BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022776
Article Type:	Research
Date Submitted by the Author:	03-Apr-2018
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Keywords:	acute heart failure, AHF, cardio-renal syndrome, CRS, real-life, renal dysfunction

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

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Target journal & format: BMJ Open - Research Articles format (counts: abstract 300 words [max 300]; 6 keywords; body 3513 words (max 4000); 74 references; 1 figure, 5 tables)

Abstract (300 words [max 300])

Objectives: Cardio-renal syndrome (CRS) is the combination of acute heart failure syndrome (AHF) and renal dysfunction (creatinine clearance [CrCl] ≤60 mL/min). Real-life data were used to compare the management and outcome of AHF with and without renal dysfunction.

Design: Prospective, multi-center.

Setting: Twenty-six academic, community, and regional hospitals in France.

Participants: 507 patients with AHF were assessed in two groups according to renal function: Group 1 (CRS patients [CrCl ≤60 mL/min]: N=335) and Group 2 (AHF patients with normal renal function [CrCl >60 mL/min]: N=172).

Results: Differences were observed (Group 1 versus Group 2) at admission for the incidence of chronic heart failure (56.42% versus 47.67%), use of furosemide (60.9% versus 52.91%), insulin (15.52% versus 9.3%), and amiodarone (14.33% versus 4.65%); additionally, more patients in Group 1 carried a defibrillator (4.78% versus 0%), had ≥2 hospitalizations in the last year (15.52% versus 5.81%), and were under the care of a cardiologist (72.24% versus 61.63%). Clinical signs were broadly similar in each group. Brain-type natriuretic peptide (BNP) and BNP prohormone were higher in Group 1 than Group 2 (1157.5 versus 534 ng/L and 5120 versus 2513 ng/mL), and more patients in Group 1 were positive for troponin (58.2% versus 44.19%), had cardiomegaly (51.04% versus 37.21%), and interstitial opacities (60.3% versus 47.67%). The only difference in emergency treatment was the use of nitrates, (higher in Group 1 [21.9% versus 12.21%]). In-hospital mortality and the percentage of patients still hospitalized after 30 days was similar between groups, but median stay was longer in Group 1 (8 days versus 6 days).

Conclusions: Renal impairment in AHF should not limit the use of loop diuretics and/or vasodilators, but early assessment of pulmonary congestion and close monitoring of the efficacy of conventional therapies is encouraged to allow rapid and appropriate implementation of alternative therapies if necessary.

Keywords: acute heart failure, AHF, cardio-renal syndrome, CRS, real-life, renal dysfunction

Strengths and limitations of this study

- Few large-scale, prospective, real-life data exist for the real-life management and outcome of patients with cardio-renal syndrome compared to acute heart failure patients without renal dysfunction.
- Cardio-renal syndrome is of prognostic importance.
- Only two groups were included (i.e. patients with or without kidney dysfunction), rather than for each stage of chronic kidney disease although the creatinine clearance cut-off (60 mL/min) is commonly used.
- Glomerular filtration rate estimations were performed by local laboratories for each center (i.e. a real-life situation), rather than standardized at a single center, although this reflects the real-life situation.

Background

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

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

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

Methods

Study design

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

Patient involvement

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

Selection of participants

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

In this analysis, only patients with known CrCl were included and were divided into those with CrCl ≤60 mL/min, i.e. renal dysfunction (Group 1) and those with CrCl >60 mL/min, i.e. normal renal function (Group 2). Glomerular filtration rate (GFR) was calculated using either the Cockroft-Gault, Modification of Diet in Renal Disease (MDRD) Study, or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations [11 12].

Study assessments

Patients' baseline characteristics, medical history, social factors, in-hospital diagnostic tests and treatment, destination after ED discharge, in-hospital mortality and length of stay were recorded by emergency physicians in a case report form, which was structured according to the progress of care. Cardiac sonographic evaluations were performed at the discretion of emergency physician. Abnormal chest X-ray was defined by the presence of cardiomegaly, and/or alveolar edema, and/or interstitial opacity, and/or pleural effusion. The choice of treatment was at the emergency physician's sole discretion, according to their usual practice. Final diagnosis of AHF was made by the emergency physician using a combination of a clinical history, abnormal chest X-ray, elevated brain-type natriuretic peptide (BNP) or BNP prohormone (proBNP), and echocardiogrpahic signs.

Although it was not possible to impose any randomization or blinding since this was an observational study, any potential bias in the study assessments was minimized by the provision of standard instructions to all participating physicians.

Data were entered into a secure database located at the Réseau Cardiologie Urgence (RESCUe) (Cardiovascular Emergency Network) Coordination Center.

Statistical analysis

Medians and interquartile ranges (IQR) are provided for continuous variables, and numbers and percentages for qualitative variables. Comparative analyses were performed using the $\chi 2$ or Fisher's test for binary variables and the Wilcoxon test for analysis of variance for continuous variables [13]. The 5% level was used to identify differences between groups that were of statistical significance ($p<0.05$). Statistical evaluations were performed using R Statistical Software (Version 3.4.1).

Results

Patient disposition and prevalence of CRS

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

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

Patient disposition is presented in Figure 1.

Baseline characteristics

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

As well as the higher incidence of chronic renal failure in Group 1, patients with CRS were more likely to have chronic HF (56.42% in Group 1 versus 47.67% in Group 2; p=0.0490). There was no difference in the incidence of any other comorbidity between groups. Patients in Group 1 were more likely than patients in Group 2 to receive furosemide (60.9% versus 52.91%; p=0.0498), insulin (15.52% versus 9.3%; p=0.0272) and amiodarone (14.33% versus

4.65%; p=0.0004) but there were no other differences between groups for medications. Additionally, patients in Group 1 were more likely to carry a defibrillator (4.48% versus 0%; p=0.0018), to have been hospitalized for HF at least twice during the last year (15.52% versus 8.81%; p=0.0031), and to be under the care of a cardiologist (72.24% versus 61.63%; p=0.0198), although there were no differences in the incidence of pacemakers between groups.

Patients in Group 1 were more likely to have a housekeeper (31.13% versus 23.26%; p=0.0170) and nurse (29.25% versus 20.93%; p=0.0359) but there was no difference between groups regarding family support, known cognitive impairment, or the incidence of being bedridden.

Hospitalization and clinical status

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

Vital signs were generally similar in Group 1 and Group 2, and there were no significant differences between groups in their means of transport to the ED (most commonly by personal means [45.76% overall]), Killip status (most patients in each group had a Killip status of 2 [53.06% overall], and signs of cardiogenic shock (2.96% overall).

Early management and diagnosis

At admission, blood samples from all patients underwent biological analysis (Table 3). As well as the differences between groups for CrCl, significant differences were observed for BNP, which was 2.2-fold higher in Group 1 than Group 2 (1157.5 ng/L versus 534 ng/L; p=0.0048), and proBNP, which was 2.0-fold higher in Group 1 than Group 2 (5120 ng/L versus 2513 ng/L; p<0.0001). Additionally, troponin was more likely to be positive in patients

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

Most patients underwent under an electrocardiogram (98.61% overall) chest X-ray (94.87% overall). Patients in Group 1 were more likely than those in Group 2 to have left bundle branch block (19.1% versus 12.79%; p=0.0461), cardiomegaly (51.04% versus 37.21%; p=0.0144), and interstitial opacities (60.3% versus 47.67%; p=0.0199).

Echography was performed for 16.17% patients overall, more often by a cardiologist (57.32% overall) than by an emergency physician (42.68% overall). There was no significant difference between groups in left ventricular ejection fraction.

Emergency treatments

Patients in Group 1 were more likely than Group 2 to receive emergency treatment of nitrates (21.19% versus 12.21%; p=0.0057), but there were no group differences in other emergency measures (furosemide, oxygen, anticoagulant, continuous positive airway pressure, non-invasive ventilation, anti-arrythmics, ionotropic agents, tracheal intubation) (Table 4). Overall 6.31% of patients received no emergency treatment, with no difference between groups.

