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ORIGINAL ARTICLE

Baseline characteristics, management, and predictors of early mortality in cardiogenic shock: insights from the FRENSHOCK registry

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Abstract

Aims Published data on cardiogenic shock (CS) are scarce and are mostly focused on small registries of selected populations. The aim of this study was to examine the current CS picture and define the independent correlates of 30 day mortality in a large non-selected cohort.

Methods and results FRENSHOCK is a prospective multicentre observational survey conducted in metropolitan French intensive care units and intensive cardiac care units between April and October 2016. There were 772 patients enrolled (mean age 65.7 ± 14.9 years; 71.5% male). Of these patients, 280 (36.3%) had ischaemic CS. Organ replacement therapies (respiratory support, circulatory support or renal replacement therapy) were used in 58.3% of patients. Mortality at 30 days was 26.0% in the overall population (16.7% to 48.0% depending on the main cause and first place of admission). Multivariate analysis showed that six independent factors were associated with a higher 30 day mortality: age [per year, odds ratio (OR) 1.06, 95% confidence interval (CI): 1.04–1.08], diuretics (OR 1.74, 95% CI: 1.05–2.88), circulatory support (OR 1.92, 95% CI: 1.12–3.29), left ventricular ejection fraction <30% (OR 2.15, 95% CI: 1.40–3.29), norepinephrine (OR 2.55, 95% CI: 1.69–3.84), and renal replacement therapy (OR 2.72, 95% CI: 1.65–4-49).

Conclusions Non-ischaemic CS accounted for more than 60% of all cases of CS. CS is still associated with significant but variable short-term mortality according to the cause and first place of admission, despite frequent use of haemodynamic support, and organ replacement therapies.

Keywords Cardiogenic shock; Epidemiology; Mortality; Organ support

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Introduction

Cardiogenic shock (CS) is a syndrome caused by a primary cardiovascular disorder in which inadequate cardiac output results in life-threatening tissue hypoperfusion associated with tissue oxygen metabolism impairment and hyperlactataemia which, depending on the severity, can result in multi-organ dysfunction and death.[1] While in clinical practice there is a spectrum of presentations, clinical trials have used specific haemodynamic parameters to define CS. The common definition of CS in the SHOCK trial[2] requires the presence of three major haemodynamic parameters: (i) persistent hypotension defined as systolic blood pressure (SBP) $<$90 mmHg (or mean arterial pressure 30 mmHg below the baseline), (ii) decreased cardiac index ($<$1.8 L/min/m^2 without support or $<$2.2 L/min/m^2 with support) with, (c) adequate or elevated filling pressure (left ventricular end-diastolic pressure $>$18 mmHg or right ventricular end-diastolic pressure $>$10 to 15 mmHg). These haemodynamic parameters, while necessary when enrolling patients in clinical trials, may not be universally applicable in clinical practice.

Inclusion criteria used to define CS in a study are not the only parameters of a study population to be considered. The study setting for prehospital, intensive cardiac care unit (ICCU) or general intensive care unit (ICU) provides patients with different characteristics and severity; hence the interest of studies on CS that recruit patients from different settings.

Ischaemic CS that complicates approximately 3–9% of the cases of acute myocardial infarction (AMI) was reported to be the most common cause of CS[3–7] and confers a severe prognosis associated with a high hospital mortality rate of 24.6–51.0%.[7–9] Data regarding non-ischaemic CS are limited[9] probably in part because all the definitions of CS used are based only on AMI CS and the major studies have focused on ischaemic CS to evaluate management (myocardial revascularization, circulatory support and medications).[2,3] However, patients with non-ischaemic CS could represent more than 50% of all the cases of CS and may be associated with a better prognosis.[10–14]

The aim of this analysis is to report the baseline characteristics, management and independent correlates of 30 day mortality in patients with CS in routine clinical practice included in the FRENSHOCK multicentre registry, regardless of the aetiology and the initial place of admission.

