40 538 40. Gargani L, Frassi F, Soldati G, et al. Ultrasound lung comets for the differential diagnosis  
41  
42 539 of acute cardiogenic dyspnoea: a comparison with natriuretic peptides. *Eur J Heart*  
43  
44 540 *Fail* 2008;**10**(1):70-7 doi: 10.1016/j.ejheart.2007.10.009.  
45  
46  
47 541 41. Yang X, Chen C, Tian J, et al. Urinary Angiotensinogen Level Predicts AKI in Acute  
48  
49 542 Decompensated Heart Failure: A Prospective, Two-Stage Study. *J Am Soc Nephrol*  
50  
51 543 2015;**26**(8):2032-41 doi: 10.1681/ASN.2014040408.  
52  
53  
54  
55  
56  
57  
58  
59

- 1  
2  
3 544 42. Elsharawy S, Raslan L, Morsy S, et al. Plasma neutrophil gelatinase-associated lipocalin  
4  
5 545 as a marker for the prediction of worsening renal function in children hospitalized for  
6  
7 546 acute heart failure. *Saudi J Kidney Dis Transpl* 2016;**27**(1):49-54 doi: 10.4103/1319-  
8  
9 547 2442.174071.
- 10  
11  
12 548 43. Ito M, Doi K, Takahashi M, et al. Plasma neutrophil gelatinase-associated lipocalin  
13  
14 549 predicts major adverse cardiovascular events after cardiac care unit discharge. *J*  
15  
16 550 *Cardiol* 2016;**67**(2):184-91 doi: 10.1016/j.jjcc.2015.05.010.
- 17  
18  
19 551 44. Medic B, Rovcanin B, Basta Jovanovic G, et al. Kidney Injury Molecule-1 and  
20  
21 552 Cardiovascular Diseases: From Basic Science to Clinical Practice. *Biomed Res Int*  
22  
23 553 2015;**2015**:854070 doi: 10.1155/2015/854070.
- 24  
25  
26  
27 554 45. *Les biomarqueurs en médecine d'urgence [French]*. 1 ed. Paris: Springer-Verlag, 2012.
- 28  
29  
30 555 46. Taub PR, Borden KC, Fard A, et al. Role of biomarkers in the diagnosis and prognosis of  
31  
32 556 acute kidney injury in patients with cardiorenal syndrome. *Expert Rev Cardiovasc*  
33  
34 557 *Ther* 2012;**10**(5):657-67 doi: 10.1586/erc.12.26.
- 35  
36  
37 558 47. Verbrugge FH, Dupont M, Steels P, et al. The kidney in congestive heart failure: 'are  
38  
39 559 natriuresis, sodium, and diuretics really the good, the bad and the ugly?'. *Eur J Heart*  
40  
41 560 *Fail* 2014;**16**(2):133-42 doi: 10.1002/ejhf.35.
- 42  
43  
44  
45 561 48. Lassus JP, Harjola VP, Peuhkurinen K, et al. Cystatin C, NT-proBNP, and inflammatory  
46  
47 562 markers in acute heart failure: insights into the cardiorenal syndrome. *Biomarkers*  
48  
49 563 2011;**16**(4):302-10 doi: 10.3109/1354750X.2011.555822.
- 50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 564 49. Legrand M, De Berardinis B, Gaggin HK, et al. Evidence of uncoupling between renal  
4  
5 565 dysfunction and injury in cardiorenal syndrome: insights from the BIONICS study.  
6  
7 566 PloS one 2014;**9**(11):e112313 doi: 10.1371/journal.pone.0112313.  
8  
9  
10 567 50. Metra M, Davison B, Bettari L, et al. Is worsening renal function an ominous prognostic  
11  
12 568 sign in patients with acute heart failure? The role of congestion and its interaction with  
13  
14 569 renal function. *Circ Heart Fail* 2012;**5**(1):54-62 doi:  
15  
16 570 10.1161/CIRCHEARTFAILURE.111.963413.  
17  
18  
19  
20 571 51. Mullens W, Verbrugge F, Nijst P, et al. Renal sodium avidity in heart failure: from  
21  
22 572 pathophysiology to treatment strategies. *European Heart Journal* 2017 doi:  
23  
24 573 10.1093/eurheartj/ehx035.  
25  
26  
27 574 52. Ferreira JP, Girerd N, Bettencourt Medeiros P, et al. Lack of Diuretic Efficiency (but Not  
28  
29 575 Low Diuresis) Early in An Acutely Decompensated Heart Failure Episode Is  
30  
31 576 Associated with Increased 180-Day Mortality. *Cardiorenal Med* 2017;**7**(2):137-49 doi:  
32  
33 577 10.1159/000455903.  
34  
35  
36  
37 578 53. Palazzuoli A, Testani JM, Ruocco G, et al. Different diuretic dose and response in acute  
38  
39 579 decompensated heart failure: Clinical characteristics and prognostic significance. *Int J*  
40  
41 580 *Cardiol* 2016;**224**:213-19 doi: 10.1016/j.ijcard.2016.09.005.  
42  
43  
44 581 54. Damman K, Testani JM. The kidney in heart failure: an update. *Eur Heart J*  
45  
46 582 2015;**36**(23):1437-44 doi: 10.1093/eurheartj/ehv010.  
47  
48  
49 583 55. Hoorn EJ, Ellison DH. Diuretic Resistance. *Am J Kidney Dis* 2017;**69**(1):136-42 doi:  
50  
51 584 10.1053/j.ajkd.2016.08.027.  
52  
53  
54  
55  
56  
57  
58  
59

- 1  
2  
3 585 56. Ray EC, Boyd-Shiwarski CR, Kleyman TR. Why Diuretics Fail Failing Hearts. *J Am Soc*  
4  
5 586 *Nephrol* 2017 doi: 10.1681/ASN.2017070797.  
6  
7  
8 587 57. Valente MA, Voors AA, Damman K, et al. Diuretic response in acute heart failure:  
9  
10 588 clinical characteristics and prognostic significance. *Eur Heart J* 2014;**35**(19):1284-93  
11  
12 589 doi: 10.1093/eurheartj/ehu065.  
13  
14  
15 590 58. ter Maaten JM, Valente MA, Damman K, et al. Diuretic response in acute heart failure-  
16  
17 591 pathophysiology, evaluation, and therapy. *Nat Rev Cardiol* 2015;**12**(3):184-92 doi:  
18  
19 592 10.1038/nrcardio.2014.215.  
20  
21  
22  
23 593 59. Bansal S, Lindenfeld J, Schrier RW. Sodium retention in heart failure and cirrhosis:  
24  
25 594 potential role of natriuretic doses of mineralocorticoid antagonist? *Circ Heart Fail*  
26  
27 595 2009;**2**(4):370-6 doi: 10.1161/CIRCHEARTFAILURE.108.821199.  
28  
29  
30 596 60. Hensen J, Abraham WT, Durr JA, et al. Aldosterone in congestive heart failure: analysis  
31  
32 597 of determinants and role in sodium retention. *Am J Nephrol* 1991;**11**(6):441-6.  
33  
34  
35 598 61. The RALES investigators. Effectiveness of spironolactone added to an angiotensin-  
36  
37 599 converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart  
38  
39 600 failure (the Randomized Aldactone Evaluation Study [RALES]). *Am J Cardiol*  
40  
41 601 1996;**78**(8):902-7.  
42  
43  
44  
45 602 62. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and  
46  
47 603 mortality in patients with severe heart failure. Randomized Aldactone Evaluation  
48  
49 604 Study Investigators. *The New England journal of medicine* 1999;**341**(10):709-17 doi:  
50  
51 605 10.1056/NEJM199909023411001.  
52  
53  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 606 63. Butler J, Anstrom KJ, Felker GM, et al. Efficacy and Safety of Spironolactone in Acute  
4  
5 607 Heart Failure: The ATHENA-HF Randomized Clinical Trial. *JAMA Cardiol* 2017 doi:  
6  
7 608 10.1001/jamacardio.2017.2198.  
8  
9  
10 609 64. Licata G, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-  
11  
12 610 volume hypertonic saline solution infusion in comparison with a high dose of  
13  
14 611 furosemide as bolus in refractory congestive heart failure: long-term effects. *Am Heart*  
15  
16 612 *J* 2003;**145**(3):459-66 doi: 10.1067/mhj.2003.166.  
17  
18  
19  
20 613 65. Paterna S, Di Pasquale P, Parrinello G, et al. Changes in brain natriuretic peptide levels  
21  
22 614 and bioelectrical impedance measurements after treatment with high-dose furosemide  
23  
24 615 and hypertonic saline solution versus high-dose furosemide alone in refractory  
25  
26 616 congestive heart failure: a double-blind study. *J Am Coll Cardiol* 2005;**45**(12):1997-  
27  
28 617 2003 doi: 10.1016/j.jacc.2005.01.059.  
29  
30  
31 618 66. Ng TM, Konopka E, Hyderi AF, et al. Comparison of bumetanide- and metolazone-based  
32  
33 619 diuretic regimens to furosemide in acute heart failure. *J Cardiovasc Pharmacol Ther*  
34  
35 620 2013;**18**(4):345-53 doi: 10.1177/1074248413482755.  
36  
37  
38  
39 621 67. Tilstone WJ, Dargie H, Dargie EN, et al. Pharmacokinetics of metolazone in normal  
40  
41 622 subjects and in patients with cardiac or renal failure. *Clin Pharmacol Ther*  
42  
43 623 1974;**16**(2):322-9.  
44  
45  
46 624 68. Wang C, Xiong B, Cai L. Effects of Tolvaptan in patients with acute heart failure: a  
47  
48 625 systematic review and meta-analysis. *BMC Cardiovasc Disord* 2017;**17**(1):164 doi:  
49  
50 626 10.1186/s12872-017-0598-y.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 627 69. Jujo K, Saito K, Ishida I, et al. Randomized pilot trial comparing tolvaptan with  
4  
5 628 furosemide on renal and neurohumoral effects in acute heart failure. *ESC Heart Fail*  
6  
7 629 2016;**3**(3):177-88 doi: 10.1002/ehf2.12088.  
8  
9  
10 630 70. Kimura K, Momose T, Hasegawa T, et al. Early administration of tolvaptan preserves  
11  
12 631 renal function in elderly patients with acute decompensated heart failure. *J Cardiol*  
13  
14 632 2016;**67**(5):399-405 doi: 10.1016/j.jjcc.2015.09.020.  
15  
16  
17 633 71. Torina AG, Silveira-Filho LM, Vilarinho KA, et al. Use of modified ultrafiltration in  
18  
19 634 adults undergoing coronary artery bypass grafting is associated with inflammatory  
20  
21 635 modulation and less postoperative blood loss: a randomized and controlled study. *J*  
22  
23 636 *Thorac Cardiovasc Surg* 2012;**144**(3):663-70 doi: 10.1016/j.jtcvs.2012.04.012.  
24  
25  
26  
27 637 72. Chew DP, Astley C, Molloy D, Vaile J, De Pasquale CG, Aylward P. Morbidity, mortality  
28  
29 638 and economic burden of renal impairment in cardiac intensive care. *Intern Med J*  
30  
31 639 2006;**36**(3):185-92 doi: 10.1111/j.1445-5994.2006.01012.x.  
32  
33  
34  
35 640 73. Schaub JA, Coca SG, Moledina DG, Gentry M, Testani JM, Parikh CR. Amino-Terminal  
36  
37 641 Pro-B-Type Natriuretic Peptide for Diagnosis and Prognosis in Patients With Renal  
38  
39 642 Dysfunction: A Systematic Review and Meta-Analysis. *JACC Heart Fail*  
40  
41 643 2015;**3**(12):977-89 doi: 10.1016/j.jchf.2015.07.014.  
42  
43  
44 644 74. Tsutamoto T, Kawahara C, Yamaji M, et al. Relationship between renal function and  
45  
46 645 serum cardiac troponin T in patients with chronic heart failure. *Eur J Heart Fail*  
47  
48 646 2009;**11**(7):653-8 doi: 10.1093/eurjhf/hfp072.  
49  
50  
51  
52 647  
53  
54  
55 648  
56  
57  
58  
59  
60

649 **Tables**

650 Table 1 Baseline characteristics of patients with confirmed acute heart failure (AHF)

651 syndrome

	All AHF patients (N=507)	Group 1 (n=335)	Group 2 (n=172)	p-value
Age, y	83 [77;88]	84 [78;89]	82 [75;88]	0.0864
Men	220 (43.39%)	144 (42.99%)	76 (44.19%)	0.8699
<b>Comorbidities</b>				
- Hypertension	353 (69.63%)	234 (69.85%)	119 (69.19%)	0.7939
- Chronic HF	271 (53.45%)	189 (56.42%)	82 (47.67%)	0.0490
- Atrial fibrillation	223 (43.98%)	151 (45.07%)	72 (41.86%)	0.4312
- Coronary heart disease	150 (29.59%)	98 (29.25%)	52 (30.23%)	0.9999
- Diabetes type I	14 (2.76%)	12 (3.58%)	2 (1.16%)	0.2589
- Diabetes type II	132 (26.04%)	93 (27.76%)	39 (22.67%)	0.1978
- Chronic renal failure	114 (22.49%)	108 (32.24%)	6 (3.49%)	<0.0001
- Chronic respiratory failure	87 (17.16%)	60 (17.91%)	27 (15.7%)	0.4565
- Known valvular disease	95 (18.74%)	70 (20.9%)	25 (14.53%)	0.0657
<b>Priori medications</b>				
- Furosemide	295 (58.19%)	204 (60.9%)	91 (52.91%)	0.0498
- ACEI/ARB	225 (44.38%)	153 (45.67%)	72 (41.86%)	0.2976
- $\beta$ - blocker	214 (42.21%)	147 (43.88%)	67 (38.95%)	0.1981
- Anticoagulant	221 (43.59%)	151 (45.07%)	70 (40.7%)	0.2442
- Aspirin	155 (30.57%)	110 (32.84%)	45 (26.16%)	0.0763
- Other antiplatelet	56 (11.05%)	37 (11.04%)	19 (11.05%)	0.7305
- Oral antidiabetic	66 (13.02%)	47 (14.03%)	19 (11.05%)	0.2150
- Insulin	68 (13.41%)	52 (15.52%)	16 (9.3%)	0.0272
- Amiodarone	56 (11.05%)	48 (14.33%)	8 (4.65%)	0.0004
- Aldosterone antagonist	38 (7.5%)	26 (7.76%)	12 (6.98%)	0.4820
- Digoxin	38 (7.5%)	18 (5.37%)	20 (11.63%)	0.0981
- Thiazidine	32 (6.31%)	21 (6.27%)	11 (6.4%)	0.7043
- None	28 (5.52%)	14 (4.18%)	14 (8.14%)	0.3808
- Unknown	13 (2.56%)	7 (2.09%)	6 (3.49%)	0.9999
<b>Pacemaker</b>				
- Single	17 (3.35%)	12 (3.58%)	5 (2.91%)	0.1061
- Dual	36 (7.1%)	27 (8.06%)	9 (5.23%)	0.2992
- Triple	6 (1.18%)	6 (1.79%)	0 (0%)	0.285
<b>Defibrillator</b>	16 (3.16%)	16 (4.78%)	0 (0%)	0.0018
<b>Prior hospitalization for HF during past year</b>				
- 0	287 (56.61%)	180 (53.73%)	107 (62.21%)	0.1397
- 1	130 (25.64%)	83 (24.78%)	47 (27.33%)	0.8556
- $\geq 2$	62 (12.23%)	52 (15.52%)	10 (5.81%)	0.0031

Followed by a cardiologist	348 (68.64%)	242 (72.24%)	106 (61.63%)	0.0198
Residence				
- At home	423 (83.43%)	287 (85.67%)	136 (79.07%)	0.0626
- Retirement institution	74 (14.6%)	43 (12.84%)	31 (18.02%)	0.1815
- Other institution	8 (1.58%)	4 (1.19%)	4 (2.33%)	0.7509
Self-sufficient	258 (50.89%)	162 (48.36%)	96 (55.81%)	0.1926
Home assistance				
- Housekeeper	151 (29.78%)	111 (33.13%)	40 (23.26%)	0.0170
- Family support	121 (23.87%)	87 (25.97%)	34 (19.77%)	0.1005
- Nurse	134 (26.43%)	98 (29.25%)	36 (20.93%)	0.0359
- Known cognitive impairment	83 (16.37%)	49 (14.63%)	34 (19.77%)	0.2579
- Bedridden	45 (8.88%)	25 (7.46%)	20 (11.63%)	0.2805

652 Data are median (IQR) age or number (%) of patients

653 Group 1: patients with CRS; Group 2: patients with normal renal function

654 AHF, acute heart failure; ADEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker;

655 HF, heart failure

656

657 Table 2 Hospitalization route and clinical status of patients with confirmed acute heart failure  
658 (AHF) syndrome

	All AHF patients (N = 507)	Group 1 (n = 335)	Group 2 (n = 172)	p-value
<b>Means of transport</b>				
- Personal	232 (45.76%)	157 (46.87%)	75 (43.6%)	0.5045
- Ambulance	89 (17.55%)	56 (16.72%)	33 (19.19%)	0.6291
- Firemen	55 (10.85%)	34 (10.15%)	21 (12.21%)	0.6530
- MICU	40 (7.89%)	29 (8.66%)	11 (6.4%)	0.4071
- Inter-hospital transfer	6 (1.18%)	5 (1.49%)	1 (0.58%)	0.4819
<b>Clinical signs</b>				
- Warm extremities	390 (76.92%)	257 (76.72%)	133 (77.33%)	0.2265
- Cold extremities	61 (12.03%)	45 (13.43%)	16 (9.3%)	0.9658
- Signs of right heart failure	216 (42.6%)	144 (42.99%)	72 (41.86%)	0.6861
- Inspiratory retraction	146 (28.8%)	107 (31.94%)	39 (22.67%)	0.0229
- Inability to speak	42 (8.28%)	25 (7.46%)	17 (9.88%)	0.5361
<b>First recorded vital signs</b>				
- Heart failure, beats/min	85 [71;102]	85 [72;102]	85 [72;104.25]	0.4861
- SBP, mmHg	140 [121;160]	140 [121;160]	140 [124;162]	0.1084
- DBP, mmHg	76 [65;90]	75 [63.5;89]	78 [67.75;92.25]	0.0262
- SBP <100 mmHg	34 (6.71%)	27 (8.06%)	7 (4.07%)	0.1300
- Respiratory rate, breaths/min	25 [20;30]	26 [20;30]	24 [20;29]	0.1585
- Pulse oximetry, %	94 [90;96.25]	94 [90;97]	94 [89;96]	0.7216
- GCS >15	48 (9.47%)	31 (9.25%)	17 (9.88%)	0.9448
- Temperature >37°C	13 (2.56%)	12 (3.58%)	1 (0.58%)	0.3669
<b>Killip status</b>				
- 1	128 (25.25%)	76 (22.69%)	52 (30.23%)	0.2611
- 2	269 (53.06%)	181 (54.03%)	88 (51.16%)	0.3000
- 3	84 (16.57%)	60 (17.91%)	24 (13.95%)	0.1057
- Signs of shock	15 (2.96%)	8 (2.39%)	7 (4.07%)	0.8915

659 Data are median (IQR) beats/minute, median (IQR) mmHg, median (IQR) breaths/minute, median (IQR) %, or

660 number (%) of patients

661 Group 1: patients with CRS; Group 2: patients with normal renal function

662 AHF, acute heart failure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; HF, heart failure; MICU,

663 mobile intensive care unit; SBP, systolic blood pressure

664

665 Table 3 Biological and diagnosis tests of patients with confirmed acute heart failure (AHF)  
666 syndrome

	All AHF patients (N=507)	Group 1 (n=335)	Group 2 (n=172)	p-value
<b>Biological analysis</b>				
- Performed	507 (100%)	335 (100%)	172 (100%)	
- Sodium, mmol/L	138 [135;141]	138 [135;141]	139 [135;141]	0.3967
- Potassium, mmol/L	4 [4;5]	4 [4;5]	4 [4;5]	0.8911
- Creatinine clearance, mL/min	50 [35;69.05]	40 [29;49.9]	78.5 [67;91]	<0.0001
- Creatinine clearance <30 mL/min	89 (17.55%)	89 (26.57%)	0 (0%)	<0.0001
- Hemoglobin, g/dL	13 [11;14]	12 [11;13]	13 [13;14]	0.0608
- Troponin positive	271 (53.45%)	195 (58.21%)	76 (44.19%)	0.0011
- BNP, ng/L	991 [507.5;2443.5]	1157.5 [569.25;2680.5]	534 [291;1292]	0.0048
- Pro-BNP, ng/L	4025 [1729;8863]	5120 [2520;12399.75]	2513 [1146.5;5376.5]	<0.0001
<b>ECG</b>				
- Performed	500 (98.61%)	329 (98.20%)	171 (99.41%)	
- Sinusal	220 (44%)	145 (43.28%)	75 (43.6%)	0.9243
- Atrial fibrillation	213 (42.01)	139 (41.49%)	74 (43.02%)	0.9999
- Driven	44 (8.8%)	33 (9.85%)	11 (6.4%)	0.1940
- AVB	21 (4.14%)	14 (4.18%)	7 (4.07%)	0.8642
- LBBB	86 (17.2%)	64 (19.1%)	22 (12.79%)	0.0461
- RBBB	59 (11.8%)	34 (10.15%)	25 (14.53%)	0.4276
- Repolarization disorder	101 (20.2%)	73 (21.79%)	28 (16.28%)	0.0905
<b>Chest X-ray</b>				
- Performed	481 (94.87%)	318 (94.92%)	163 (94.76%)	
- Normal	24 (4.73%)	11 (3.28%)	13 (7.56%)	0.1999
- Cardiomegaly	235 (48.86%)	171 (51.04%)	64 (37.21%)	0.0144
- Interstitial opacities	284 (59.04%)	202 (60.3%)	82 (47.67%)	0.0199
- Alveolar opacities	108 (22.45%)	64 (19.1%)	44 (25.58%)	0.0503
<b>Echography</b>				
- Performed	82 (16.17%)	55 (16.41%)	27 (15.72%)	
- By cardiologist	47 (57.32%)	36 (10.75%)	11 (6.4%)	0.0589
- Satisfactory	23 (4.54%)	18 (5.37%)	5 (2.91%)	0.2784
- Intermediate	14 (2.76%)	11 (3.28%)	3 (1.74%)	0.2781
- Weak	2 (0.39%)	2 (0.6%)	0 (0%)	0.8091
- By emergency physician	35 (42.68%)	19 (5.67%)	16 (9.3%)	0.0589
- Satisfactory	8 (1.58%)	1 (0.3%)	7 (4.07%)	0.0022
- Intermediate	19 (3.75%)	12 (3.58%)	7 (4.07%)	0.8919
- Weak	8 (1.58%)	1 (0.3%)	7 (4.07%)	0.0022
- LVEF				

	- >50 %	32 (39.02%)	23 (6.87%)	9 (5.23%)	0.6175
	- 35-50 %	26 (31.71%)	18 (5.37%)	8 (4.65%)	0.9754
	- <35 %	19 (23.17%)	11 (3.28%)	8 (4.65%)	0.4884
	- Dilated RV	18 (21.95%)	11 (3.28%)	7 (4.07%)	0.7448
	- VC diameter, mm	21 (25.61%)	15 (4.48%)	6 (3.49%)	0.8233

667 Data are median (IQR) mmol/L, mL/min (IQR) median, median (IQR) g/dL, median (IQR) ng/L, or number (%)

668 of patients

669 Group 1: patients with CRS; Group 2: patients with normal renal function

670 AHF, acute heart failure; AVB, atrioventricular block; BNP, brain natriuretic peptide; ECG, electrocardiogram;

671 HF, heart failure; IVC, inferior vena cava; LBBB, left bundle branch block; LVEF, left ventricular ejection

672 fraction; RBBB, right bundle branch block; RV, right ventricle; US, ultrasound

673

674 Table 4 Emergency treatment of patients with confirmed acute heart failure (AHF) syndrome

	All AHF patients (N=507)	Group 1 (n=335)	Group 2 (n=172)	p-value
Furosemide	376 (74.16%)	252 (75.22%)	124 (72.09%)	0.2620
Oxygen	337 (66.47%)	225 (67.16%)	112 (65.12%)	0.4342
Nitrates	92 (18.15%)	71 (21.19%)	21 (12.21%)	0.0057
Anticoagulant	37 (7.3%)	22 (6.57%)	15 (8.72%)	0.9999
CPAP	8 (1.58%)	6 (1.79%)	2 (1.16%)	0.2374
NIV	45 (8.88%)	30 (8.96%)	15 (8.72%)	0.5800
Antiarrhythmics	23 (4.54%)	15 (4.48%)	8 (4.65%)	0.6009
Inotropic agents	3 (0.59%)	3 (0.9%)	0 (0%)	0.1126
Tracheal intubation	1 (0.2%)	1 (0.3%)	0 (0%)	0.2017
None	32 (6.31%)	17 (5.07%)	15 (8.72%)	0.5841

