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### ► To cite this version:

Kim Volle, Hamid Merdji, Vincent Bataille, Nicolas Lamblin, François Roubille, et al.. Ventilation strategies in cardiogenic shock: insights from the FRENSHOCK observational registry. *Clinical Research in Cardiology*, 2024, 10.1007/s00392-024-02551-x . hal-04751201

**HAL Id: hal-04751201**

**<https://hal.science/hal-04751201v1>**

Submitted on 24 Oct 2024

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# Ventilation strategies in cardiogenic shock: insights from the FRENSHOCK observational registry

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**Keywords:**

Cardiogenic shock; Mechanical ventilation; Mortality; Non-invasive ventilation; Prognosis.

# Abstract

## Background:

Despite scarce data, invasive mechanical ventilation (MV) is widely suggested as first-line ventilatory support in cardiogenic shock (CS) patients. We assessed the real-life use of different ventilation strategies in CS and their influence on short and mid-term prognosis.

## Methods:

FRENSHOCK was a prospective registry including 772 CS patients from 49 centers in France. Patients were categorized into three groups according to the ventilatory supports during hospitalization: no mechanical ventilation group (NV), non-invasive ventilation alone group (NIV), and invasive mechanical ventilation group (MV). We compared clinical characteristics, management, and occurrence of death and major adverse event (MAE) (death, heart transplantation or ventricular assist device) at 30 days and 1 year between the three groups.

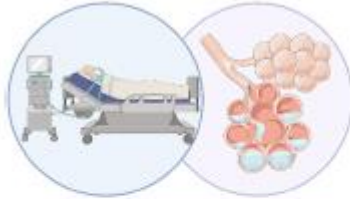
## Results:

Seven hundred sixty-eight patients were included in this analysis. Mean age was 66 years and 71% were men. Among them, 359 did not receive any ventilatory support (46.7%), 118 only NIV (15.4%), and 291 MV (37.9%). MV patients presented more severe CS with more skin mottling, higher lactate levels, and higher use of vasoactive drugs and mechanical circulatory support. MV was associated with higher mortality and MAE at 30 days (HR 1.41 [1.05-1.90] and 1.52 [1.16-1.99] vs NV). No difference in mortality (HR 0.79 [0.49-1.26]) or MAE (HR 0.83 [0.54-1.27]) was found between NIV patients and NV patients. Similar results were found at 1-year follow-up.

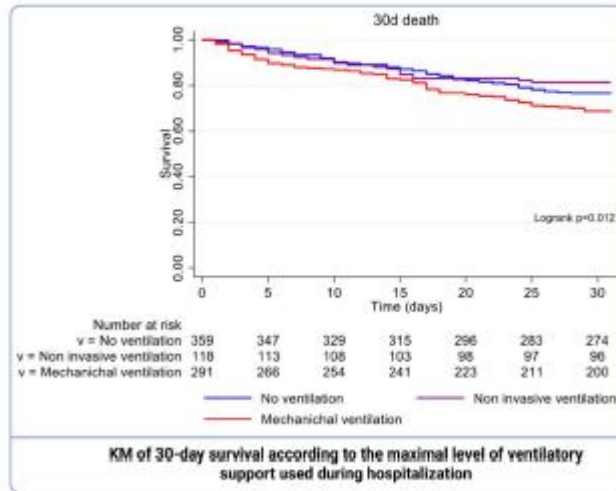
## Conclusions:

Our study suggests that using NIV is safe in selected patients with less profound CS and no other MV indication. NCT02703038.

## Short and mid-term prognosis according to ventilation strategies in unselected patients with cardiogenic shock



- 49 centers
- 768 Cardiogenic shock:
  - 359 (46.7%) without ventilation
  - 118 (15.4%) with NIV only
  - 291 (37.9%) with MV
- More severe CS in patient under MV
- No difference in mortality between NIV patients and patients without ventilation



## Abbreviations

- CICardiac index
- CRP C-reactive protein
- CRT Capillary refill time
- CS Cardiogenic shock
- ESC European Society of Cardiology
- ESICM European Society of Intensive Care Medicine
- eGFR Estimated glomerular filtration rate
- IABP Intra-aortic balloon pump
- ICCU Intensive cardiac care unit
- ICU Intensive care unit
- LVEF Left ventricular ejection fraction
- MAE Major adverse events
- MAP Mean arterial pressure
- MI Myocardial infarction
- MCS Mechanical circulatory support
- MV Mechanical ventilation
- NIV Noninvasive ventilation
- NV No ventilation
- PCI Percutaneous coronary intervention
- RRT Renal replacement therapy
- SAP Systolic arterial pressure
- VA-ECMO Venoarterial-extracorporeal membrane oxygenation

# Introduction

Cardiogenic shock (CS) is consensually considered as a primary cardiac dysfunction with low cardiac output leading to critical end-organ hypoperfusion [1, 2]. The most frequent causes of CS are non-ischemic cardiomyopathy and myocardial infarction [3–5]. Despite recent therapeutic advances in medication and intervention, the short-term mortality of CS remains high between 30 and 50% [5–7].

CS patients usually present an increase in pulmonary capillary pressures responsible for an alteration in gas exchange revealed by acute pulmonary oedema (APE) and respiratory distress (57%) requiring oxygen support and, for the most severe (43%), mechanical ventilation (MV)[8]. These ventilatory therapies, such as non-invasive ventilation (NIV) and MV have been increasingly used in recent years, although no prospective trial has been conducted to date in CS [8]. Most recommendations propose MV as first-line ventilatory support in CS but are based on a low level of evidence (1C), i.e., expert consensus [1, 2, 9–13]. Nevertheless, the use of MV is frequently associated with excess mortality even in CS patients and its prolonged use is associated with increased length of stay, increased morbidity and mortality, and significant loss of autonomy in case of survival [14]. NIV is recommended as first-line treatment for APE with hypoxia ( $SpO_2 < 90\%$ ) with a class IIa grade [13] since it reduces the need for intubation and early mortality compared to traditional oxygen therapy. According to the Frank–Starling law, the effects of MV in CS may be difficult to predict. On one hand, the pathophysiology effects of NIV may be beneficial in CS patients with decreased LVEF as it may increase cardiac output. On the other hand, when there is isolated right ventricular (RV) dysfunction, positive pressure may be detrimental as the increase in RV afterload may precipitate or aggravate RV failure, explaining why NIV was contraindicated for a long time in CS. Besides, CS patients may have encephalopathy leading to difficulties to conduct NIV [15–17].