Outcomes

Precipitating factors were not determined in 42.21% of cases overall, with no overall difference between groups (Table 5). The most common determined precipitating factors were infection (25.25% overall), arrythmia (15.19% overall), and hypertension (10.65% overall). Diabetes decompensation was considered to be the precipitating factor for AHF in 2.99% of patients in Group 1 but none in Group 2 (p=0.0110). There were no other group differences in precipitating factors.

There was no difference between groups in discharge destination (which was most often cardiology [28.01% overall]), and the discharge destination was deemed appropriate for a similar number of patients in each group (75.35% overall).

Neither in-hospital mortality (5.92% overall) nor the percentage of patients still hospitalized at 30 days (6.31% overall) were significantly different between Group 1 and Group 2. However, the median length of stay was 2 days longer in Group 1 than in Group 2 (8 days versus 6 days; p=0.0327) (Table 5).

Discussion

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

expected to recover once normal hemodynamic function is restored. It is therefore important to use biomarkers to provide a more precise assessment of kidney function than serum creatinine [27 28]. Equations to estimate GFR have replaced 24-hour creatinine clearance measurement in EDs because of the difficulty of urine collection. Creatinine clearance, urea clearance, net sodium excretion, and fractional excretion of sodium calculated over 6 hours can be used to evaluate kidney function and to define the natriuretic response precisely [29]. Conversely, the proportion of patients with a history of chronic renal injury is likely to be under-estimated due to memory bias.

The overall baseline characteristics, clinical status, biological and diagnostic tests, emergency treatment, and outcome of the patients included in this sub-analysis was similar to the overall population in the DeFSSICA study; however, some differences were observed between AHF patients with and without renal dysfunction. As would be expected due to reduced kidney excretion [30], and as described elsewhere [31-34], BNP and pro-BNP levels were higher in patients with CRS than in AHF patients with normal renal function and the percentage of troponin positive patients was also higher in the CRS group. These biomarkers probably reflect the congestion status and remain formally recommended for the management of AHF patients, especially for their prognostic value. The appropriate use of loop diuretics and/or vasodilators [35] in the CRS group, as well as in the AHF group without renal dysfunction, may explain in part the similar intra-hospital mortality rate in each group and the similar proportion of AHF patients with and without renal dysfunction who were still in hospital at 30 days after ED admission. Importantly, therefore, the prognosis of CRS patients was not significantly different using loop diuretics and/or nitrates to those without renal dysfunction. As such, it appears that the correct congestive assessment is vital in this complex clinical situation with concomitant failures in two organs.

Worsening renal function (WRF), which leads to a progressive loss of kidney function [30], is a factor for poor long-term prognosis [21 36 37] and Ferreira et al [2] showed that all formulae used to estimate renal function showed a strong and independent association with cardiovascular mortality, with eGFR or CrCl rates under 60 mL/min being associated with increasing cardiovascular mortality. As such, the use of loop diuretics has been considered to be deleterious to long-term renal function, probably since impaired renal function can have etiologies other than those related to congestion. However, despite WRF, Testani et al have recently shown an improvement in prognosis in AHF patients when loop diuretics are used [9]. Moreover, for patients treated for AHF, kidney injury appears to be more common in those with an altered ejection fraction than in those with a preserved ejection fraction [37]. However, despite these differences in pathophysiology and etiology between AHF patients with and without renal dysfunction, patient outcome is similar [38 39] meaning that renal dysfunction does not have an impact on outcome in AHF patients. Overall, the results of the sub-analysis of the DeFSSICA survey data for AHF patients with and without renal dysfunction support this conclusion. Although a small but statistically significant increase in the length of hospital stay from 6 to 8 days was observed in CRS patients, who showed a greater incidence of certain co-morbidities (inspiratory retraction, left bundle branch block, cardiomegaly and interstitial opacities), there was no difference in in-hospital mortality or in the number of patients still hospitalized at 30 days post-admission. Additionally, there was no difference in ejection fraction in CRS patients compared to AHF patients with normal renal function.

Recent publications suggest that appropriate, fast-acting decongesting therapies, as recommended by international guidelines, improve the prognosis for AHF patients as long as such therapies are introduced early, even if renal impairment develops at the same time [8]. Furthermore, it appears that renal impairment in AHF patients does not have an adverse

impact on patient prognosis provided that the congestion is improved. Renal function should be assessed according to the level of patient congestion, and so tools for the assessment of congestion, such as the BNP or proBNP biomarkers [40], lung ultrasound (LUS) B-lines (38), or the assessment of the dimensions and compliance of the inferior vena cava are vital. Novel biomarkers such as urinary angiotensinogen [41], neutrophil gelatinase-associated lipocalin [42 43], kidney injury molecule-1 [44], interleukin-18 [45 46], N-acetyl-β-d-glucosaminidase [47], cystatine C [48 49] or a combination of some or all of these could also be used to improve the diagnosis of acute kidney injury. Furthermore, the assessment of diuresis and natriuresis, which reflect both glomerular and tubular function, could offer a more successful strategy to achieve decongestion [47 50 51]. Ferreira et al [52] and Palazzuoli et al [53] have recently demonstrated that the lack of a diuretic response is a more important prognostic factor than the use of loop diuretics. This suggests a new diagnostic challenge, i.e. to assess the patient's response to diuretics [54-57]. However, despite some proposals to define diuretic resistance (e.g. persistent congestion despite adequate and escalating doses of diuretic with >80 mg furosemide/day, amount of sodium excreted as a percentage of filtered load <0.2%, failure to excrete ≥90 mmol of sodium within 72 hours of a 160 mg oral furosemide dose given twice daily) and the means of evaluation (e.g. weight loss per unit of 40 mg furosemide [or equivalent], net fluid loss/mg of loop diuretic [40 mg of furosemide or equivalent] during hospitalization, natriuretic response to furosemide as the ratio of urinary sodium to urinary furosemide) [58], there is currently no consensus for commonly accepted standards. Additionally, it is important that any alteration of GFR should be interpreted in the context of the deterioration of the clinical situation.

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

results appear to cast doubt on these favorable conclusions [63]. Combined therapies have also been evaluated, including hypotonic saline serum in combination with diuretic therapy to improve diuresis [64 65] and mannitol in combination with furosemide [58], although their benefit in diuretic-resistant patients is not confirmed. The addition of metozalone to furosemide could be of interest because of its capacity to produce diuresis even in patients with low GFR [66 67], although metozalone is not yet marketed in France. In a recent meta-analysis, Wang and al have shown that tolvaptan, an oral vasopressin V_2-receptor antagonist, may also represent an alternative therapy in WRF [68], and several studies have demonstrated that it can decrease the rate of WRF in patients treated with furosemide [69 70]. Finally, venous ultrafiltration allows a controlled hydrosodic depletion by subtracting isotonic fluid while diuretics allow the subtraction of hypotonic fluid. Other studies also suggest that the effectiveness of ultrafiltration is associated with a reduction in inflammatory cytokines [71]. These and other approaches in patients with cardiac insufficiency and resistance to diuretics have recently been reviewed [58].

The CRS analysis using data from the DeFSSICA survey has some limitations. First, only two groups have been analyzed (i.e. patients with or without kidney dysfunction), although chronic kidney disease is characterized by 5 stages. However, the CrCl threshold of 60 mL/min is commonly used [2 34 72-74] and is considered to be satisfactory for this analysis, especially since the small number of patients would not allow a thorough analysis for five sub-categories. The choice of a CrCl threshold of 30 mL/min could have led to a greater chance of obtaining a significant difference between groups in terms of outcome, but the 60 mL/min cut-off is more widely used. Second, since the data used are observational, it was not possible to impose any randomization or blinding, and the number of patients in each group was not balanced. Third, GFR assessments were performed by local laboratories for each center, rather than standardized at a single center, and repeated measures of GFR could have

improved their accuracy and comparability. The use of different formulae to evaluate CrCl in a chronic disease state but in an acute context without knowledge of the baseline value reflects the real-life situation. While potentially problematic, with the possibility of some incorrect classification of CKD, numerous previous studies of the impact of renal failure in AHF have used a similar approach [2 34 72]. Finally, it was not possible to sub-classify different types of CRS is this analysis since Kidney Disease Improving Global Outcomes (KDIGO) data were not collected.