675 Data are number (%) of patients

676 Group 1: patients with CRS; Group 2: patients with normal renal function

677 AHF, acute heart failure; CPAP, continuous positive airway pressure; NIV, non-invasive ventilation



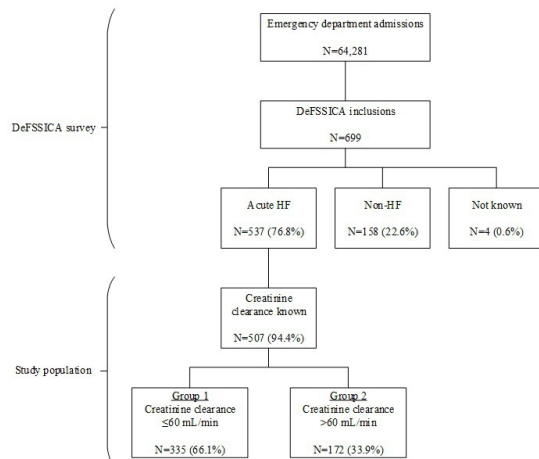
678 Table 5 Outcomes of patients with confirmed acute heart failure (AHF) syndrome

	All AHF patients (N=507)	Group 1 (n=335)	Group 2 (n=172)	p-value
<b>Precipitating factors</b>				
- Unknown	214 (42.21%)	138 (41.19%)	76 (44.19%)	0.8196
- Infection	128 (25.25%)	84 (25.07%)	44 (25.58%)	0.8947
- Rhythm disorder	77 (15.19%)	47 (14.03%)	30 (17.44%)	0.6683
- Hypertension	54 (10.65%)	39 (11.64%)	15 (8.72%)	0.1865
- Non-adherence to treatment	30 (5.92%)	17 (5.07%)	13 (7.56%)	0.9165
- Acute coronary syndrome	21 (4.14%)	15 (4.48%)	6 (3.49%)	0.3237
- Eating disorder	20 (3.94%)	14 (4.18%)	6 (3.49%)	0.3906
- Diabetes decompensation	10 (1.97%)	10 (2.99%)	0 (0%)	0.0110
<b>Discharge destination</b>				
- Cardiology	142 (28.01%)	100 (29.85%)	42 (24.42%)	0.3301
- Geriatric medicine	61 (12.03%)	34 (10.15%)	27 (15.7%)	0.0552
- Other medical unit	99 (19.53%)	67 (20%)	32 (18.6%)	0.9806
- CICU	62 (12.23%)	42 (12.54%)	20 (11.63%)	0.9999
- Resuscitation unit	16 (3.16%)	11 (3.28%)	5 (2.91%)	0.9786
- ED hospitalization unit	74 (14.6%)	48 (14.33%)	26 (15.12%)	0.7187
- Back home	26 (5.13%)	14 (4.18%)	12 (6.98%)	0.1391
- Other	24 (4.73%)	18 (5.37%)	6 (3.49%)	0.7828
<b>Destination considered appropriate</b>	<b>382 (75.35%)</b>	<b>246 (73.43%)</b>	<b>136 (79.07%)</b>	<b>0.1306</b>
<b>Outcome</b>				
- In-hospital mortality	30 (5.92%)	24 (7.16%)	6 (3.49%)	0.9711
- Still hospitalized at 30 days	32 (6.31%)	20 (5.97%)	12 (6.98%)	0.9999
<b>Length of stay, days</b>	<b>7 [4;13]</b>	<b>8 [4;13]</b>	<b>6 [3;12]</b>	<b>0.0327</b>

679 Data are number (%) of patients or median (IQR) days

680 Group 1: patients with CRS; Group 2: patients with normal renal function

681 AHF, acute heart failure



TITLE: Figure 1 Patient disposition

LEGEND: DeFSSICA, Description de la Filière de Soins dans les Syndromes d'Insuffisance Cardiaque Aigue; HF, heart failure

338x190mm (96 x 96 DPI)

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies**

**TITLE: Impact of renal dysfunction on the management and outcome of acute heart failure: results from the French prospective, multicenter, DeFSSICA survey**

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9
		(b) Describe any methods used to examine subgroups and interactions	9
		(c) Explain how missing data were addressed	NA
		(d) If applicable, explain how loss to follow-up was addressed	NA
		(e) Describe any sensitivity analyses	NA

<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10 and Figure 1
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	14-17
<b>Limitations</b>			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Impact of renal dysfunction on the management and outcome of acute heart failure: results from the French prospective, multicenter, DeFSSICA survey

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022776.R1
Article Type:	Research
Date Submitted by the Author:	21-Jun-2018
Complete List of Authors:	<p>dos Reis, Dominique; Val de Grâce Medical School, Ministère de la Défense</p> <p>Fratlicelli, Laurie; Centre Hospitalier de Vienne Lucien Hussenel, RESCUE Network</p> <p>Bassand, Adrien; CHRU Nancy, Emergency Department; CHRU Nancy, CIC-P</p> <p>Manzo-Silberman, Stéphane; Hopital Lariboisiere, Department of Cardiology; INSERM UMR-S-942</p> <p>Peschanski, Nicolas; Centre Hospitalier Eure-Seine, Emergency Department</p> <p>Charpentier, Sandrine; Hopital de Ranguueil, Emergency Department; Universite Toulouse III Paul Sabatier</p> <p>Elbaz, Meyer; Hopital de Ranguueil, Department of Cardiology</p> <p>Savary, Dominique; Annecy-Genevois, Emergency Department and Intensive Care Unit</p> <p>Bonnefoy-Cudraz, Eric; Hôpital Cardiologique de Lyon, Department of Cardiology</p> <p>Laribi, Said; Centre Hospitalier Regional Universitaire de Tours, Emergency Department; INSERM UMR-S-942, Université Paris-Diderot, Sorbonne</p> <p>Henry, Patrick; Hopital Lariboisiere, Department of Cardiology; INSERM UMR-S-942, Université Paris-Diderot, Sorbonne</p> <p>Guerraoui, Abdallah; Groupement Hospitalier Edouard Herriot, Emergency Department; Universite Claude Bernard Lyon 1</p> <p>Tazarourte, Karim; University Hospital, Hospices Civils, Lyon, Emergency Medicine; University Lyon 1, Health Services and Performance Research Laboratory, EA 7425</p> <p>Chouihed, Tahar; CHRU Nancy, SAMU-SMUR-SAU; Institut Lorrain du Coeur et des Vaisseaux</p> <p>El Khoury, Carlos; Centre Hospitalier de Vienne Lucien Hussenel, Emergency Department and RESCUE Network</p>
<b>Primary Subject Heading</b>:	Emergency medicine
Secondary Subject Heading:	Cardiovascular medicine, Renal medicine
Keywords:	acute heart failure, AHF, cardio-renal syndrome, CRS, real-life, renal dysfunction

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



SCHOLARONE™  
Manuscripts

1 Impact of renal dysfunction on the management and outcome of acute heart failure: results  
2 from the French prospective, multicenter, DeFSSICA survey

3 Dominique dos Reis, MD<sup>1</sup>, Laurie Fraticelli PhD<sup>2</sup>, Adrien Bassand, MD<sup>3</sup>, Stéphane Manzo-  
4 Silberman, MD, PhD<sup>4</sup>, Nicolas Peschanski, MD, PhD<sup>5</sup>, Sandrine Charpentier, MD, PhD<sup>6</sup>,  
5 Meyer Elbaz, MD, PhD<sup>7</sup>, Dominique Savary, MD<sup>8</sup>, Eric Bonnefoy-Cudraz, MD, PhD<sup>9</sup>, Said  
6 Laribi, MD, PhD<sup>10</sup>, Patrick Henry, MD, PhD<sup>11</sup>, Abdallah Guerraoui, MD<sup>12</sup>, Karim Tazarourte,  
7 MD, PhD<sup>13</sup>, Tahar Chouihed, MD<sup>14</sup>, Carlos El Khoury, MD, PhD<sup>15</sup>

8 <sup>1</sup>Val de Grâce Medical School, Ministère de la Défense, Paris, France ([d.dosreis@live.fr](mailto:d.dosreis@live.fr));

9 <sup>2</sup>RESCUe Network, Lucien Hussel Hospital, Vienne, France ([l.fraticelli@resuval.fr](mailto:l.fraticelli@resuval.fr));

10 <sup>3</sup>SAMU-SMUR-SAU Nancy, Hôpital Central, CHRU Nancy, France

11 ([adrienbassand@gmail.com](mailto:adrienbassand@gmail.com)); <sup>4</sup>Lariboisière Hospital, Department of Cardiology, Paris, France

12 and INSERM UMR-S 942, Université Paris-Diderot, Sorbonne Paris Cité, Paris, France

13 ([stephane.manzosilberman@aphp.fr](mailto:stephane.manzosilberman@aphp.fr)); <sup>5</sup>Emergency Department, SAMU 27, Eure Seine

14 Evreux Hospital, France ([bansbari@gmail.com](mailto:bansbari@gmail.com)); <sup>6</sup>Emergency Department, Rangueil

15 University Hospital, Toulouse, France; INSERM, U1027, Toulouse, France; Université

16 Toulouse III – Paul Sabatier, Toulouse, France ([charpentier.s@chu-toulouse.fr](mailto:charpentier.s@chu-toulouse.fr)); <sup>7</sup>Department

17 of Cardiology, Rangueil Hospital, Toulouse, France ([elbaz.m@chu-toulouse.fr](mailto:elbaz.m@chu-toulouse.fr)); <sup>8</sup>Emergency

18 Department and Intensive Care Unit, Annecy-Genevois, Metz-Tessy, France

19 ([savaryd@wanadoo.fr](mailto:savaryd@wanadoo.fr)); <sup>9</sup>Department of Cardiology, Hôpital Cardiologique de Lyon, Lyon,

20 France ([eric.bonnefoy-cudraz@chu-lyon.fr](mailto:eric.bonnefoy-cudraz@chu-lyon.fr)); <sup>10</sup>Emergency Medicine Department, University

21 Hospital of Tours; INSERM UMR-S 942, Université Paris-Diderot, Sorbonne Paris Cité,

22 Paris, France ([s.laribi@chu-tours.fr](mailto:s.laribi@chu-tours.fr)); <sup>11</sup>Lariboisière Hospital, Department of Cardiology,

23 Paris, France; INSERM UMR-S 942, Université Paris-Diderot, Sorbonne Paris Cité, Paris,

24 France ([patrick.henry@aphp.fr](mailto:patrick.henry@aphp.fr)); <sup>12</sup>Calydial Dialysis Department, Lucien Hussel Hospital,

25 Vienne, France ([abdallah.guerraoui@calyodial.org](mailto:abdallah.guerraoui@calyodial.org)); <sup>13</sup>Emergency Department, Edouard

1  
2  
3 26 Herriot Hospital, Lyon, France; Univ. Lyon, Claude Bernard Lyon 1 University, HESPER EA  
4  
5 27 7425, Lyon, France ([karim.tazarourte@chu-lyon.fr](mailto:karim.tazarourte@chu-lyon.fr)); <sup>14</sup>SAMU-SMUR-SAU Nancy, Hôpital  
6  
7 28 Central, CHRU Nancy, France; Centre d'Investigation Clinique Plurithématique 1433, Institut  
8  
9 29 Lorrain du Cœur et des Vaisseaux, Vandoeuvre-les-Nancy France; INSERM U1116,  
10  
11 30 Université de Lorraine, Nancy, France ([t.chouihed@gmail.com](mailto:t.chouihed@gmail.com)); <sup>15</sup>Emergency Department  
12  
13 31 and RESCUE Network, Lucien Hessel Hospital, Vienne, France; Univ. Lyon, Claude Bernard  
14  
15 32 Lyon 1 University, HESPER EA 7425, Lyon, France ([c.elkhoury@vienne.fr](mailto:c.elkhoury@vienne.fr))  
16  
17  
18

19 **Corresponding author:**

20  
21  
22 34 Carlos El Khoury, MD, PhD  
23  
24 35 Emergency Department and RESCUE Network, Lucien Hessel Hospital, Vienne, France;  
25  
26 36 Univ. Lyon, Claude Bernard Lyon 1 University, HESPER EA 7425, Lyon, France  
27  
28  
29 37 Tél. +33 (0) 4 7431 3257; Mob. +33 (0) 6 2410 4024; email [c.elkhoury@resuval.fr](mailto:c.elkhoury@resuval.fr)  
30  
31

32 **Target journal & format:** BMJ Open - Research Articles format (counts: abstract 300 words  
33  
34 [max 300]; 6 keywords; body 3719 words (max 4000); 83 references; 1 figure, 5 tables).  
35  
36  
37  
38  
39  
40



1  
2  
3 41 **Abstract (300 words [max 300])**  
4  
5

6 42 **Objectives:** Cardio-renal syndrome (CRS) is the combination of acute heart failure syndrome  
7  
8 43 (AHF) and renal dysfunction (creatinine clearance [CrCl]  $\leq 60$  mL/min). Real-life data were  
9  
10 44 used to compare the management and outcome of AHF with and without renal dysfunction.  
11  
12

13 45 **Design:** Prospective, multi-center.  
14  
15

16 46 **Setting:** Twenty-six academic, community, and regional hospitals in France.  
17  
18

19 47 **Participants:** 507 patients with AHF were assessed in two groups according to renal  
20  
21 48 function: Group 1 (CRS patients [CrCl  $\leq 60$  mL/min]: N=335) and Group 2 (AHF patients  
22  
23 49 with normal renal function [CrCl  $> 60$  mL/min]: N=172).  
24  
25  
26

27 50 **Results:** Differences were observed (Group 1 versus Group 2) at admission for the incidence  
28  
29 51 of chronic heart failure (56.42% versus 47.67%), use of furosemide (60.9% versus 52.91%),  
30  
31 52 insulin (15.52% versus 9.3%), and amiodarone (14.33% versus 4.65%); additionally, more  
32  
33 53 patients in Group 1 carried a defibrillator (4.78% versus 0%), had  $\geq 2$  hospitalizations in the  
34  
35 54 last year (15.52% versus 5.81%), and were under the care of a cardiologist (72.24% versus  
36  
37 55 61.63%). Clinical signs were broadly similar in each group. Brain-type natriuretic peptide  
38  
39 56 (BNP) and BNP prohormone were higher in Group 1 than Group 2 (1157.5 versus 534 ng/L  
40  
41 57 and 5120 versus 2513 ng/mL), and more patients in Group 1 were positive for troponin  
42  
43 58 (58.2% versus 44.19%), had cardiomegaly (51.04% versus 37.21%), and interstitial opacities  
44  
45 59 (60.3% versus 47.67%). The only difference in emergency treatment was the use of nitrates,  
46  
47 60 (higher in Group 1 [21.9% versus 12.21%]). In-hospital mortality and the percentage of  
48  
49 61 patients still hospitalized after 30 days was similar between groups, but median stay was  
50  
51 62 longer in Group 1 (8 days versus 6 days).  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 63 **Conclusions:** Renal impairment in AHF should not limit the use of loop diuretics and/or  
4  
5 64 vasodilators, but early assessment of pulmonary congestion and close monitoring of the  
6  
7 65 efficacy of conventional therapies is encouraged to allow rapid and appropriate  
8  
9 66 implementation of alternative therapies if necessary.  
10  
11  
12 67  
13  
14  
15 68  
16  
17  
18 69  
19  
20  
21 70 **Keywords:** acute heart failure, AHF, cardio-renal syndrome, CRS, real-life, renal dysfunction  
22  
23  
24  
25 71  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 72 **Strengths and limitations of this study**  
4  
5

- 6 73 • Few large-scale, prospective, real-life data exist for the real-life management and  
7  
8 74 outcome of patients with cardio-renal syndrome compared to acute heart failure patients  
9  
10 75 without renal dysfunction.  
11  
12 76 • Cardio-renal syndrome is of prognostic importance.  
13  
14 77 • Only two groups were included (i.e. patients with or without kidney dysfunction), rather  
15  
16 78 than for each stage of chronic kidney disease although the creatinine clearance cut-off (60  
17  
18 79 mL/min) is commonly used.  
19  
20 80 • Glomerular filtration rate estimations were performed by local laboratories for each  
21  
22 81 center (i.e. a real-life situation), rather than standardized at a single center, although this  
23  
24 82 reflects the real-life situation.  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 84 **Background**

85 Heart failure (HF) has an incidence of approximately 2% in adults in developed countries [1]  
86 and mainly affects elderly patients, who may have multiple comorbidities. One such  
87 comorbidity, impaired renal function, has been shown to be a stronger predictor of mortality  
88 than impaired cardiac function [2 3] and can be present in 50% of patients treated for acute  
89 HF (AHF) [4]. The prognostic importance of the association of renal dysfunction (creatinine  
90 clearance [CrCl]  $\leq 60$  mL/min) and AHF (cardio-renal syndrome [CRS]) has only been  
91 demonstrated recently. This represents a complex pathophysiological condition that has been  
92 classified into 5 stages [5 6]. It is worth noting that this is a mechanistic classification and the  
93 patients' clinical management must consider the full clinical presentation..

94 Even moderate degrees of renal insufficiency are independently associated with an increased  
95 risk of mortality from any cause in patients with HF [7]. As such, CRS can lead to hesitancy  
96 among some clinicians to implement appropriate treatments for HF, such as diuretics, due to  
97 the effect that these may have to worsen the renal insufficiency. However, additional  
98 prospective research is needed and current recommendations are to maintain such treatments  
99 in CRS patients [8 9] although the emergency physician should make an appropriate risk  
100 risk:benefit assessment for each patient.

101 In this context, a sub-analysis was conducted using real-life data from the DeFSSICA study  
102 (Description de la Filière de Soins dans les Syndromes d'Insuffisance Cardiaque Aigue), a  
103 large-scale, prospective study that was conducted in patients with suspected dyspnea of  
104 cardiac origin in emergency departments (EDs) throughout France [10]. The aim of this sub-  
105 analysis was to compare the management and outcome of CRS patients to AHF patients  
106 without renal dysfunction in France using novel real-life data, based on the hypothesis that

1  
2  
3 107 CRS and AHF patients would have the same outcome if the management of CRS was based  
4  
5 108 on that for AHF patients without renal dysfunction.  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 109 **Methods**

4  
5  
6 110 *Study design*

7  
8  
9 111 This was a prospective, multi-center study in patients presenting with suspected heart failure  
10 112 dyspnea in 26 EDs in academic, community, and regional hospitals (the DeFSSICA study) for  
11 113 which the rationale and design are reported elsewhere [10]. The study received approval from  
12 114 the National Commission for Liberties and Data Protection (Commission Nationale de  
13 115 l'Informatique et des Libertés) (number DR-2014-543) and the Advisory Committee on the  
14 116 Treatment of Information in the field of Health Research (Comité Consultatif sur le  
15 117 Traitement de l'Information en matière de Recherche dans le Domaine de la Santé) (number  
16 118 14-291). The study did not affect the patient-physician relationship or the patient's care and  
17 119 follow-up.

18  
19  
20 120 *Patient involvement*

21  
22 121 Written information regarding the objectives of the survey was provided to all patients prior  
23 122 to their inclusion. The research question was based on the prognostic importance of CRS and  
24 123 a need for real-life data on the management and outcome of CRS patients. Patients were not  
25 124 involved in the design, recruitment, and conduct of the study, and there is no plan to  
26 125 disseminate the results specifically to the patients who provided data used in this analysis.

27  
28  
29 126 *Selection of participants*

30  
31  
32 127 In the DeFSSICA survey, patients >18 years of age with dyspnea compatible with acute HF,  
33 128 defined as dyspnea associated with peripheral edema and/or pulmonary crackles and/or  
34 129 excessive weight gain and/or use of furosemide, were eligible for inclusion after ED  
35 130 admission and prior to chest X-ray and laboratory tests. Patient enrollment occurred between  
36 131 16 June 2014 and 7 July 2014.

1  
2  
3 132 In this analysis, only patients with known CrCl were included and were divided into those  
4  
5 133 with CrCl  $\leq$ 60 mL/min, i.e. renal dysfunction (Group 1) and those with CrCl >60 mL/min, i.e.  
6  
7 134 normal renal function (Group 2). Glomerular filtration rate (GFR) was calculated using either  
8  
9 135 the Cockcroft-Gault (9 centers), Modification of Diet in Renal Disease (MDRD) Study (12  
10  
11 136 centers), or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations (14  
12  
13 137 centers) (8 centers used two methods and 18 centers used one method) [11 12].  
14  
15

### 16 138 *Study assessments*

17  
18  
19 139 Patients' baseline characteristics, medical history, social factors, in-hospital diagnostic tests  
20  
21 140 and treatment, destination after ED discharge, in-hospital mortality and length of stay were  
22  
23 141 recorded by emergency physicians in a case report form, which was structured according to  
24  
25 142 the progress of care. Cardiac sonographic evaluations were performed at the discretion of the  
26  
27 143 emergency physician. Abnormal chest X-ray was defined by the presence of cardiomegaly,  
28  
29 144 and/or alveolar edema, and/or interstitial opacity, and/or pleural effusion. The choice of  
30  
31 145 treatment was at the emergency physician's discretion, and according to his/her usual  
32  
33 146 practice. Final diagnosis of AHF was made by the emergency physician using a combination  
34  
35 147 of a clinical history, abnormal chest X-ray, elevated brain-type natriuretic peptide (BNP) or  
36  
37 148 BNP prohormone (proBNP), and echocardiographic signs.  
38  
39  
40  
41

42 149 Although it was not possible to impose any randomization or blinding since this was an  
43  
44 150 observational study, any potential bias in the study assessments was minimized by the  
45  
46 151 provision of standard instructions to all participating physicians.  
47  
48

49 152 Data were entered into a secure database located at the Réseau Cardiologie Urgence  
50  
51 153 (RESCUe) (Cardiovascular Emergency Network) Coordination Center.  
52  
53

### 54 154 *Statistical analysis*

55  
56  
57  
58  
59  
60

1  
2  
3 155 Medians and interquartile ranges (IQR) are provided for continuous variables, and numbers  
4  
5 156 and percentages for qualitative variables. Comparative analyses were performed using the  $\chi^2$   
6  
7 157 or Fisher's test for binary variables and the Wilcoxon test for analysis of variance for  
8  
9 158 continuous variables [13]. The 5% level was used to identify differences between groups that  
10  
11 159 were of statistical significance ( $p < 0.05$ ). Statistical evaluations were performed using R  
12  
13 160 Statistical Software (Version 3.4.1).

14  
15  
16  
17 161

For peer review only



## 162 **Results**

### 163 *Patient disposition and prevalence of CRS*

164 A total of 64,281 ED consultations took place during the survey period and 699 patients with  
165 dyspnea of cardiac origin were included in DEFSSICA study. Of these, 537 patients were  
166 identified as having AHF, of whom only those with known CrCl (N=507) were included in  
167 this analysis.

168 Patients in Group 1 (N=335 [66.1%]) had renal dysfunction (CrCl  $\leq$ 60 mL/min) and  
169 comprised the population with CRS. In this group, 99 patients (29.6%) had severe renal  
170 dysfunction (Stage 4 or 5: CrCl:  $<$ 30 mL/min) and 120 (35.8%) had a known history of  
171 chronic renal failure. All patients in Group 2 (N=172 [33.9%]) had normal renal function  
172 (CrCl  $>$ 60 mL/min).

173 Patient disposition is presented in Figure 1.

### 174 *Baseline characteristics*

175 The baseline characteristics of patients in Group 1 and Group 2 are shown in Table 1. There  
176 was no difference between Group 1 and Group 2 in age (median [IQR]: 84 [88-79] years and  
177 82 [75-88] years;  $p=0.09$ ) or sex distribution (42.99% male in Group 1 and 44.19% male in  
178 Group 2;  $p=0.87$ ).

179 As well as the higher incidence of chronic renal failure in Group 1, patients with CRS were  
180 more likely to have chronic HF (56.42% in Group 1 versus 47.67% in Group 2;  $p<0.05$ ).