Several registries provide conflicting results regarding the effect of NIV in the management of CS patients. For some, NIV is associated with an increased risk of complications and mortality probably due to delayed orotracheal intubation, whereas for others it seems to be effective and safe in this indication [8, 14, 18]. In all cases, the delay in the initiation of adapted ventilatory support seems to be associated with an over risk of mortality [19].

Based on the largest European prospective cohort of unselected CS to date, we aimed to assess characteristics and outcomes of CS according to the type of ventilatory support used. Our secondary objective was to determine prognostic factors of the need for MV in CS patients.

## Methods

### Patient population

FRENSHOCK is a prospective multicenter observational registry conducted in metropolitan France for 6 months between April and October 2016 in intensive care unit (ICU) and intensive cardiac care units (ICCU) (NCT02703038). The methods used for this registry have been previously described [5, 20]. Briefly, the primary objective was to evaluate CS patients'

characteristics, management, and outcomes, with a new modified definition of CS as seen in routine clinical practice, on a nationwide scale.

All adult patients ( $\geq 18$  years old) with CS were prospectively included in this registry if they met at least one criterion of each of the following three components: (1) hemodynamic criteria, defined as low systolic arterial pressure (SAP)  $< 90$  mmHg and/or the need for maintenance with vasopressors/inotropes and/or a low CI  $< 2.2$  L/min/m<sup>2</sup>; (2) left and/or right-heart overload, defined by clinical, radiology, blood tests, echocardiography, or invasive hemodynamics' signs; and (3) signs of organ malperfusion, which could be clinical and/or biologic. Patients admitted after cardiopulmonary resuscitation were included if they fulfilled previously defined CS criteria. Patients could be included regardless of CS etiology, and whether CS was primary or secondary. Exclusion criteria were refusal or inability to consent. A diagnosis of CS was refuted in favor of alternative diagnoses, such as septic shock, refractory cardiac arrest, and post-cardiotomy CS [5, 20].

All institutions were invited to participate in the study, including university teaching hospitals, general and regional hospitals, as well as public and private hospitals that manage CS patients (ICCU, surgical ICUs, medical ICUs, and general ICUs).

The study was conducted in accordance with the guidelines for good clinical practice and French law. Written consent was obtained for all the patients. The data recorded and their handling and storage were reviewed and approved by the CCTIRS (French Health Research Data Processing Advisory Committee) (n° 15.897) and the CNIL (French Data Protection Agency) (n° DR-2016-109).

## **Data collection**

Data on baseline characteristics, including demographics (age, gender, body mass index, social status), risk factors (hypertension, diabetes, current smoking, hypercholesterolemia, family history of coronary artery disease), and medical history [cardiomyopathy, myocardial infarction (MI), stroke, peripheral artery disease, chronic kidney disease, active cancer, chronic obstructive lung disease], were collected as previously mentioned. Clinical, biologic, and echocardiographic data were collected within the first 24 h after admission. Up to three CS triggers were determined for each patient by the local investigator, that is, ischemic (Type 1 or Type-2 acute myocardial infarction according to European guidelines); ventricular and supraventricular arrhythmia; conduction disorder; infectious disease; non-compliance (poor compliance with medical treatment or hygiene and diet rules, for example, stopping or skipping an angiotensin-converting enzyme inhibitor or beta-blocker treatment, deviation from a low sodium diet, etc.); or iatrogenesis. Investigators could also note other existing factors or etiologies. Such triggering factors were indicated as 'other'. Information regarding the use of cardiac procedures, that is, coronary angiography and/or percutaneous coronary intervention (PCI); right-heart catheterization; the need for medications (inotropes, vasopressors, diuretics, and fibrinolysis) and organ replacement therapies such as MV (invasive or noninvasive); temporary mechanical circulatory support [intraaortic balloon pump (IABP); venoarterial-extracorporeal membrane oxygenation (VA-ECMO) or Impella R (Abiomed, Danvers, MA, USA)]; and renal replacement therapy (RRT) (continuous or intermittent) were collected. In-hospital complications were noted, such as stroke, bleeding and transfusions, hemolysis, thrombocytopenia, nosocomial infections, vascular



complications, and death. Information on mortality was obtained directly by the local investigators (cause and date) through a 30-day and a 1-year follow-up.

## Statistical analysis

Continuous variables were reported as means (SD) or medians and interquartile ranges when appropriate. Discrete variables were described in numbers and percentages. Patients were categorized into three groups according to the maximal ventilatory supports used during hospitalization: no mechanical ventilation group (NV), non-invasive ventilation alone group (NIV), and invasive mechanical ventilation group (MV). Thus, patients who required invasive ventilation after NIV were classified into the MV group. We compared clinical characteristics, management, and occurrence of death and major adverse event (MAE) (death, heart transplantation or ventricular assist device) at 30 days and 1 year between the three groups. Differences between groups were tested using analyses of variance or Mann–Whitney non-parametric tests for continuous variables and using  $\chi^2$  or Fisher's exact tests for categorical variables. Factors independently associated with the use of MV were studied using multiple logistic regression. Survival analyses were conducted using the Kaplan–Meier method. Statistical analyses were performed using Stata (*Stata Statistical Software SE/17.0. StataCorp LLC. College Station. TX. USA.*). For all analyses, two-sided  $p$  values  $< 0.05$  were considered significant.

# Results

## Study population

A total of 768 CS patients were included in 49 centers, among whom 359 (46.7%) did not require ventilation, 118 (15.4%) required NIV, and 291 (37.9%) MV. Clinical characteristics of these patients are presented in Table 1. The mean age, gender, and risk factors were similar in the three groups. There was no difference regarding medical history except less history of previous heart disease in the MV group (47.8 vs 50 in NIV and 64.9% in NV groups,  $p < 0.001$ ). MV patients were less frequently under long-term cardiological treatments than those under NIV or NV (Beta-blockers, ACE inhibitors or ARB2, Furosemide, and anti-aldosterone).

The most frequent CS triggers were ischemia, ventricular, and supraventricular arrhythmia without between groups difference except for ischemia, which was less frequent in NV group (29% vs 45.8 and 45%,  $p < 0.001$ ).

The clinical, echography, and biologic presentations are presented in Table 2. Patients in the MV group were more often hospitalized in the ICU versus ICCU than patients under NIV or NV (58.8% vs 15.5 and 10.9% respectively,  $p < 0.001$ ). MV patients presented with more previous cardiac arrest (21.3 vs 6.8 and 2.2%,  $p < 0.001$ ), more skin mottling (51.4 vs 34.2 and 29.9%,  $p < 0.001$ ), and higher lactate at admission than NIV or NV group (3.8 vs 2.7 vs 2.3 mmol/L,  $p < 0.001$ ). Renal and hepatic functions were similar between groups. There were no between groups difference regarding echocardiography at admission besides tricuspid annular peak systolic velocity tissue doppler imaging which was higher in the MV group than NIV or NV (10 vs 8 vs 7 cm/s,  $p < 0.001$ ).