Conclusion

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

Funding

This work was supported by Novartis France, but the Sponsor was not involved in the study protocol, methods, or choice of centers.

Competing interests

CEK and has received grants from Novartis (other than this work), Daiichy Sankyo, and Boehringer Ingleheim.

NP reports has acted as a paid consultant for Vygon SA.

SC reports personal fees from Novartis (other than this work).

LF is an employee of RESCUe Network.

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

Authors' contributions

SMZ, NP, SC, ME, DS, EBC, SL, PH, TC, and CEK conceived the study, designed the trial, and obtained research funding. TC and CEK supervised the conduct of the trial and data collection. NP, SC, DS and TC undertook recruitment of participating centers and patients. LF managed the data, including quality control, provided statistical advice and analyzed the data. DdR, LF, AB, AG, KT, TC and CEK drafted the manuscript, and all authors contributed substantially to its revision. All authors reviewed and approved the final version of the manuscript and are accountable for its content.

Consent for publication

Not applicable since no individual patient is identified.

Availability of data and material

No additional data available.

Acknowledgements

The authors thank the emergency physicians and cardiologists and patients who participated in this survey at the following centers: CHU Toulouse, CHU Rouen, CHU Clermont Ferrand, CHU Nancy, CHR Metz-Thionville-Hôpital de Mercy, Hôpital Lariboisière-Paris, CHR Annecy Genevois, CHU Lyon-Hôp, Edouard Herriot, CHRU de Lille, Chu De Caen, CHU Nice-Hôpital Saint-Roch, CHU de Grenoble, Hôpital Bicêtre-Paris, Hôpital St Louis Paris, CH I Meulan, CH d'Avignon, CH Jacques Lacarin–Vichy, CH d'Aix En Provence, CH Fleyriat –Bourg En Bresse, CH Bourgoin Jallieu, CHU de Saint Etienne, CH du Forez Montbrison-Feurs, CH de Firminy, CH Villefranche-Sur-Saône, CHU De Brest, CH Henri Mondor, CH de Vienne.

The authors also thank the RESCUe Network for the practical implementation of this survey and statistical analysis and Novartis France for its financial support.

Dr Andrew Lane (Lane Medical Writing), funded by the RESCUe network, provided professional medical writing assistance in the preparation and development of the manuscript in accordance with the European Medical Writers Association guidelines and Good Publication Practice.

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Tables

Table 1 Baseline characteristics of patients with confirmed acute heart failure (AHF) 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
Comorbidities				
- 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
Priori medications				
- 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
- β- 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
Pacemaker				
- 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
Defibrillator	16 (3.16%)	16 (4.78%)	0 (0%)	0.0018
Prior hospitalization for HF during past year				
- 0	287 (56.61%)	180 (53.73%)	107 (62.21%)	0.1397
- 1	130 (25.64%)	83 (24.78%)	47 (27.33%)	0.8556
- ≥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

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

	All AHF patients (N = 507)	Group 1 (n = 335)	Group 2 (n = 172)	p-value
Means of transport				
- 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
Clinical signs				
- 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
First recorded vital signs				
- 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
Killip status				
- 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

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

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

AHF, acute heart failure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; HF, heart failure; MICU, mobile intensive care unit; SBP, systolic blood pressure

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
Biological analysis				
- 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
ECG				
- 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
Chest X-ray				
- 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
Echography				
- 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

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

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

AHF, acute heart failure; AVB, atrioventricular block; BNP, brain natriuretic peptide; ECG, electrocardiogram; HF, heart failure; IVC, inferior vena cava; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; RBBB, right bundle branch block; RV, right ventricle; US, ultrasound

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
Antiarrythmics	23 (4.54%)	15 (4.48%)	8 (4.65%)	0.6009
Ionotropic 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

Data are number (%) of patients

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

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

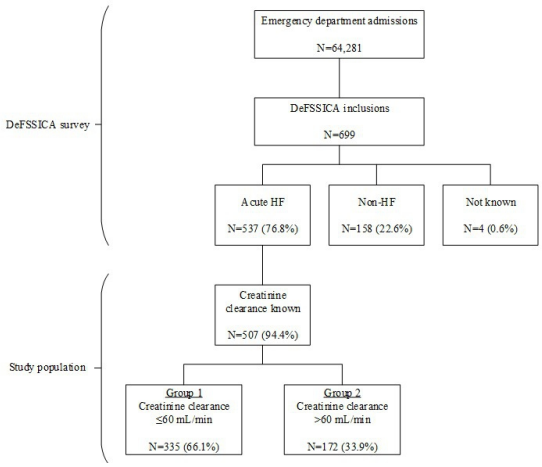
Table 5 Outcomes of patients with confirmed acute heart failure (AHF) syndrome

	All AHF patients (N=507)	Group 1 (n=335)	Group 2 (n=172)	p-value
Precipitating factors				
- 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
Discharge destination				
- 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
Destination considered appropriate	382 (75.35%)	246 (73.43%)	136 (79.07%)	0.1306
Outcome				
- 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
Length of stay, days	7 [4;13]	8 [4;13]	6 [3;12]	0.0327

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

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

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
Introduction			
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
Methods			
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

Results			
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
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-17
Limitations			
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
Other information			
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.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022776.R1
Article Type:	Research
Date Submitted by the Author:	21-Jun-2018
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Primary Subject Heading:	Emergency medicine
Secondary Subject Heading:	Cardiovascular medicine, Renal medicine
Keywords:	acute heart failure, AHF, cardio-renal syndrome, CRS, real-life, renal dysfunction

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

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Target journal & format: BMJ Open - Research Articles format (counts: abstract 300 words [max 300]; 6 keywords; body 3719 words (max 4000); 83 references; 1 figure, 5 tables).

Abstract (300 words [max 300])

Objectives: Cardio-renal syndrome (CRS) is the combination of acute heart failure syndrome (AHF) and renal dysfunction (creatinine clearance [CrCl] ≤60 mL/min). Real-life data were used to compare the management and outcome of AHF with and without renal dysfunction.

Design: Prospective, multi-center.

Setting: Twenty-six academic, community, and regional hospitals in France.

Participants: 507 patients with AHF were assessed in two groups according to renal function: Group 1 (CRS patients [CrCl ≤60 mL/min]: N=335) and Group 2 (AHF patients with normal renal function [CrCl >60 mL/min]: N=172).

Results: Differences were observed (Group 1 versus Group 2) at admission for the incidence of chronic heart failure (56.42% versus 47.67%), use of furosemide (60.9% versus 52.91%), insulin (15.52% versus 9.3%), and amiodarone (14.33% versus 4.65%); additionally, more patients in Group 1 carried a defibrillator (4.78% versus 0%), had ≥2 hospitalizations in the last year (15.52% versus 5.81%), and were under the care of a cardiologist (72.24% versus 61.63%). Clinical signs were broadly similar in each group. Brain-type natriuretic peptide (BNP) and BNP prohormone were higher in Group 1 than Group 2 (1157.5 versus 534 ng/L and 5120 versus 2513 ng/mL), and more patients in Group 1 were positive for troponin (58.2% versus 44.19%), had cardiomegaly (51.04% versus 37.21%), and interstitial opacities (60.3% versus 47.67%). The only difference in emergency treatment was the use of nitrates, (higher in Group 1 [21.9% versus 12.21%]). In-hospital mortality and the percentage of patients still hospitalized after 30 days was similar between groups, but median stay was longer in Group 1 (8 days versus 6 days).

Conclusions: Renal impairment in AHF should not limit the use of loop diuretics and/or vasodilators, but early assessment of pulmonary congestion and close monitoring of the efficacy of conventional therapies is encouraged to allow rapid and appropriate implementation of alternative therapies if necessary.

Keywords: acute heart failure, AHF, cardio-renal syndrome, CRS, real-life, renal dysfunction

Strengths and limitations of this study

- Few large-scale, prospective, real-life data exist for the real-life management and outcome of patients with cardio-renal syndrome compared to acute heart failure patients without renal dysfunction.
- Cardio-renal syndrome is of prognostic importance.
- Only two groups were included (i.e. patients with or without kidney dysfunction), rather than for each stage of chronic kidney disease although the creatinine clearance cut-off (60 mL/min) is commonly used.
- Glomerular filtration rate estimations were performed by local laboratories for each center (i.e. a real-life situation), rather than standardized at a single center, although this reflects the real-life situation.