181 There was no difference in the incidence of any other comorbidity between groups. Patients in  
182 Group 1 were more likely than patients in Group 2 to receive furosemide (60.9% versus  
183 52.91%;  $p<0.05$ ), insulin (15.52% versus 9.3%;  $p=0.03$ ) and amiodarone (14.33% versus

1  
2  
3 184 4.65%;  $p < 0.01$ ) but there were no other differences between groups for medications.  
4  
5 185 Additionally, patients in Group 1 were more likely to have been hospitalized for HF at least  
6  
7 186 twice during the last year (15.52% versus 8.81%;  $p < 0.01$ ), and to be under the care of a  
8  
9 187 cardiologist (72.24% versus 61.63%;  $p = 0.02$ ). The incidence of patients carrying a  
10  
11 188 defibrillator and of pacemakers (single, dual, or triple) are not presented since the sample  
12  
13 189 sizes were small ( $N = 16$  and  $N = 17$ ,  $N = 36$ , and  $N = 6$ , respectively) and so the data were not  
14  
15 190 considered sufficiently robust. Patients in Group 1 were more likely to have a housekeeper  
16  
17 191 (31.13% versus 23.26%;  $p = 0.02$ ) and nurse (29.25% versus 20.93%;  $p = 0.04$ ) but there was no  
18  
19 192 difference between groups regarding family support, known cognitive impairment, or the  
20  
21 193 incidence of being bedridden.  
22  
23  
24

#### 25 194 *Hospitalization and clinical status*

26  
27  
28 195 Although there were few statistically significant differences between groups in hospitalization  
29  
30 196 and clinical status parameters (Table 2) there was a consistent trend towards more congestion  
31  
32 197 in Group 1, including higher levels of dyspnea, more pulmonary infiltrates on chest X-ray,  
33  
34 198 higher BNP and proBNP (Table 3 and below).  
35  
36  
37

38 199 There were no significant differences between groups in their means of transport to the ED  
39  
40 200 (most commonly by personal means [45.76% overall]), Killip status (most patients in each  
41  
42 201 group had a Killip status of 2 [53.06% overall]), and signs of cardiogenic shock (2.96%  
43  
44 202 overall).  
45  
46

#### 47 203 *Early management and diagnosis*

48  
49  
50 204 At admission, blood samples from all patients underwent biological analysis (Table 3). As  
51  
52 205 well as the differences between groups for CrCl, significant differences were observed for  
53  
54 206 BNP, which was 2.2-fold higher in Group 1 than Group 2 (1157.5 ng/L versus 534 ng/L;  
55  
56  
57  
58  
59  
60

207 p<0.01), and proBNP, which was 2.0-fold higher in Group 1 than Group 2 (5120 ng/L versus  
208 2513 ng/L; p<0.01). Additionally, troponin was more likely to be positive in patients in Group  
209 1 than Group 2 (58.21% versus 44.19%; p<0.01). There were no differences between groups  
210 for sodium, potassium, or hemoglobin.

211 Most patients underwent under an electrocardiogram (98.61% overall) chest X-ray (94.87%  
212 overall). Patients in Group 1 were more likely than those in Group 2 to have left bundle  
213 branch block (19.1% versus 12.79%; p<0.05), cardiomegaly (51.04% versus 37.21%;  
214 p=0.01), and interstitial opacities (60.3% versus 47.67%; p=0.02).

215 Echography was only performed for 82 patients and so the data were not considered  
216 sufficiently robust for inclusion in the analysis.

#### 217 *Emergency treatments*

218 Patients in Group 1 were more likely than Group 2 to receive emergency treatment of nitrates  
219 (21.19% versus 12.21%; p<0.01), but there were no group differences in other emergency  
220 measures (furosemide, oxygen, anticoagulant, continuous positive airway pressure, non-  
221 invasive ventilation, anti-arrhythmics, inotropic agents, tracheal intubation) (Table 4). Overall  
222 6.31% of patients received no emergency treatment, with no difference between groups.

#### 223 *Outcomes*

224 Precipitating factors were not determined in 42.21% of cases overall, with no overall  
225 difference between groups (Table 5). The most common determined precipitating factors were  
226 infection (25.25% overall), arrhythmia (15.19% overall), and hypertension (10.65% overall).  
227 Diabetes decompensation was considered to be the precipitating factor for AHF in 2.99% of  
228 patients in Group 1 but none in Group 2 (p=0.01). There were no other group differences in  
229 precipitating factors.

1  
2  
3 230 There was no difference between groups in discharge destination (which was most often  
4  
5 231 cardiology [28.01% overall]), and the discharge destination was deemed appropriate for a  
6  
7 232 similar number of patients in each group (75.35% overall).  
8  
9

10 233 Neither in-hospital mortality (5.92% overall) nor the percentage of patients still hospitalized  
11  
12 234 at 30 days (6.31% overall) were significantly different between Group 1 and Group 2.  
13

14 235 However, the median length of stay was 2 days longer in Group 1 than in Group 2 (8 days  
15  
16 236 versus 6 days;  $p=0.03$ ) (Table 5).  
17  
18

19  
20 237  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 238 Discussion

239 The DeFSSICA study was a large-scale, prospective, real-life study conducted following  
240 admission of AHF patients to EDs throughout France. As such, the data are primarily  
241 applicable to the French population, although wider extrapolation is possible due to  
242 coherences with similar studies in other geographical regions. The overall DeFSSICA study  
243 data are presented elsewhere [10] and the present sub-analysis reports real-life data from sub-  
244 groups of AHF patients with or without concomitant renal dysfunction, based on a CrCl  
245 threshold of 60 mL/min. The results show that AHF admissions to EDs are often associated  
246 with renal impairment, with almost two-thirds of AHF admissions having CrCl  $\leq$ 60 mL/min.  
247 This prevalence is comparable to published data from France [14], Italy [15 16], Poland [17],  
248 Spain [18 19], Taiwan [20], and the USA [21-23], as well as from pan-European [24 25] and  
249 wider international studies [26]. In these studies [14-26], the prevalence of renal impairment  
250 on admission of AHF patients ranged from 54.5% to 64%, including 12.4 to 27.4% of patients  
251 with severe renal insufficiency. Patients with a history of chronic renal failure ranged from  
252 21.4% to 32.5%, which is also comparable to the findings of the DeFSSICA survey. However,  
253 it should be noted that impaired cardiac function leads to reduced renal perfusion, which  
254 could be in addition to an underlying chronic renal insufficiency. Additionally, increased  
255 abdominal pressure at admission that can result from ascites can lead to renal vein  
256 compression and reduced GFR at admission, which could also result in elevated serum  
257 creatinine. It is likely, therefore, that a proportion of acute kidney injury diagnosed at  
258 admission based on serum creatinine could be due to temporary changes in perfusion  
259 pressures rather than kidney damage *per se*; these functional reductions in GFR would be  
260 expected to recover once normal hemodynamic function is restored. While it is therefore  
261 important to consider the use of biomarkers to provide a more precise assessment of kidney  
262 function than serum creatinine [27 28] it is also important to note that the evidence supporting

1  
2  
3 263 the preferential use of novel biomarkers rather than serum creatinine to detect acute kidney  
4  
5 264 injury can be inconsistent and remains an area for further research [29-32].  
6  
7

8 265 The overall baseline characteristics, clinical status, biological and diagnostic tests, emergency  
9  
10 266 treatment, and outcome of the patients included in this sub-analysis was similar to the overall  
11  
12 267 population in the DeFSSICA study; however, some differences were observed between AHF  
13  
14 268 patients with and without renal dysfunction, including a trend towards more congestion in  
15  
16 269 patients with CRS. As would be expected due to reduced kidney excretion [33], and as  
17  
18 270 described elsewhere [34-37], BNP and pro-BNP levels were higher in patients with CRS than  
19  
20 271 in AHF patients with normal renal function and the percentage of troponin positive patients  
21  
22 272 was also higher in the CRS group. These biomarkers probably reflect the congestion status  
23  
24 273 and remain formally recommended for the management of AHF patients, especially for their  
25  
26 274 prognostic value. The appropriate use of loop diuretics and/or vasodilators [38] in the CRS  
27  
28 275 group, as well as in the AHF group without renal dysfunction, may explain in part the similar  
29  
30 276 intra-hospital mortality rate in each group and the similar proportion of AHF patients with and  
31  
32 277 without renal dysfunction who were still in hospital 30 days after ED admission. Importantly,  
33  
34 278 therefore, the prognosis of CRS patients was not significantly different using loop diuretics  
35  
36 279 and/or nitrates to those without renal dysfunction. As such, it appears that the correct  
37  
38 280 congestive assessment is vital in this complex clinical situation with concomitant failures in  
39  
40 281 two organs.  
41  
42  
43  
44

45 282 Worsening renal function (WRF), which leads to a progressive loss of kidney function [33], is  
46  
47 283 a factor for poor long-term prognosis [21 39 40] and Ferreira et al [2] showed that all  
48  
49 284 formulae used to estimate renal function showed a strong and independent association with  
50  
51 285 cardiovascular mortality, with eGFR or CrCl rates under 60 mL/min being associated with  
52  
53 286 increasing cardiovascular mortality. As such, the use of loop diuretics has been considered to  
54  
55 287 be deleterious to long-term renal function, probably since impaired renal function can have  
56  
57  
58  
59  
60

1  
2  
3 288 etiologies other than those related to congestion. However, despite WRF, Testani et al have  
4  
5 289 recently shown an improvement in prognosis in AHF patients when loop diuretics are used  
6  
7 290 [9]. Moreover, for patients treated for AHF, kidney injury appears to be more common in  
8  
9 291 those with an altered ejection fraction than in those with a preserved ejection fraction [40].  
10  
11 292 However, despite these differences in pathophysiology and etiology between AHF patients  
12  
13 293 with and without renal dysfunction, patient outcome is similar [41 42] meaning that renal  
14  
15 294 dysfunction does not have an impact on outcome in AHF patients. Overall, the results of the  
16  
17 295 sub-analysis of the DeFSSICA survey data for AHF patients with and without renal  
18  
19 296 dysfunction support this conclusion. Although a small but statistically significant increase in  
20  
21 297 the length of hospital stay from 6 to 8 days was observed in CRS patients, who showed a  
22  
23 298 greater incidence of certain co-morbidities (inspiratory retraction, left bundle branch block,  
24  
25 299 cardiomegaly and interstitial opacities), there was no difference in in-hospital mortality or in  
26  
27 300 the number of patients still hospitalized at 30 days post-admission. Additionally, there was no  
28  
29 301 difference in ejection fraction in CRS patients compared to AHF patients with normal renal  
30  
31 302 function.  
32  
33  
34  
35

36 303 Recent publications suggest that appropriate, fast-acting decongesting therapies, as  
37  
38 304 recommended by international guidelines, improve the prognosis for AHF patients as long as  
39  
40 305 such therapies are introduced early, even if renal impairment develops at the same time [8].  
41  
42 306 Furthermore, it appears that renal impairment in AHF patients does not have an adverse  
43  
44 307 impact on patient prognosis provided that the congestion is improved. Renal function should  
45  
46 308 be assessed according to the level of patient congestion, and so tools for the assessment of  
47  
48 309 congestion, such as the BNP or proBNP biomarkers [43], lung ultrasound (LUS) B-lines (38),  
49  
50 310 or the assessment of the dimensions and compliance of the inferior vena cava are vital.  
51  
52 311 Additionally, hemoconcentration monitoring can be useful for monitoring congestion [44] and  
53  
54 312 several routinely assessed biological parameters, e.g. serum protein, albumin, hemoglobin,  
55  
56  
57  
58  
59  
60

1  
2  
3 313 and hematocrit, have been proposed as surrogate markers [45]. Furthermore, formulae have  
4  
5 314 been developed to indirectly estimate plasma volume using hemoglobin and/or hematocrit  
6  
7 315 data [46 47]. Novel biomarkers such as urinary angiotensinogen [48], neutrophil gelatinase-  
8  
9 316 associated lipocalin [49 50], kidney injury molecule-1 [51], interleukin-18 [52 53], N-acetyl-  
10  
11 317  $\beta$ -d-glucosaminidase [54], cystatine C [55 56] or a combination of some or all of these could  
12  
13 318 also be used to improve the diagnosis of acute kidney injury, with the caveat that the use of  
14  
15 319 such biomarkers can be inconsistent as described earlier. The assessment of diuresis and  
16  
17 320 natriuresis, which reflect both glomerular and tubular function, could offer a strategy to  
18  
19 321 achieve decongestion [54 57 58]. Ferreira et al [59] and Palazzuoli et al [60] showed that the  
20  
21 322 lack of a diuretic response is a more important prognostic factor than the use of loop diuretics.  
22  
23 323 This suggests a new diagnostic challenge, i.e. to assess the patient's response to diuretics [61-  
24  
25 324 64]. However, despite some proposals to define diuretic resistance (e.g. persistent congestion  
26  
27 325 despite adequate and escalating doses of diuretic with >80 mg furosemide/day, amount of  
28  
29 326 sodium excreted as a percentage of filtered load <0.2%, failure to excrete  $\geq$ 90 mmol of  
30  
31 327 sodium within 72 hours of a 160 mg oral furosemide dose given twice daily) and the means of  
32  
33 328 evaluation (e.g. weight loss per unit of 40 mg furosemide [or equivalent], net fluid loss/mg of  
34  
35 329 loop diuretic [40 mg of furosemide or equivalent] during hospitalization, natriuretic response  
36  
37 330 to furosemide) [65], there is currently no consensus for commonly accepted standards.  
38  
39 331 Additionally, it is important that any alteration of GFR should be interpreted in the context of  
40  
41 332 the deterioration of the clinical situation.  
42  
43  
44  
45

46  
47 333 Another alternative therapy in CRS is the use of mineralocorticoid antagonists. These have  
48  
49 334 been associated with an improvement in both congestion [66 67] and mortality in HF patients  
50  
51 335 [68 69], although the ATHENA-HF trial results are less conclusive [70]. Combined therapies  
52  
53 336 have also been evaluated, including hypotonic saline serum in combination with diuretic  
54  
55 337 therapy to improve diuresis [71 72] and mannitol in combination with furosemide [65],  
56  
57  
58  
59



1  
2  
3 338 although their benefit in diuretic-resistant patients is not confirmed. The addition of  
4  
5 339 metozalone to furosemide could be of interest because of its capacity to produce diuresis even  
6  
7 340 in patients with low GFR [73 74]. In a meta-analysis, Wang and al showed that tolvaptan, an  
8  
9 341 oral vasopressin V<sub>2</sub>-receptor antagonist, may also represent an alternative therapy in WRF  
10  
11 342 [75]. Several studies have shown that tolvaptan can decrease WRF in patients treated with  
12  
13 343 furosemide [76 77]. Finally, venous ultrafiltration allows controlled hydrosodic depletion by  
14  
15 344 subtracting isotonic fluid, compared to diuretics that allow the subtraction of hypotonic fluid.  
16  
17  
18 345 Other studies suggest that the effectiveness of ultrafiltration is associated with a reduction in  
19  
20 346 inflammatory cytokines [78]. These and other approaches in patients with cardiac  
21  
22 347 insufficiency and resistance to diuretics have recently been reviewed [65].  
23  
24

25 348 The CRS analysis using data from the DeFSSICA survey has some limitations. First, only two  
26  
27 349 groups have been analyzed (i.e. patients with or without renal dysfunction), whereas chronic  
28  
29 350 kidney disease is characterized by 5 stages [5]. However, as noted earlier, this is a  
30  
31 351 mechanistic classification and in the present analysis the use of the CrCl threshold of 60  
32  
33 352 mL/min, which is commonly used to define renal dysfunction [2 37 79-81], is considered to  
34  
35 353 be satisfactory, especially since the small number of patients would not allow a thorough  
36  
37  
38 354 analysis for five sub-categories. However, the pathophysiology of WRF in AHF is complex  
39  
40 355 [82] and using a spot measurement of serum creatinine to classify CRS has limitations. This  
41  
42 356 approach does not allow the separation of patients with acute and chronic CRS: in the present  
43  
44 357 study, 35.8% of patients included in the CRS group had a history of chronic renal failure and  
45  
46 358 so may not have suffered any acute change in renal function, whereas patients with acute  
47  
48 359 changes in serum creatinine compared to their own baseline but not fulfilling the <60 mL/min  
49  
50 360 criterion would not have been included in the CRS group. That said, the presence of renal  
51  
52 361 failure on admission remains strongly associated with a poor prognosis irrespective of the  
53  
54 362 anterior renal status and despite the lack of WRF in the first 5 days [83]. While the choice of a  
55  
56  
57  
58  
59  
60

1  
2  
3 363 CrCl threshold of 30 mL/min could have led to a greater chance of obtaining a significant  
4  
5 364 difference between groups in terms of outcome, we based our analysis on the 60 mL/min cut-  
6  
7 365 off since it is more widely used. Second, since the data used are observational, it was not  
8  
9 366 possible to impose any randomization or blinding, and the number of patients in each group  
10  
11 367 was not balanced. Third, GFR assessments were performed by local laboratories for each  
12  
13 368 center, rather than standardized at a single center, and repeated measures of GFR could have  
14  
15 369 improved their accuracy and comparability. The use of different formulae to evaluate CrCl in  
16  
17 370 a chronic disease state and an acute context without knowledge of the baseline value reflects  
18  
19 371 the real-life situation. While potentially problematic, with the possibility of some incorrect  
20  
21 372 classification of CKD, numerous previous studies of the impact of renal failure in AHF have  
22  
23 373 used a similar approach [2 37 79]. Finally, it was not possible to sub-classify different types  
24  
25 374 of CRS in this analysis since Kidney Disease Improving Global Outcomes (KDIGO) data  
26  
27 375 were not collected, although as described earlier the small number of patients would not have  
28  
29 376 allowed a thorough analysis for each sub-category.  
30  
31  
32  
33

### 377 **Conclusion**

378 These real-life data suggested that CRS patients have the same outcome as AHF patients  
379 without renal dysfunction when the treatment of the former group is modeled on that for the  
380 latter group. This finding should not limit the use of loop diuretics and/or vasodilators as long  
381 as the patient presents congestion as assessed using biomarkers and ultrasound. The use of  
382 diuretic treatment should be based on a more rapid diagnosis of congestion and evaluation of  
383 an inadequate response to diuretics, allowing the rapid and appropriate implementation of  
384 alternative therapies if necessary.  
385

1  
2  
3 386 **Funding**  
4

5  
6 387 This work was supported by Novartis France, but the Sponsor was not involved in the study  
7  
8 388 protocol, methods, or choice of centers.  
9

10  
11 389 **Competing interests**  
12

13  
14 390 CEK and has received grants from Novartis (other than this work), Daiichy Sankyo, and  
15  
16 391 Boehringer Ingleheim.  
17

18  
19 392 NP reports has acted as a paid consultant for Vygon SA.  
20

21  
22 393 SC reports personal fees from Novartis (other than this work).  
23

24  
25 394 LF is an employee of RESCUe Network.  
26

27  
28 395 DdR, AB, SMZ, ME, DS, EBC, SL, PH, AG, KT and TC have no competing interests.  
29

30  
31  
32 396 **Authors' contributions**  
33

34  
35 397 SMZ, NP, SC, ME, DS, EBC, SL, PH, TC, and CEK conceived the study, designed the trial,  
36  
37 398 and obtained research funding. TC and CEK supervised the conduct of the trial and data  
38  
39 399 collection. NP, SC, DS and TC undertook recruitment of participating centers and patients. LF  
40  
41 400 managed the data, including quality control, provided statistical advice and analyzed the data.  
42

43  
44 401 DdR, LF, AB, AG, KT, TC and CEK drafted the manuscript, and all authors contributed  
45  
46 402 substantially to its revision. All authors reviewed and approved the final version of the  
47  
48 403 manuscript and are accountable for its content.  
49

50  
51 404 **Consent for publication**  
52

53  
54 405 Not applicable since no individual patient is identified.  
55  
56  
57  
58  
59  
60

1  
2  
3 406 **Data sharing statement**  
4

5  
6 407 The database supporting the results presented in this article can be shared on reasonable  
7  
8 408 request.  
9

10  
11 409 **Acknowledgements**  
12

13  
14 410 The authors thank the emergency physicians and cardiologists and patients who participated  
15  
16 411 in this survey at the following centers: CHU Toulouse, CHU Rouen, CHU Clermont Ferrand,  
17  
18 412 CHU Nancy, CHR Metz-Thionville-Hôpital de Mercy, Hôpital Lariboisière-Paris, CHR  
19  
20 413 Annecy Genevois, CHU Lyon-Hôp, Edouard Herriot, CHRU de Lille, Chu De Caen, CHU  
21  
22 414 Nice-Hôpital Saint-Roch, CHU de Grenoble, Hôpital Bicêtre-Paris, Hôpital St Louis Paris,  
23  
24 415 CH I Meulan, CH d'Avignon, CH Jacques Lacarin-Vichy, CH d'Aix En Provence, CH  
25  
26 416 Fleyriat –Bourg En Bresse, CH Bourgoin Jallieu, CHU de Saint Etienne, CH du Forez  
27  
28 417 Montbrison-Feurs, CH de Firminy, CH Villefranche-Sur-Saône, CHU De Brest, CH Henri  
29  
30 418 Mondor, CH de Vienne.  
31  
32

33  
34 419 The authors also thank the RESCUE Network for the practical implementation of this survey  
35  
36 420 and statistical analysis and Novartis France for its financial support.  
37

38  
39 421 Dr Andrew Lane (Lane Medical Writing), funded by the RESCUE network, provided  
40  
41 422 professional medical writing assistance in the preparation and development of the manuscript  
42  
43 423 in accordance with the European Medical Writers Association guidelines and Good  
44  
45 424 Publication Practice.  
46  
47

48  
49 425  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

426 **References**

- 427 1. Sayago-Silva I, Garcia-Lopez F, Segovia-Cubero J. Epidemiology of heart failure in Spain  
428 over the last 20 years. *Rev Esp Cardiol (Engl Ed)* 2013;**66**(8):649-56 doi:  
429 10.1016/j.rec.2013.03.012.
- 430 2. Ferreira JP, Girerd N, Pellicori P, et al. Renal function estimation and Cockcroft-Gault  
431 formulas for predicting cardiovascular mortality in population-based, cardiovascular  
432 risk, heart failure and post-myocardial infarction cohorts: The Heart 'OMics' in  
433 AGEing (HOMAGE) and the high-risk myocardial infarction database initiatives.  
434 *BMC Med* 2016;**14**(1):181 doi: 10.1186/s12916-016-0731-2.
- 435 3. Hillege HL, Girbes AR, de Kam PJ, et al. Renal function, neurohormonal activation, and  
436 survival in patients with chronic heart failure. *Circulation* 2000;**102**(2):203-10.
- 437 4. Damman K, Valente MA, Voors AA, et al. Renal impairment, worsening renal function,  
438 and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J*  
439 2014;**35**(7):455-69 doi: 10.1093/eurheartj/eh386.
- 440 5. Ronco C, Haapio M, House AA, et al. Cardiorenal syndrome. *J Am Coll Cardiol*  
441 2008;**52**(19):1527-39 doi: 10.1016/j.jacc.2008.07.051.
- 442 6. Ronco C, House AA, Haapio M. Cardiorenal syndrome: refining the definition of a  
443 complex symbiosis gone wrong. *Intensive Care Med* 2008;**34**(5):957-62 doi:  
444 10.1007/s00134-008-1017-8.
- 445 7. Dries DL, Exner DV, Domanski MJ, et al. The prognostic implications of renal  
446 insufficiency in asymptomatic and symptomatic patients with left ventricular systolic  
447 dysfunction. *J Am Coll Cardiol* 2000;**35**(3):681-9.