## **In-hospital management**

In-hospital management and parameters at discharge are presented in Table 3. The MV group received more volume expansion during the first 24 h of management than the NIV or NV groups (56.7 vs 49.2 vs 27.5%,  $p < 0.01$ ). During hospitalization, they benefited from higher doses of inotropes and vasopressors (dobutamine, norepinephrine, and epinephrine). Moreover, organs support was more frequently used in this group with higher use of acute mechanical circulatory support (MCS) (36.8 vs 8.5 vs 6.4%,  $p < 0.01$ ) mainly by VA-ECMO support (71% in the MV group), and higher use of RRT in the VM group (27.2 vs 8.5 vs 8.4%  $p < 0.01$ ). On the contrary, there was a more common use of diuretics (89.4% vs 74.6% in the MV group,  $p < 0.01$ ) and less acute MCS use (6.4%) from different types with a predominance of IABP (65.2%) in the NV group.

Half of CS patients had undergone coronary angiography. A 3-vessel disease was found in about 20% of the cases but only the culprit lesion was revascularized in about 80% without significant differences between groups. There were also no differences regarding right-heart catheterization, pacemaker or defibrillator implantation, or radiofrequency ablation.

## **CS prognosis according to ventilatory support**

At discharge, LVEF was significantly higher in patients in the MV group (41 vs 32.1 vs 31.7%,  $p < 0.01$ ). Patients in the MV group were hospitalized longer (20 vs 16 days,  $p < 0.01$ ) but without difference in the discharge mode (home, rehabilitation, or care center).

At 30 days, MV group presented higher mortality (crude HR (MV vs No Ventilation) 1.41 [1.05–1.90],  $p = 0.022$  and Fig. 1, log-rank  $p = 0.012$ ) and a higher rate of major adverse events (death, heart transplantation or ventricular assistance) as compared with others groups (crude HR (MV vs No Ventilation) 1.52 [1.16–1.99],  $p = 0.003$  and Fig. 2, log-rank  $p = 0.002$ ). At 1 year, the between-groups difference subsists (Supplementary Fig. 1, log-rank  $p = 0.052$ ), especially with a higher mortality for MV patients (crude HR (MV vs No Ventilation) 1.28 [1.02–1.61],  $p = 0.032$ ).

Interestingly after adjustment for known independent predictors of 30-day mortality [5] (age, LVEF < 30%, mechanical circulatory support, RRT, use of norepinephrine and use of diuretics), the between groups difference in 30-day all-cause mortality disappears (Supplementary Table 1).

No difference in all-cause mortality (Crude HR (NIV vs No Ventilation) 0.79 [0.49–1.26],  $p = 0.315$ ) or MAE (Crude HR (NIV vs No Ventilation) 0.83 [0.54–1.27],  $p = 0.399$ ) was found between NIV and NV groups either at 30-day or 1-year (Crude HR (NIV vs No Ventilation) 0.95 [0.69–1.31],  $p = 0.752$  for all-cause mortality).

Among MV group, no difference in terms of 30-day mortality was found between patients intubated directly ( $n = 237$ , 84%) and patients first ventilated by NIV and then intubated ( $n = 44$ , 16%) (respectively 31.7 and 31.8%,  $p = 0.899$ ) (Supplementary Fig. 2). No difference was found neither between patients intubated directly, patients first ventilated by NIV and then

intubated within 24 h ( $n = 28$ , 10%), or patients first ventilated by NIV and then intubated after 24 h ( $n = 16$ , 6%) (respectively 31.7, 28.6 and 37.5%,  $p = 0.899$ ) (Supplemental Fig. 3).

**Table 1** Clinical characteristics at admission according to the maximal level of ventilatory support used during hospitalisation