Methods

Patient population

FRENSHOCK is a prospective multicentre observational study conducted in metropolitan France during a 6 month period between April and October 2016 in ICU and ICCU (NCT02703038). The methods used for this registry have been previously described.[15] Briefly, the primary objective was to evaluate the characteristics, management, and outcomes of CS patients, with a new modified definition of CS (Supporting information, *Table S1*) as seen in routine clinical practice, on a nation-wide 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: (i) haemodynamic criteria, defined as a low SBP $<$90 mmHg and/or the need for maintenance with vasopressors/inotropes and/or a low cardiac index $<$2.2 L/min/m^2; (ii) left and/or right heart pressure elevation, defined by clinical signs, radiology, blood tests, echocardiography, or signs of invasive haemodynamic overload; and (iii) signs of organ malperfusion, which could be clinical and/or biological. Patients admitted after cardiopulmonary resuscitation were included if they fulfilled previously defined CS criteria. Patients could be included regardless of CS aetiology, and whether CS was primary or secondary. Exclusion criteria were refusal or the inability to consent and a diagnosis of CS refuted in favour of alternative diagnoses, such as septic shock, refractory cardiac arrest and post-cardiotomy CS.[15]

All institutions were invited to participate in the study, including university teaching hospitals, general and regional hospitals, public and private hospitals that manage CS patients (ICCUs, 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 infraction (MI), stroke, peripheral artery disease (PAD), chronic kidney disease (CKD), active cancer, chronic obstructive lung disease], were collected as previously mentioned.[15] Clinical, biological, and echocardiographic data within the first 24 h after admission were collected. Up to three CS triggers were determined for each patient by the local investigator, that is, ischaemic (Type 1 or Type 2 AMI 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 aetiologies. 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 mechanical ventilation (invasive or non-invasive); temporary mechanical circulatory support [intra-aortic balloon pump (IABP); extracorporeal membrane oxygenation or Impella® (Abiomed, Danvers, MA, USA)]; and renal replacement therapy (continuous or intermittent) were collected.

In-hospital complications, such as stroke, bleeding and transfusions, haemolysis, thrombocytopenia, nosocomial infections, vascular complications, and death, were noted. Information on mortality was obtained directly by the local investigators (cause and date).

Statistical analysis

Continuous variables are reported as means (SD) or medians and interquartile ranges when appropriate. Discrete variables are described in numbers and percentages. Groups (30 day survivors and non-survivors) were compared by analysis of variance for continuous variables and χ^2 or Fisher's exact test for discrete variables. Odds ratios (ORs) are presented with their 95% confidence intervals (CIs).

To determine independent predictors of in-hospital all-cause mortality, binary logistic regression analyses were used, with a threshold <0.10 for variable elimination. Variables included in the final models were selected ad hoc based on their physiological relevance and potential to be associated with outcomes. Two multivariable analyses were conducted. The first included only variables available on admission: age, gender, type of institution, risk factors, comorbidities, and causes of CS. A sensitivity analysis was performed, and lactate peak was added to the covariates in the main analysis. The second model added in-hospital management variables (first place of admission; respiratory, circulatory, or renal support; use of inotropes, vasopressors, diuretics, and fibrinolysis in the first 24 h; and myocardial revascularization). This analysis was repeated on the subset of patients with ischaemic CS.

Analyses were repeated using forward stepwise analysis to assess the consistency of results. Collinearity was assessed by calculating variance inflation factors. Statistical analyses were performed using IBM SPSS 23.0 (IBM SPSS Inc.). For all analyses, two-sided P values <0.05 were considered significant.

Results

Study population

A total of 772 CS patients were included in 49 centres. Clinical characteristics are presented in *Table 1*. CS criteria used to define CS are reported in *Table S2*. The main criteria were hypotension and/or echocardiographic parameters for the haemodynamic criteria, clinical parameters for the overload criteria, and biological parameters for the organ malperfusion criteria. Less than 8% of the patients were diagnosed based on invasive parameters of CS. Mean age of the population was 65.7 (±14.9) years with a predominance of men (71.5%). The rate of hypertension, dyslipidaemia, diabetes mellitus, and current smoking were high, respectively, 47.2%, 35.9%, 28.1%, and 26.7%. A history of cardiac disease was reported in 56.1% (29.8% coronary artery disease), previous PCI in 21.5%, previous stroke in 8.0%, PAD in 11.8%, and CKD in 21.2%.

At admission, mean SBP was 101 (±25) mmHg and mean heart rate was 96 (±30) bpm (*Table 2*). Clinical signs of left and right heart failure were frequent with 72.5% and 50% respectively. Mottling was reported in 37.5% of the cases.

The main triggers of CS (not mutually exclusive) were ischaemic (36.3%), supra ventricular arrhythmias (13.3%), ventricular arrhythmias (12.6%), and infectious disease (11.9%) (*Figure 1*). Cardiac arrest occurred in 10.3% of patients.