- 1  
2  
3 448 8. Hanberg JS, Tang WHW, Wilson FP, et al. An exploratory analysis of the competing  
4  
5 449 effects of aggressive decongestion and high-dose loop diuretic therapy in the DOSE  
6  
7 450 trial. *Int J Cardiol* 2017;**241**:277-82 doi: 10.1016/j.ijcard.2017.03.114.  
8  
9  
10 451 9. Testani JM, Ter Maaten JM. Decongestion in Acute Heart Failure: Does the End Justify the  
11  
12 452 Means? *JACC Heart Fail* 2016;**4**(7):589-90 doi: 10.1016/j.jchf.2016.03.024.  
13  
14  
15 453 10. Chouihed T, Manzo-Silberman S, Peschanski N, et al. Management of suspected acute  
16  
17 454 heart failure dyspnea in the emergency department: results from the French  
18  
19 455 prospective multicenter DeFSSICA survey. *Scand J Trauma Resusc Emerg Med*  
20  
21 456 2016;**24**(1):112 doi: 10.1186/s13049-016-0300-x.  
22  
23  
24  
25 457 11. National Institute of Diabetes and Digestive and Kidney Diseases. Estimating glomerular  
26  
27 458 filtration rate (GFR) 2015. [https://www.niddk.nih.gov/health-information/health-](https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr/estimating/Pages/estimating.aspx)  
28  
29 459 [communication-programs/nkdep/lab-evaluation/gfr/estimating/Pages/estimating.aspx](https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr/estimating/Pages/estimating.aspx).  
30  
31 460 Accessed 21 June 2018.  
32  
33  
34  
35 461 12. Botev R, Mallie JP, Couchoud C, et al. Estimating glomerular filtration rate: Cockcroft-  
36  
37 462 Gault and Modification of Diet in Renal Disease formulas compared to renal inulin  
38  
39 463 clearance. *Clin J Am Soc Nephrol* 2009;**4**(5):899-906 doi: 10.2215/CJN.05371008.  
40  
41  
42 464 13. Ancelle T. *Statistique Epidémiologique*. 3rd ed. Paris: Maloine, 2011.  
43  
44  
45 465 14. Logeart D, Isnard R, Resche-Rigon M, et al. Current aspects of the spectrum of acute  
46  
47 466 heart failure syndromes in a real-life setting: the OFICA study. *Eur J Heart Fail*  
48  
49 467 2013;**15**(4):465-76 doi: 10.1093/eurjhf/hfs189.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 468 15. Oliva F, Mortara A, Cacciatore G, et al. Acute heart failure patient profiles, management  
4  
5 469 and in-hospital outcome: results of the Italian Registry on Heart Failure Outcome. *Eur*  
6  
7 470 *J Heart Fail* 2012;**14**(11):1208-17 doi: 10.1093/eurjhf/hfs117.  
8  
9  
10 471 16. Tavazzi L, Maggioni AP, Lucci D, et al. Nationwide survey on acute heart failure in  
11  
12 472 cardiology ward services in Italy. *Eur Heart J* 2006;**27**(10):1207-15 doi:  
13  
14 473 10.1093/eurheartj/ehi845.  
15  
16  
17 474 17. Straburzynska-Migaj E, Kaluzna-Oleksy M, Maggioni AP, et al. Patients with heart  
18  
19 475 failure and concomitant chronic obstructive pulmonary disease participating in the  
20  
21 476 Heart Failure Pilot Survey (ESC-HF Pilot) - Polish population. *Arch Med Sci*  
22  
23 477 2015;**11**(4):743-50 doi: 10.5114/aoms.2014.47878.  
24  
25  
26  
27 478 18. Conde-Martel A, Formiga F, Perez-Bocanegra C, et al. Clinical characteristics and one-  
28  
29 479 year survival in heart failure patients more than 85 years of age compared with  
30  
31 480 younger. *Eur J Intern Med* 2013;**24**(4):339-45 doi: 10.1016/j.ejim.2013.01.005.  
32  
33  
34 481 19. Llorens P, Escoda R, Miró O, et al. Characteristics and clinical course of patients with  
35  
36 482 acute heart failure and the therapeutic measures applied in Spanish emergency  
37  
38 483 departments: based on the EAHFE registry (Epidemiology of Acute Heart Failure in  
39  
40 484 Emergency Departments). *Emergencias* 2015;**27**:11-22.  
41  
42  
43  
44 485 20. Chang H-Y, Wang C-C, Wu Y-W, et al. One-Year Outcomes of Acute Decompensated  
45  
46 486 Systolic Heart Failure in Taiwan: Lessons from TSOC-HFrEF Registry *Acta*  
47  
48 487 *Cardiologica Sinica* 2017;**33**(2):127-38  
49  
50  
51 488 21. Abraham WT, Fonarow GC, Albert NM, et al. Predictors of in-hospital mortality in  
52  
53 489 patients hospitalized for heart failure: insights from the Organized Program to Initiate  
54  
55  
56  
57  
58  
59

- 1  
2  
3 490 Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). J  
4  
5 491 Am Coll Cardiol 2008;**52**(5):347-56 doi: 10.1016/j.jacc.2008.04.028.  
6  
7  
8 492 22. Adams KF, Jr., Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients  
9  
10 493 hospitalized for heart failure in the United States: rationale, design, and preliminary  
11  
12 494 observations from the first 100,000 cases in the Acute Decompensated Heart Failure  
13  
14 495 National Registry (ADHERE). Am Heart J 2005;**149**(2):209-16 doi:  
15  
16 496 10.1016/j.ahj.2004.08.005.  
17  
18  
19  
20 497 23. Diercks DB, Fonarow GC, Kirk JD, et al. Risk stratification in women enrolled in the  
21  
22 498 Acute Decompensated Heart Failure National Registry Emergency Module  
23  
24 499 (ADHERE-EM). Acad Emerg Med 2008;**15**(2):151-8 doi: 10.1111/j.1553-  
25  
26 500 2712.2008.00030.x.  
27  
28  
29 501 24. Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme-- a  
30  
31 502 survey on the quality of care among patients with heart failure in Europe. Part 1:  
32  
33 503 patient characteristics and diagnosis. Eur Heart J 2003;**24**(5):442-63.  
34  
35  
36  
37 504 25. Nieminen MS, Brutsaert D, Dickstein K, et al. EuroHeart Failure Survey II (EHFS II): a  
38  
39 505 survey on hospitalized acute heart failure patients: description of population. Eur  
40  
41 506 Heart J 2006;**27**(22):2725-36 doi: 10.1093/eurheartj/ehl193.  
42  
43  
44 507 26. Follath F, Yilmaz MB, Delgado JF, et al. Clinical presentation, management and  
45  
46 508 outcomes in the Acute Heart Failure Global Survey of Standard Treatment (ALARM-  
47  
48 509 HF). Intensive Care Med 2011;**37**(4):619-26 doi: 10.1007/s00134-010-2113-0.  
49  
50  
51 510 27. Molitoris BA, Levin A, Warnock DG, et al. Improving outcomes of acute kidney injury:  
52  
53 511 report of an initiative. Nat Clin Pract Nephrol 2007;**3**(8):439-42 doi:  
54  
55 512 10.1038/ncpneph0551.  
56  
57  
58  
59



- 1  
2  
3 513 28. Waikar SS, Bonventre JV. Creatinine kinetics and the definition of acute kidney injury. J  
4  
5 514 Am Soc Nephrol 2009;**20**(3):672-9 doi: 10.1681/ASN.2008070669.  
6  
7  
8 515 29. Breidthardt T, Sabti Z, Ziller R, et al. Diagnostic and prognostic value of cystatin C in  
9  
10 516 acute heart failure. Clin Biochem 2017;**50**(18):1007-13 doi:  
11  
12 517 10.1016/j.clinbiochem.2017.07.016.  
13  
14  
15 518 30. Breidthardt T, Socrates T, Drexler B, et al. Plasma neutrophil gelatinase-associated  
16  
17 519 lipocalin for the prediction of acute kidney injury in acute heart failure. Crit Care  
18  
19 520 2012;**16**(1):R2 doi: 10.1186/cc10600.  
20  
21  
22  
23 521 31. Maisel AS, Wettersten N, van Veldhuisen DJ, et al. Neutrophil Gelatinase-Associated  
24  
25 522 Lipocalin for Acute Kidney Injury During Acute Heart Failure Hospitalizations: The  
26  
27 523 AKINESIS Study. J Am Coll Cardiol 2016;**68**(13):1420-31 doi:  
28  
29 524 10.1016/j.jacc.2016.06.055.  
30  
31  
32 525 32. Meersch M, Schmidt C, Hoffmeier A, et al. Prevention of cardiac surgery-associated AKI  
33  
34 526 by implementing the KDIGO guidelines in high risk patients identified by biomarkers:  
35  
36 527 the PrevAKI randomized controlled trial. Intensive Care Med 2017;**43**(11):1551-61  
37  
38 528 doi: 10.1007/s00134-016-4670-3.  
39  
40  
41  
42 529 33. Tuegel C, Bansal N. Heart failure in patients with kidney disease. Heart 2017 doi:  
43  
44 530 10.1136/heartjnl-2016-310794|.  
45  
46  
47 531 34. Anwaruddin S, Lloyd-Jones DM, Baggish A, et al. Renal function, congestive heart  
48  
49 532 failure, and amino-terminal pro-brain natriuretic peptide measurement: results from  
50  
51 533 the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. J  
52  
53 534 Am Coll Cardiol 2006;**47**(1):91-7 doi: 10.1016/j.jacc.2005.08.051.  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 535 35. Group NW, Wu AH, Jaffe AS, et al. National Academy of Clinical Biochemistry  
4  
5 536 laboratory medicine practice guidelines: use of cardiac troponin and B-type natriuretic  
6  
7 537 peptide or N-terminal proB-type natriuretic peptide for etiologies other than acute  
8  
9 538 coronary syndromes and heart failure. *Clin Chem* 2007;**53**(12):2086-96 doi:  
10  
11 539 10.1373/clinchem.2007.095679.
- 12  
13  
14 540 36. Lamb EJ, Vickery S, Price CP. Amino-terminal pro-brain natriuretic peptide to diagnose  
15  
16 541 congestive heart failure in patients with impaired kidney function. *J Am Coll Cardiol*  
17  
18 542 2006;**48**(5):1060-1; author reply 61 doi: 10.1016/j.jacc.2006.06.019.
- 19  
20  
21  
22 543 37. Vickery S, Price CP, John RI, et al. B-type natriuretic peptide (BNP) and amino-terminal  
23  
24 544 proBNP in patients with CKD: relationship to renal function and left ventricular  
25  
26 545 hypertrophy. *Am J Kidney Dis* 2005;**46**(4):610-20 doi: 10.1053/j.ajkd.2005.06.017.
- 27  
28  
29 546 38. Peacock WF, Emerman C, Costanzo MR, et al. Early vasoactive drugs improve heart  
30  
31 547 failure outcomes. *Congest Heart Fail* 2009;**15**(6):256-64 doi: 10.1111/j.1751-  
32  
33 548 7133.2009.00112.x.
- 34  
35  
36  
37 549 39. Damman K, Navis G, Voors AA, et al. Worsening renal function and prognosis in heart  
38  
39 550 failure: systematic review and meta-analysis. *J Card Fail* 2007;**13**(8):599-608 doi:  
40  
41 551 10.1016/j.cardfail.2007.04.008.
- 42  
43  
44 552 40. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart  
45  
46 553 failure: prognostic and therapeutic implications from a prospective cohort study.  
47  
48 554 *Circulation* 2004;**109**(8):1004-9 doi: 10.1161/01.CIR.0000116764.53225.A9.
- 49  
50  
51 555 41. Abebe TB, Gebreyohannes EA, Tefera YG, Abegaz TM. Patients with HFpEF and HFrEF  
52  
53 556 have different clinical characteristics but similar prognosis: a retrospective cohort  
54  
55 557 study. *BMC Cardiovasc Disord* 2016;**16**(1):232 doi: 10.1186/s12872-016-0418-9.

- 1  
2  
3 558 42. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes  
4  
5 559 within the heart failure spectrum. *Circulation* 2011;**123**(18):2006-13; discussion 14  
6  
7 560 doi: 10.1161/CIRCULATIONAHA.110.954388.  
8  
9  
10 561 43. Gargani L, Frassi F, Soldati G, et al. Ultrasound lung comets for the differential diagnosis  
11  
12 562 of acute cardiogenic dyspnoea: a comparison with natriuretic peptides. *Eur J Heart*  
13  
14 563 *Fail* 2008;**10**(1):70-7 doi: 10.1016/j.ejheart.2007.10.009.  
15  
16  
17 564 44. Ahmad T, Testani JM. Haemoconcentration as a treatment goal in heart failure: ready for  
18  
19 565 prime time? *Eur J Heart Fail* 2017;**19**(2):237-40 doi: 10.1002/ejhf.715.  
20  
21  
22 566 45. Girerd N, Seronde MF, Coiro S, et al. Integrative Assessment of Congestion in Heart  
23  
24 567 Failure Throughout the Patient Journey. *JACC Heart Fail* 2018;**6**(4):273-85 doi:  
25  
26 568 10.1016/j.jchf.2017.09.023.  
27  
28  
29 569 46. Mentz RJ, Kjeldsen K, Rossi GP, et al. Decongestion in acute heart failure. *Eur J Heart*  
30  
31 570 *Fail* 2014;**16**(5):471-82 doi: 10.1002/ejhf.74.  
32  
33  
34 571 47. Duarte K, Monnez JM, Albuissou E, et al. Prognostic Value of Estimated Plasma Volume  
35  
36 572 in Heart Failure. *JACC Heart Fail* 2015;**3**(11):886-93 doi: 10.1016/j.jchf.2015.06.014.  
37  
38  
39 573 48. Yang X, Chen C, Tian J, et al. Urinary Angiotensinogen Level Predicts AKI in Acute  
40  
41 574 Decompensated Heart Failure: A Prospective, Two-Stage Study. *J Am Soc Nephrol*  
42  
43 575 2015;**26**(8):2032-41 doi: 10.1681/ASN.2014040408.  
44  
45  
46  
47 576 49. Elsharawy S, Raslan L, Morsy S, et al. Plasma neutrophil gelatinase-associated lipocalin  
48  
49 577 as a marker for the prediction of worsening renal function in children hospitalized for  
50  
51 578 acute heart failure. *Saudi J Kidney Dis Transpl* 2016;**27**(1):49-54 doi: 10.4103/1319-  
52  
53 579 2442.174071.  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 580 50. Ito M, Doi K, Takahashi M, et al. Plasma neutrophil gelatinase-associated lipocalin  
4  
5 581 predicts major adverse cardiovascular events after cardiac care unit discharge. *J*  
6  
7 582 *Cardiol* 2016;**67**(2):184-91 doi: 10.1016/j.jjcc.2015.05.010.  
8  
9  
10 583 51. Medic B, Rovcanin B, Basta Jovanovic G, et al. Kidney Injury Molecule-1 and  
11  
12 584 Cardiovascular Diseases: From Basic Science to Clinical Practice. *Biomed Res Int*  
13  
14 585 2015;**2015**:854070 doi: 10.1155/2015/854070.  
16  
17 586 52. *Les biomarqueurs en médecine d'urgence [French]*. 1 ed. Paris: Springer-Verlag, 2012.  
19  
20 587 53. Taub PR, Borden KC, Fard A, Maisel A. Role of biomarkers in the diagnosis and  
21  
22 588 prognosis of acute kidney injury in patients with cardiorenal syndrome. *Expert Rev*  
23  
24 589 *Cardiovasc Ther* 2012;**10**(5):657-67 doi: 10.1586/erc.12.26.  
26  
27  
28 590 54. Verbrugge FH, Dupont M, Steels P, et al. The kidney in congestive heart failure: 'are  
29  
30 591 natriuresis, sodium, and diuretics really the good, the bad and the ugly?'. *Eur J Heart*  
31  
32 592 *Fail* 2014;**16**(2):133-42 doi: 10.1002/ejhf.35.  
34  
35 593 55. Lassus JP, Harjola VP, Peuhkurinen K, et al. Cystatin C, NT-proBNP, and inflammatory  
36  
37 594 markers in acute heart failure: insights into the cardiorenal syndrome. *Biomarkers*  
38  
39 595 2011;**16**(4):302-10 doi: 10.3109/1354750X.2011.555822.  
41  
42  
43 596 56. Legrand M, De Berardinis B, Gaggin HK, et al. Evidence of uncoupling between renal  
44  
45 597 dysfunction and injury in cardiorenal syndrome: insights from the BIONICS study.  
46  
47 598 *PloS one* 2014;**9**(11):e112313 doi: 10.1371/journal.pone.0112313.  
49  
50 599 57. Metra M, Davison B, Bettari L, et al. Is worsening renal function an ominous prognostic  
51  
52 600 sign in patients with acute heart failure? The role of congestion and its interaction with  
53  
54  
55  
56  
57  
58  
59

- 1  
2  
3 601 renal function. *Circ Heart Fail* 2012;**5**(1):54-62 doi:  
4  
5 602 10.1161/CIRCHEARTFAILURE.111.963413.  
6  
7  
8 603 58. Mullens W, Verbrugge F, Nijst P, Tang W. Renal sodium avidity in heart failure: from  
9  
10 604 pathophysiology to treatment strategies. *European Heart Journal* 2017 doi:  
11  
12 605 10.1093/eurheartj/ehx035.  
13  
14  
15 606 59. Ferreira JP, Girerd N, Bettencourt Medeiros P, et al. Lack of diuretic efficiency (but not  
16  
17 607 low diuresis) early in an acutely decompensated heart failure episode is associated  
18  
19 608 with increased 180-day mortality. *Cardiorenal Med* 2017;**7**(2):137-49 doi:  
20  
21 609 10.1159/000455903.  
22  
23  
24  
25 610 60. Palazzuoli A, Testani JM, Ruocco G, et al. Different diuretic dose and response in acute  
26  
27 611 decompensated heart failure: Clinical characteristics and prognostic significance. *Int J*  
28  
29 612 *Cardiol* 2016;**224**:213-19 doi: 10.1016/j.ijcard.2016.09.005.  
30  
31  
32  
33 613 61. Damman K, Testani JM. The kidney in heart failure: an update. *Eur Heart J*  
34  
35 614 2015;**36**(23):1437-44 doi: 10.1093/eurheartj/ehv010.  
36  
37  
38 615 62. Hoorn EJ, Ellison DH. Diuretic Resistance. *Am J Kidney Dis* 2017;**69**(1):136-42 doi:  
39  
40 616 10.1053/j.ajkd.2016.08.027.  
41  
42  
43 617 63. Ray EC, Boyd-Shiwerski CR, Kleyman TR. Why Diuretics fail failing hearts. *J Am Soc*  
44  
45 618 *Nephrol* 2017 doi: 10.1681/ASN.2017070797.  
46  
47  
48 619 64. Valente MA, Voors AA, Damman K, et al. Diuretic response in acute heart failure:  
49  
50 620 clinical characteristics and prognostic significance. *Eur Heart J* 2014;**35**(19):1284-93  
51  
52 621 doi: 10.1093/eurheartj/ehu065.  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 622 65. ter Maaten JM, Valente MA, Damman K, et al. Diuretic response in acute heart failure-  
4 pathophysiology, evaluation, and therapy. *Nat Rev Cardiol* 2015;**12**(3):184-92 doi:  
5 623 10.1038/nrcardio.2014.215.  
6  
7 624  
8  
9  
10 625 66. Bansal S, Lindenfeld J, Schrier RW. Sodium retention in heart failure and cirrhosis:  
11 potential role of natriuretic doses of mineralocorticoid antagonist? *Circ Heart Fail*  
12 626 2009;**2**(4):370-6 doi: 10.1161/CIRCHEARTFAILURE.108.821199.  
13  
14 627  
15  
16  
17 628 67. Hensen J, Abraham WT, Durr JA, Schrier RW. Aldosterone in congestive heart failure:  
18 analysis of determinants and role in sodium retention. *Am J Nephrol* 1991;**11**(6):441-  
19 629 6.  
20  
21 630  
22  
23  
24  
25 631 68. The RALES investigators. Effectiveness of spironolactone added to an angiotensin-  
26 converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart  
27 632 failure (the Randomized Aldactone Evaluation Study [RALES]). *Am J Cardiol*  
28 633 1996;**78**(8):902-7.  
29  
30 634  
31  
32  
33  
34 635 69. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and  
35 mortality in patients with severe heart failure. Randomized Aldactone Evaluation  
36 636 Study Investigators. *The New England journal of medicine* 1999;**341**(10):709-17 doi:  
37 637 10.1056/NEJM199909023411001.  
38  
39 638  
40  
41  
42  
43  
44 639 70. Butler J, Anstrom KJ, Felker GM, et al. Efficacy and safety of spironolactone in acute  
45 heart failure: The ATHENA-HF Randomized Clinical Trial. *JAMA Cardiol* 2017 doi:  
46 640 10.1001/jamacardio.2017.2198.  
47  
48 641  
49  
50  
51 642 71. Licata G, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-  
52 volume hypertonic saline solution infusion in comparison with a high dose of  
53 643

- 1  
2  
3 644 furosemide as bolus in refractory congestive heart failure: long-term effects. *Am Heart*  
4  
5 645 *J* 2003;**145**(3):459-66 doi: 10.1067/mhj.2003.166.  
6  
7  
8 646 72. Paterna S, Di Pasquale P, Parrinello G, et al. Changes in brain natriuretic peptide levels  
9  
10 647 and bioelectrical impedance measurements after treatment with high-dose furosemide  
11  
12 648 and hypertonic saline solution versus high-dose furosemide alone in refractory  
13  
14 649 congestive heart failure: a double-blind study. *J Am Coll Cardiol* 2005;**45**(12):1997-  
15  
16 650 2003 doi: 10.1016/j.jacc.2005.01.059.  
17  
18  
19  
20 651 73. Ng TM, Konopka E, Hyderi AF, et al. Comparison of bumetanide- and metolazone-based  
21  
22 652 diuretic regimens to furosemide in acute heart failure. *J Cardiovasc Pharmacol Ther*  
23  
24 653 2013;**18**(4):345-53 doi: 10.1177/1074248413482755.  
25  
26  
27 654 74. Tilstone WJ, Dargie H, Dargie EN, et al. Pharmacokinetics of metolazone in normal  
28  
29 655 subjects and in patients with cardiac or renal failure. *Clin Pharmacol Ther*  
30  
31 656 1974;**16**(2):322-9.  
32  
33  
34  
35 657 75. Wang C, Xiong B, Cai L. Effects of Tolvaptan in patients with acute heart failure: a  
36  
37 658 systematic review and meta-analysis. *BMC Cardiovasc Disord* 2017;**17**(1):164 doi:  
38  
39 659 10.1186/s12872-017-0598-y.  
40  
41  
42 660 76. Jujo K, Saito K, Ishida I, et al. Randomized pilot trial comparing tolvaptan with  
43  
44 661 furosemide on renal and neurohumoral effects in acute heart failure. *ESC Heart Fail*  
45  
46 662 2016;**3**(3):177-88 doi: 10.1002/ehf2.12088.  
47  
48  
49  
50 663 77. Kimura K, Momose T, Hasegawa T, et al. Early administration of tolvaptan preserves  
51  
52 664 renal function in elderly patients with acute decompensated heart failure. *J Cardiol*  
53  
54 665 2016;**67**(5):399-405 doi: 10.1016/j.jjcc.2015.09.020.  
55  
56  
57  
58  
59  
60

- 1  
2  
3 666 78. Torina AG, Silveira-Filho LM, Vilarinho KA, et al. Use of modified ultrafiltration in  
4  
5 667 adults undergoing coronary artery bypass grafting is associated with inflammatory  
6  
7 668 modulation and less postoperative blood loss: a randomized and controlled study. *J*  
8  
9 669 *Thorac Cardiovasc Surg* 2012;**144**(3):663-70 doi: 10.1016/j.jtcvs.2012.04.012.  
10  
11  
12 670 79. Chew DP, Astley C, Molloy D, et al. Morbidity, mortality and economic burden of renal  
13  
14 671 impairment in cardiac intensive care. *Intern Med J* 2006;**36**(3):185-92 doi:  
15  
16 672 10.1111/j.1445-5994.2006.01012.x.  
17  
18  
19 673 80. Schaub JA, Coca SG, Moledina DG, et al. Amino-Terminal Pro-B-Type Natriuretic  
20  
21 674 Peptide for Diagnosis and Prognosis in Patients With Renal Dysfunction: A  
22  
23 675 Systematic Review and Meta-Analysis. *JACC Heart Fail* 2015;**3**(12):977-89 doi:  
24  
25 676 10.1016/j.jchf.2015.07.014.  
26  
27  
28  
29 677 81. Tsutamoto T, Kawahara C, Yamaji M, et al. Relationship between renal function and  
30  
31 678 serum cardiac troponin T in patients with chronic heart failure. *Eur J Heart Fail*  
32  
33 679 2009;**11**(7):653-8 doi: 10.1093/eurjhf/hfp072.  
34  
35  
36  
37 680 82. Aronson D, Abassi Z, Allon E, Burger AJ. Fluid loss, venous congestion, and worsening  
38  
39 681 renal function in acute decompensated heart failure. *Eur J Heart Fail* 2013;**15**(6):637-  
40  
41 682 43 doi: 10.1093/eurjhf/hft036.  
42  
43  
44 683 83. Shirakabe A, Hata N, Kobayashi N, et al. Worsening renal function definition is  
45  
46 684 insufficient for evaluating acute renal failure in acute heart failure. *ESC Heart Fail*  
47  
48 685 2018;**5**(3):322-31 doi: 10.1002/ehf2.12264.  
49  
50  
51 686  
52  
53  
54  
55 687