|  | No ventilation<br>( $n=359$ ) |            | Non-invasive ventilation<br>( $n=118$ ) |            | Mechanical ventilation<br>( $n=291$ ) |            | $p$    |
|--|-------------------------------|------------|---|------------|---------------------------------------|------------|--------|
| Male gender                            | 260                           | 72.4       | 75                                      | 63.6       | 214                                   | 73.5       | 0.111  |
| Age (years), mean $\pm$ SD             | 68.0                          | $\pm 13.5$ | 69.1                                    | $\pm 16.1$ | 61.7                                  | $\pm 15.0$ | 0.963  |
| BMI ( $\text{kg/m}^2$ ), mean $\pm$ SD | 25.3                          | $\pm 5.5$  | 26.2                                    | $\pm 6.1$  | 26.4                                  | $\pm 5.4$  | 0.062  |
| $n$                                    | 340                           |            | 118                                     |            | 283                                   |            |        |
| Risk factors, $n$ (%)                  |                               |            |   |            |                                       |            |        |
| Current smoker                         | 91/351                        | 25.9       | 32/116                                  | 27.6       | 83/269                                | 30.9       | 0.397  |
| Diabetes mellitus                      | 110/358                       | 30.7       | 35/118                                  | 29.7       | 71/291                                | 24.4       | 0.189  |
| Arterial hypertension                  | 170                           | 47.4       | 62                                      | 52.5       | 131                                   | 45.0       | 0.385  |
| Dyslipidaemia                          | 121                           | 33.7       | 52                                      | 44.1       | 103                                   | 35.4       | 0.122  |
| Medical history, $n$ (%)               |                               |            |   |            |                                       |            |        |
| History of cardiac disease             | 233                           | 64.9       | 59                                      | 50.0       | 139                                   | 47.8       | <0.001 |
| Ischaemic                              | 123                           | 34.3       | 35                                      | 29.7       | 71                                    | 24.4       | 0.024  |
| Hypertrophic                           | 8                             | 2.2        | 2                                       | 1.7        | 1                                     | 0.3        | 0.092  |
| Idiopathic                             | 48                            | 13.4       | 8                                       | 6.8        | 22                                    | 7.6        | 0.021  |
| Toxic                                  | 26                            | 7.2        | 3                                       | 2.5        | 5                                     | 1.7        | 0.002  |
| Multisite pacing                       | 34/358                        | 9.5        | 12/118                                  | 10.2       | 17/291                                | 5.8        | 0.169  |
| Defibrillator                          | 76/358                        | 21.2       | 19/118                                  | 16.1       | 31/291                                | 10.7       | 0.041  |
| CABG                                   | 30/358                        | 8.4        | 11/118                                  | 9.3        | 20/291                                | 6.9        | 0.652  |
| PCI                                    | 92/358                        | 25.7       | 26/118                                  | 22.0       | 48/291                                | 16.5       | 0.018  |
| Peripheral artery disease              | 43/358                        | 12.0       | 16/118                                  | 13.6       | 32/291                                | 11.0       | 0.763  |
| Ischemic stroke                        | 29/358                        | 8.1        | 6/118                                   | 5.1        | 25/291                                | 8.6        | 0.472  |
| Chronic renal failure                  | 94/358                        | 26.3       | 28/118                                  | 23.7       | 41/291                                | 14.1       | 0.568  |
| COPD                                   | 25/358                        | 7.0        | 7/118                                   | 5.9        | 18/291                                | 6.2        | 0.884  |
| Active neoplasy                        | 23/358                        | 6.4        | 5/118                                   | 4.2        | 23/291                                | 7.9        | 0.392  |
| Previous medications, $n$ (%)          |                               |            |   |            |                                       |            |        |
| Aspirin                                | 126                           | 35.1       | 50                                      | 42.4       | 111                                   | 38.1       | 0.345  |
| P2Y12 inhibitor                        | 56                            | 15.6       | 22                                      | 18.6       | 48                                    | 16.5       | 0.740  |
| Statins                                | 138                           | 38.4       | 53                                      | 44.9       | 94                                    | 32.3       | 0.044  |
| Betablockers                           | 165                           | 46.0       | 57                                      | 48.3       | 92                                    | 31.6       | <0.001 |
| Vitamin K antagonist                   | 98                            | 27.3       | 26                                      | 22.0       | 40                                    | 13.8       | 0.361  |
| Direct oral anticoagulant              | 29                            | 8.1        | 13                                      | 11.0       | 14                                    | 4.8        | 0.067  |
| ACE inhibitors or ARB                  | 147                           | 41.0       | 57                                      | 48.3       | 86                                    | 29.6       | <0.001 |
| Sacubitril/valsartan                   | 12                            | 3.5        | 2                                       | 1.8        | 4                                     | 1.5        | 0.265  |
| Furosemide                             | 213                           | 59.3       | 66                                      | 55.9       | 96                                    | 33.0       | <0.001 |
| Aldosterone antagonist                 | 73                            | 20.3       | 11                                      | 9.3        | 24                                    | 8.3        | <0.001 |
| Amiodarone                             | 65                            | 18.9       | 20                                      | 17.1       | 46                                    | 15.9       | 0.613  |
| Proton pump inhibitor                  | 144                           | 40.8       | 43                                      | 36.8       | 88                                    | 30.7       | 0.030  |
| Triggers                               |                               |            |   |            |                                       |            |        |
| Ischaemic                              | 104                           | 29.0       | 54                                      | 45.8       | 131                                   | 45.0       | <0.001 |
| Mechanical                             | 12                            | 3.3        | 3                                       | 2.5        | 8                                     | 2.8        | 0.958  |
| Ventricular arrhythmia                 | 35                            | 9.8        | 14                                      | 11.9       | 49                                    | 16.8       | 0.025  |
| Atrial arrhythmia                      | 62                            | 17.3       | 13                                      | 11.0       | 33                                    | 11.3       | 0.057  |
| Conductive disorders                   | 7                             | 2.0        | 2                                       | 1.7        | 9                                     | 3.1        | 0.653  |
| Infectious                             | 32                            | 8.9        | 13                                      | 11.0       | 50                                    | 17.2       | 0.006  |
| Non compliance                         | 22                            | 6.1        | 5                                       | 4.2        | 3                                     | 1.0        | 0.002  |
| Iatrogenic                             | 41                            | 11.4       | 4                                       | 3.4        | 15                                    | 5.2        | 0.002  |
| Other                                  | 46                            | 12.8       | 11                                      | 9.3        | 44                                    | 15.1       | 0.281  |
| None/undefined                         | 73                            | 20.3       | 15                                      | 12.7       | 22                                    | 7.6        | <0.001 |

ACE angiotensin-converting enzyme, ARB angiotensin-receptor blocker, BMI body mass index, CABG coronary artery bypass graft, COPD chronic obstructive pulmonary disease, PCI percutaneous coronary intervention, SD standard deviation

**Table 2** Clinical, echography, and biologic presentation according to the maximal level of ventilatory support used during hospitalization