Most patients had multiple organ failure as evidenced by kidney dysfunction, hepatic cytolysis and cholestasis, and lactate elevation.

Seven hundred and sixty patients (98.5%) had an echocardiography at admission. Left ventricular ejection fraction (LVEF) $<40\%$ was reported in 80.7% of the patients and $<30\%$ in 61.4%.

Vitals parameters at 24 h after admission are detailed in *Table S3*.

In-hospital management

In-hospital management is reported in *Table 3*. Most patients were directly admitted in ICCU (56.1%); 23.1% were admitted

Table 1 Clinical characteristics at admission according to vital status at 30 days

	Overall population (n = 772)	30 day survivors (n = 571)	30 day non-survivors (n = 201)	P value
Age, mean ± SD, years	65.7 ± 14.9	64.0 ± 14.8	70.4 ± 14.3	<0.001
Male, *n* (%)	552 (71.5)	407 (71.3)	145 (72.1)	0.82
Body mass index, mean ± SD, kg/m^2	25.8 ± 5.6	25.9 ± 5.5	25.6 ± 5.9	0.47
Employment status, *n* (%)				
Employed	128 (16.6)	108 (18.9)	20 (10)	<0.001
Unemployed	25 (3.1)	21 (3.7)	4 (2.0)	
Househusband/wife	14 (1.8)	12 (2.1)	2 (1.0)	
Disability	56 (7.3)	35 (6.1)	21 (10.4)	
Retired	448 (58.0)	308 (53.9)	140 (69.7)	
Risk factors, *n* (%)				
Current smoker	206 (26.7)	159 (27.8)	47 (23.4)	0.22
Diabetes mellitus	217 (28.1)	166 (29.1)	51 (25.4)	0.41
Hypertension	364 (47.2)	263 (46.1)	101 (50.2)	0.51
Dyslipidaemia	277 (35.9)	205 (35.9)	72 (35.8)	0.84
Medical history, *n* (%)				
History of cardiac disease	433 (56.1)	312 (54.6)	121 (60.2)	0.34
Ischaemic	230 (29.8)	169 (29.6)	61 (30.3)	0.84
Hypertrophic	11 (1.4)	9 (1.6)	2 (1.0)	0.55
Toxic	34 (4.4)	28 (4.9)	6 (3.0)	0.17
Idiopathic	78 (10.1)	56 (9.8)	22 (10.9)	0.65
Multisite pacing	63 (8.2)	45 (7.9)	18 (9.0)	0.75
Defibrillator	127 (16.5)	96 (16.8)	31 (15.4)	0.75
Coronary artery bypass grafting	62 (8.0)	43 (7.5)	19 (9.5)	0.58
Percutaneous coronary intervention	166 (21.5)	123 (21.5)	43 (21.4)	0.84
Peripheral artery disease	91 (11.8)	72 (12.6)	19 (9.5)	0.41
Stroke	62 (8.0)	42 (7.4)	20 (10.0)	0.43
Chronic renal failure	164 (21.2)	104 (18.2)	60 (29.9)	0.002
Dialysis	11 (1.4)	8 (1.4)	3 (1.5)	0.84
Chronic obstructive pulmonary disease	50 (6.5)	33 (5.8)	17 (8.5)	0.35
Active cancer	51 (6.6)	36 (6.3)	15 (7.5)	0.72
Previous medications, *n* (%)				
Aspirin	288 (37.3)	210 (36.8)	78 (38.8)	0.63
P2Y12 inhibitors	126 (16.3)	96 (16.8)	30 (14.9)	0.57
Statins	286 (37.0)	210 (36.8)	76 (37.8)	0.69
Beta blockers	316 (41.0)	232 (40.6)	84 (41.8)	0.68
Vitamin K antagonist	165 (21.4)	108 (18.9)	57 (28.4)	0.01
Direct oral anticoagulant	56 (7.3)	48 (8.4)	8 (4.0)	0.08
ACE inhibitors or ARB	292 (37.8)	213 (37.3)	79 (39.3)	0.63
Sacubitril/valsartan	18 (2.3)	15 (2.6)	3 (1.5)	0.40
Loop diuretics	376 (48.7)	266 (46.6)	110 (54.7)	0.11
Aldosterone antagonist	108 (14.0)	82 (14.4)	26 (12.9)	0.60
Amiodarone	132 (17.6)	98 (17.5)	34 (17.7)	0.95
Proton pump inhibitor	276 (36.4)	206 (36.6)	70 (35.7)	0.83

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; SD, standard deviation.

in ICU, and 13.3% were transferred from another centre (emergency or another department).