Background

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

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

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

CRS and AHF patients would have the same outcome if the management of CRS was based on that for AHF patients without renal dysfunction.

Methods

Study design

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

Patient involvement

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

Selection of participants

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

In this analysis, only patients with known CrCl were included and were divided into those with CrCl ≤60 mL/min, i.e. renal dysfunction (Group 1) and those with CrCl >60 mL/min, i.e. normal renal function (Group 2). Glomerular filtration rate (GFR) was calculated using either the Cockroft-Gault (9 centers), Modification of Diet in Renal Disease (MDRD) Study (12 centers), or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations (14 centers) (8 centers used two methods and 18 centers used one method) [11 12].

Study assessments

Patients' baseline characteristics, medical history, social factors, in-hospital diagnostic tests and treatment, destination after ED discharge, in-hospital mortality and length of stay were recorded by emergency physicians in a case report form, which was structured according to the progress of care. Cardiac sonographic evaluations were performed at the discretion of the emergency physician. Abnormal chest X-ray was defined by the presence of cardiomegaly, and/or alveolar edema, and/or interstitial opacity, and/or pleural effusion. The choice of treatment was at the emergency physician's discretion, and according to his/her usual practice. Final diagnosis of AHF was made by the emergency physician using a combination of a clinical history, abnormal chest X-ray, elevated brain-type natriuretic peptide (BNP) or BNP prohormone (proBNP), and echocardiogrpahic signs.

Although it was not possible to impose any randomization or blinding since this was an observational study, any potential bias in the study assessments was minimized by the provision of standard instructions to all participating physicians.

Data were entered into a secure database located at the Réseau Cardiologie Urgence (RESCUe) (Cardiovascular Emergency Network) Coordination Center.

Statistical analysis

Medians and interquartile ranges (IQR) are provided for continuous variables, and numbers and percentages for qualitative variables. Comparative analyses were performed using the $\chi 2$ or Fisher's test for binary variables and the Wilcoxon test for analysis of variance for continuous variables [13]. The 5% level was used to identify differences between groups that were of statistical significance ($p<0.05$). Statistical evaluations were performed using R Statistical Software (Version 3.4.1).

Results

Patient disposition and prevalence of CRS

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

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

Patient disposition is presented in Figure 1.

Baseline characteristics

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

As well as the higher incidence of chronic renal failure in Group 1, patients with CRS were more likely to have chronic HF (56.42% in Group 1 versus 47.67% in Group 2; p<0.05). There was no difference in the incidence of any other comorbidity between groups. Patients in Group 1 were more likely than patients in Group 2 to receive furosemide (60.9% versus 52.91%; p<0.05), insulin (15.52% versus 9.3%; p=0.03) and amiodarone (14.33% versus

4.65%; p<0.01) but there were no other differences between groups for medications. Additionally, patients in Group 1 were more likely to have been hospitalized for HF at least twice during the last year (15.52% versus 8.81%; p<0.01), and to be under the care of a cardiologist (72.24% versus 61.63%; p=0.02). The incidence of patients carrying a defibrillator and of pacemakers (single, dual, or triple) are not presented since the sample sizes were small (N=16 and N=17, N=36, and N=6, respectively) and so the data were not considered sufficiently robust. Patients in Group 1 were more likely to have a housekeeper (31.13% versus 23.26%; p=0.02) and nurse (29.25% versus 20.93%; p=0.04) but there was no difference between groups regarding family support, known cognitive impairment, or the incidence of being bedridden.

Hospitalization and clinical status

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

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

Early management and diagnosis

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

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

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

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

Emergency treatments

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

Outcomes

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

There was no difference between groups in discharge destination (which was most often cardiology [28.01% overall]), and the discharge destination was deemed appropriate for a similar number of patients in each group (75.35% overall).

Neither in-hospital mortality (5.92% overall) nor the percentage of patients still hospitalized at 30 days (6.31% overall) were significantly different between Group 1 and Group 2. However, the median length of stay was 2 days longer in Group 1 than in Group 2 (8 days versus 6 days; p=0.03) (Table 5).

Discussion

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

the preferential use of novel biomarkers rather than serum creatinine to detect acute kidney injury can be inconsistent and remains an area for further research [29-32].

The overall baseline characteristics, clinical status, biological and diagnostic tests, emergency treatment, and outcome of the patients included in this sub-analysis was similar to the overall population in the DeFSSICA study; however, some differences were observed between AHF patients with and without renal dysfunction, including a trend towards more congestion in patients with CRS. As would be expected due to reduced kidney excretion [33], and as described elsewhere [34-37], BNP and pro-BNP levels were higher in patients with CRS than in AHF patients with normal renal function and the percentage of troponin positive patients was also higher in the CRS group. These biomarkers probably reflect the congestion status and remain formally recommended for the management of AHF patients, especially for their prognostic value. The appropriate use of loop diuretics and/or vasodilators [38] in the CRS group, as well as in the AHF group without renal dysfunction, may explain in part the similar intra-hospital mortality rate in each group and the similar proportion of AHF patients with and without renal dysfunction who were still in hospital 30 days after ED admission. Importantly, therefore, the prognosis of CRS patients was not significantly different using loop diuretics and/or nitrates to those without renal dysfunction. As such, it appears that the correct congestive assessment is vital in this complex clinical situation with concomitant failures in two organs.

Worsening renal function (WRF), which leads to a progressive loss of kidney function [33], is a factor for poor long-term prognosis [21 39 40] and Ferreira et al [2] showed that all formulae used to estimate renal function showed a strong and independent association with cardiovascular mortality, with eGFR or CrCl rates under 60 mL/min being associated with increasing cardiovascular mortality. As such, the use of loop diuretics has been considered to be deleterious to long-term renal function, probably since impaired renal function can have

etiologies other than those related to congestion. However, despite WRF, Testani et al have recently shown an improvement in prognosis in AHF patients when loop diuretics are used [9]. Moreover, for patients treated for AHF, kidney injury appears to be more common in those with an altered ejection fraction than in those with a preserved ejection fraction [40]. However, despite these differences in pathophysiology and etiology between AHF patients with and without renal dysfunction, patient outcome is similar [41 42] meaning that renal dysfunction does not have an impact on outcome in AHF patients. Overall, the results of the sub-analysis of the DeFSSICA survey data for AHF patients with and without renal dysfunction support this conclusion. Although a small but statistically significant increase in the length of hospital stay from 6 to 8 days was observed in CRS patients, who showed a greater incidence of certain co-morbidities (inspiratory retraction, left bundle branch block, cardiomegaly and interstitial opacities), there was no difference in in-hospital mortality or in the number of patients still hospitalized at 30 days post-admission. Additionally, there was no difference in ejection fraction in CRS patients compared to AHF patients with normal renal function.

Recent publications suggest that appropriate, fast-acting decongesting therapies, as recommended by international guidelines, improve the prognosis for AHF patients as long as such therapies are introduced early, even if renal impairment develops at the same time [8]. Furthermore, it appears that renal impairment in AHF patients does not have an adverse impact on patient prognosis provided that the congestion is improved. Renal function should be assessed according to the level of patient congestion, and so tools for the assessment of congestion, such as the BNP or proBNP biomarkers [43], lung ultrasound (LUS) B-lines (38), or the assessment of the dimensions and compliance of the inferior vena cava are vital. Additionally, hemoconcentration monitoring can be useful for monitoring congestion [44] and several routinely assessed biological parameters, e.g. serum protein, albumin, hemoglobin,

and hematocrit, have been proposed as surrogate markers [45]. Furthermore, formulae have been developed to indirectly estimate plasma volume using hemoglobin and/or hematocrit data [46 47]. Novel biomarkers such as urinary angiotensinogen [48], neutrophil gelatinase-associated lipocalin [49 50], kidney injury molecule-1 [51], interleukin-18 [52 53], N-acetyl-β-d-glucosaminidase [54], cystatine C [55 56] or a combination of some or all of these could also be used to improve the diagnosis of acute kidney injury, with the caveat that the use of such biomarkers can be inconsistent as described earlier. The assessment of diuresis and natriuresis, which reflect both glomerular and tubular function, could offer a strategy to achieve decongestion [54 57 58]. Ferreira et al [59] and Palazzuoli et al [60] showed that the lack of a diuretic response is a more important prognostic factor than the use of loop diuretics. This suggests a new diagnostic challenge, i.e. to assess the patient's response to diuretics [61-64]. However, despite some proposals to define diuretic resistance (e.g. persistent congestion despite adequate and escalating doses of diuretic with >80 mg furosemide/day, amount of sodium excreted as a percentage of filtered load <0.2%, failure to excrete ≥90 mmol of sodium within 72 hours of a 160 mg oral furosemide dose given twice daily) and the means of evaluation (e.g. weight loss per unit of 40 mg furosemide [or equivalent], net fluid loss/mg of loop diuretic [40 mg of furosemide or equivalent] during hospitalization, natriuretic response to furosemide) [65], there is currently no consensus for commonly accepted standards. Additionally, it is important that any alteration of GFR should be interpreted in the context of the deterioration of the clinical situation.