|  | No ventilation<br>(n=359) |       | Non-invasive ventilation<br>(n=118) |       | Mechanical ventilation<br>(n=291) |       | p      |
|--|---------------------------|-------|-------------------------------------|-------|-----------------------------------|-------|--------|
| Admission unit, n (%)                          |                           |       |                                     |       |                                   |       | <0.001 |
| ICCU   | 236                       | 89.1  | 87                                  | 84.5  | 91                                | 41.2  |        |
| ICU  | 29                        | 10.9  | 16                                  | 15.5  | 130                               | 58.8  |        |
| Clinical presentation at admission             |                           |       |                                     |       |                                   |       |        |
| Heart rate (bpm), mean ± SD                    | 93                        | ±28   | 96                                  | ±32   | 99                                | ±30   | 0.041  |
| n  | 358                       |       | 118                                 |       | 290                               |       |        |
| SBP (mmHg), mean ± SD                          | 100                       | ±23   | 103                                 | ±24   | 102                               | ±28   | 0.439  |
| n  | 358                       |       | 118                                 |       | 291                               |       |        |
| DBP (mmHg), mean ± SD                          | 64                        | ±17   | 65                                  | ±18   | 62                                | ±18   | 0.103  |
| n  | 358                       |       | 118                                 |       | 290                               |       |        |
| Sinus rhythm, n (%)                            | 177/356                   | 49.7  | 60/118                              | 50.9  | 159/291                           | 54.6  | 0.449  |
| Mottling, n (%)                                | 88/294                    | 29.9  | 39/114                              | 34.2  | 128/249                           | 51.4  | <0.001 |
| Cardiac arrest, n (%)                          | 8                         | 2.2   | 8                                   | 6.8   | 62                                | 21.3  | <0.001 |
| Blood tests at admission                       |                           |       |                                     |       |                                   |       |        |
| Sodium (mmol/l), mean ± SD                     | 134                       | ±6    | 136                                 | ±5    | 135                               | ±6    | 0.003  |
| n  | 351                       |       | 118                                 |       | 289                               |       |        |
| eGFR (mL/min/1.73 m <sup>2</sup> ), mean ± SD  | 47.1                      | ±26.3 | 50.4                                | ±23.9 | 52.4                              | ±27.9 | 0.041  |
| n  | 346                       |       | 117                                 |       | 286                               |       |        |
| Bilirubin (mg/L), median (IQR)                 | 21 (11–32)                |       | 18 (11–31)                          |       | 13 (8–22)                         |       | <0.001 |
| n  | 250                       |       | 81                                  |       | 211                               |       |        |
| Hemoglobin (g/dL), mean ± SD                   | 12.6                      | ±2.3  | 12.6                                | ±2.3  | 12.4                              | ±2.5  | 0.741  |
| n  | 347                       |       | 118                                 |       | 287                               |       |        |
| Arterial blood lactates (mmol/l), median (IQR) | 2.3 (1.7–3.7)             |       | 2.7 (2.0–4.0)                       |       | 3.8 (2.0–6.0)                     |       | <0.001 |
| n  | 291                       |       | 109                                 |       | 282                               |       |        |
| ASAT (IU/L), median (IQR)                      | 89 (397–342)              |       | 54 (29–123)                         |       | 103 (44–291)                      |       | 0.022  |
| n  | 271                       |       | 60                                  |       | 214                               |       |        |
| ALAT (IU/L), median (IQR)                      | 61 (26–236)               |       | 38 (21–89)                          |       | 62 (30–171)                       |       | 0.014  |
| n  | 276                       |       | 62                                  |       | 219                               |       |        |
| Nt proBNP (pg/mL), median (IQR)                | 12,711 (5003–30,289)      |       | 7708 (3659–13,352)                  |       | 6541 (3466–13,700)                |       | 0.012  |
| n  | 116                       |       | 22                                  |       | 85                                |       |        |
| BNP (pg/mL), median (IQR)                      | 1437 (646–3274)           |       | 1193 (477–2436)                     |       | 882 (271–2090)                    |       | 0.010  |
| n  | 119                       |       | 66                                  |       | 79                                |       |        |
| CRP (mg/L), median (IQR)                       | 27 (10–55)                |       | 29 (8–60)                           |       | 37 (8–107)                        |       | 0.333  |
| n  | 219                       |       | 54                                  |       | 133                               |       |        |
| Baseline echography                            |                           |       |                                     |       |                                   |       |        |
| LVEF (%), mean ± SD                            | 25.8                      | ±13.6 | 27.8                                | ±12.7 | 26.4                              | ±13.3 | 0.398  |
| n  | 354                       |       | 117                                 |       | 289                               |       |        |
| TAPSE (mm), mean ± SD                          | 12.7                      | ±4.8  | 13.7                                | ±4.3  | 14.5                              | ±5.2  | 0.019  |
| n  | 142                       |       | 21                                  |       | 96                                |       |        |
| PSVtdi (cm/s), median (IQR)                    | 7 (6–9)                   |       | 8 (7–10)                            |       | 10 (7–13)                         |       | <0.001 |
| n  | 101                       |       | 25                                  |       | 80                                |       |        |
| Severe mitral regurgitation, n (%)             | 66/337                    | 19.6  | 14/114                              | 12.3  | 27/279                            | 9.7   | 0.002  |
| Severe aortic stenosis, n (%)                  | 15/354                    | 4.2   | 8/118                               | 6.8   | 13/284                            | 4.6   | 0.523  |
| Severe aortic regurgitation, n (%)             | 5/351                     | 1.4   | 0/116                               | 0.0   | 5/285                             | 1.8   | 0.479  |

ALAT alanine aminotransferase, ASAT aspartate aminotransferase, CRP C-Reactive Protein, DBP Diastolic Blood Pressure, ICU intensive care unit, ICCU intensive cardiac care unit, IQR interquartile range, LVEF left ventricular ejection fraction, PSVtdi peak systolic velocity tissue doppler imaging, SBP systolic blood pressure, SD standard deviation, TAPSE tricuspid annular plane systolic excursion

**Table 3** In-hospital management and outcomes according to the maximal level of ventilatory support used during hospitalization