Intravenous diuretics were used in 82% of the cases. Dobutamine was the most used inotrope (81.9%) at low to intermediate doses (5–10 μg/kg/min). Norepinephrine was used in 53.1% of the patients, a dobutamine—norepinephrine combination in 45.6%, and epinephrine in 12.4%. Use of levosimendan (7.4%), dopamine (0.3%), milrinone (1.8%), and enoximone (0.4%) was minimal. Use of invasive and non-invasive ventilation was 37.9% and 25.9%, respectively. Circulatory support was provided in 18.6% of the cases. Extracorporeal life support was the most frequent type of assistance (85/143, 59.4%). Finally, renal replacement therapy was provided in 15.8% of the cases. Overall, 41.7% had no organ support (no respiratory, or circulatory support, and no renal replacement therapy).

Coronary angiography was performed in 399 patients (51.7%), 63.7% of whom had significant coronary disease (one-vessel, two-vessel, and three-vessel disease in 20.1%, 22.8%, and 21.8%, respectively). A PCI was performed for 54.4% of those who had a coronary angiogram.

Thirty-day outcome and correlates

In-hospital complications are listed in *Table S4*. Pneumonia was the most frequent infection reported (19.7%) and the rate of severe bleeding was 12.4% (mainly digestive bleeding) (*Figure 2*).

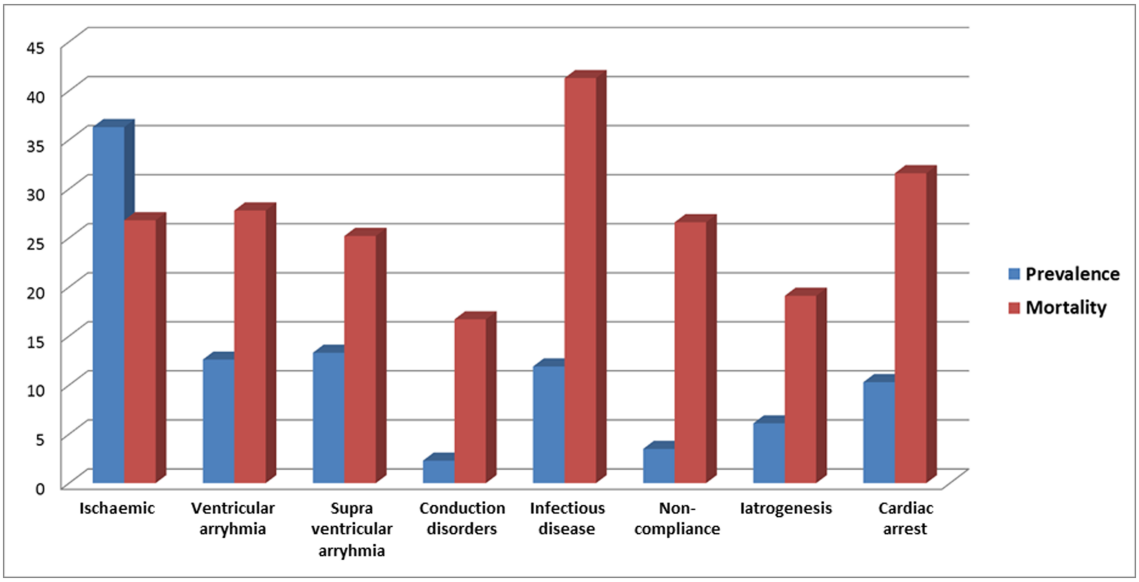
At Day 30, two patients were lost to follow-up (0.26%). Mortality rate at 30 days was 26.0% in the overall population and differed according to initial place of admission [22.2% for

Table 2 Clinical, echocardiographic and biological presentation according to vital status at 30 days