Another alternative therapy in CRS is the use of mineralocorticoid antagonists. These have been associated with an improvement in both congestion [66 67] and mortality in HF patients [68 69], although the ATHENA-HF trial results are less conclusive [70]. Combined therapies have also been evaluated, including hypotonic saline serum in combination with diuretic therapy to improve diuresis [71 72] and mannitol in combination with furosemide [65],

although their benefit in diuretic-resistant patients is not confirmed. The addition of metozalone to furosemide could be of interest because of its capacity to produce diuresis even in patients with low GFR [73 74]. In a meta-analysis, Wang and al showed that tolvaptan, an oral vasopressin V_2-receptor antagonist, may also represent an alternative therapy in WRF [75]. Several studies have shown that tolvaptan can decrease WRF in patients treated with furosemide [76 77]. Finally, venous ultrafiltration allows controlled hydrosodic depletion by subtracting isotonic fluid, compared to diuretics that allow the subtraction of hypotonic fluid. Other studies suggest that the effectiveness of ultrafiltration is associated with a reduction in inflammatory cytokines [78]. These and other approaches in patients with cardiac insufficiency and resistance to diuretics have recently been reviewed [65].

The CRS analysis using data from the DeFSSICA survey has some limitations. First, only two groups have been analyzed (i.e. patients with or without renal dysfunction), whereas chronic kidney disease is characterized by 5 stages [5]. However, as noted earlier, this is a mechanistic classification and in the present analysis the use of the CrCl threshold of 60 mL/min, which is commonly used to define renal dysfunction [2 37 79-81], is considered to be satisfactory, especially since the small number of patients would not allow a thorough analysis for five sub-categories. However, the pathophysiology of WRF in AHF is complex [82] and using a spot measurement of serum creatinine to classify CRS has limitations. This approach does not allow the separation of patients with acute and chronic CRS: in the present study, 35.8% of patients included in the CRS group had a history of chronic renal failure and so may not have suffered any acute change in renal function, whereas patients with acute changes in serum creatinine compared to their own baseline but not fulfilling the <60 mL/min criterion would not have been included in the CRS group. That said, the presence of renal failure on admission remains strongly associated with a poor prognosis irrespective of the anterior renal status and despite the lack of WRF in the first 5 days [83]. While the choice of a

CrCl threshold of 30 mL/min could have led to a greater chance of obtaining a significant difference between groups in terms of outcome, we based our analysis on the 60 mL/min cut-off since it is more widely used. Second, since the data used are observational, it was not possible to impose any randomization or blinding, and the number of patients in each group was not balanced. Third, GFR assessments were performed by local laboratories for each center, rather than standardized at a single center, and repeated measures of GFR could have improved their accuracy and comparability. The use of different formulae to evaluate CrCl in a chronic disease state and an acute context without knowledge of the baseline value reflects the real-life situation. While potentially problematic, with the possibility of some incorrect classification of CKD, numerous previous studies of the impact of renal failure in AHF have used a similar approach [2 37 79]. Finally, it was not possible to sub-classify different types of CRS in this analysis since Kidney Disease Improving Global Outcomes (KDIGO) data were not collected, although as described earlier the small number of patients would not have allowed a thorough analysis for each sub-category.

Conclusion

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

Funding

This work was supported by Novartis France, but the Sponsor was not involved in the study protocol, methods, or choice of centers.

Competing interests

CEK and has received grants from Novartis (other than this work), Daiichy Sankyo, and Boehringer Ingleheim.

NP reports has acted as a paid consultant for Vygon SA.

SC reports personal fees from Novartis (other than this work).

LF is an employee of RESCUe Network.

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

Authors' contributions

SMZ, NP, SC, ME, DS, EBC, SL, PH, TC, and CEK conceived the study, designed the trial, and obtained research funding. TC and CEK supervised the conduct of the trial and data collection. NP, SC, DS and TC undertook recruitment of participating centers and patients. LF managed the data, including quality control, provided statistical advice and analyzed the data. DdR, LF, AB, AG, KT, TC and CEK drafted the manuscript, and all authors contributed substantially to its revision. All authors reviewed and approved the final version of the manuscript and are accountable for its content.

Consent for publication

Not applicable since no individual patient is identified.

Data sharing statement

The database supporting the results presented in this article can be shared on reasonable request.

Acknowledgements

The authors thank the emergency physicians and cardiologists and patients who participated in this survey at the following centers: CHU Toulouse, CHU Rouen, CHU Clermont Ferrand, CHU Nancy, CHR Metz-Thionville-Hôpital de Mercy, Hôpital Lariboisière-Paris, CHR Annecy Genevois, CHU Lyon-Hôp, Edouard Herriot, CHRU de Lille, Chu De Caen, CHU Nice-Hôpital Saint-Roch, CHU de Grenoble, Hôpital Bicêtre-Paris, Hôpital St Louis Paris, CH I Meulan, CH d'Avignon, CH Jacques Lacarin–Vichy, CH d'Aix En Provence, CH Fleyriat –Bourg En Bresse, CH Bourgoin Jallieu, CHU de Saint Etienne, CH du Forez Montbrison-Feurs, CH de Firminy, CH Villefranche-Sur-Saône, CHU De Brest, CH Henri Mondor, CH de Vienne.

The authors also thank the RESCUe Network for the practical implementation of this survey and statistical analysis and Novartis France for its financial support.

Dr Andrew Lane (Lane Medical Writing), funded by the RESCUe network, provided professional medical writing assistance in the preparation and development of the manuscript in accordance with the European Medical Writers Association guidelines and Good Publication Practice.

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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
Comorbidities				
- 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
Priori medications				
- 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
- β- 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
Prior hospitalization for HF during past year				
- 0	287 (56.61%)	180 (53.73%)	107 (62.21%)	0.14
- 1	130 (25.64%)	83 (24.78%)	47 (27.33%)	0.86
- ≥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
Residence				
- 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

Self-sufficient	258 (50.89%)	162 (48.36%)	96 (55.81%)	0.19
Home assistance				
- 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

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

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

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

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

	All AHF patients (N = 507)	Group 1 (n = 335)	Group 2 (n = 172)	p-value
Means of transport				
- 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
Clinical signs				
- 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
First recorded vital signs				
- 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
Killip status				
- 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

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

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

AHF, acute heart failure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; HF, heart failure; MICU, mobile intensive care unit; SBP, systolic blood pressure

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

	All AHF patients (N=507)	Group 1 (n=335)	Group 2 (n=172)	p-value
Biological analysis				
- 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
ECG				
- 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
Chest X-ray				
- 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

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

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

AHF, acute heart failure; AVB, atrioventricular block; BNP, brain natriuretic peptide; ECG, electrocardiogram; HF, heart failure; IVC, inferior vena cava; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; RBBB, right bundle branch block; RV, right ventricle; US, ultrasound

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
Antiarrythmics	23 (4.54%)	15 (4.48%)	8 (4.65%)	0.60
Ionotropic 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