|   | No ventilation(n=359) |      | Non-invasive ventilation<br>(n=118) |      | Mechanical<br>ventilation(n=291) |      | p       |
|---|-----------------------|------|-------------------------------------|------|----------------------------------|------|---------|
| <b>Medications used, n (%)</b>            |                       |      |                                     |      |                                  |      |         |
| Diuretics                                 | 321                   | 89.4 | 95                                  | 80.5 | 217                              | 74.6 | < 0.001 |
| Volume expander                           | 98                    | 27.4 | 58                                  | 49.2 | 165                              | 56.7 | < 0.001 |
| Dobutamine                                | 307                   | 85.5 | 87                                  | 73.7 | 238                              | 81.8 | 0.014   |
| If yes, maximum dose (g/kg/min):          |                       |      |                                     |      |                                  |      | < 0.001 |
| 5-10                                      | 215                   | 70.0 | 65                                  | 74.7 | 125                              | 52.5 |         |
| 10-15                                     | 54                    | 17.6 | 16                                  | 18.4 | 66                               | 27.7 |         |
| >15                                       | 16                    | 5.2  | 2                                   | 2.3  | 29                               | 12.2 |         |
| Unknown                                   | 22                    | 7.2  | 4                                   | 4.6  | 18                               | 7.6  |         |
| Norepinephrine                            | 137                   | 38.2 | 34                                  | 28.8 | 239                              | 82.1 | < 0.001 |
| If yes, maximum dose (mg/h):              |                       |      |                                     |      |                                  |      | < 0.001 |
| < 1                                       | 39                    | 28.5 | 12                                  | 35.3 | 35                               | 14.6 |         |
| 1-5                                       | 70                    | 51.1 | 13                                  | 38.2 | 132                              | 55.2 |         |
| >5  | 12                    | 8.8  | 5                                   | 14.7 | 58                               | 24.3 |         |
| Unknown                                   | 16                    | 11.7 | 4                                   | 11.8 | 14                               | 5.9  |         |
| Epinephrine                               | 12                    | 3.3  | 6                                   | 5.1  | 77                               | 26.5 | 0.001   |
| If yes, maximum dose (mg/h):              |                       |      |                                     |      |                                  |      | 0.684   |
| < 1                                       | 5                     | 41.7 | 2                                   | 33.3 | 27                               | 35.1 |         |
| 1-5                                       | 4                     | 33.3 | 4                                   | 66.7 | 32                               | 41.6 |         |
| >5  | 1                     | 8.3  | 0                                   | 0.0  | 13                               | 16.9 |         |
| Unknown                                   | 2                     | 16.7 | 0                                   | 0.0  | 5                                | 6.5  |         |
| Norepinephrine + dobutamine combination   | 121                   | 33.7 | 29                                  | 24.6 | 202                              | 69.4 | < 0.001 |
| Levosimendan                              | 32                    | 8.9  | 4                                   | 3.4  | 21                               | 7.2  | 0.137   |
| Dopamine                                  | 1                     | 0.3  | 0                                   | 0.0  | 1                                | 0.3  | 1.000   |
| Isoprenaline                              | 11                    | 3.1  | 2                                   | 1.7  | 19                               | 6.5  | 0.035   |
| Antiarrhythmic                            | 141                   | 39.3 | 36                                  | 30.5 | 121                              | 41.6 | 0.111   |
| Transfusion                               | 25/358                | 7.0  | 14/118                              | 11.9 | 89/291                           | 30.6 | < 0.001 |
| Fibrinolysis                              | 6/358                 | 1.7  | 1/118                               | 0.9  | 6/291                            | 2.1  | 0.807   |
| <b>Organ replacement therapies, n (%)</b> |                       |      |                                     |      |                                  |      |         |
| Mechanical circulatory support            | 23/358                | 6.4  | 10/118                              | 8.5  | 107/291                          | 36.8 | < 0.001 |
| if yes:                                   |                       |      |                                     |      |                                  |      |         |
| IABP                                      | 15/23                 | 65.2 | 4/9                                 | 44.4 | 29/107                           | 27.1 | 0.002   |
| Impella                                   | 4/23                  | 17.4 | 0/9                                 | 0.0  | 22/107                           | 20.6 | 0.419   |
| VA-ECMO                                   | 4/23                  | 17.4 | 4/9                                 | 44.4 | 76/107                           | 71.0 | < 0.001 |
| Renal replacement therapy                 | 30                    | 8.4  | 10                                  | 8.5  | 79                               | 27.2 | < 0.001 |
| <b>Invasive cardiology, n (%)</b>         |                       |      |                                     |      |                                  |      |         |
| CAG                                       | 168                   | 46.8 | 56                                  | 47.5 | 173                              | 59.5 | 0.004   |
| If yes:                                   |                       |      |                                     |      |                                  |      | 0.009   |
| CAG result                                |                       |      |                                     |      |                                  |      |         |
| Normal                                    | 42                    | 25.0 | 10                                  | 17.9 | 22                               | 12.7 |         |
| 1-Mono                                    | 26                    | 15.5 | 12                                  | 21.4 | 41                               | 23.7 |         |
| 2-Bi                                      | 43                    | 25.6 | 15                                  | 26.8 | 33                               | 19.1 |         |
| 3-Tri                                     | 39                    | 23.2 | 11                                  | 19.6 | 37                               | 21.4 |         |
| Unknown                                   | 18                    | 10.7 | 8                                   | 14.3 | 40                               | 23.1 |         |
| Culprit lesion                            | 101/126               | 80.2 | 36/46                               | 78.3 | 119/145                          | 82.1 | 0.829   |
| Any PCI                                   | 84                    | 23.4 | 29                                  | 24.6 | 104                              | 35.7 | 0.001   |
| Any PCI (even in a second time)           | 91                    | 25.4 | 30                                  | 25.4 | 105                              | 36.1 | 0.007   |
| Right heart catheterisation               | 44                    | 12.3 | 18                                  | 15.3 | 59                               | 20.3 | 0.020   |
| Pace-maker implantation                   | 18/340                | 5.3  | 5/116                               | 4.3  | 12/276                           | 4.4  | 0.832   |

**Table 3** (continued)

|   | No ventilation(n=359) |          | Non-invasive ventilation (n=118) |          | Mechanical ventilation(n=291) |          | <i>p</i> |
|---|-----------------------|----------|----------------------------------|----------|-------------------------------|----------|----------|
| Defibrillator implantation                      | 21/340                | 6.2      | 5/116                            | 4.3      | 11/276                        | 4.0      | 0.431    |
| Radiofrequency ablation                         | 10/340                | 2.9      | 3/116                            | 2.6      | 4/276                         | 1.5      | 0.426    |
| Discharge parameters                            |                       |          |                                  |          |                               |          |          |
| LVEF (%), mean +/- SD                           | 31.7                  | +/- 13.9 | 32.1                             | +/- 13.3 | 41                            | +/- 14.0 | < 0.001  |
| <i>n</i>  | 207                   |          | 82                               |          | 150                           |          |          |
| LVEF variation*, mean +/- SD                    | 5.5                   | +/- 11.0 | 4.5                              | +/- 11.1 | 14.7                          | +/- 17.3 | < 0.001  |
| <i>n</i>  | 205                   |          | 81                               |          | 150                           |          |          |
| Length of stay in ICU/CCUU (days), median (IQR) | 10 (7-16)             |          | 11 (6-18)                        |          | 14 (8-26)                     |          | 0.002    |
| <i>n</i>  | 196                   |          | 64                               |          | 180                           |          |          |
| Length of stay in hospital (days), median (IQR) | 16 (11-24)            |          | 16 (10-28)                       |          | 20 (13-37)                    |          | 0.001    |
| <i>n</i>  | 219                   |          | 78                               |          | 139                           |          |          |
| Discharge mode                                  |                       |          |                                  |          |                               |          |          |
| Home  | 89                    | 29.9     | 29                               | 28.7     | 53                            | 21.5     |          |
| Rehabilitation                                  | 22                    | 7.4      | 12                               | 11.9     | 10                            | 4.0      |          |
| Transferred (other center/other department)     | 103                   | 34.6     | 34                               | 33.7     | 77                            | 31.2     |          |
| Death   | 83                    | 27.9     | 24                               | 23.8     | 107                           | 43.3     |          |
| Other   | 1                     | 0.3      | 2                                | 2.0      | 0                             | 0.0      |          |
| Registration on transplant waiting list         | 13/275                | 4.7      | 7/112                            | 6.3      | 20/235                        | 8.5      | 0.221    |
| Prognosis                                       |                       |          |                                  |          |                               |          |          |
| 30-day mortality                                | 85                    | 23.7     | 22                               | 18.6     | 92                            | 31.6     | 0.011    |
| 30-day MACE                                     | 99                    | 27.6     | 27                               | 22.9     | 113                           | 38.8     | 0.001    |
| 1-year mortality**                              | 152                   | 42.3     | 49                               | 41.5     | 145                           | 49.8     | 0.114    |