	Overall population (n = 772)	30 day survivors (n = 571)	30 day non-survivors (n = 201)	P value
Clinical presentation at admission				
Heart rate, mean ± SD, bpm	96 ± 30	95 ± 30	98 ± 27	0.19
SBP, mean ± SD, mmHg	101 ± 25	103 ± 25	96 ± 26	<0.001
DBP, mean ± SD, mmHg	63 ± 17	64 ± 17	59 ± 17	<0.001
Sinus rhythm, n (%)	399 (52.0)	308 (54.3)	91 (45.3)	0.03
Cardiac arrest, n (%)	79 (10.3)	54 (9.5)	25 (12.4)	0.12
Mottling, n (%)	248 (37.5) N = 660	169 (37.1)	79 (45.7)	0.045
Blood tests at admission, median (IQR)				
Sodium, mmol/L	135 (132–139) N = 760	136 (132–139) N = 559	135 (131–139) N = 201	0.15
eGFR, mL/min/1.73 m^2	46 (28–67) N = 751	49 (32–70) N = 553	38 (23–54) N = 198	<0.001
Bilirubin, mg/L	16 (9–29) N = 544	16 (9.5–28) N = 395	17 (9–31) N = 149	0.17
Haemoglobin, g/dL	12.6 (11.0–14.0) N = 754	13.0 (11.0–14.0) N = 555	12.0 (11.0–14.0) N = 199	0.02
Arterial blood lactates, mmol/L	3.0 (2.0–4.75) N = 684	2.9 (2.0–4.2) N = 499	3 (2.0–5.0) N = 185	<0.001
ASAT, IU/L	90.0 (39.0–301.0) N = 547	80.50 (37.0–286.3) N = 396	121.00 (46.0–468.0) N = 151	0.92
ALAT, IU/L	59.0 (27.0–183.0) N = 459	58.0 (26.0–182.0) N = 407	62.0 (31.0–199.8) N = 152	0.81
Nt proBNP, pg/mL	9277 [4045; 23810] n = 224	7503 [3504; 16 845] n = 156	13 701 [5 386; 35 000] n = 68	<0.001
BNP, pg/mL	1150 [476; 2778] n = 264	1082 [441; 2561] n = 205	1670 [762; 3484] n = 59	0.04
CRP, mg/L	28 (9–69) N = 406	26 (9–62) N = 300	40 (9–96.5) N = 106	0.001
Baseline echocardiography				
LVEF, mean ± SD, %	26 ± 13	27 ± 13.5	24.5 ± 13	0.004
N = 763	N = 564	N = 199		
TAPSE, mm; median (IQR)	13 [10–16]	13 [10–17]	12 [9–16]	0.6
N = 772	N = 195	N = 60		
PSVtdi, cm/s; median (IQR)	8 [6–11]	8 [6–11]	9 [7–11]	0.23
N = 206	N = 155	N = 51		
Severe mitral regurgitation, n (%)	107 (14.6)	79 (14.5)	28 (14.5)	0.96
Severe aortic stenosis, n (%)	36 (4.7)	22 (3.9)	14 (7.1)	0.03
Severe aortic regurgitation, n (%)	10 (1.3)	6 (1.1)	4 (2.1)	0.28
Unknown	117 (15.2)	36 (17.9)	81 (14.2)	0.24

ACE, angiotensin-converting enzyme; ALAT, alanine aminotransferase; ARB, angiotensin-receptor blocker; ASAT, aspartate aminotransferase; CRP, C-reactive protein; DBP, diastolic blood pressure; PSVtdi, peak systolic velocity tissue Doppler imaging; SBP, systolic blood pressure; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion.

Figure 1 Cardiogenic shock trigger (in blue) and associated 30 day mortality (in red). For all patients who meet the FRENSHOCK criteria (n = 772), the cardiogenic shock trigger and the associated 30 day mortality are summarized. Up to three CS triggers (not mutually exclusive) were identified by the local investigator for each patient (i.e. ischaemic, ventricular, and supraventricular arrhythmia, conduction disorder, infectious disease, non-compliance or iatrogenesis).



ICCU, 31.5% for ICU, and 36.4% for patients transferred from another centre (emergency or another department); P = 0.04]. Mortality at 30 days was numerically higher but non-significant with a higher number of CS triggers (21.4%: absent, 27.3%: one, 27.5%: two, and 37.5%: three or more).

Baseline characteristics and 30 day mortality

Clinical characteristics according to vital status at 30 days are presented in *Table 1*. Overall, non-survivors at 30 days were older (70.4 ± 14.3 years vs. 64.0 ± 14.8 years) with similar gender ratios. No significant difference was observed in risk factors and comorbidities except for CKD (30 day survivors: 18.2%; 30 day non-survivors: 29.9%).