Data are number (%) of patients

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

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

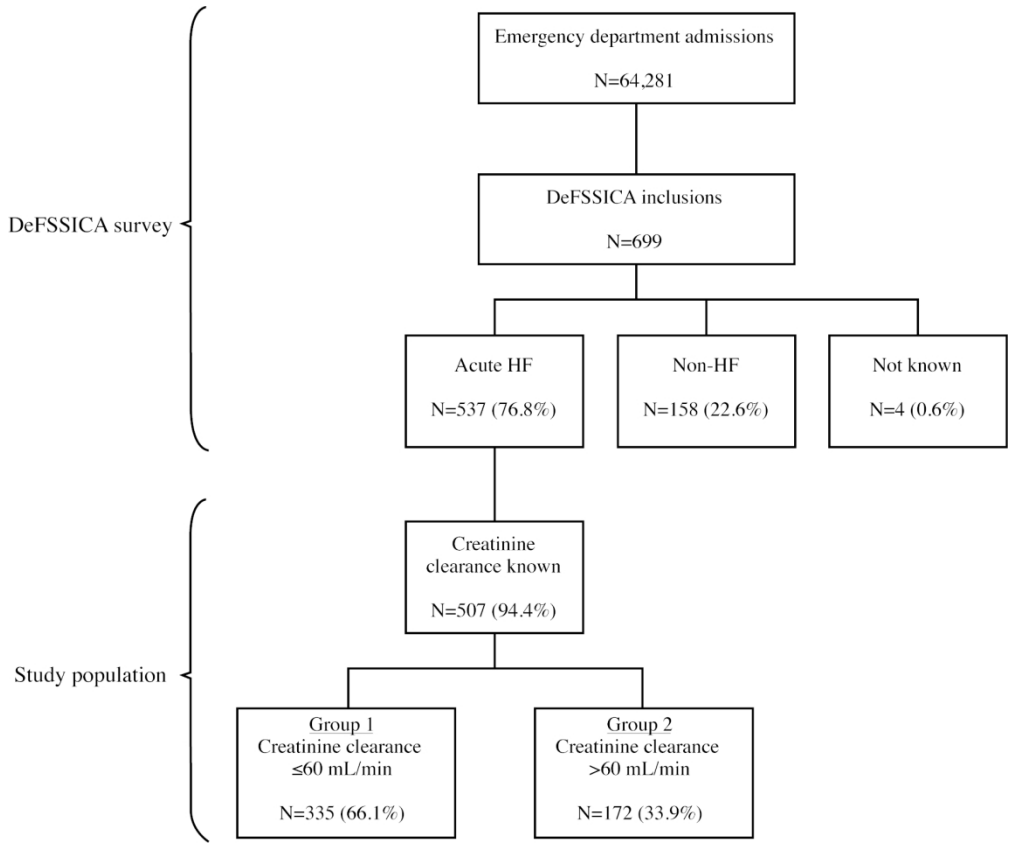
Table 5 Outcomes of patients with confirmed acute heart failure (AHF) syndrome

	All AHF patients (N=507)	Group 1 (n=335)	Group 2 (n=172)	p-value
Precipitating factors				
- 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
Discharge destination				
- 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
Destination considered appropriate	382 (75.35%)	246 (73.43%)	136 (79.07%)	0.13
Outcome				
- 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
Length of stay, days	7 (4;13)	8 (4;13)	6 (3;12)	0.03

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

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

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
Introduction			
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
Methods			
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

Results			
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
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-17
Limitations			
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
Other information			
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.

BMJ Open

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

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

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

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

Abstract (300 words [max 300])

Objectives: Cardio-renal syndrome (CRS) is the combination of acute heart failure syndrome (AHF) and renal dysfunction (creatinine clearance [CrCl] ≤60 mL/min). Real-life data were used to compare the management and outcome of AHF with and without renal dysfunction.

Design: Prospective, multi-center.

Setting: Twenty-six academic, community, and regional hospitals in France.

Participants: 507 patients with AHF were assessed in two groups according to renal function: Group 1 (CRS patients [CrCl ≤60 mL/min]: N=335) and Group 2 (AHF patients with normal renal function [CrCl >60 mL/min]: N=172).

Results: Differences were observed (Group 1 versus Group 2) at admission for the incidence of chronic heart failure (56.42% versus 47.67%), use of furosemide (60.9% versus 52.91%), insulin (15.52% versus 9.3%), and amiodarone (14.33% versus 4.65%); additionally, more patients in Group 1 carried a defibrillator (4.78% versus 0%), had ≥2 hospitalizations in the last year (15.52% versus 5.81%), and were under the care of a cardiologist (72.24% versus 61.63%). Clinical signs were broadly similar in each group. Brain-type natriuretic peptide (BNP) and BNP prohormone were higher in Group 1 than Group 2 (1157.5 versus 534 ng/L and 5120 versus 2513 ng/mL), and more patients in Group 1 were positive for troponin (58.2% versus 44.19%), had cardiomegaly (51.04% versus 37.21%), and interstitial opacities (60.3% versus 47.67%). The only difference in emergency treatment was the use of nitrates, (higher in Group 1 [21.9% versus 12.21%]). In-hospital mortality and the percentage of patients still hospitalized after 30 days was similar between groups, but median stay was longer in Group 1 (8 days versus 6 days).

Conclusions: Renal impairment in AHF should not limit the use of loop diuretics and/or vasodilators, but early assessment of pulmonary congestion and close monitoring of the efficacy of conventional therapies is encouraged to allow rapid and appropriate implementation of alternative therapies if necessary.

Keywords: acute heart failure, AHF, cardio-renal syndrome, CRS, real-life, renal dysfunction

Strengths and limitations of this study

- A large-scale, prospective, real-life study for the management and outcome of patients with cardio-renal syndrome compared to acute heart failure patients without renal dysfunction.
- Only two groups were included (i.e. patients with or without kidney dysfunction), rather than for each stage of chronic kidney disease although the creatinine clearance cut-off (60 mL/min) is commonly used.
- Glomerular filtration rate was calculated using three different methods.
- Glomerular filtration rate estimations were performed by local laboratories for each center (i.e. a real-life situation).
- There was no clearance monitoring after hospital discharge.

Background

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

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

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

CRS and AHF patients would have the same outcome if the management of CRS was based on that for AHF patients without renal dysfunction.

Methods

Study design

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

Patient involvement

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

Selection of participants

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

admission and prior to chest X-ray and laboratory tests. Patient enrollment occurred between 16 June 2014 and 7 July 2014.

In this analysis, only patients with known CrCl were included and were divided into those with CrCl ≤60 mL/min, i.e. renal dysfunction (Group 1) and those with CrCl >60 mL/min, i.e. normal renal function (Group 2). Glomerular filtration rate (GFR) was calculated using either the Cockroft-Gault (9 centers), Modification of Diet in Renal Disease (MDRD) Study (12 centers), or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations (14 centers) (8 centers used two methods and 18 centers used one method) [11 12].

Study assessments

Patients' baseline characteristics, medical history, social factors, in-hospital diagnostic tests and treatment, destination after ED discharge, in-hospital mortality and length of stay were recorded by emergency physicians in a case report form, which was structured according to the progress of care. Cardiac sonographic evaluations were performed at the discretion of the emergency physician. Abnormal chest X-ray was defined by the presence of cardiomegaly, and/or alveolar edema, and/or interstitial opacity, and/or pleural effusion. The choice of treatment was at the emergency physician's discretion, and according to his/her usual practice. Final diagnosis of AHF was made by the emergency physician using a combination of a clinical history, abnormal chest X-ray, elevated brain-type natriuretic peptide (BNP) or BNP prohormone (proBNP), and echocardiogrpahic signs.

Although it was not possible to impose any randomization or blinding since this was an observational study, any potential bias in the study assessments was minimized by the provision of standard instructions to all participating physicians.

Data were entered into a secure database located at the Réseau Cardiologie Urgence (RESCUe) (Cardiovascular Emergency Network) Coordination Center.

Statistical analysis

Medians and interquartile ranges (IQR) are provided for continuous variables, and numbers and percentages for qualitative variables. Comparative analyses were performed using the $\chi 2$ or Fisher's test for binary variables and the Wilcoxon test for analysis of variance for continuous variables [13]. The 5% level was used to identify differences between groups that were of statistical significance ($p<0.05$). Statistical evaluations were performed using R Statistical Software (Version 3.4.1).