CAG coronary artery angiography, VA-ECMO venoarterial-extracorporeal membrane oxygenation, IABP intra-aortic balloon pump, ICU intensive care unit, ICCU intensive cardiac care unit, LVEF left ventricular ejection fraction, MACE major cardiovascular adverse event defined by death or heart transplantation, or LVAD/BI-VAD support, PCI percutaneous coronary intervention

\*At discharge compared with admission

\*\*Sachant qu'il y a 3% de perdus de vue à 1 an

**Table 4** Factors associated with the use of invasive mechanical ventilation

|                              | Odds ratio | 95% CI     | <i>p</i>  |
|------------------------------|------------|------------|-----------|
| Age (years)*                 | 0.97       | 0.95-0.98  | < 0.001   |
| Trigger: infection           | 2.55       | 1.49-4.35  | 0.001     |
| Trigger: non compliance      | 0.17       | 0.05-0.60  | 0.006     |
| Ongoing furosemide treatment | 0.47       | 0.32-0.68  | < 0.001   |
| Cardiac arrest               | 5.48       | 2.89-10.39 | < 0.001   |
| Mottling                     | 2.25       | 1.54-3.29  | < 0.001   |
| Lactates                     |            |            |           |
|                              | Tertile 1  | 1.00       | Ref       |
|                              | Tertile 2  | 1.33       | 0.85-2.08 |
|                              | Tertile 3  | 2.13       | 1.30-3.48 |
|                              | Unknown    | 0.30       | 0.12-0.70 |

*n* = 657. Hosmer - Lemeshow goodness of fit *p* = 0.327

CI confidence interval

\*For 1 year more

### Death within 30 days

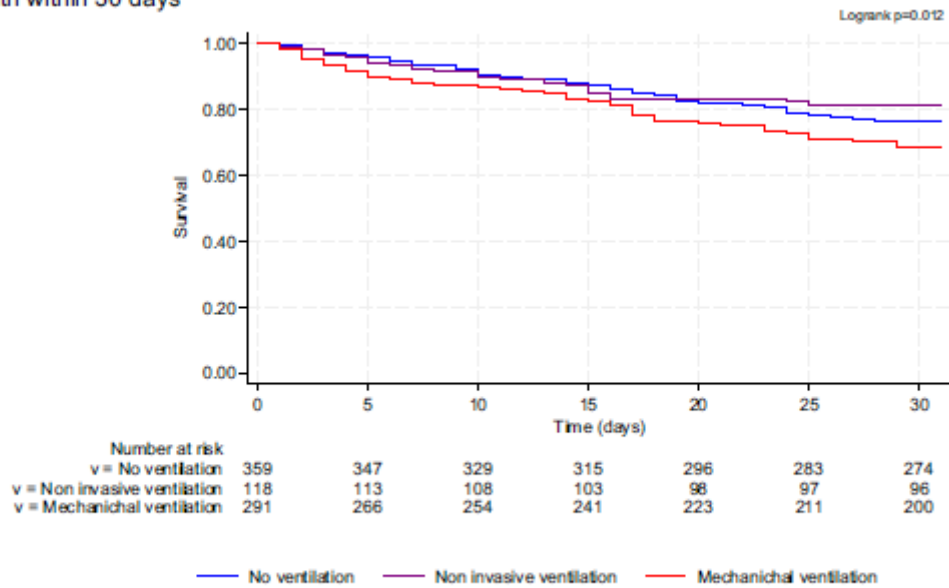


Fig. 1 30 day survival according to the maximal level of ventilatory support used during hospitalization

### Death, heart transplant, or assistance within 30 days

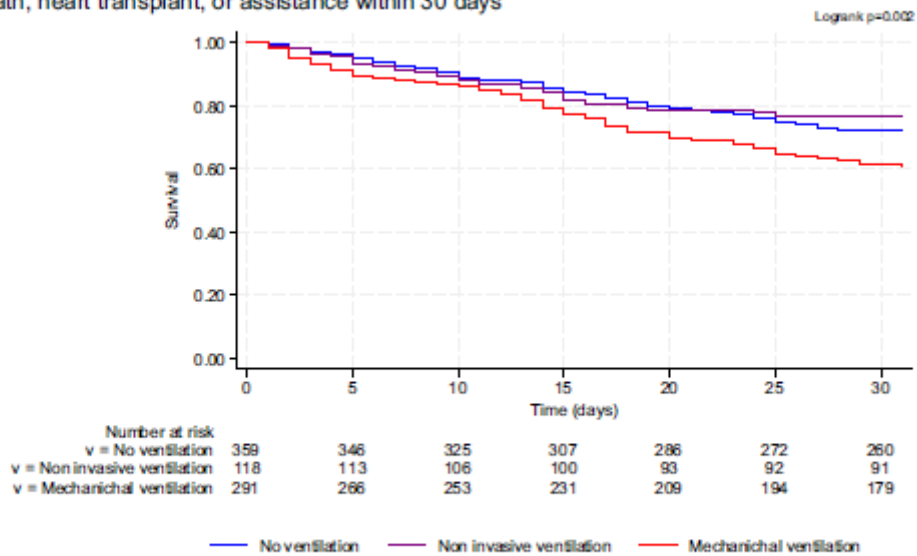


Fig. 2 30 day survival free from heart transplantation or LVAD/BiVAD support according to the maximal level of ventilatory support used during hospitalization. BiVAD, biventricular assist device or total artificial heart; LVAD, left ventricular assist device

## Factors associated with the use of invasive mechanical ventilation

Factors associated with increased use for MV (Table 4) are previous cardiac arrest (OR 5.48,  $p < 0.001$ ), infectious CS trigger (OR 2.55,  $p 0.001$ ), presence of mottling (OR 2.25,  $p < 0.01$ ), and higher lactate at admission (OR 2.13 for the third tertile of lactate,  $p 0.003$ ). On the other hand, older patients (OR 0.97 for 1 year more,  $p < 0.001$ ), non-observant patients (OR 0.17;  $p = 0.001$ ), and those on long-term furosemide were less managed by MV (OR 0.47;  $p = 0.006$ ).

## Discussion

To our knowledge, this study is one of the first studies to provide information about contemporary use of different ventilation modalities and their associated outcomes in a large, unselected cohort of CS patients. First, we reported the use of ventilatory support in 1 on 2 CS patients with NIV alone in 15.4% of the cases and MV in 37.9%. Second, compared to NV and NIV, MV was associated with the worst prognosis at 30 days in terms of all-cause mortality and MAE (mortality, heart transplantation, or LVAD/BiVAD) probably due to a more severe CS presentation. Third and more importantly, NIV was not associated with increased mortality or MAE even after adjustment for severity of disease as compared with patients not ventilated. Fourth, MV was used for more severe and younger patients with mixed shock.