688 **Tables**

689 Table 1 Baseline characteristics of patients with confirmed acute heart failure (AHF)

690 syndrome

	All AHF patients (N=507)	Group 1 (n=335)	Group 2 (n=172)	p-value
Age, y	83 [77;88]	84 [78;89]	82 [75;88]	0.09
Men	220 (43.39%)	144 (42.99%)	76 (44.19%)	0.87
<b>Comorbidities</b>				
- Hypertension	353 (69.63%)	234 (69.85%)	119 (69.19%)	0.79
- Chronic HF	271 (53.45%)	189 (56.42%)	82 (47.67%)	<0.05
- Atrial fibrillation	223 (43.98%)	151 (45.07%)	72 (41.86%)	0.43
- Coronary heart disease	150 (29.59%)	98 (29.25%)	52 (30.23%)	1.00
- Diabetes type I	14 (2.76%)	12 (3.58%)	2 (1.16%)	0.26
- Diabetes type II	132 (26.04%)	93 (27.76%)	39 (22.67%)	0.20
- Chronic renal failure	114 (22.49%)	108 (32.24%)	6 (3.49%)	<0.01
- Chronic respiratory failure	87 (17.16%)	60 (17.91%)	27 (15.7%)	0.46
- Known valvular disease	95 (18.74%)	70 (20.9%)	25 (14.53%)	0.07
<b>Priori medications</b>				
- Furosemide	295 (58.19%)	204 (60.9%)	91 (52.91%)	<0.05
- ACEI/ARB	225 (44.38%)	153 (45.67%)	72 (41.86%)	0.30
- $\beta$ - blocker	214 (42.21%)	147 (43.88%)	67 (38.95%)	0.20
- Anticoagulant	221 (43.59%)	151 (45.07%)	70 (40.7%)	0.24
- Aspirin	155 (30.57%)	110 (32.84%)	45 (26.16%)	0.08
- Other antiplatelet	56 (11.05%)	37 (11.04%)	19 (11.05%)	0.73
- Oral antidiabetic	66 (13.02%)	47 (14.03%)	19 (11.05%)	0.22
- Insulin	68 (13.41%)	52 (15.52%)	16 (9.3%)	0.03
- Amiodarone	56 (11.05%)	48 (14.33%)	8 (4.65%)	<0.01
- Aldosterone antagonist	38 (7.5%)	26 (7.76%)	12 (6.98%)	0.48
- Digoxin	38 (7.5%)	18 (5.37%)	20 (11.63%)	0.10
- Thiazidine	32 (6.31%)	21 (6.27%)	11 (6.4%)	0.70
- None	28 (5.52%)	14 (4.18%)	14 (8.14%)	0.38
- Unknown	13 (2.56%)	7 (2.09%)	6 (3.49%)	1.00
<b>Prior hospitalization for HF during past year</b>				
- 0	287 (56.61%)	180 (53.73%)	107 (62.21%)	0.14
- 1	130 (25.64%)	83 (24.78%)	47 (27.33%)	0.86
- $\geq 2$	62 (12.23%)	52 (15.52%)	10 (5.81%)	<0.01
Followed by a cardiologist	348 (68.64%)	242 (72.24%)	106 (61.63%)	0.02
<b>Residence</b>				
- At home	423 (83.43%)	287 (85.67%)	136 (79.07%)	0.06
- Retirement institution	74 (14.6%)	43 (12.84%)	31 (18.02%)	0.18
- Other institution	8 (1.58%)	4 (1.19%)	4 (2.33%)	0.75

1					
2					
3	Self-sufficient	258 (50.89%)	162 (48.36%)	96 (55.81%)	0.19
4	Home assistance				
5	- Housekeeper	151 (29.78%)	111 (33.13%)	40 (23.26%)	0.02
6	- Family support	121 (23.87%)	87 (25.97%)	34 (19.77%)	0.10
7	- Nurse	134 (26.43%)	98 (29.25%)	36 (20.93%)	0.04
8	- Known cognitive				
9	impairment	83 (16.37%)	49 (14.63%)	34 (19.77%)	0.26
10	- Bedridden	45 (8.88%)	25 (7.46%)	20 (11.63%)	0.28

691 Data are median (IQR) age or number (%) of patients

692 Group 1: patients with CRS; Group 2: patients with normal renal function

693 AHF, acute heart failure; ADEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker;

694 HF, heart failure

695

696 Table 2 Hospitalization route and clinical status of patients with confirmed acute heart failure  
697 (AHF) syndrome

	All AHF patients (N = 507)	Group 1 (n = 335)	Group 2 (n = 172)	p-value
<b>Means of transport</b>				
- Personal	232 (45.76%)	157 (46.87%)	75 (43.6%)	0.50
- Ambulance	89 (17.55%)	56 (16.72%)	33 (19.19%)	0.63
- Firemen	55 (10.85%)	34 (10.15%)	21 (12.21%)	0.65
- MICU	40 (7.89%)	29 (8.66%)	11 (6.4%)	0.41
- Inter-hospital transfer	6 (1.18%)	5 (1.49%)	1 (0.58%)	0.48
<b>Clinical signs</b>				
- Warm extremities	390 (76.92%)	257 (76.72%)	133 (77.33%)	0.23
- Cold extremities	61 (12.03%)	45 (13.43%)	16 (9.3%)	0.97
- Signs of right heart failure	216 (42.6%)	144 (42.99%)	72 (41.86%)	0.69
- Inspiratory retraction	146 (28.8%)	107 (31.94%)	39 (22.67%)	0.02
- Inability to speak	42 (8.28%)	25 (7.46%)	17 (9.88%)	0.54
<b>First recorded vital signs</b>				
- Heart failure, beats/min	85 [71;102]	85 [72;102]	85 [72;104.25]	0.49
- SBP, mmHg	140 [121;160]	140 [121;160]	140 [124;162]	0.11
- DBP, mmHg	76 [65;90]	75 [63.5;89]	78 [67.75;92.25]	0.03
- SBP <100 mmHg	34 (6.71%)	27 (8.06%)	7 (4.07%)	0.13
- Respiratory rate, breaths/min	25 [20;30]	26 [20;30]	24 [20;29]	0.16
- Pulse oximetry, %	94 [90;96.25]	94 [90;97]	94 [89;96]	0.72
- GCS <15	48 (9.47%)	31 (9.25%)	17 (9.88%)	0.94
- Temperature >37°C	13 (2.56%)	12 (3.58%)	1 (0.58%)	0.37
<b>Killip status</b>				
- 1	128 (25.25%)	76 (22.69%)	52 (30.23%)	0.26
- 2	269 (53.06%)	181 (54.03%)	88 (51.16%)	0.30
- 3	84 (16.57%)	60 (17.91%)	24 (13.95%)	0.11
- Signs of shock	15 (2.96%)	8 (2.39%)	7 (4.07%)	0.89

698 Data are median (IQR) beats/minute, median (IQR) mmHg, median (IQR) breaths/minute, median (IQR) %, or

699 number (%) of patients

700 Group 1: patients with CRS; Group 2: patients with normal renal function

701 AHF, acute heart failure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; HF, heart failure; MICU,

702 mobile intensive care unit; SBP, systolic blood pressure

703

704 Table 3 Biological and diagnosis tests of patients with confirmed acute heart failure (AHF)  
705 syndrome

	All AHF patients (N=507)	Group 1 (n=335)	Group 2 (n=172)	p-value
<b>Biological analysis</b>				
- Performed	507 (100%)	335 (100%)	172 (100%)	
- Sodium, mmol/L	138 [135;141]	138 [135;141]	139 [135;141]	0.40
- Potassium, mmol/L	4 [4;5]	4 [4;5]	4 [4;5]	0.89
- Creatinine clearance, mL/min	50 [35;69.05]	40 [29;49.9]	78.5 [67;91]	<0.01
- Creatinine clearance <30 mL/min	89 (17.55%)	89 (26.57%)	0 (0%)	<0.01
- Hemoglobin, g/dL	13 [11;14]	12 [11;13]	13 [13;14]	0.06
- Troponin positive	271 (53.45%)	195 (58.21%)	76 (44.19%)	<0.01
- BNP, ng/L	991 [507.5;2443.5]	1157.5 [569.25;2680.5]	534 [291;1292]	<0.01
- Pro-BNP, ng/L	4025 [1729;8863]	5120 [2520;12399.75]	2513 [1146.5;5376.5]	<0.01
<b>ECG</b>				
- Performed	500 (98.61%)	329 (98.20%)	171 (99.41%)	
- Sinusal	220 (44%)	145 (43.28%)	75 (43.6%)	0.92
- Atrial fibrillation	213 (42.01)	139 (41.49%)	74 (43.02%)	1.00
- Driven	44 (8.8%)	33 (9.85%)	11 (6.4%)	0.19
- AVB	21 (4.14%)	14 (4.18%)	7 (4.07%)	0.86
- LBBB	86 (17.2%)	64 (19.1%)	22 (12.79%)	<0.05
- RBBB	59 (11.8%)	34 (10.15%)	25 (14.53%)	0.43
- Repolarization disorder	101 (20.2%)	73 (21.79%)	28 (16.28%)	0.09
<b>Chest X-ray</b>				
- Performed	481 (94.87%)	318 (94.92%)	163 (94.76%)	
- Normal	24 (4.73%)	11 (3.28%)	13 (7.56%)	0.20
- Cardiomegaly	235 (48.86%)	171 (51.04%)	64 (37.21%)	0.01
- Interstitial opacities	284 (59.04%)	202 (60.3%)	82 (47.67%)	0.02
- Alveolar opacities	108 (22.45%)	64 (19.1%)	44 (25.58%)	0.05

706 Data are median (IQR) mmol/L, median (IQR) mL/min, median (IQR) g/dL, median (IQR) ng/L, or number (%)

707 of patients

708 Group 1: patients with CRS; Group 2: patients with normal renal function

709 AHF, acute heart failure; AVB, atrioventricular block; BNP, brain natriuretic peptide; ECG, electrocardiogram;

710 HF, heart failure; IVC, inferior vena cava; LBBB, left bundle branch block; LVEF, left ventricular ejection

711 fraction; RBBB, right bundle branch block; RV, right ventricle; US, ultrasound

712

713 Table 4 Emergency treatment of patients with confirmed acute heart failure (AHF) syndrome

	All AHF patients (N=507)	Group 1 (n=335)	Group 2 (n=172)	p-value
Furosemide	376 (74.16%)	252 (75.22%)	124 (72.09%)	0.26
Oxygen	337 (66.47%)	225 (67.16%)	112 (65.12%)	0.43
Nitrates	92 (18.15%)	71 (21.19%)	21 (12.21%)	0.01
Anticoagulant	37 (7.3%)	22 (6.57%)	15 (8.72%)	1.00
CPAP	8 (1.58%)	6 (1.79%)	2 (1.16%)	0.24
NIV	45 (8.88%)	30 (8.96%)	15 (8.72%)	0.58
Antiarrhythmics	23 (4.54%)	15 (4.48%)	8 (4.65%)	0.60
Inotropic agents	3 (0.59%)	3 (0.9%)	0 (0%)	0.11
Tracheal intubation	1 (0.2%)	1 (0.3%)	0 (0%)	0.20
None	32 (6.31%)	17 (5.07%)	15 (8.72%)	0.58

714 Data are number (%) of patients

715 Group 1: patients with CRS; Group 2: patients with normal renal function

716 AHF, acute heart failure; CPAP, continuous positive airway pressure; NIV, non-invasive ventilation

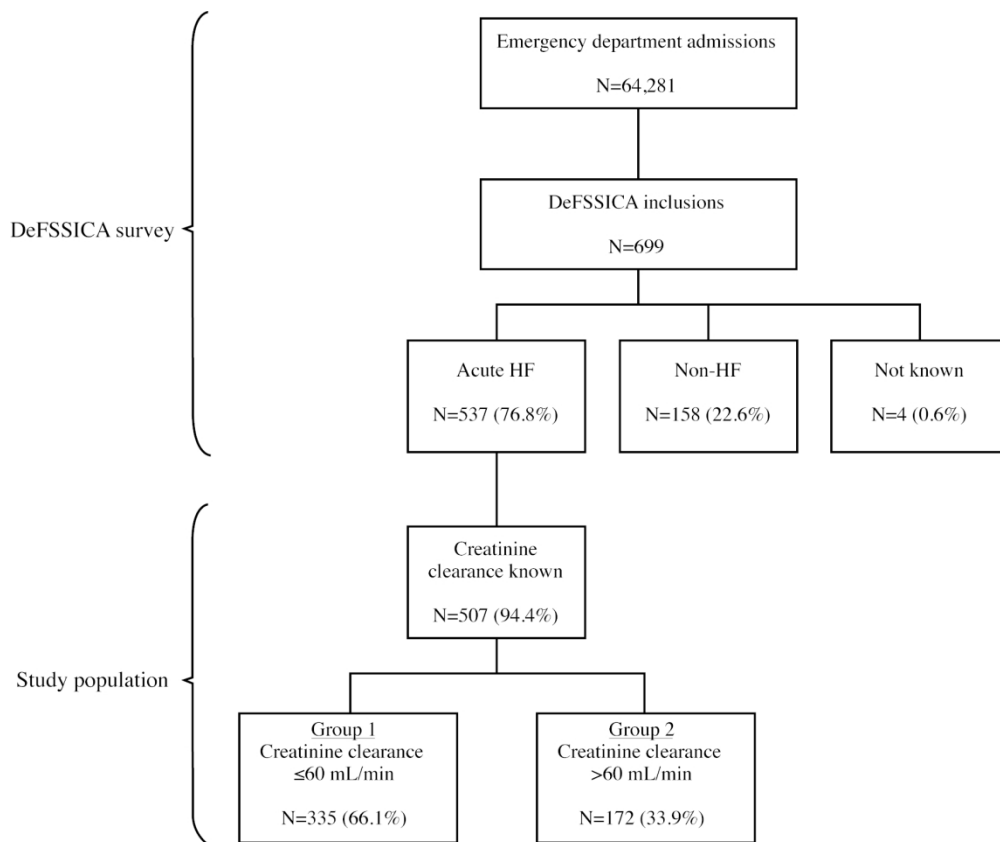
717 Table 5 Outcomes of patients with confirmed acute heart failure (AHF) syndrome

	All AHF patients (N=507)	Group 1 (n=335)	Group 2 (n=172)	p-value
<b>Precipitating factors</b>				
- Unknown	214 (42.21%)	138 (41.19%)	76 (44.19%)	0.82
- Infection	128 (25.25%)	84 (25.07%)	44 (25.58%)	0.89
- Rhythm disorder	77 (15.19%)	47 (14.03%)	30 (17.44%)	0.67
- Hypertension	54 (10.65%)	39 (11.64%)	15 (8.72%)	0.19
- Non-adherence to treatment	30 (5.92%)	17 (5.07%)	13 (7.56%)	0.92
- Acute coronary syndrome	21 (4.14%)	15 (4.48%)	6 (3.49%)	0.32
- Eating disorder	20 (3.94%)	14 (4.18%)	6 (3.49%)	0.39
- Diabetes decompensation	10 (1.97%)	10 (2.99%)	0 (0%)	0.01
<b>Discharge destination</b>				
- Cardiology	142 (28.01%)	100 (29.85%)	42 (24.42%)	0.33
- Geriatric medicine	61 (12.03%)	34 (10.15%)	27 (15.7%)	0.06
- Other medical unit	99 (19.53%)	67 (20%)	32 (18.6%)	0.98
- CICU	62 (12.23%)	42 (12.54%)	20 (11.63%)	1.00
- Resuscitation unit	16 (3.16%)	11 (3.28%)	5 (2.91%)	0.98
- ED hospitalization unit	74 (14.6%)	48 (14.33%)	26 (15.12%)	0.72
- Back home	26 (5.13%)	14 (4.18%)	12 (6.98%)	0.14
- Other	24 (4.73%)	18 (5.37%)	6 (3.49%)	0.78
<b>Destination considered appropriate</b>	<b>382 (75.35%)</b>	<b>246 (73.43%)</b>	<b>136 (79.07%)</b>	<b>0.13</b>
<b>Outcome</b>				
- In-hospital mortality	30 (5.92%)	24 (7.16%)	6 (3.49%)	0.97
- Still hospitalized at 30 days	32 (6.31%)	20 (5.97%)	12 (6.98%)	1.00
<b>Length of stay, days</b>	<b>7 (4;13)</b>	<b>8 (4;13)</b>	<b>6 (3;12)</b>	<b>0.03</b>

718 Data are number (%) of patients or median (IQR) days

719 Group 1: patients with CRS; Group 2: patients with normal renal function

720 AHF, acute heart failure



TITLE: Figure 1 Patient disposition

LEGEND: DeFSSICA, Description de la Filière de Soins dans les Syndromes d’Insuffisance Cardiaque Aigue;  
HF, heart failure

158x133mm (300 x 300 DPI)

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies**

**TITLE: Impact of renal dysfunction on the management and outcome of acute heart failure: results from the French prospective, multicenter, DeFSSICA survey**

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9
		(b) Describe any methods used to examine subgroups and interactions	9
		(c) Explain how missing data were addressed	NA
		(d) If applicable, explain how loss to follow-up was addressed	NA
		(e) Describe any sensitivity analyses	NA



<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10 and Figure 1
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	14-17
<b>Limitations</b>			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Impact of renal dysfunction on the management and outcome of acute heart failure: results from the French prospective, multicenter, DeFSSICA survey

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-022776.R2
Article Type:	Research
Date Submitted by the Author:	08-Oct-2018
Complete List of Authors:	<p>dos Reis, Dominique; Val de Grâce Medical School, Ministère de la Défense</p> <p>Fratlicelli, Laurie; Centre Hospitalier de Vienne Lucien Hussenel, RESCUE Network</p> <p>Bassand, Adrien; CHRU Nancy, Emergency Department; CHRU Nancy, CIC-P</p> <p>Manzo-Silberman, Stéphane; Hopital Lariboisiere, Department of Cardiology; INSERM UMR-S-942</p> <p>Peschanski, Nicolas; Centre Hospitalier Eure-Seine, Emergency Department</p> <p>Charpentier, Sandrine; Hopital de Ranguueil, Emergency Department; Universite Toulouse III Paul Sabatier</p> <p>Elbaz, Meyer; Hopital de Ranguueil, Department of Cardiology</p> <p>Savary, Dominique; Annecy-Genevois, Emergency Department and Intensive Care Unit</p> <p>Bonnefoy-Cudraz, Eric; Hôpital Cardiologique de Lyon, Department of Cardiology</p> <p>Laribi, Said; Centre Hospitalier Regional Universitaire de Tours, Emergency Department; INSERM UMR-S-942, Université Paris-Diderot, Sorbonne</p> <p>Henry, Patrick; Hopital Lariboisiere, Department of Cardiology; INSERM UMR-S-942, Université Paris-Diderot, Sorbonne</p> <p>Guerraoui, Abdallah; Groupement Hospitalier Edouard Herriot, Emergency Department; Universite Claude Bernard Lyon 1</p> <p>Tazarourte, Karim; University Hospital, Hospices Civils, Lyon, Emergency Medicine; University Lyon 1, Health Services and Performance Research Laboratory, EA 7425</p> <p>Chouihed, Tahar; CHRU Nancy, SAMU-SMUR-SAU; Institut Lorrain du Coeur et des Vaisseaux</p> <p>El Khoury, Carlos; Centre Hospitalier de Vienne Lucien Hussenel, Emergency Department and RESCUE Network</p>
<b>Primary Subject Heading</b>:	Emergency medicine
Secondary Subject Heading:	Cardiovascular medicine, Renal medicine
Keywords:	acute heart failure, AHF, cardio-renal syndrome, CRS, real-life, renal dysfunction

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



SCHOLARONE™  
Manuscripts

1  
2  
3 1 Impact of renal dysfunction on the management and outcome of acute heart failure: results  
4  
5 2 from the French prospective, multicenter, DeFSSICA survey  
6  
7  
8 3 Dominique dos Reis, MD<sup>1</sup>, Laurie Fraticelli PhD<sup>2</sup>, Adrien Bassand, MD<sup>3</sup>, Stéphane Manzo-  
9  
10 4 Silberman, MD, PhD<sup>4</sup>, Nicolas Peschanski, MD, PhD<sup>5</sup>, Sandrine Charpentier, MD, PhD<sup>6</sup>,  
11  
12 5 Meyer Elbaz, MD, PhD<sup>7</sup>, Dominique Savary, MD<sup>8</sup>, Eric Bonnefoy-Cudraz, MD, PhD<sup>9</sup>, Said  
13  
14 6 Laribi, MD, PhD<sup>10</sup>, Patrick Henry, MD, PhD<sup>11</sup>, Abdallah Guerraoui, MD<sup>12</sup>, Karim Tazarourte,  
15  
16 7 MD, PhD<sup>13</sup>, Tahar Chouihed, MD<sup>14</sup>, Carlos El Khoury, MD, PhD<sup>15</sup>  
17  
18  
19  
20  
21 8 <sup>1</sup>Val de Grâce Medical School, Ministère de la Défense, Paris, France ([d.dosreis@live.fr](mailto:d.dosreis@live.fr));  
22  
23 9 <sup>2</sup>RESCUe Network, Lucien Hussel Hospital, Vienne, France ([l.fraticelli@resuval.fr](mailto:l.fraticelli@resuval.fr));  
24  
25  
26 10 <sup>3</sup>SAMU-SMUR-SAU Nancy, Hôpital Central, CHRU Nancy, France  
27  
28 11 ([adrienbassand@gmail.com](mailto:adrienbassand@gmail.com)); <sup>4</sup>Lariboisière Hospital, Department of Cardiology, Paris, France  
29  
30 12 and INSERM UMR-S 942, Université Paris-Diderot, Sorbonne Paris Cité, Paris, France  
31  
32 13 ([stephane.manzosilberman@aphp.fr](mailto:stephane.manzosilberman@aphp.fr)); <sup>5</sup>Emergency Department, SAMU 27, Eure Seine  
33  
34 14 Evreux Hospital, France ([bansbari@gmail.com](mailto:bansbari@gmail.com)); <sup>6</sup>Emergency Department, Ranguéil  
35  
36 15 University Hospital, Toulouse, France; INSERM, U1027, Toulouse, France; Université  
37  
38 16 Toulouse III – Paul Sabatier, Toulouse, France ([charpentier.s@chu-toulouse.fr](mailto:charpentier.s@chu-toulouse.fr)); <sup>7</sup>Department  
39  
40 17 of Cardiology, Ranguéil Hospital, Toulouse, France ([elbaz.m@chu-toulouse.fr](mailto:elbaz.m@chu-toulouse.fr)); <sup>8</sup>Emergency  
41  
42 18 Department and Intensive Care Unit, Annecy-Genevois, Metz-Tessy, France  
43  
44 19 ([savaryd@wanadoo.fr](mailto:savaryd@wanadoo.fr)); <sup>9</sup>Department of Cardiology, Hôpital Cardiologique de Lyon, Lyon,  
45  
46 20 France ([eric.bonnefoy-cudraz@chu-lyon.fr](mailto:eric.bonnefoy-cudraz@chu-lyon.fr)); <sup>10</sup>Emergency Medicine Department, University  
47  
48 21 Hospital of Tours; INSERM UMR-S 942, Université Paris-Diderot, Sorbonne Paris Cité,  
49  
50 22 Paris, France ([s.laribi@chu-tours.fr](mailto:s.laribi@chu-tours.fr)); <sup>11</sup>Lariboisière Hospital, Department of Cardiology,  
51  
52 23 Paris, France; INSERM UMR-S 942, Université Paris-Diderot, Sorbonne Paris Cité, Paris,  
53  
54 24 France ([patrick.henry@aphp.fr](mailto:patrick.henry@aphp.fr)); <sup>12</sup>Calydial Dialysis Department, Lucien Hussel Hospital,  
55  
56 25 Vienne, France ([abdallah.guerraoui@calydial.org](mailto:abdallah.guerraoui@calydial.org)); <sup>13</sup>Emergency Department, Edouard

1  
2  
3 26 Herriot Hospital, Lyon, France; Univ. Lyon, Claude Bernard Lyon 1 University, HESPER EA  
4  
5 27 7425, Lyon, France ([karim.tazarourte@chu-lyon.fr](mailto:karim.tazarourte@chu-lyon.fr)); <sup>14</sup>SAMU-SMUR-SAU Nancy, Hôpital  
6  
7 28 Central, CHRU Nancy, France; Centre d'Investigation Clinique Plurithématique 1433, Institut  
8  
9 29 Lorrain du Cœur et des Vaisseaux, Vandoeuvre-les-Nancy France; INSERM U1116,  
10  
11 30 Université de Lorraine, Nancy, France ([t.chouihed@gmail.com](mailto:t.chouihed@gmail.com)); <sup>15</sup>Emergency Department  
12  
13 31 and RESCUE Network, Lucien Hessel Hospital, Vienne, France; Univ. Lyon, Claude Bernard  
14  
15 32 Lyon 1 University, HESPER EA 7425, Lyon, France ([c.elkhoury@resuval.fr](mailto:c.elkhoury@resuval.fr))  
16  
17  
18  
19

20 33 **Corresponding author:**

21  
22  
23 34 Carlos El Khoury, MD, PhD  
24  
25 35 Emergency Department and RESCUE Network, Lucien Hessel Hospital, Vienne, France;  
26  
27 36 Univ. Lyon, Claude Bernard Lyon 1 University, HESPER EA 7425, Lyon, France  
28  
29  
30 37 Tél. +33 (0) 4 7431 3257; Mob. +33 (0) 6 2410 4024; email [c.elkhoury@resuval.fr](mailto:c.elkhoury@resuval.fr)  
31  
32  
33

34 38 **Target journal & format:** BMJ Open - Research Articles format (counts: abstract 300 words  
35  
36 39 [max 300]; 6 keywords; body 3476 words (max 4000); 79 references; 1 figure, 5 tables).  
37  
38  
39  
40

1  
2  
3 **41 Abstract (300 words [max 300])**  
4  
5

6 **42 Objectives:** Cardio-renal syndrome (CRS) is the combination of acute heart failure syndrome  
7  
8  
9 **43 (AHF) and renal dysfunction (creatinine clearance [CrCl]  $\leq$ 60 mL/min). Real-life data were**  
10  
11 **44 used to compare the management and outcome of AHF with and without renal dysfunction.**  
12

13  
14 **45 Design:** Prospective, multi-center.  
15

16  
17 **46 Setting:** Twenty-six academic, community, and regional hospitals in France.  
18