Results

Patient disposition and prevalence of CRS

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

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

Patient disposition is presented in Figure 1.

Baseline characteristics

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

As well as the higher incidence of chronic renal failure in Group 1, patients with CRS were more likely to have chronic HF (56.42% in Group 1 versus 47.67% in Group 2; p<0.05). There was no difference in the incidence of any other comorbidity between groups. Patients in Group 1 were more likely than patients in Group 2 to receive furosemide (60.9% versus 52.91%; p<0.05), insulin (15.52% versus 9.3%; p=0.03) and amiodarone (14.33% versus

4.65%; p<0.01) but there were no other differences between groups for medications. Additionally, patients in Group 1 were more likely to have been hospitalized for HF at least twice during the last year (15.52% versus 8.81%; p<0.01), and to be under the care of a cardiologist (72.24% versus 61.63%; p=0.02). The incidence of patients carrying a defibrillator and of pacemakers (single, dual, or triple) are not presented since the sample sizes were small (N=16 and N=17, N=36, and N=6, respectively) and so the data were not considered sufficiently robust. Patients in Group 1 were more likely to have a housekeeper (31.13% versus 23.26%; p=0.02) and nurse (29.25% versus 20.93%; p=0.04) but there was no difference between groups regarding family support, known cognitive impairment, or the incidence of being bedridden.

Hospitalization and clinical status

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

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

Early management and diagnosis

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

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

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

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

Emergency treatments

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

Outcomes

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

There was no difference between groups in discharge destination (which was most often cardiology [28.01% overall]), and the discharge destination was deemed appropriate for a similar number of patients in each group (75.35% overall).

Neither in-hospital mortality (5.92% overall) nor the percentage of patients still hospitalized at 30 days (6.31% overall) were significantly different between Group 1 and Group 2. However, the median length of stay was 2 days longer in Group 1 than in Group 2 (8 days versus 6 days; p=0.03) (Table 5).

Discussion

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

the preferential use of novel biomarkers rather than serum creatinine to detect acute kidney injury can be inconsistent and remains an area for further research [29-32].

The overall baseline characteristics, clinical status, biological and diagnostic tests, emergency treatment, and outcome of the patients included in this sub-analysis was similar to the overall population in the DeFSSICA study; however, some differences were observed between AHF patients with and without renal dysfunction, including a trend towards more congestion in patients with CRS. As would be expected due to reduced kidney excretion [33], and as described elsewhere [34-37], BNP and pro-BNP levels were higher in patients with CRS than in AHF patients with normal renal function and the percentage of troponin positive patients was also higher in the CRS group. These biomarkers probably reflect the congestion status and remain formally recommended for the management of AHF patients, especially for their prognostic value. The appropriate use of loop diuretics and/or vasodilators [38] in the CRS group, as well as in the AHF group without renal dysfunction, may explain in part the similar intra-hospital mortality rate in each group and the similar proportion of AHF patients with and without renal dysfunction who were still in hospital 30 days after ED admission. Importantly, therefore, the prognosis of CRS patients was not significantly different using loop diuretics and/or nitrates to those without renal dysfunction. As such, it appears that the correct congestive assessment is vital in this complex clinical situation with concomitant failures in two organs.

Recent publications suggest that appropriate, fast-acting decongesting therapies, as recommended by international guidelines, improve the prognosis for AHF patients as long as such therapies are introduced early, even if renal impairment develops at the same time [8]. Furthermore, it appears that renal impairment in AHF patients does not have an adverse impact on patient prognosis provided that the congestion is improved. Renal function should be assessed according to the level of patient congestion, and so tools for the assessment of

congestion, such as the BNP or proBNP biomarkers [39], lung ultrasound (LUS) B-lines (38), or the assessment of the dimensions and compliance of the inferior vena cava are vital. Additionally, hemoconcentration monitoring can be useful for monitoring congestion and significantly improves the short-term outcome of AHF patients [40]and several routinely assessed biological parameters, e.g. serum protein, albumin, hemoglobin, and hematocrit, have been proposed as surrogate markers [41]. Furthermore, formulae have been developed to indirectly estimate plasma volume using hemoglobin and/or hematocrit data [42 43]. Further research is needed to establish the ability of novel biomarkers such as urinary angiotensinogen [44], neutrophil gelatinase-associated lipocalin [45 46], kidney injury molecule-1 [47], interleukin-18 [48 49], N-acetyl-β-d-glucosaminidase [50], cystatine C [51 52] or a combination of some or all of these could also be used to improve clinical decision making and therapy. The assessment of diuresis and natriuresis, which reflect both glomerular and tubular function, could offer a strategy to achieve decongestion [50 53 54]. Ferreira et al [55] and Palazzuoli et al [56] showed that the lack of a diuretic response is a more important prognostic factor than the use of loop diuretics. This suggests a new diagnostic challenge, i.e. to assess the patient's response to diuretics [57-60]. However, despite some proposals to define diuretic resistance (e.g. persistent congestion despite adequate and escalating doses of diuretic with >80 mg furosemide/day, amount of sodium excreted as a percentage of filtered load <0.2%, failure to excrete ≥90 mmol of sodium within 72 hours of a 160 mg oral furosemide dose given twice daily) and the means of evaluation (e.g. weight loss per unit of 40 mg furosemide [or equivalent], net fluid loss/mg of loop diuretic [40 mg of furosemide or equivalent] during hospitalization, natriuretic response to furosemide) [61], there is currently no consensus for commonly accepted standards. Additionally, it is important that any alteration of GFR should be interpreted in the context of the deterioration of the clinical situation.

Another alternative therapy in CRS is the use of mineralocorticoid antagonists. These have been associated with an improvement in both congestion [62 63] and mortality in HF patients [64 65], although the ATHENA-HF trial results are less conclusive [66]. Combined therapies have also been evaluated, including hypotonic saline serum in combination with diuretic therapy to improve diuresis [67 68] and mannitol in combination with furosemide [61], although their benefit in diuretic-resistant patients is not confirmed. The addition of metozalone to furosemide could be of interest because of its capacity to produce diuresis even in patients with low GFR [69 70]. In a meta-analysis, Wang and al showed that tolvaptan, an oral vasopressin V_2-receptor antagonist, may also represent an alternative therapy in WRF [71]. Several studies have shown that tolvaptan can decrease WRF in patients treated with furosemide [72 73]. Finally, venous ultrafiltration allows controlled hydrosodic depletion by subtracting isotonic fluid, compared to diuretics that allow the subtraction of hypotonic fluid. Other studies suggest that the effectiveness of ultrafiltration is associated with a reduction in inflammatory cytokines [74]. These and other approaches in patients with cardiac insufficiency and resistance to diuretics have recently been reviewed [61].

The CRS analysis using data from the DeFSSICA survey has some limitations. First, only two groups have been analyzed (i.e. patients with or without renal dysfunction), whereas chronic kidney disease is characterized by 5 stages [5]. However, as noted earlier, this is a mechanistic classification and in the present analysis the use of the CrCl threshold of 60 mL/min, which is commonly used to define renal dysfunction [2 37 75-77], is considered to be satisfactory, especially since the small number of patients would not allow a thorough analysis for five sub-categories. However, the pathophysiology of WRF in AHF is complex [78] and using a spot measurement of serum creatinine to classify CRS has limitations. This approach does not allow the separation of patients with acute and chronic CRS: in the present study, 35.8% of patients included in the CRS group had a history of chronic renal failure and

so may not have suffered any acute change in renal function, whereas patients with acute changes in serum creatinine compared to their own baseline but not fulfilling the <60 mL/min criterion would not have been included in the CRS group. That said, the presence of renal failure on admission remains strongly associated with a poor prognosis irrespective of the anterior renal status and despite the lack of WRF in the first 5 days [79]. While the choice of a CrCl threshold of 30 mL/min could have led to a greater chance of obtaining a significant difference between groups in terms of outcome, we based our analysis on the 60 mL/min cut-off since it is more widely used. Second, since the data used are observational, it was not possible to impose any randomization or blinding, and the number of patients in each group was not balanced. Third, GFR assessments were performed by local laboratories for each center, rather than standardized at a single center, and repeated measures of GFR could have improved their accuracy and comparability. The use of different formulae to evaluate CrCl in a chronic disease state and an acute context without knowledge of the baseline value reflects the real-life situation. While potentially problematic, with the possibility of some incorrect classification of CKD, numerous previous studies of the impact of renal failure in AHF have used a similar approach [2 37 75]. Finally, it was not possible to sub-classify different types of CRS in this analysis since Kidney Disease Improving Global Outcomes (KDIGO) data were not collected, although as described earlier the small number of patients would not have allowed a thorough analysis for each sub-category.