When APE is accompanied with reduced LV systolic function, the application of positive end-expiratory pressure (PEEP) offers several theoretical benefits [21]. PEEP can effectively alleviate congestion by decreasing venous return, increasing transmural pressure, and reducing LV afterload. These mechanisms collectively contribute to the enhancement of oxygenation levels, mitigation of hypercapnia, and alleviation of acidosis. In addition, MV can lessen the burden of breathing workload, leading to a reduction in myocardial oxygen consumption when combined with PEEP.

Data about ventilatory support strategies in CS are scarce. *Hongisto et al.* reported the use of MV in 63% and NIV in 12% of their 219 CS patients from diverse etiologies [14]. The inclusion of patients in different centers (from primary to tertiary) and unit (ICU and ICCU), and the use of a specific definition (FRENSHOCK definition) of CS allowing inclusion of patients from ischemic and non-ischemic etiologies but also patients with less profound shock [5, 20], probably explain lower use of ventilatory support especially MV in our cohort (15.4 and 37.9% of patients with NIV and MV, respectively). Furthermore, patients were categorized according to the maximal level of ventilatory support used during hospitalization in our registry whereas they defined their groups according to the maximum intensity of ventilatory support during the first 24 h of management. As indication, type, and timing of ventilatory support not only depend on shock severity but also on clinicians' expertise and habits, we assume that the use of the maximum level of support during hospitalization probably better reflects CS severity and evolution.

As previously observed, MV was associated with severe prognosis with higher 30-day mortality and MAE in our cohort as compared with other groups reflecting in part more severe shock [14]. Interestingly, we did not find any difference in terms of mortality or MAE at 30 days between NIV and NV groups. This is a major point of this study since to date, place of NIV in CS management is obvious: at best not recommended and at worst contraindicated by consensus or guidelines [1, 2, 9–11]. The decision to intubate and start invasive MV is often multi-factorial considering respiratory (clinical signs of respiratory failure, oxygenation index), neuropsychological (agitation, consciousness disorders) and hemodynamic parameters (vasopressor dose, lactate level and progress in multiorgan failure or implantation of an acute mechanical support) [21]. To date, however, there is no consensus or guidelines specifying the category of patients most likely to benefit from intubation in circulatory shock states, nor is there guidance on the optimal timing for it, due to the lack of available evidence. Caution is only advised in case of hypotension or right ventricular dysfunction due to possible undesirable effect of PEEP on right ventricular afterload and



function. Moreover, due to ventricular interdependence, NIV influences on the RV can ultimately affect left ventricular (LV) performance. A dilated, pressure-overloaded RV can displace the interventricular septum toward the LV, decreasing LV preload and stroke volume. Guidelines do not recommend using NIV in patients presenting with acute coronary syndrome or APE and suffering from shock or low blood pressure, or requiring urgent coronary revascularization. In many studies regarding the use of NIV in APE or acute kidney injury, the presence of low blood pressure, need for vasoactive medications or shock have been considered as exclusion criteria or as criteria for intubation [15–17].

NIV presents several advantages as compared with MV. NIV allows patients to communicate, eat, move at least to some extent, and breathe spontaneously. By avoiding endotracheal intubation and invasive MV, the risks of nosocomial infections, ventilator-associated pneumonia, and injuries related to the intubation procedure itself are diminished [22]. Moreover, the use of profound sedation with loss of vasomotor tone can be avoided, this might be especially beneficial in patients presenting with symptoms of shock, in whom the sedatives may further increase hypotension [22, 23].

Our study suggests that using NIV is safe in selected patients with less profound shock CS and no other MV indication (mixed shock, post-cardiac arrest management). But special attention should be paid to CS patients under NIV support due to the risk of worsening hypotension and state of consciousness. Patients should be managed and monitored closely and promptly intubated without improvement or in case of degradation (respiratory and/or hemodynamic) under NIV support.

Future dedicated studies should prospectively investigate this major topic, but none are currently reported on [clinicaltrials.gov](http://clinicaltrials.gov).

## **Limitations**

There are some limitations to be acknowledged. First, data from patients who died before informed consent was obtained were not collected and recorded in the database because of administrative regulations. Thus, it cannot be excluded that the most severe patients i.e., with several comorbidities, frailty, or multiple end-stage organ failure could not have been admitted in ICU/ICCU for futility or have been deceased before inclusion. This could be a source of bias resulting in an underestimation of mortality. Second, the choice of ventilation strategy was not protocolized and was left at the discretion of the physician in charge. In addition, the specific reasons for intubation and MV (for example, potential confusion / neurologic dysfunction from CS, hemodynamic instability, aMCS location) are unfortunately not available in our data set because our register does not have been designed for this. However, as our study was carried out in line with the state of the art, is multicentric and included ICCU and ICU patients, we believe it reflects the usual indications for the use of NIV and MV, mainly based on “common sense”, hemodynamic, respiratory and neurologic parameters [21]. Timing and escalation of ventilation strategies were based on standard clinical practice and progressive management (where possible), which involved starting with NIV, followed by therapeutic escalation with IMV as recently recommended by expert advice [25]. However, the study reflects real-life practice in university and non-university, public and private hospitals in France through a large nationwide collection of CS patients. Third, a global severity score such as the SOFA score, the SAPS II, or the Charlson comorbidity index would have been useful for comparing the initial severity of different groups of patients. But

these scores were not recorded, and we were not able to use the SCAI SHOCK Stage Classification given that it was not yet available at the time of our study.

## **Conclusion**

Due to the lack of available data, levels of evidence to guide ventilatory support strategies in CS patients are low to date. In this large prospective nationwide registry of unselected CS, we report that NIV can be safely used for respiratory failure management in properly selected CS patients in clinical practice. Nevertheless, given the increasing use of ventilation in cardiogenic shock, futures dedicated studies appear necessary to address this issue and confirm our findings.

## **Acknowledgements**

FRENSHOCK is a registry of the French Society of Cardiology, managed by its Emergency and Acute Cardiovascular Care Working Group. Our thanks go out to all the devoted personnel of Societe Francaise de Cardiologie who participate in the upkeep of the registry. The authors are deeply indebted to all the physicians who took care of the patients at the participating institutions.

## **Funding**

Open access funding provided by Universite Toulouse III - Paul Sabatier. The study was sponsored by the Federation Francaise de Cardiologie and was funded by unrestricted grants from Daiichi- Sankyo and Maquet SAS.

## **Data availability**

Data are available from the corresponding author upon reasonable request.

## **Declarations**

## **Conflict of interest**

The authors declare that they have no conflict of interest.

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