19  
20  
21 **47 Participants:** 507 patients with AHF were assessed in two groups according to renal  
22  
23 **48 function: Group 1 (CRS patients [CrCl  $\leq$ 60 mL/min]: N=335) and Group 2 (AHF patients**  
24  
25 **49 with normal renal function [CrCl  $>$ 60 mL/min]: N=172).**  
26  
27

28  
29 **50 Results:** Differences were observed (Group 1 versus Group 2) at admission for the incidence  
30  
31 **51 of chronic heart failure (56.42% versus 47.67%), use of furosemide (60.9% versus 52.91%),**  
32  
33 **52 insulin (15.52% versus 9.3%), and amiodarone (14.33% versus 4.65%); additionally, more**  
34  
35 **53 patients in Group 1 carried a defibrillator (4.78% versus 0%), had  $\geq$ 2 hospitalizations in the**  
36  
37 **54 last year (15.52% versus 5.81%), and were under the care of a cardiologist (72.24% versus**  
38  
39 **55 61.63%). Clinical signs were broadly similar in each group. Brain-type natriuretic peptide**  
40  
41 **56 (BNP) and BNP prohormone were higher in Group 1 than Group 2 (1157.5 versus 534 ng/L**  
42  
43 **57 and 5120 versus 2513 ng/mL), and more patients in Group 1 were positive for troponin**  
44  
45 **58 (58.2% versus 44.19%), had cardiomegaly (51.04% versus 37.21%), and interstitial opacities**  
46  
47 **59 (60.3% versus 47.67%). The only difference in emergency treatment was the use of nitrates,**  
48  
49 **60 (higher in Group 1 [21.9% versus 12.21%]). In-hospital mortality and the percentage of**  
50  
51 **61 patients still hospitalized after 30 days was similar between groups, but median stay was**  
52  
53 **62 longer in Group 1 (8 days versus 6 days).**  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 63 **Conclusions:** Renal impairment in AHF should not limit the use of loop diuretics and/or  
4  
5 64 vasodilators, but early assessment of pulmonary congestion and close monitoring of the  
6  
7 65 efficacy of conventional therapies is encouraged to allow rapid and appropriate  
8  
9  
10 66 implementation of alternative therapies if necessary.  
11  
12

13 67  
14  
15

16 68  
17  
18

19 69  
20  
21

22  
23 70 **Keywords:** acute heart failure, AHF, cardio-renal syndrome, CRS, real-life, renal dysfunction  
24  
25

26 71  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 72 **Strengths and limitations of this study**  
4  
5

- 6 73 • A large-scale, prospective, real-life study for the management and outcome of patients  
7  
8 74 with cardio-renal syndrome compared to acute heart failure patients without renal  
9  
10 75 dysfunction.  
11  
12 76 • Only two groups were included (i.e. patients with or without kidney dysfunction), rather  
13  
14 77 than for each stage of chronic kidney disease although the creatinine clearance cut-off (60  
15  
16 78 mL/min) is commonly used.  
17  
18 79 • Glomerular filtration rate was calculated using three different methods.  
19  
20 80 • Glomerular filtration rate estimations were performed by local laboratories for each  
21  
22 81 center (i.e. a real-life situation).  
23  
24 82 • There was no clearance monitoring after hospital discharge.  
25  
26  
27  
28  
29  
30  
31 83  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## 84 **Background**

85 Heart failure (HF) has an incidence of approximately 2% in adults in developed countries [1]  
86 and mainly affects elderly patients, who may have multiple comorbidities. One such  
87 comorbidity, impaired renal function, has been shown to be a stronger predictor of mortality  
88 than impaired cardiac function [2 3] and can be present in 50% of patients treated for acute  
89 HF (AHF) [4]. The prognostic importance of the association of renal dysfunction (creatinine  
90 clearance [CrCl]  $\leq 60$  mL/min) and AHF (cardio-renal syndrome [CRS]) has only been  
91 demonstrated recently. This represents a complex pathophysiological condition that has been  
92 classified into 5 stages [5 6]. It is worth noting that this is a mechanistic classification and the  
93 patients' clinical management must consider the full clinical presentation..

94 Even moderate degrees of renal insufficiency are independently associated with an increased  
95 risk of mortality from any cause in patients with HF [7]. As such, CRS can lead to hesitancy  
96 among some clinicians to implement appropriate treatments for HF, such as diuretics, due to  
97 the effect that these may have to worsen the renal insufficiency. However, additional  
98 prospective research is needed and current recommendations are to maintain such treatments  
99 in CRS patients [8 9] although the emergency physician should make an appropriate risk  
100 risk:benefit assessment for each patient.

101 In this context, a sub-analysis was conducted using real-life data from the DeFSSICA study  
102 (Description de la Filière de Soins dans les Syndromes d'Insuffisance Cardiaque Aigue), a  
103 large-scale, prospective study that was conducted in patients with suspected dyspnea of  
104 cardiac origin in emergency departments (EDs) throughout France [10]. The aim of this sub-  
105 analysis was to compare the management and outcome of CRS patients to AHF patients  
106 without renal dysfunction in France using novel real-life data, based on the hypothesis that

1  
2  
3 107 CRS and AHF patients would have the same outcome if the management of CRS was based  
4  
5 108 on that for AHF patients without renal dysfunction.  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

## 109 **Methods**

### 110 *Study design*

111 This was a prospective, multi-center study in patients presenting with suspected heart failure  
112 dyspnea in 26 EDs in academic, community, and regional hospitals (the DeFSSICA study) for  
113 which the rationale and design are reported elsewhere [10]. The study received approval from  
114 the National Commission for Liberties and Data Protection (Commission Nationale de  
115 l'Informatique et des Libertés) (number DR-2014-543) and the Advisory Committee on the  
116 Treatment of Information in the field of Health Research (Comité Consultatif sur le  
117 Traitement de l'Information en matière de Recherche dans le Domaine de la Santé) (number  
118 14-291). Written information regarding the objectives of the survey was provided to all  
119 patients prior to their inclusion according to French law. Each participating physician  
120 presented the study to the patient and/or the patient's family. The patient and/or the patient's  
121 family could choose for the patient to withdraw from the study at any time. The study did not  
122 affect the patient-physician relationship or the patient's care and follow-up.

### 123 *Patient involvement*

124 The research question was based on the prognostic importance of CRS and a need for real-life  
125 data on the management and outcome of CRS patients. Patients were not involved in the  
126 design, recruitment, and conduct of the study, and there is no plan to disseminate the results  
127 specifically to the patients who provided data used in this analysis.

### 128 *Selection of participants*

129 In the DeFSSICA survey, patients >18 years of age with dyspnea compatible with acute HF,  
130 defined as dyspnea associated with peripheral edema and/or pulmonary crackles and/or  
131 excessive weight gain and/or use of furosemide, were eligible for inclusion after ED

1  
2  
3 132 admission and prior to chest X-ray and laboratory tests. Patient enrollment occurred between  
4  
5 133 16 June 2014 and 7 July 2014.  
6  
7

8  
9 134 In this analysis, only patients with known CrCl were included and were divided into those  
10  
11 135 with CrCl  $\leq$ 60 mL/min, i.e. renal dysfunction (Group 1) and those with CrCl >60 mL/min, i.e.  
12  
13 136 normal renal function (Group 2). Glomerular filtration rate (GFR) was calculated using either  
14  
15 137 the Cockcroft-Gault (9 centers), Modification of Diet in Renal Disease (MDRD) Study (12  
16  
17 138 centers), or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations (14  
18  
19 139 centers) (8 centers used two methods and 18 centers used one method) [11 12].  
20  
21  
22

#### 23 140 *Study assessments*

24  
25  
26 141 Patients' baseline characteristics, medical history, social factors, in-hospital diagnostic tests  
27  
28 142 and treatment, destination after ED discharge, in-hospital mortality and length of stay were  
29  
30 143 recorded by emergency physicians in a case report form, which was structured according to  
31  
32 144 the progress of care. Cardiac sonographic evaluations were performed at the discretion of the  
33  
34 145 emergency physician. Abnormal chest X-ray was defined by the presence of cardiomegaly,  
35  
36 146 and/or alveolar edema, and/or interstitial opacity, and/or pleural effusion. The choice of  
37  
38 147 treatment was at the emergency physician's discretion, and according to his/her usual  
39  
40 148 practice. Final diagnosis of AHF was made by the emergency physician using a combination  
41  
42 149 of a clinical history, abnormal chest X-ray, elevated brain-type natriuretic peptide (BNP) or  
43  
44 150 BNP prohormone (proBNP), and echocardiographic signs.  
45  
46  
47  
48  
49

50  
51 151 Although it was not possible to impose any randomization or blinding since this was an  
52  
53 152 observational study, any potential bias in the study assessments was minimized by the  
54  
55 153 provision of standard instructions to all participating physicians.  
56  
57  
58  
59  
60

1  
2  
3 154 Data were entered into a secure database located at the Réseau Cardiologie Urgence  
4  
5 155 (RESCUe) (Cardiovascular Emergency Network) Coordination Center.  
6  
7

8  
9 156 *Statistical analysis*  
10

11  
12 157 Medians and interquartile ranges (IQR) are provided for continuous variables, and numbers  
13  
14 158 and percentages for qualitative variables. Comparative analyses were performed using the  $\chi^2$   
15  
16 159 or Fisher's test for binary variables and the Wilcoxon test for analysis of variance for  
17  
18 160 continuous variables [13]. The 5% level was used to identify differences between groups that  
19  
20 161 were of statistical significance ( $p < 0.05$ ). Statistical evaluations were performed using R  
21  
22 162 Statistical Software (Version 3.4.1).  
23  
24  
25  
26  
27 163  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 164 **Results**

### 165 *Patient disposition and prevalence of CRS*

166 A total of 64,281 ED consultations took place during the survey period and 699 patients with  
167 dyspnea of cardiac origin were included in DEFSSICA study. Of these, 537 patients were  
168 identified as having AHF, of whom only those with known CrCl (N=507) were included in  
169 this analysis.

170 Patients in Group 1 (N=335 [66.1%]) had renal dysfunction (CrCl  $\leq$ 60 mL/min) and  
171 comprised the population with CRS. In this group, 99 patients (29.6%) had severe renal  
172 dysfunction (Stage 4 or 5: CrCl:  $<$ 30 mL/min) and 120 (35.8%) had a known history of  
173 chronic renal failure. All patients in Group 2 (N=172 [33.9%]) had normal renal function  
174 (CrCl  $>$ 60 mL/min).

175 Patient disposition is presented in Figure 1.

### 176 *Baseline characteristics*

177 The baseline characteristics of patients in Group 1 and Group 2 are shown in Table 1. There  
178 was no difference between Group 1 and Group 2 in age (median [IQR]: 84 [88-79] years and  
179 82 [75-88] years;  $p=0.09$ ) or sex distribution (42.99% male in Group 1 and 44.19% male in  
180 Group 2;  $p=0.87$ ).

181 As well as the higher incidence of chronic renal failure in Group 1, patients with CRS were  
182 more likely to have chronic HF (56.42% in Group 1 versus 47.67% in Group 2;  $p<0.05$ ).

183 There was no difference in the incidence of any other comorbidity between groups. Patients in  
184 Group 1 were more likely than patients in Group 2 to receive furosemide (60.9% versus  
185 52.91%;  $p<0.05$ ), insulin (15.52% versus 9.3%;  $p=0.03$ ) and amiodarone (14.33% versus

186 4.65%;  $p<0.01$ ) but there were no other differences between groups for medications.

187 Additionally, patients in Group 1 were more likely to have been hospitalized for HF at least  
188 twice during the last year (15.52% versus 8.81%;  $p<0.01$ ), and to be under the care of a  
189 cardiologist (72.24% versus 61.63%;  $p=0.02$ ). The incidence of patients carrying a  
190 defibrillator and of pacemakers (single, dual, or triple) are not presented since the sample  
191 sizes were small ( $N=16$  and  $N=17$ ,  $N=36$ , and  $N=6$ , respectively) and so the data were not  
192 considered sufficiently robust. Patients in Group 1 were more likely to have a housekeeper  
193 (31.13% versus 23.26%;  $p=0.02$ ) and nurse (29.25% versus 20.93%;  $p=0.04$ ) but there was no  
194 difference between groups regarding family support, known cognitive impairment, or the  
195 incidence of being bedridden.

#### 196 *Hospitalization and clinical status*

197 Although there were few statistically significant differences between groups in hospitalization  
198 and clinical status parameters (Table 2) there was a consistent trend towards more congestion  
199 in Group 1, including higher levels of dyspnea, more pulmonary infiltrates on chest X-ray,  
200 higher BNP and proBNP (Table 3 and below).

201 There were no significant differences between groups in their means of transport to the ED  
202 (most commonly by personal means [45.76% overall]), Killip status (most patients in each  
203 group had a Killip status of 2 [53.06% overall], and signs of cardiogenic shock (2.96%  
204 overall).

#### 205 *Early management and diagnosis*

206 At admission, blood samples from all patients underwent biological analysis (Table 3). As  
207 well as the differences between groups for CrCl, significant differences were observed for  
208 BNP, which was 2.2-fold higher in Group 1 than Group 2 (1157.5 ng/L versus 534 ng/L;

209 p<0.01), and proBNP, which was 2.0-fold higher in Group 1 than Group 2 (5120 ng/L versus  
210 2513 ng/L; p<0.01). Additionally, troponin was more likely to be positive in patients in Group  
211 1 than Group 2 (58.21% versus 44.19%; p<0.01). There were no differences between groups  
212 for sodium, potassium, or hemoglobin.

213 Most patients underwent under an electrocardiogram (98.61% overall) chest X-ray (94.87%  
214 overall). Patients in Group 1 were more likely than those in Group 2 to have left bundle  
215 branch block (19.1% versus 12.79%; p<0.05), cardiomegaly (51.04% versus 37.21%;  
216 p=0.01), and interstitial opacities (60.3% versus 47.67%; p=0.02).

217 Echography was only performed for 82 patients and so the data were not considered  
218 sufficiently robust for inclusion in the analysis.

### 219 *Emergency treatments*

220 Patients in Group 1 were more likely than Group 2 to receive emergency treatment of nitrates  
221 (21.19% versus 12.21%; p<0.01), but there were no group differences in other emergency  
222 measures (furosemide, oxygen, anticoagulant, continuous positive airway pressure, non-  
223 invasive ventilation, anti-arrhythmics, inotropic agents, tracheal intubation) (Table 4). Overall  
224 6.31% of patients received no emergency treatment, with no difference between groups.

### 225 *Outcomes*

226 Precipitating factors were not determined in 42.21% of cases overall, with no overall  
227 difference between groups (Table 5). The most common determined precipitating factors were  
228 infection (25.25% overall), arrhythmia (15.19% overall), and hypertension (10.65% overall).  
229 Diabetes decompensation was considered to be the precipitating factor for AHF in 2.99% of  
230 patients in Group 1 but none in Group 2 (p=0.01). There were no other group differences in  
231 precipitating factors.



1  
2  
3 232 There was no difference between groups in discharge destination (which was most often  
4  
5 233 cardiology [28.01% overall]), and the discharge destination was deemed appropriate for a  
6  
7  
8 234 similar number of patients in each group (75.35% overall).  
9

10  
11 235 Neither in-hospital mortality (5.92% overall) nor the percentage of patients still hospitalized  
12  
13 236 at 30 days (6.31% overall) were significantly different between Group 1 and Group 2.  
14

15 237 However, the median length of stay was 2 days longer in Group 1 than in Group 2 (8 days  
16  
17  
18 238 versus 6 days;  $p=0.03$ ) (Table 5).  
19

20  
21 239  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 240 Discussion

241 The DeFSSICA study was a large-scale, prospective, real-life study conducted following  
242 admission of AHF patients to EDs throughout France. As such, the data are primarily  
243 applicable to the French population, although wider extrapolation is possible due to  
244 coherences with similar studies in other geographical regions. The overall DeFSSICA study  
245 data are presented elsewhere [10] and the present sub-analysis reports real-life data from sub-  
246 groups of AHF patients with or without concomitant renal dysfunction, based on a CrCl  
247 threshold of 60 mL/min. The results show that AHF admissions to EDs are often associated  
248 with renal impairment, with almost two-thirds of AHF admissions having CrCl  $\leq$ 60 mL/min.  
249 This prevalence is comparable to published data from France [14], Italy [15 16], Poland [17],  
250 Spain [18 19], Taiwan [20], and the USA [21-23], as well as from pan-European [24 25] and  
251 wider international studies [26]. In these studies [14-26], the prevalence of renal impairment  
252 on admission of AHF patients ranged from 54.5% to 64%, including 12.4 to 27.4% of patients  
253 with severe renal insufficiency. Patients with a history of chronic renal failure ranged from  
254 21.4% to 32.5%, which is also comparable to the findings of the DeFSSICA survey. However,  
255 it should be noted that impaired cardiac function leads to reduced renal perfusion, which  
256 could be in addition to an underlying chronic renal insufficiency. Additionally, increased  
257 abdominal pressure at admission that can result from ascites can lead to renal vein  
258 compression and reduced GFR at admission, which could also result in elevated serum  
259 creatinine. It is likely, therefore, that a proportion of acute kidney injury diagnosed at  
260 admission based on serum creatinine could be due to temporary changes in perfusion  
261 pressures rather than kidney damage *per se*; these functional reductions in GFR would be  
262 expected to recover once normal hemodynamic function is restored. While it is therefore  
263 important to consider the use of biomarkers to provide a more precise assessment of kidney  
264 function than serum creatinine [27 28] it is also important to note that the evidence supporting

1  
2  
3 265 the preferential use of novel biomarkers rather than serum creatinine to detect acute kidney  
4  
5 266 injury can be inconsistent and remains an area for further research [29-32].  
6  
7

8  
9 267 The overall baseline characteristics, clinical status, biological and diagnostic tests, emergency  
10  
11 268 treatment, and outcome of the patients included in this sub-analysis was similar to the overall  
12  
13 269 population in the DeFSSICA study; however, some differences were observed between AHF  
14  
15 270 patients with and without renal dysfunction, including a trend towards more congestion in  
16  
17 271 patients with CRS. As would be expected due to reduced kidney excretion [33], and as  
18  
19 272 described elsewhere [34-37], BNP and pro-BNP levels were higher in patients with CRS than  
20  
21 273 in AHF patients with normal renal function and the percentage of troponin positive patients  
22  
23 274 was also higher in the CRS group. These biomarkers probably reflect the congestion status  
24  
25 275 and remain formally recommended for the management of AHF patients, especially for their  
26  
27 276 prognostic value. The appropriate use of loop diuretics and/or vasodilators [38] in the CRS  
28  
29 277 group, as well as in the AHF group without renal dysfunction, may explain in part the similar  
30  
31 278 intra-hospital mortality rate in each group and the similar proportion of AHF patients with and  
32  
33 279 without renal dysfunction who were still in hospital 30 days after ED admission. Importantly,  
34  
35 280 therefore, the prognosis of CRS patients was not significantly different using loop diuretics  
36  
37 281 and/or nitrates to those without renal dysfunction. As such, it appears that the correct  
38  
39 282 congestive assessment is vital in this complex clinical situation with concomitant failures in  
40  
41 283 two organs.  
42  
43  
44  
45  
46  
47

48  
49 284 Recent publications suggest that appropriate, fast-acting decongesting therapies, as  
50  
51 285 recommended by international guidelines, improve the prognosis for AHF patients as long as  
52  
53 286 such therapies are introduced early, even if renal impairment develops at the same time [8].  
54  
55 287 Furthermore, it appears that renal impairment in AHF patients does not have an adverse  
56  
57 288 impact on patient prognosis provided that the congestion is improved. Renal function should  
58  
59 289 be assessed according to the level of patient congestion, and so tools for the assessment of  
60

1  
2  
3 290 congestion, such as the BNP or proBNP biomarkers [39], lung ultrasound (LUS) B-lines (38),  
4  
5 291 or the assessment of the dimensions and compliance of the inferior vena cava are vital.  
6  
7 292 Additionally, hemoconcentration monitoring can be useful for monitoring congestion and  
8  
9 293 significantly improves the short-term outcome of AHF patients [40] and several routinely  
10 294 assessed biological parameters, e.g. serum protein, albumin, hemoglobin, and hematocrit,  
11  
12 295 have been proposed as surrogate markers [41]. Furthermore, formulae have been developed to  
13  
14 296 indirectly estimate plasma volume using hemoglobin and/or hematocrit data [42 43]. Further  
15  
16 297 research is needed to establish the ability of novel biomarkers such as urinary angiotensinogen  
17  
18 298 [44], neutrophil gelatinase-associated lipocalin [45 46], kidney injury molecule-1 [47],  
19  
20 299 interleukin-18 [48 49], N-acetyl- $\beta$ -d-glucosaminidase [50], cystatine C [51 52] or a  
21  
22 300 combination of some or all of these could also be used to improve clinical decision making  
23  
24 301 and therapy. The assessment of diuresis and natriuresis, which reflect both glomerular and  
25  
26 302 tubular function, could offer a strategy to achieve decongestion [50 53 54]. Ferreira et al [55]  
27  
28 303 and Palazzuoli et al [56] showed that the lack of a diuretic response is a more important  
29  
30 304 prognostic factor than the use of loop diuretics. This suggests a new diagnostic challenge, i.e.  
31  
32 305 to assess the patient's response to diuretics [57-60]. However, despite some proposals to  
33  
34 306 define diuretic resistance (e.g. persistent congestion despite adequate and escalating doses of  
35  
36 307 diuretic with >80 mg furosemide/day, amount of sodium excreted as a percentage of filtered  
37  
38 308 load <0.2%, failure to excrete  $\geq$ 90 mmol of sodium within 72 hours of a 160 mg oral  
39  
40 309 furosemide dose given twice daily) and the means of evaluation (e.g. weight loss per unit of  
41  
42 310 40 mg furosemide [or equivalent], net fluid loss/mg of loop diuretic [40 mg of furosemide or  
43  
44 311 equivalent] during hospitalization, natriuretic response to furosemide) [61], there is currently  
45  
46 312 no consensus for commonly accepted standards. Additionally, it is important that any  
47  
48 313 alteration of GFR should be interpreted in the context of the deterioration of the clinical  
49  
50 314 situation.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 315 Another alternative therapy in CRS is the use of mineralocorticoid antagonists. These have  
4  
5 316 been associated with an improvement in both congestion [62 63] and mortality in HF patients  
6  
7 317 [64 65], although the ATHENA-HF trial results are less conclusive [66]. Combined therapies  
8  
9 318 have also been evaluated, including hypotonic saline serum in combination with diuretic  
10  
11 319 therapy to improve diuresis [67 68] and mannitol in combination with furosemide [61],  
12  
13 320 although their benefit in diuretic-resistant patients is not confirmed. The addition of  
14  
15 321 metozalone to furosemide could be of interest because of its capacity to produce diuresis even  
16  
17 322 in patients with low GFR [69 70]. In a meta-analysis, Wang and al showed that tolvaptan, an  
18  
19 323 oral vasopressin V<sub>2</sub>-receptor antagonist, may also represent an alternative therapy in WRF  
20  
21 324 [71]. Several studies have shown that tolvaptan can decrease WRF in patients treated with  
22  
23 325 furosemide [72 73]. Finally, venous ultrafiltration allows controlled hydrosodic depletion by  
24  
25 326 subtracting isotonic fluid, compared to diuretics that allow the subtraction of hypotonic fluid.  
26  
27 327 Other studies suggest that the effectiveness of ultrafiltration is associated with a reduction in  
28  
29 328 inflammatory cytokines [74]. These and other approaches in patients with cardiac  
30  
31 329 insufficiency and resistance to diuretics have recently been reviewed [61].

32  
33 330 The CRS analysis using data from the DeFSSICA survey has some limitations. First, only two  
34  
35 331 groups have been analyzed (i.e. patients with or without renal dysfunction), whereas chronic  
36  
37 332 kidney disease is characterized by 5 stages [5]. However, as noted earlier, this is a  
38  
39 333 mechanistic classification and in the present analysis the use of the CrCl threshold of 60  
40  
41 334 mL/min, which is commonly used to define renal dysfunction [2 37 75-77], is considered to  
42  
43 335 be satisfactory, especially since the small number of patients would not allow a thorough  
44  
45 336 analysis for five sub-categories. However, the pathophysiology of WRF in AHF is complex  
46  
47 337 [78] and using a spot measurement of serum creatinine to classify CRS has limitations. This  
48  
49 338 approach does not allow the separation of patients with acute and chronic CRS: in the present  
50  
51 339 study, 35.8% of patients included in the CRS group had a history of chronic renal failure and  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 340 so may not have suffered any acute change in renal function, whereas patients with acute  
4  
5 341 changes in serum creatinine compared to their own baseline but not fulfilling the <60 mL/min  
6  
7 342 criterion would not have been included in the CRS group. That said, the presence of renal  
8  
9 343 failure on admission remains strongly associated with a poor prognosis irrespective of the  
10  
11 344 anterior renal status and despite the lack of WRF in the first 5 days [79]. While the choice of a  
12  
13 345 CrCl threshold of 30 mL/min could have led to a greater chance of obtaining a significant  
14  
15 346 difference between groups in terms of outcome, we based our analysis on the 60 mL/min cut-  
16  
17 347 off since it is more widely used. Second, since the data used are observational, it was not  
18  
19 348 possible to impose any randomization or blinding, and the number of patients in each group  
20  
21 349 was not balanced. Third, GFR assessments were performed by local laboratories for each  
22  
23 350 center, rather than standardized at a single center, and repeated measures of GFR could have  
24  
25 351 improved their accuracy and comparability. The use of different formulae to evaluate CrCl in  
26  
27 352 a chronic disease state and an acute context without knowledge of the baseline value reflects  
28  
29 353 the real-life situation. While potentially problematic, with the possibility of some incorrect  
30  
31 354 classification of CKD, numerous previous studies of the impact of renal failure in AHF have  
32  
33 355 used a similar approach [2 37 75]. Finally, it was not possible to sub-classify different types  
34  
35 356 of CRS in this analysis since Kidney Disease Improving Global Outcomes (KDIGO) data  
36  
37 357 were not collected, although as described earlier the small number of patients would not have  
38  
39 358 allowed a thorough analysis for each sub-category.