Conclusion

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

an inadequate response to diuretics, allowing the rapid and appropriate implementation of alternative therapies if necessary.

Funding

This work was supported by Novartis France, but the Sponsor was not involved in the study protocol, methods, or choice of centers.

Competing interests

CEK and has received grants from Novartis (other than this work), Daiichy Sankyo, and Boehringer Ingleheim.

NP reports has acted as a paid consultant for Vygon SA.

SC reports personal fees from Novartis (other than this work).

LF is an employee of RESCUe Network.

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

Authors' contributions

SMS, NP, SC, ME, DS, EBC, SL, PH, TC, and CEK conceived the study, designed the trial, and obtained research funding. TC and CEK supervised the conduct of the trial and data collection. NP, SC, DS and TC undertook recruitment of participating centers and patients. LF managed the data, including quality control, provided statistical advice and analyzed the data. DdR, LF, AB, AG, KT, TC and CEK drafted the manuscript, and all authors contributed substantially to its revision. All authors reviewed and approved the final version of the manuscript and are accountable for its content.

Consent for publication

Not applicable since no individual patient is identified.

Data sharing statement

The database supporting the results presented in this article can be shared on reasonable request.

Acknowledgements

The authors thank the emergency physicians and cardiologists and patients who participated in this survey at the following centers: CHU Toulouse, CHU Rouen, CHU Clermont Ferrand, CHU Nancy, CHR Metz-Thionville-Hôpital de Mercy, Hôpital Lariboisière-Paris, CHR Annecy Genevois, CHU Lyon-Hôp, Edouard Herriot, CHRU de Lille, Chu De Caen, CHU Nice-Hôpital Saint-Roch, CHU de Grenoble, Hôpital Bicêtre-Paris, Hôpital St Louis Paris, CH I Meulan, CH d'Avignon, CH Jacques Lacarin–Vichy, CH d'Aix En Provence, CH Fleyriat –Bourg En Bresse, CH Bourgoin Jallieu, CHU de Saint Etienne, CH du Forez Montbrison-Feurs, CH de Firminy, CH Villefranche-Sur-Saône, CHU De Brest, CH Henri Mondor, CH de Vienne.

The authors also thank the RESCUe Network for the practical implementation of this survey and statistical analysis and Novartis France for its financial support.

Dr Andrew Lane (Lane Medical Writing), funded by the RESCUe network, provided professional medical writing assistance in the preparation and development of the manuscript in accordance with the European Medical Writers Association guidelines and Good Publication Practice.

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Tables

Table 1 Baseline characteristics of patients with confirmed acute heart failure (AHF) 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
Comorbidities				
- 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
Priori medications				
- 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
- β- 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
Prior hospitalization for HF during past year				
- 0	287 (56.61%)	180 (53.73%)	107 (62.21%)	0.14
- 1	130 (25.64%)	83 (24.78%)	47 (27.33%)	0.86
- ≥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
Residence				

- 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
Self-sufficient	258 (50.89%)	162 (48.36%)	96 (55.81%)	0.19
Home assistance				
- 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

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

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

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

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

	All AHF patients (N = 507)	Group 1 (n = 335)	Group 2 (n = 172)	p-value
Means of transport				
- 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
Clinical signs				
- 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
First recorded vital signs				
- 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
Killip status				
- 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

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

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

AHF, acute heart failure; DBP, diastolic blood pressure; GCS, Glasgow Coma Scale; HF, heart failure; MICU, mobile intensive care unit; SBP, systolic blood pressure

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

	All AHF patients (N=507)	Group 1 (n=335)	Group 2 (n=172)	p-value
Biological analysis				
- 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
ECG				
- 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
Chest X-ray				
- 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

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

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

AHF, acute heart failure; AVB, atrioventricular block; BNP, brain natriuretic peptide; ECG, electrocardiogram; HF, heart failure; IVC, inferior vena cava; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; RBBB, right bundle branch block; RV, right ventricle; US, ultrasound

685

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
Antiarrythmics	23 (4.54%)	15 (4.48%)	8 (4.65%)	0.60
Ionotropic 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
Precipitating factors				
- 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
Discharge destination				
- 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
Destination considered appropriate	382 (75.35%)	246 (73.43%)	136 (79.07%)	0.13
Outcome				
- 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
Length of stay, days	7 (4;13)	8 (4;13)	6 (3;12)	0.03

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

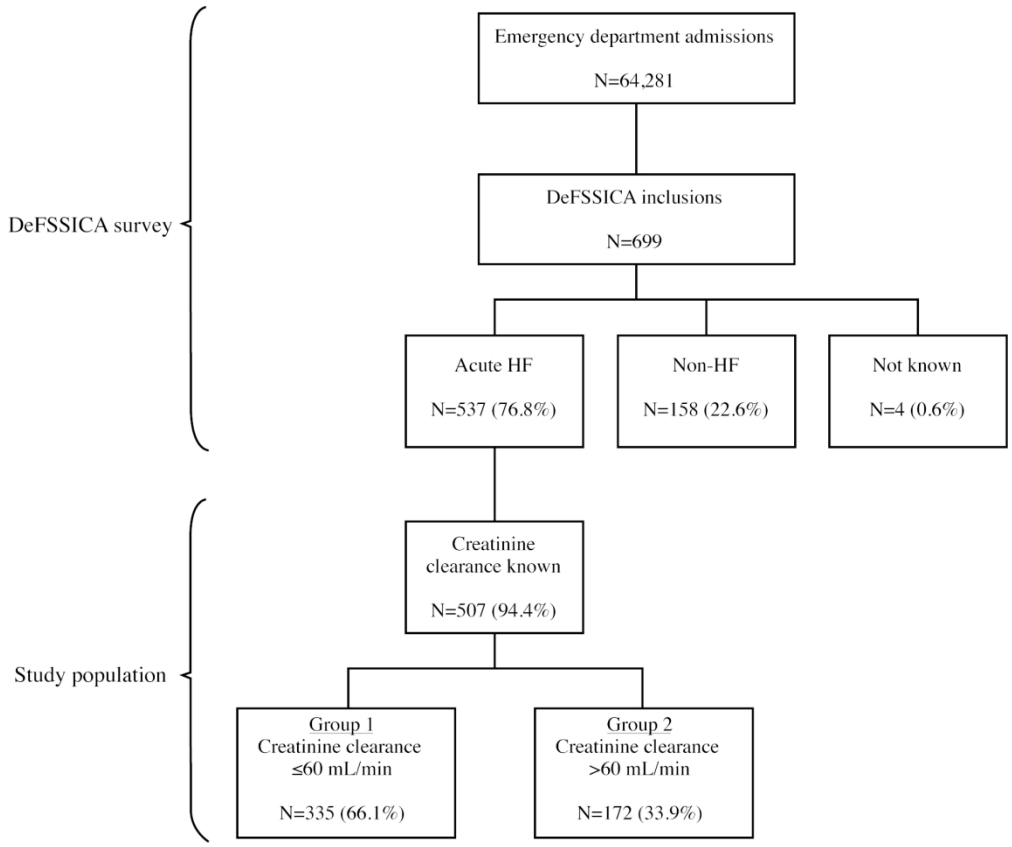
694

Figure title and legend

Figure 1

Title: Patient disposition

Legend: DeFSSICA, Description de la Filière de Soins dans les Syndromes d'Insuffisance Cardiaque Aigue; HF, 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
Introduction			
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
Methods			
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

Results			
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
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-17
Limitations			
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
Other information			
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.