Cardiogenic shock mortality also depended on the trigger (*Figure 1*). In the overall population, ischaemia was the most frequent CS trigger while infectious disease was more frequent in non-survivors (18.9% vs. 9.5%). The proportion of cardiac arrests was numerically higher in non-survivors. In resuscitated cardiac arrest patients, mortality was 31.6% (and 48.8% in non-ischaemic cardiac arrest).

At admission, non-survivors had a lower SBP and diastolic blood pressure, a higher heart rate and less sinus rhythm (*Table 2*). They had a lower LVEF (24.5% ± 13 vs. 27% ± 13.5) and more severe aortic stenosis (7.1% vs. 3.9%). They had higher arterial blood lactate and inflammatory markers (C-reactive protein), more severe kidney failure and lower haemoglobin.

Outcomes in relation to early management

In-hospital management according to vital status at 30 days is presented in *Table 3*. The rate of intravenous diuretics was numerically higher in survivors group (83.9 vs. 76.6%). Dobutamine was prescribed for 85.6% of the non-survivors compared with 80.6% of the survivors, for whom numerically, higher doses (>15 μg/kg/min) were fewer. Epinephrine and norepinephrine were used more often in non-survivors. Invasive respiratory support was more frequent in non-survivors (46.2% vs. 35%) as were renal replacement therapy and circulatory support.

Coronary angiography was performed in 55.7% of survivors and 40.3% of non-survivors ($P < 0.001$). However, the number of diseased vessels and the rate of PCI were similar in both groups.

Most in-hospital complications were similar in survivors and non-survivors, except for stroke (non-survivors: 9%; vs. survivors: 3.2%) (*Table S4*). Pneumonia was the most common infectious complication in both groups (19.7%).

Independent correlates of 30 day mortality

Factors related to 30 day mortality are reported in *Tables 4* and *5*. At admission, age (per year: OR 1.03, 95% CI: 1.02–1.05), infectious trigger (OR 2.10, 95% CI: 1.26–3.50), and LVEF <30% (OR 1.79, 95% CI: 1.21–2.64) were independently associated with higher mortality at 30 days. High lac-

Table 3 In-hospital management according to vital status at 30 days

	Overall population (n = 772)	30 day survivors (n = 571)	30 day non-survivors (n = 201)	P value
Medications used, *n* (%)				
Diuretics	633 (82.0)	479 (83.9)	154 (76.6)	0.05
Volume expander	321 (41.6)	242 (42.4)	79 (39.3)	0.18
Dobutamine	632 (81.9)	460 (80.6)	172 (85.6)	0.11
Maximum dose:				
5–10 μg/kg/min	405/632 (52.5)	322/460 (56.4)	83/172 (41.3)	
10–15 μg/kg/min	136/632 (17.6)	76/460 (13.3)	60/172 (29.9)	
>15 μg/kg/min	47/632 (6.1)	29/460 (5.1)	18/172 (9.0)	
Unknown	184/632 (23.8)	144/460 (25.2)	40/172 (19.9)	
Norepinephrine	410 (53.1)	271 (47.5)	139 (69.2)	<0.001
Epinephrine	95 (12.4)	58 (10.2)	37 (18.6)	<0.001
Norepinephrine and dobutamine combination	352 (45.6%)	225 (39.4)	127 (63.2)	<0.001
Levosimendan	57 (7.4)	42 (7.4)	15 (7.5)	0.55
Dopamine	2 (0.3)	0 (0)	2 (0.3)	0.03
Isoprenaline	32 (4.1)	27 (4.7)	5 (2.5)	0.22
Antiarrhythmic	298 (38.6)	217 (38.0)	81 (40.3)	0.45
Transfusion	128 (16.6)	87 (15.2)	41 (20.4)	0.05
Fibrinolysis	13 (1.7)	11 (1.9)	2 (1.0)	0.15
Organ replacement therapies, *n* (%)				
Respiratory support				
Invasive	291 (37.9)	199 (35.0)	92 (46.2)	0.005
Non-invasive	199 (25.9)	157 (27.6)	42 (21.1)	0.04
Mechanical circulatory support	143 (18.6)	96 (16.8)	47 (23.5)	0.04
IABP	48/143 (34.3)	30/96 (31.9)	18/47 (32.1)	0.22
Impella	26/143 (18.6)	17/96 (18.1)	9/47 (19.6)	0.99
ECLS	85/143 (60.7)	52/96 (55.3)	33/47 (71.7)	0.06
Renal replacement therapy	122 (15.8)	67 (11.7)	55 (27.5)	<0.001
Invasive cardiology, *n* (%)				
CAG	399 (51.7)	318 (55.7)	81 (40.3)	<0.001
1-VD	80/399 (20.1)	65/399 (20.4)	15/399 (18.5)	0.46
2-VD	91/399 (22.8)	74/399 (23.3)	17/399 (21.0)	
3-VD	87/399 (21.8)	64/399 (20.1)	23/399 (28.4)	
Culprit lesion	256/399 (64.2)	196/399 (61.6)	60/399 (74.1)	0.08
Any PCI	217/399 (54.4)	171 (53.8)	46 (56.8)	0.63
Right heart catheterization	121 (15.7)	102 (17.9)	19 (9.5)	0.01
Pace-maker implantation	35 (4.5)	31 (4.0)	4 (2.0)	0.05
Defibrillator implantation	37 (4.8)	36 (6.3)	1 (0.5)	0.02
Radiofrequency ablation	33 (4.5%)	28 (5.1%)	5 (2.7%)	0.16