## 359 **Conclusion**

360 These real-life data suggested that CRS patients have the same outcome as AHF patients  
361 without renal dysfunction when the treatment of the former group is modeled on that for the  
362 latter group. This finding should not limit the use of loop diuretics and/or vasodilators as long  
363 as the patient presents congestion as assessed using biomarkers and ultrasound. The use of  
364 diuretic treatment should be based on a more rapid diagnosis of congestion and evaluation of

1  
2  
3 365 an inadequate response to diuretics, allowing the rapid and appropriate implementation of  
4  
5 366 alternative therapies if necessary.  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3 367 **Funding**  
4  
5

6 368 This work was supported by Novartis France, but the Sponsor was not involved in the study  
7  
8 369 protocol, methods, or choice of centers.  
9  
10

11  
12 370 **Competing interests**  
13  
14

15 371 CEK and has received grants from Novartis (other than this work), Daiichy Sankyo, and  
16  
17 372 Boehringer Ingleheim.  
18

19  
20 373 NP reports has acted as a paid consultant for Vygon SA.  
21  
22

23  
24 374 SC reports personal fees from Novartis (other than this work).  
25  
26

27 375 LF is an employee of RESCUe Network.  
28  
29

30 376 DdR, AB, SMZ, ME, DS, EBC, SL, PH, AG, KT and TC have no competing interests.  
31  
32

33  
34 377 **Authors' contributions**  
35  
36

37 378 SMS, NP, SC, ME, DS, EBC, SL, PH, TC, and CEK conceived the study, designed the trial,  
38  
39 379 and obtained research funding. TC and CEK supervised the conduct of the trial and data  
40  
41 380 collection. NP, SC, DS and TC undertook recruitment of participating centers and patients. LF  
42  
43 381 managed the data, including quality control, provided statistical advice and analyzed the data.  
44  
45 382 DdR, LF, AB, AG, KT, TC and CEK drafted the manuscript, and all authors contributed  
46  
47 383 substantially to its revision. All authors reviewed and approved the final version of the  
48  
49 384 manuscript and are accountable for its content.  
50  
51  
52

53  
54 385 **Consent for publication**  
55  
56

57 386 Not applicable since no individual patient is identified.  
58  
59  
60



1  
2  
3 387 **Data sharing statement**  
4  
5

6 388 The database supporting the results presented in this article can be shared on reasonable  
7  
8 389 request.  
9

10  
11  
12 390 **Acknowledgements**  
13  
14

15 391 The authors thank the emergency physicians and cardiologists and patients who participated  
16  
17 392 in this survey at the following centers: CHU Toulouse, CHU Rouen, CHU Clermont Ferrand,  
18  
19 393 CHU Nancy, CHR Metz-Thionville-Hôpital de Mercy, Hôpital Lariboisière-Paris, CHR  
20  
21 394 Annecy Genevois, CHU Lyon-Hôp, Edouard Herriot, CHRU de Lille, Chu De Caen, CHU  
22  
23 395 Nice-Hôpital Saint-Roch, CHU de Grenoble, Hôpital Bicêtre-Paris, Hôpital St Louis Paris,  
24  
25 396 CH I Meulan, CH d'Avignon, CH Jacques Lacarin–Vichy, CH d'Aix En Provence, CH  
26  
27 397 Fleyriat –Bourg En Bresse, CH Bourgoin Jallieu, CHU de Saint Etienne, CH du Forez  
28  
29 398 Montbrison-Feurs, CH de Firminy, CH Villefranche-Sur-Saône, CHU De Brest, CH Henri  
30  
31 399 Mondor, CH de Vienne.  
32  
33  
34  
35

36  
37 400 The authors also thank the RESCUE Network for the practical implementation of this survey  
38  
39 401 and statistical analysis and Novartis France for its financial support.  
40  
41

42 402 Dr Andrew Lane (Lane Medical Writing), funded by the RESCUE network, provided  
43  
44 403 professional medical writing assistance in the preparation and development of the manuscript  
45  
46 404 in accordance with the European Medical Writers Association guidelines and Good  
47  
48 405 Publication Practice.  
49  
50

51  
52  
53 406  
54  
55  
56  
57  
58  
59  
60

407 **References**

- 408 1. Sayago-Silva I, Garcia-Lopez F, Segovia-Cubero J. Epidemiology of heart failure in Spain  
409 over the last 20 years. *Rev Esp Cardiol (Engl Ed)* 2013;**66**(8):649-56 doi:  
410 10.1016/j.rec.2013.03.012.
- 411 2. Ferreira JP, Girerd N, Pellicori P, et al. Renal function estimation and Cockcroft-Gault  
412 formulas for predicting cardiovascular mortality in population-based, cardiovascular  
413 risk, heart failure and post-myocardial infarction cohorts: The Heart 'OMics' in AGEing  
414 (HOMAGE) and the high-risk myocardial infarction database initiatives. *BMC Med*  
415 2016;**14**(1):181 doi: 10.1186/s12916-016-0731-2.
- 416 3. Hillege HL, Girbes AR, de Kam PJ, et al. Renal function, neurohormonal activation, and  
417 survival in patients with chronic heart failure. *Circulation* 2000;**102**(2):203-10.
- 418 4. Damman K, Valente MA, Voors AA, et al. Renal impairment, worsening renal function, and  
419 outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J*  
420 2014;**35**(7):455-69 doi: 10.1093/eurheartj/eh386.
- 421 5. Ronco C, Haapio M, House AA, et al. Cardiorenal syndrome. *J Am Coll Cardiol*  
422 2008;**52**(19):1527-39 doi: 10.1016/j.jacc.2008.07.051.
- 423 6. Ronco C, House AA, Haapio M. Cardiorenal syndrome: refining the definition of a complex  
424 symbiosis gone wrong. *Intensive Care Med* 2008;**34**(5):957-62 doi: 10.1007/s00134-  
425 008-1017-8.
- 426 7. Dries DL, Exner DV, Domanski MJ, et al. The prognostic implications of renal insufficiency  
427 in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J*  
428 *Am Coll Cardiol* 2000;**35**(3):681-9.

- 1  
2  
3 429 8. Hanberg JS, Tang WHW, Wilson FP, et al. An exploratory analysis of the competing effects  
4  
5 430 of aggressive decongestion and high-dose loop diuretic therapy in the DOSE trial. *Int J*  
6  
7 431 *Cardiol* 2017;**241**:277-82 doi: 10.1016/j.ijcard.2017.03.114[published Online First:  
8  
9 432 Epub Date]].
- 10  
11  
12  
13 433 9. Testani JM, Ter Maaten JM. Decongestion in Acute Heart Failure: Does the End Justify the  
14  
15 434 Means? *JACC Heart Fail* 2016;**4**(7):589-90 doi: 10.1016/j.jchf.2016.03.024[published  
16  
17 435 Online First: Epub Date]].
- 18  
19  
20  
21 436 10. Chouihed T, Manzo-Silberman S, Peschanski N, et al. Management of suspected acute heart  
22  
23 437 failure dyspnea in the emergency department: results from the French prospective  
24  
25 438 multicenter DeFSSICA survey. *Scand J Trauma Resusc Emerg Med* 2016;**24**(1):112  
26  
27 439 doi: 10.1186/s13049-016-0300-x[published Online First: Epub Date]].
- 30  
31 440 11. Diseases NIDaDK. Estimating glomerular filtration rate (GFR). Secondary Estimating  
32  
33 441 glomerular filtration rate (GFR) 2015. [https://www.niddk.nih.gov/health-](https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr/estimating/Pages/estimating.aspx)  
34  
35 442 [information/health-communication-programs/nkdep/lab-](https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr/estimating/Pages/estimating.aspx)  
36  
37 443 [evaluation/gfr/estimating/Pages/estimating.aspx](https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr/estimating/Pages/estimating.aspx).
- 38  
39  
40  
41 444 12. Botev R, Mallie JP, Couchoud C, et al. Estimating glomerular filtration rate: Cockcroft-  
42  
43 445 Gault and Modification of Diet in Renal Disease formulas compared to renal inulin  
44  
45 446 clearance. *Clin J Am Soc Nephrol* 2009;**4**(5):899-906 doi:  
46  
47 447 10.2215/CJN.05371008[published Online First: Epub Date]].
- 48  
49  
50  
51 448 13. Ancelle T. *Statistique Epidémiologique*. 3rd ed. Paris: Maloine, 2011.
- 52  
53  
54  
55 449 14. Logeart D, Isnard R, Resche-Rigon M, et al. Current aspects of the spectrum of acute heart  
56  
57 450 failure syndromes in a real-life setting: the OFICA study. *Eur J Heart Fail*  
58  
59 451 2013;**15**(4):465-76 doi: 10.1093/eurjhf/hfs189[published Online First: Epub Date]].

- 1  
2  
3 452 15. Oliva F, Mortara A, Cacciatore G, et al. Acute heart failure patient profiles, management  
4  
5 453 and in-hospital outcome: results of the Italian Registry on Heart Failure Outcome. *Eur*  
6  
7 454 *J Heart Fail* 2012;**14**(11):1208-17 doi: 10.1093/eurjhf/hfs117.
- 8  
9  
10  
11 455 16. Tavazzi L, Maggioni AP, Lucci D, et al. Nationwide survey on acute heart failure in  
12  
13 456 cardiology ward services in Italy. *Eur Heart J* 2006;**27**(10):1207-15 doi:  
14  
15 457 10.1093/eurheartj/ehi845.
- 16  
17  
18  
19 458 17. Straburzynska-Migaj E, Kaluzna-Oleksy M, Maggioni AP, et al. Patients with heart failure  
20  
21 459 and concomitant chronic obstructive pulmonary disease participating in the Heart  
22  
23 460 Failure Pilot Survey (ESC-HF Pilot) - Polish population. *Arch Med Sci* 2015;**11**(4):743-  
24  
25 461 50 doi: 10.5114/aoms.2014.47878.
- 26  
27  
28  
29 462 18. Conde-Martel A, Formiga F, Perez-Bocanegra C, et al. Clinical characteristics and one-year  
30  
31 463 survival in heart failure patients more than 85 years of age compared with younger. *Eur*  
32  
33 464 *J Intern Med* 2013;**24**(4):339-45 doi: 10.1016/j.ejim.2013.01.005.
- 34  
35  
36  
37 465 19. Llorens P, Escoda R, Miró O, et al. Characteristics and clinical course of patients with acute  
38  
39 466 heart failure and the therapeutic measures applied in Spanish emergency departments:  
40  
41 467 based on the EAHFE registry (Epidemiology of Acute Heart Failure in Emergency  
42  
43 468 Departments). *Emergencias* 2015;**27**:11-22.
- 44  
45  
46  
47 469 20. Chang H-Y, Wang C-C, Wu Y-W, et al. One-year outcomes of acute decompensated  
48  
49 470 systolic heart failure in Taiwan: lessons from TSOC-HFrEF Registry *Acta Cardiologica*  
50  
51 471 *Sinica* 2017;**33**(2):127-38.
- 52  
53  
54  
55 472 21. Abraham WT, Fonarow GC, Albert NM, et al. Predictors of in-hospital mortality in patients  
56  
57 473 hospitalized for heart failure: insights from the Organized Program to Initiate Lifesaving  
58  
59 474 Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *J Am Coll*

- 1  
2  
3 475 Cardiol 2008;**52**(5):347-56 doi: 10.1016/j.jacc.2008.04.028[published Online First:  
4  
5 476 Epub Date]].  
6  
7  
8  
9 477 22. Adams KF, Jr., Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients  
10  
11 478 hospitalized for heart failure in the United States: rationale, design, and preliminary  
12  
13 479 observations from the first 100,000 cases in the Acute Decompensated Heart Failure  
14  
15 480 National Registry (ADHERE). Am Heart J 2005;**149**(2):209-16 doi:  
16  
17 481 10.1016/j.ahj.2004.08.005[published Online First: Epub Date]].  
18  
19  
20  
21 482 23. Diercks DB, Fonarow GC, Kirk JD, et al. Risk stratification in women enrolled in the Acute  
22  
23 483 Decompensated Heart Failure National Registry Emergency Module (ADHERE-EM).  
24  
25 484 Acad Emerg Med 2008;**15**(2):151-8 doi: 10.1111/j.1553-2712.2008.00030.x[published  
26  
27 485 Online First: Epub Date]].  
28  
29  
30  
31 486 24. Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme-- a  
32  
33 487 survey on the quality of care among patients with heart failure in Europe. Part 1: patient  
34  
35 488 characteristics and diagnosis. Eur Heart J 2003;**24**(5):442-63  
36  
37  
38  
39 489 25. Nieminen MS, Brutsaert D, Dickstein K, et al. EuroHeart Failure Survey II (EHFS II): a  
40  
41 490 survey on hospitalized acute heart failure patients: description of population. Eur Heart  
42  
43 491 J 2006;**27**(22):2725-36 doi: 10.1093/eurheartj/ehl193[published Online First: Epub  
44  
45 492 Date]].  
46  
47  
48  
49 493 26. Follath F, Yilmaz MB, Delgado JF, et al. Clinical presentation, management and outcomes  
50  
51 494 in the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF).  
52  
53 495 Intensive Care Med 2011;**37**(4):619-26 doi: 10.1007/s00134-010-2113-0[published  
54  
55 496 Online First: Epub Date]].  
56  
57  
58  
59  
60

- 1  
2  
3 497 27. Molitoris BA, Levin A, Warnock DG, et al. Improving outcomes of acute kidney injury:  
4  
5 498 report of an initiative. *Nat Clin Pract Nephrol* 2007;**3**(8):439-42 doi:  
6  
7 499 10.1038/ncpneph0551.  
8  
9  
10  
11 500 28. Waikar SS, Bonventre JV. Creatinine kinetics and the definition of acute kidney injury. *J*  
12  
13 501 *Am Soc Nephrol* 2009;**20**(3):672-9 doi: 10.1681/ASN.2008070669.  
14  
15  
16 502 29. Breidthardt T, Sabti Z, Ziller R, et al. Diagnostic and prognostic value of cystatin C in acute  
17  
18 heart failure. *Clin Biochem* 2017;**50**(18):1007-13 doi:  
19 503 10.1016/j.clinbiochem.2017.07.016.  
20  
21 504  
22  
23  
24 505 30. Breidthardt T, Socrates T, Drexler B, et al. Plasma neutrophil gelatinase-associated lipocalin  
25  
26 for the prediction of acute kidney injury in acute heart failure. *Crit Care* 2012;**16**(1):R2  
27 506 doi: 10.1186/cc10600.  
28  
29 507  
30  
31  
32 508 31. Maisel AS, Wettersten N, van Veldhuisen DJ, et al. Neutrophil Gelatinase-Associated  
33  
34 Lipocalin for Acute Kidney Injury During Acute Heart Failure Hospitalizations: The  
35 509 AKINESIS Study. *J Am Coll Cardiol* 2016;**68**(13):1420-31 doi:  
36  
37 510 10.1016/j.jacc.2016.06.055.  
38  
39 511  
40  
41  
42 512 32. Meersch M, Schmidt C, Hoffmeier A, et al. Prevention of cardiac surgery-associated AKI  
43  
44 by implementing the KDIGO guidelines in high risk patients identified by biomarkers:  
45 513 the PrevAKI randomized controlled trial. *Intensive Care Med* 2017;**43**(11):1551-61 doi:  
46  
47 514 10.1007/s00134-016-4670-3.  
48  
49 515  
50  
51  
52 516 33. Tuegel C, Bansal N. Heart failure in patients with kidney disease. *Heart* 2017 doi:  
53  
54 10.1136/heartjnl-2016-310794.  
55 517  
56  
57  
58  
59  
60

- 1  
2  
3 518 34. Anwaruddin S, Lloyd-Jones DM, Baggish A, et al. Renal function, congestive heart failure,  
4  
5 519 and amino-terminal pro-brain natriuretic peptide measurement: results from the ProBNP  
6  
7 520 Investigation of Dyspnea in the Emergency Department (PRIDE) Study. *J Am Coll*  
8  
9  
10 521 *Cardiol* 2006;**47**(1):91-7 doi: 10.1016/j.jacc.2005.08.051.  
11  
12  
13 522 35. Nacv Writing Group, Wu AH, Jaffe AS, et al. National Academy of Clinical Biochemistry  
14  
15 523 laboratory medicine practice guidelines: use of cardiac troponin and B-type natriuretic  
16  
17 524 peptide or N-terminal proB-type natriuretic peptide for etiologies other than acute  
18  
19 525 coronary syndromes and heart failure. *Clin Chem* 2007;**53**(12):2086-96 doi:  
20  
21 526 10.1373/clinchem.2007.095679.  
22  
23  
24  
25 527 36. Lamb EJ, Vickery S, Price CP. Amino-terminal pro-brain natriuretic peptide to diagnose  
26  
27 528 congestive heart failure in patients with impaired kidney function. *J Am Coll Cardiol*  
28  
29 529 2006;**48**(5):1060-1; author reply 61 doi: 10.1016/j.jacc.2006.06.019.  
30  
31  
32  
33 530 37. Vickery S, Price CP, John RI, et al. B-type natriuretic peptide (BNP) and amino-terminal  
34  
35 531 proBNP in patients with CKD: relationship to renal function and left ventricular  
36  
37 532 hypertrophy. *Am J Kidney Dis* 2005;**46**(4):610-20 doi: 10.1053/j.ajkd.2005.06.017.  
38  
39  
40  
41 533 38. Peacock WF, Emerman C, Costanzo MR, et al. Early vasoactive drugs improve heart failure  
42  
43 534 outcomes. *Congest Heart Fail* 2009;**15**(6):256-64 doi: 10.1111/j.1751-  
44  
45 535 7133.2009.00112.x.  
46  
47  
48  
49 536 39. Gargani L, Frassi F, Soldati G, et al. Ultrasound lung comets for the differential diagnosis  
50  
51 537 of acute cardiogenic dyspnoea: a comparison with natriuretic peptides. *Eur J Heart Fail*  
52  
53 538 2008;**10**(1):70-7 doi: 10.1016/j.ejheart.2007.10.009.  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 539 40. Breidhardt T, Weidmann ZM, Twerenbold R, et al. Impact of haemoconcentration during  
4  
5 540 acute heart failure therapy on mortality and its relationship with worsening renal  
6  
7 541 function. *Eur J Heart Fail* 2017;**19**(2):226-36 doi: 10.1002/ejhf.667.  
9  
10  
11 542 41. Girerd N, Seronde MF, Coiro S, et al. Integrative assessment of congestion in heart failure  
12  
13 543 throughout the patient journey. *JACC Heart Fail* 2018;**6**(4):273-85 doi:  
14  
15 544 10.1016/j.jchf.2017.09.023.  
17  
18  
19 545 42. Mentz RJ, Kjeldsen K, Rossi GP, et al. Decongestion in acute heart failure. *Eur J Heart Fail*  
20  
21 546 2014;**16**(5):471-82 doi: 10.1002/ejhf.74.  
23  
24  
25 547 43. Duarte K, Monnez JM, Albuissou E, et al. Prognostic value of estimated plasma volume in  
26  
27 548 heart failure. *JACC Heart Fail* 2015;**3**(11):886-93 doi: 10.1016/j.jchf.2015.06.014.  
28  
29  
30 549 44. Yang X, Chen C, Tian J, et al. Urinary angiotensinogen level predicts AKI in acute  
31  
32 550 decompensated heart failure: a prospective, two-stage study. *J Am Soc Nephrol*  
33  
34 551 2015;**26**(8):2032-41 doi: 10.1681/ASN.2014040408.  
36  
37  
38 552 45. Elsharawy S, Raslan L, Morsy S, et al. Plasma neutrophil gelatinase-associated lipocalin as  
39  
40 553 a marker for the prediction of worsening renal function in children hospitalized for acute  
41  
42 554 heart failure. *Saudi J Kidney Dis Transpl* 2016;**27**(1):49-54 doi: 10.4103/1319-  
43  
44 555 2442.174071.  
46  
47  
48 556 46. Ito M, Doi K, Takahashi M, et al. Plasma neutrophil gelatinase-associated lipocalin predicts  
49  
50 557 major adverse cardiovascular events after cardiac care unit discharge. *J Cardiol*  
51  
52 558 2016;**67**(2):184-91 doi: 10.1016/j.jjcc.2015.05.010.  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 559 47. Medic B, Rovcanin B, Basta Jovanovic G, et al. Kidney Injury Molecule-1 and  
4  
5 560 cardiovascular diseases: from basic science to clinical practice. *Biomed Res Int*  
6  
7 561 2015;**2015**:854070 doi: 10.1155/2015/854070.  
8  
9  
10  
11 562 48. *Les biomarqueurs en médecine d'urgence [French]*. 1 ed. Paris: Springer-Verlag, 2012.  
12  
13  
14 563 49. Taub PR, Borden KC, Fard A, et al. Role of biomarkers in the diagnosis and prognosis of  
15  
16 564 acute kidney injury in patients with cardiorenal syndrome. *Expert Rev Cardiovasc Ther*  
17  
18 565 2012;**10**(5):657-67 doi: 10.1586/erc.12.26.  
19  
20  
21  
22 566 50. Verbrugge FH, Dupont M, Steels P, et al. The kidney in congestive heart failure: 'are  
23  
24 567 natriuresis, sodium, and diuretics really the good, the bad and the ugly?'. *Eur J Heart*  
25  
26 568 *Fail* 2014;**16**(2):133-42 doi: 10.1002/ejhf.35.  
27  
28  
29  
30 569 51. Lassus JP, Harjola VP, Peuhkurinen K, et al. Cystatin C, NT-proBNP, and inflammatory  
31  
32 570 markers in acute heart failure: insights into the cardiorenal syndrome. *Biomarkers*  
33  
34 571 2011;**16**(4):302-10 doi: 10.3109/1354750X.2011.555822.  
35  
36  
37  
38 572 52. Legrand M, De Berardinis B, Gaggin HK, et al. Evidence of uncoupling between renal  
39  
40 573 dysfunction and injury in cardiorenal syndrome: insights from the BIONICS study. *PloS*  
41  
42 574 *one* 2014;**9**(11):e112313 doi: 10.1371/journal.pone.0112313.  
43  
44  
45  
46 575 53. Metra M, Davison B, Bettari L, et al. Is worsening renal function an ominous prognostic  
47  
48 576 sign in patients with acute heart failure? The role of congestion and its interaction with  
49  
50 577 renal function. *Circ Heart Fail* 2012;**5**(1):54-62 doi:  
51  
52 578 10.1161/CIRCHEARTFAILURE.111.963413.  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 579 54. Mullens W, Verbrugge F, Nijst P, et al. Renal sodium avidity in heart failure: from  
4  
5 580 pathophysiology to treatment strategies. *European Heart Journal* 2017 doi:  
6  
7 581 10.1093/eurheartj/ehx035.  
8  
9  
10  
11 582 55. Ferreira JP, Girerd N, Bettencourt Medeiros P, et al. Lack of diuretic efficiency (but not low  
12  
13 583 diuresis) early in an acutely decompensated heart failure episode is associated with  
14  
15 584 increased 180-day mortality. *Cardiorenal Med* 2017;**7**(2):137-49 doi:  
16  
17 585 10.1159/000455903.  
18  
19  
20  
21 586 56. Palazzuoli A, Testani JM, Ruocco G, et al. Different diuretic dose and response in acute  
22  
23 587 decompensated heart failure: clinical characteristics and prognostic significance. *Int J*  
24  
25 588 *Cardiol* 2016;**224**:213-19 doi: 10.1016/j.ijcard.2016.09.005.  
26  
27  
28  
29 589 57. Damman K, Testani JM. The kidney in heart failure: an update. *Eur Heart J*  
30  
31 590 2015;**36**(23):1437-44 doi: 10.1093/eurheartj/ehv010.  
32  
33  
34  
35 591 58. Hoorn EJ, Ellison DH. Diuretic resistance. *Am J Kidney Dis* 2017;**69**(1):136-42 doi:  
36  
37 592 10.1053/j.ajkd.2016.08.027.  
38  
39  
40  
41 593 59. Ray EC, Boyd-Shiwariski CR, Kleyman TR. Why diuretics fail failing hearts. *J Am Soc*  
42  
43 594 *Nephrol* 2017 doi: 10.1681/ASN.2017070797.  
44  
45  
46 595 60. Valente MA, Voors AA, Damman K, et al. Diuretic response in acute heart failure: clinical  
47  
48 596 characteristics and prognostic significance. *Eur Heart J* 2014;**35**(19):1284-93 doi:  
49  
50 597 10.1093/eurheartj/ehu065.  
51  
52  
53  
54 598 61. ter Maaten JM, Valente MA, Damman K, et al. Diuretic response in acute heart failure-  
55  
56 599 pathophysiology, evaluation, and therapy. *Nat Rev Cardiol* 2015;**12**(3):184-92 doi:  
57  
58 600 10.1038/nrcardio.2014.215.  
59  
60