CAG, coronary angiogram; ECLS, extracorporeal life support; IABP, intra-aortic balloon pump; INV, invasive; NI, non-invasive; PCI, percutaneous coronary intervention; VD, vessel disease.

tate levels (>4 mmol/l) were also associated with higher mortality (OR 2.07, 95% CI: 1.19–3.58).

With full adjustment (Model 2), independent factors associated with mortality at 30 days were (*Table 5*): age [per year (OR 1.06, 95% CI: 1.04–1.08)], LVEF <30% (OR 2.15, 95% CI: 1.40–3.29), circulatory support (OR 1.92, 95% CI: 1.12–3.29), renal replacement therapy (OR 2.72, 95% CI 1.65–4.49), and the use of norepinephrine (OR 2.55, 95% CI: 1.69–3.84) and of diuretics (OR 1.74, 95% CI: 1.05–2.88). In addition, invasive (OR 1.14, 95% CI: 0.68–1.90) and non-invasive respiratory support (OR 0.83, 95% CI: 0.51–1.34), PCI (OR 0.64, 95% CI: 0.41–1.01) and dobutamine (OR 1.27, 95% CI: 0.74–2.19) were not associated with 30 day-mortality in our analysis.

Similarly, in patients with ischaemic CS, the use of PCI was not associated with a significantly lower mortality (OR 0.63, 95% CI: 0.32–1.25).

Table S5 describes all ORs and 95% CIs of all variables tested in Models 1 and 2.

Discussion

To date, the FRENSHOCK registry is the largest European prospective, observational multicentre study on CS that describes a contemporary cohort of unselected patients with CS, from a broad spectrum of aetiologies. The main findings and the originality of this study are the diversity of patient profiles and CS aetiologies linked to the inclusion of patients in different departments (ICU, ICCU, etc.). Although ischaemia remains the primary trigger, it represented only 36.3% of the causes of CS. Secondary, mortality rate at 30 days was 26.0% in the overall population but varied according to the trigger and the first place of admission (ICU, ICCU, transfer from another hospital), and ranged from 16.7% to 48.0%. Finally, six independent factors (age, LVEF <30%, circulatory support, renal replacement therapy, the use of norepinephrine and diuretics) were associated with higher mortality at 30 days.

Figure 2 Central illustration: the FRENSHOCK registry—a real-life picture of cardiogenic shock in France. CS, cardiogenic shock; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; RRT, renal replacement therapy.