- 1  
2  
3 601 62. Bansal S, Lindenfeld J, Schrier RW. Sodium retention in heart failure and cirrhosis:  
4  
5 602 potential role of natriuretic doses of mineralocorticoid antagonist? *Circ Heart Fail*  
6  
7 603 2009;**2**(4):370-6 doi: 10.1161/CIRCHEARTFAILURE.108.821199.  
8  
9  
10  
11 604 63. Hensen J, Abraham WT, Durr JA, et al. Aldosterone in congestive heart failure: analysis of  
12  
13 605 determinants and role in sodium retention. *Am J Nephrol* 1991;**11**(6):441-6  
14  
15  
16 606 64. The RALES investigators. Effectiveness of spironolactone added to an angiotensin-  
17  
18 607 converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart  
19  
20 608 failure (the Randomized Aldactone Evaluation Study [RALES]). *Am J Cardiol*  
21  
22 609 1996;**78**(8):902-7.  
23  
24  
25  
26 610 65. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality  
27  
28 611 in patients with severe heart failure. Randomized Aldactone Evaluation Study  
29  
30 612 Investigators. *New Engl J Med* 1999;**341**(10):709-17 doi:  
31  
32 613 10.1056/NEJM199909023411001.  
33  
34  
35  
36 614 66. Butler J, Anstrom KJ, Felker GM, et al. Efficacy and safety of spironolactone in acute heart  
37  
38 615 failure: the ATHENA-HF Randomized Clinical Trial. *JAMA Cardiol* 2017 doi:  
39  
40 616 10.1001/jamacardio.2017.2198.  
41  
42  
43  
44 617 67. Licata G, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-  
45  
46 618 volume hypertonic saline solution infusion in comparison with a high dose of  
47  
48 619 furosemide as bolus in refractory congestive heart failure: long-term effects. *Am Heart*  
49  
50 620 *J* 2003;**145**(3):459-66 doi: 10.1067/mhj.2003.166.  
51  
52  
53  
54 621 68. Paterna S, Di Pasquale P, Parrinello G, et al. Changes in brain natriuretic peptide levels and  
55  
56 622 bioelectrical impedance measurements after treatment with high-dose furosemide and  
57  
58 623 hypertonic saline solution versus high-dose furosemide alone in refractory congestive  
59  
60

- 1  
2  
3 624 heart failure: a double-blind study. *J Am Coll Cardiol* 2005;**45**(12):1997-2003 doi:  
4  
5 625 10.1016/j.jacc.2005.01.059.  
6  
7  
8  
9 626 69. Ng TM, Konopka E, Hyderi AF, et al. Comparison of bumetanide- and metolazone-based  
10  
11 627 diuretic regimens to furosemide in acute heart failure. *J Cardiovasc Pharmacol Ther*  
12  
13 628 2013;**18**(4):345-53 doi: 10.1177/1074248413482755.  
14  
15  
16  
17 629 70. Tilstone WJ, Dargie H, Dargie EN, et al. Pharmacokinetics of metolazone in normal  
18  
19 630 subjects and in patients with cardiac or renal failure. *Clin Pharmacol Ther*  
20  
21 631 1974;**16**(2):322-9.  
22  
23  
24  
25 632 71. Wang C, Xiong B, Cai L. Effects of Tolvaptan in patients with acute heart failure: a  
26  
27 633 systematic review and meta-analysis. *BMC Cardiovasc Disord* 2017;**17**(1):164 doi:  
28  
29 634 10.1186/s12872-017-0598-y.  
30  
31  
32  
33 635 72. Jujo K, Saito K, Ishida I, et al. Randomized pilot trial comparing tolvaptan with furosemide  
34  
35 636 on renal and neurohumoral effects in acute heart failure. *ESC Heart Fail* 2016;**3**(3):177-  
36  
37 637 88 doi: 10.1002/ehf2.12088.  
38  
39  
40  
41 638 73. Kimura K, Momose T, Hasegawa T, et al. Early administration of tolvaptan preserves renal  
42  
43 639 function in elderly patients with acute decompensated heart failure. *J Cardiol*  
44  
45 640 2016;**67**(5):399-405 doi: 10.1016/j.jjcc.2015.09.020.  
46  
47  
48  
49 641 74. Torina AG, Silveira-Filho LM, Vilarinho KA, et al. Use of modified ultrafiltration in adults  
50  
51 642 undergoing coronary artery bypass grafting is associated with inflammatory modulation  
52  
53 643 and less postoperative blood loss: a randomized and controlled study. *J Thorac*  
54  
55 644 *Cardiovasc Surg* 2012;**144**(3):663-70 doi: 10.1016/j.jtcvs.2012.04.012.  
56  
57  
58  
59  
60

- 1  
2  
3 645 75. Chew DP, Astley C, Molloy D, et al. Morbidity, mortality and economic burden of renal  
4  
5 646 impairment in cardiac intensive care. *Intern Med J* 2006;**36**(3):185-92 doi:  
6  
7 647 10.1111/j.1445-5994.2006.01012.x.  
8  
9  
10  
11 648 76. Schaub JA, Coca SG, Moledina DG, et al. Amino-terminal pro-B-type natriuretic peptide  
12  
13 649 for diagnosis and prognosis in patients with renal dysfunction: a systematic review and  
14  
15 650 meta-analysis. *JACC Heart Fail* 2015;**3**(12):977-89 doi: 10.1016/j.jchf.2015.07.014.  
16  
17  
18  
19 651 77. Tsutamoto T, Kawahara C, Yamaji M, et al. Relationship between renal function and serum  
20  
21 652 cardiac troponin T in patients with chronic heart failure. *Eur J Heart Fail*  
22  
23 653 2009;**11**(7):653-8 doi: 10.1093/eurjhf/hfp072.  
24  
25  
26  
27 654 78. Aronson D, Abassi Z, Allon E, et al. Fluid loss, venous congestion, and worsening renal  
28  
29 655 function in acute decompensated heart failure. *Eur J Heart Fail* 2013;**15**(6):637-43 doi:  
30  
31 656 10.1093/eurjhf/hft036.  
32  
33  
34  
35 657 79. Shirakabe A, Hata N, Kobayashi N, et al. Worsening renal function definition is insufficient  
36  
37 658 for evaluating acute renal failure in acute heart failure. *ESC Heart Fail* 2018;**5**(3):322-  
38  
39 659 31 doi: 10.1002/ehf2.12264.  
40  
41  
42  
43 660

661 **Tables**662 Table 1 Baseline characteristics of patients with confirmed acute heart failure (AHF)  
663 syndrome

	All AHF patients (N=507)	Group 1 (n=335)	Group 2 (n=172)	p-value
Age, y	83 [77;88]	84 [78;89]	82 [75;88]	0.09
Men	220 (43.39%)	144 (42.99%)	76 (44.19%)	0.87
<b>Comorbidities</b>				
- Hypertension	353 (69.63%)	234 (69.85%)	119 (69.19%)	0.79
- Chronic HF	271 (53.45%)	189 (56.42%)	82 (47.67%)	<0.05
- Atrial fibrillation	223 (43.98%)	151 (45.07%)	72 (41.86%)	0.43
- Coronary heart disease	150 (29.59%)	98 (29.25%)	52 (30.23%)	1.00
- Diabetes type I	14 (2.76%)	12 (3.58%)	2 (1.16%)	0.26
- Diabetes type II	132 (26.04%)	93 (27.76%)	39 (22.67%)	0.20
- Chronic renal failure	114 (22.49%)	108 (32.24%)	6 (3.49%)	<0.01
- Chronic respiratory failure	87 (17.16%)	60 (17.91%)	27 (15.7%)	0.46
- Known valvular disease	95 (18.74%)	70 (20.9%)	25 (14.53%)	0.07
<b>Priori medications</b>				
- Furosemide	295 (58.19%)	204 (60.9%)	91 (52.91%)	<0.05
- ACEI/ARB	225 (44.38%)	153 (45.67%)	72 (41.86%)	0.30
- $\beta$ - blocker	214 (42.21%)	147 (43.88%)	67 (38.95%)	0.20
- Anticoagulant	221 (43.59%)	151 (45.07%)	70 (40.7%)	0.24
- Aspirin	155 (30.57%)	110 (32.84%)	45 (26.16%)	0.08
- Other antiplatelet	56 (11.05%)	37 (11.04%)	19 (11.05%)	0.73
- Oral antidiabetic	66 (13.02%)	47 (14.03%)	19 (11.05%)	0.22
- Insulin	68 (13.41%)	52 (15.52%)	16 (9.3%)	0.03
- Amiodarone	56 (11.05%)	48 (14.33%)	8 (4.65%)	<0.01
- Aldosterone antagonist	38 (7.5%)	26 (7.76%)	12 (6.98%)	0.48
- Digoxin	38 (7.5%)	18 (5.37%)	20 (11.63%)	0.10
- Thiazidine	32 (6.31%)	21 (6.27%)	11 (6.4%)	0.70
- None	28 (5.52%)	14 (4.18%)	14 (8.14%)	0.38
- Unknown	13 (2.56%)	7 (2.09%)	6 (3.49%)	1.00
<b>Prior hospitalization for HF during past year</b>				
- 0	287 (56.61%)	180 (53.73%)	107 (62.21%)	0.14
- 1	130 (25.64%)	83 (24.78%)	47 (27.33%)	0.86
- $\geq 2$	62 (12.23%)	52 (15.52%)	10 (5.81%)	<0.01
Followed by a cardiologist	348 (68.64%)	242 (72.24%)	106 (61.63%)	0.02
<b>Residence</b>				

- At home	423 (83.43%)	287 (85.67%)	136 (79.07%)	0.06
- Retirement institution	74 (14.6%)	43 (12.84%)	31 (18.02%)	0.18
- Other institution	8 (1.58%)	4 (1.19%)	4 (2.33%)	0.75
<b>Self-sufficient</b>	<b>258 (50.89%)</b>	<b>162 (48.36%)</b>	<b>96 (55.81%)</b>	<b>0.19</b>
<b>Home assistance</b>				
- Housekeeper	151 (29.78%)	111 (33.13%)	40 (23.26%)	0.02
- Family support	121 (23.87%)	87 (25.97%)	34 (19.77%)	0.10
- Nurse	134 (26.43%)	98 (29.25%)	36 (20.93%)	0.04
- Known cognitive impairment	83 (16.37%)	49 (14.63%)	34 (19.77%)	0.26
- Bedridden	45 (8.88%)	25 (7.46%)	20 (11.63%)	0.28

664 Data are median (IQR) age or number (%) of patients

665 Group 1: patients with CRS; Group 2: patients with normal renal function

666 AHF, acute heart failure; ADEL, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker;

667 HF, heart failure

668

669 Table 2 Hospitalization route and clinical status of patients with confirmed acute heart failure  
670 (AHF) syndrome

	All AHF patients (N = 507)	Group 1 (n = 335)	Group 2 (n = 172)	p-value
<b>Means of transport</b>				
- Personal	232 (45.76%)	157 (46.87%)	75 (43.6%)	0.50
- Ambulance	89 (17.55%)	56 (16.72%)	33 (19.19%)	0.63
- Firemen	55 (10.85%)	34 (10.15%)	21 (12.21%)	0.65
- MICU	40 (7.89%)	29 (8.66%)	11 (6.4%)	0.41
- Inter-hospital transfer	6 (1.18%)	5 (1.49%)	1 (0.58%)	0.48
<b>Clinical signs</b>				
- Warm extremities	390 (76.92%)	257 (76.72%)	133 (77.33%)	0.23
- Cold extremities	61 (12.03%)	45 (13.43%)	16 (9.3%)	0.97
- Signs of right heart failure	216 (42.6%)	144 (42.99%)	72 (41.86%)	0.69
- Inspiratory retraction	146 (28.8%)	107 (31.94%)	39 (22.67%)	0.02
- Inability to speak	42 (8.28%)	25 (7.46%)	17 (9.88%)	0.54
<b>First recorded vital signs</b>				
- Heart failure, beats/min	85 [71;102]	85 [72;102]	85 [72;104.25]	0.49
- SBP, mmHg	140 [121;160]	140 [121;160]	140 [124;162]	0.11
- DBP, mmHg	76 [65;90]	75 [63.5;89]	78 [67.75;92.25]	0.03
- SBP <100 mmHg	34 (6.71%)	27 (8.06%)	7 (4.07%)	0.13
- Respiratory rate, breaths/min	25 [20;30]	26 [20;30]	24 [20;29]	0.16
- Pulse oximetry, %	94 [90;96.25]	94 [90;97]	94 [89;96]	0.72
- GCS <15	48 (9.47%)	31 (9.25%)	17 (9.88%)	0.94
- Temperature >37°C	13 (2.56%)	12 (3.58%)	1 (0.58%)	0.37
<b>Killip status</b>				
- 1	128 (25.25%)	76 (22.69%)	52 (30.23%)	0.26
- 2	269 (53.06%)	181 (54.03%)	88 (51.16%)	0.30
- 3	84 (16.57%)	60 (17.91%)	24 (13.95%)	0.11
- Signs of shock	15 (2.96%)	8 (2.39%)	7 (4.07%)	0.89

671 Data are median (IQR) beats/minute, median (IQR) mmHg, median (IQR) breaths/minute, median (IQR) %, or  
672 number (%) of patients

673 Group 1: patients with CRS; Group 2: patients with normal renal function

674 AHF, acute heart failure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; HF, heart failure; MICU,

675 mobile intensive care unit; SBP, systolic blood pressure



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

676

For peer review only

677 Table 3 Biological and diagnosis tests of patients with confirmed acute heart failure (AHF)  
678 syndrome

	All AHF patients (N=507)	Group 1 (n=335)	Group 2 (n=172)	p-value
<b>Biological analysis</b>				
- Performed	507 (100%)	335 (100%)	172 (100%)	
- Sodium, mmol/L	138 [135;141]	138 [135;141]	139 [135;141]	0.40
- Potassium, mmol/L	4 [4;5]	4 [4;5]	4 [4;5]	0.89
- Creatinine clearance, mL/min	50 [35;69.05]	40 [29;49.9]	78.5 [67;91]	<0.01
- Creatinine clearance <30 mL/min	89 (17.55%)	89 (26.57%)	0 (0%)	<0.01
- Hemoglobin, g/dL	13 [11;14]	12 [11;13]	13 [13;14]	0.06
- Troponin positive	271 (53.45%)	195 (58.21%)	76 (44.19%)	<0.01
- BNP, ng/L	991 [507.5;2443.5]	1157.5 [569.25;2680.5]	534 [291;1292]	<0.01
- Pro-BNP, ng/L	4025 [1729;8863]	5120 [2520;12399.75]	2513 [1146.5;5376.5]	<0.01
<b>ECG</b>				
- Performed	500 (98.61%)	329 (98.20%)	171 (99.41%)	
- Sinusal	220 (44%)	145 (43.28%)	75 (43.6%)	0.92
- Atrial fibrillation	213 (42.01)	139 (41.49%)	74 (43.02%)	1.00
- Driven	44 (8.8%)	33 (9.85%)	11 (6.4%)	0.19
- AVB	21 (4.14%)	14 (4.18%)	7 (4.07%)	0.86
- LBBB	86 (17.2%)	64 (19.1%)	22 (12.79%)	<0.05
- RBBB	59 (11.8%)	34 (10.15%)	25 (14.53%)	0.43
- Repolarization disorder	101 (20.2%)	73 (21.79%)	28 (16.28%)	0.09
<b>Chest X-ray</b>				
- Performed	481 (94.87%)	318 (94.92%)	163 (94.76%)	
- Normal	24 (4.73%)	11 (3.28%)	13 (7.56%)	0.20
- Cardiomegaly	235 (48.86%)	171 (51.04%)	64 (37.21%)	0.01
- Interstitial opacities	284 (59.04%)	202 (60.3%)	82 (47.67%)	0.02
- Alveolar opacities	108 (22.45%)	64 (19.1%)	44 (25.58%)	0.05

679 Data are median (IQR) mmol/L, median (IQR) mL/min, median (IQR) g/dL, median (IQR) ng/L, or number (%)

680 of patients

681 Group 1: patients with CRS; Group 2: patients with normal renal function

682 AHF, acute heart failure; AVB, atrioventricular block; BNP, brain natriuretic peptide; ECG, electrocardiogram;

683 HF, heart failure; IVC, inferior vena cava; LBBB, left bundle branch block; LVEF, left ventricular ejection

684 fraction; RBBB, right bundle branch block; RV, right ventricle; US, ultrasound

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

685

For peer review only

686 Table 4 Emergency treatment of patients with confirmed acute heart failure (AHF) syndrome

	All AHF patients (N=507)	Group 1 (n=335)	Group 2 (n=172)	p-value
Furosemide	376 (74.16%)	252 (75.22%)	124 (72.09%)	0.26
Oxygen	337 (66.47%)	225 (67.16%)	112 (65.12%)	0.43
Nitrates	92 (18.15%)	71 (21.19%)	21 (12.21%)	0.01
Anticoagulant	37 (7.3%)	22 (6.57%)	15 (8.72%)	1.00
CPAP	8 (1.58%)	6 (1.79%)	2 (1.16%)	0.24
NIV	45 (8.88%)	30 (8.96%)	15 (8.72%)	0.58
Antiarrhythmics	23 (4.54%)	15 (4.48%)	8 (4.65%)	0.60
Inotropic agents	3 (0.59%)	3 (0.9%)	0 (0%)	0.11
Tracheal intubation	1 (0.2%)	1 (0.3%)	0 (0%)	0.20
None	32 (6.31%)	17 (5.07%)	15 (8.72%)	0.58

687 Data are number (%) of patients

688 Group 1: patients with CRS; Group 2: patients with normal renal function

689 AHF, acute heart failure; CPAP, continuous positive airway pressure; NIV, non-invasive ventilation

690 Table 5 Outcomes of patients with confirmed acute heart failure (AHF) syndrome

	All AHF patients (N=507)	Group 1 (n=335)	Group 2 (n=172)	p-value
<b>Precipitating factors</b>				
- Unknown	214 (42.21%)	138 (41.19%)	76 (44.19%)	0.82
- Infection	128 (25.25%)	84 (25.07%)	44 (25.58%)	0.89
- Rhythm disorder	77 (15.19%)	47 (14.03%)	30 (17.44%)	0.67
- Hypertension	54 (10.65%)	39 (11.64%)	15 (8.72%)	0.19
- Non-adherence to treatment	30 (5.92%)	17 (5.07%)	13 (7.56%)	0.92
- Acute coronary syndrome	21 (4.14%)	15 (4.48%)	6 (3.49%)	0.32
- Eating disorder	20 (3.94%)	14 (4.18%)	6 (3.49%)	0.39
- Diabetes decompensation	10 (1.97%)	10 (2.99%)	0 (0%)	0.01
<b>Discharge destination</b>				
- Cardiology	142 (28.01%)	100 (29.85%)	42 (24.42%)	0.33
- Geriatric medicine	61 (12.03%)	34 (10.15%)	27 (15.7%)	0.06
- Other medical unit	99 (19.53%)	67 (20%)	32 (18.6%)	0.98
- CICU	62 (12.23%)	42 (12.54%)	20 (11.63%)	1.00
- Resuscitation unit	16 (3.16%)	11 (3.28%)	5 (2.91%)	0.98
- ED hospitalization unit	74 (14.6%)	48 (14.33%)	26 (15.12%)	0.72
- Back home	26 (5.13%)	14 (4.18%)	12 (6.98%)	0.14
- Other	24 (4.73%)	18 (5.37%)	6 (3.49%)	0.78
<b>Destination considered appropriate</b>	<b>382 (75.35%)</b>	<b>246 (73.43%)</b>	<b>136 (79.07%)</b>	<b>0.13</b>
<b>Outcome</b>				
- In-hospital mortality	30 (5.92%)	24 (7.16%)	6 (3.49%)	0.97
- Still hospitalized at 30 days	32 (6.31%)	20 (5.97%)	12 (6.98%)	1.00
<b>Length of stay, days</b>	<b>7 (4;13)</b>	<b>8 (4;13)</b>	<b>6 (3;12)</b>	<b>0.03</b>

691 Data are number (%) of patients or median (IQR) days

692 Group 1: patients with CRS; Group 2: patients with normal renal function

693 AHF, acute heart failure

694

1  
2  
3 695 **Figure title and legend**  
4  
5

6 696 Figure 1  
7  
8

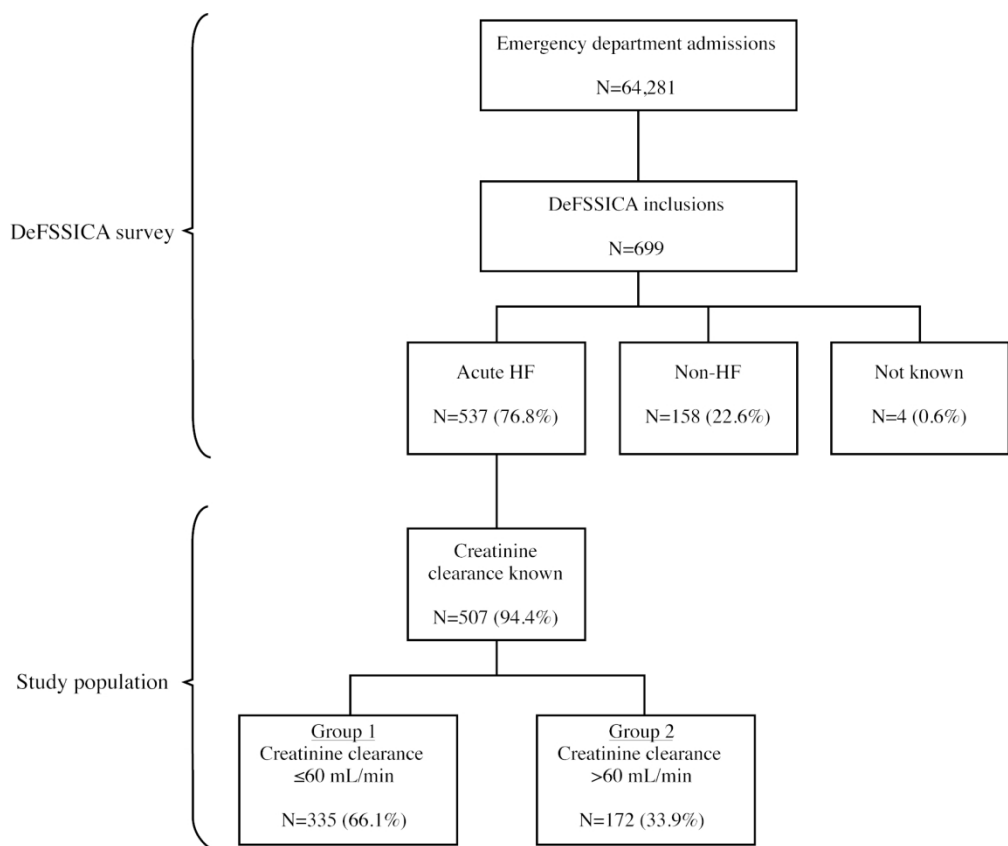
9 697 Title: Patient disposition  
10  
11

12 698 Legend: DeFSSICA, Description de la Filière de Soins dans les Syndromes d'Insuffisance  
13  
14

15 699 Cardiaque Aigue; HF, heart failure  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



TITLE: Figure 1 Patient disposition

LEGEND: DeFSSICA, Description de la Filière de Soins dans les Syndromes d'Insuffisance Cardiaque Aigue; HF, heart failure

158x133mm (300 x 300 DPI)

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of cohort studies****TITLE: Impact of renal dysfunction on the management and outcome of acute heart failure: results from the French prospective, multicenter, DeFSSICA survey**

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9
		(b) Describe any methods used to examine subgroups and interactions	9
		(c) Explain how missing data were addressed	NA
		(d) If applicable, explain how loss to follow-up was addressed	NA
		(e) Describe any sensitivity analyses	NA



<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10 and Figure 1
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(b) Report category boundaries when continuous variables were categorized	NA
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	14-17
<b>Limitations</b>			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).