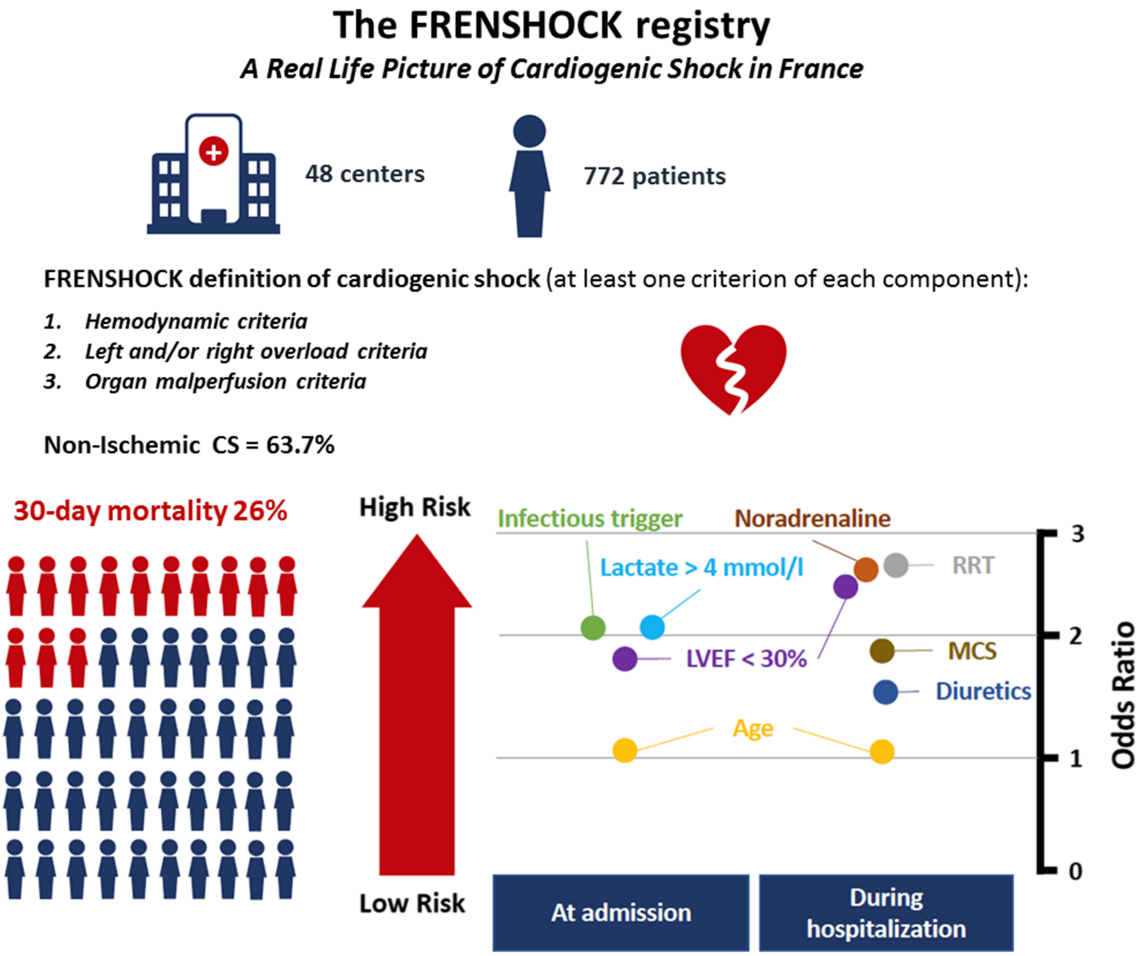


Table 4 Characteristics that affect 30 day mortality for all patients with cardiogenic shock (adjusted for clinical characteristics)

	OR (95% CI)	*P* value
Age (per year)	1.03 (1.02–1.05)	<0.001
Infectious trigger	2.10 (1.26–3.50)	0.005
LVEF <30%	1.79 (1.21–2.64)	0.004
Lactate level		
<2 mmol/L	Ref	
≥2 and <4 mmol/L	1.61 (0.92–2.83)	0.09
≥4 mmol/L	2.07 (1.19–3.58)	0.01

CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio.

Table 5 Independent variables associated with 30 day mortality in all patients with cardiogenic shock (adjusted for clinical characteristics and management)

	OR (95% CI)	*P* value
Age (per year)	1.06 (1.04–1.08)	<0.001
LVEF <30%	2.15 (1.40–3.29)	<0.001
Mechanical circulatory support	1.92 (1.12–3.29)	0.02
Renal replacement therapy	2.72 (1.65–4-49)	<0.001
Use of norepinephrine	2.55 (1.69–3.84)	<0.001
Use of diuretics	1.74 (1.05–2.88)	0.03

CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio.

An inadequate definition of cardiogenic shock in current practice

Numerous definitions of CS have been suggested, but it is broadly recognized as a state of low cardiac output resulting in end-organ hypoperfusion. The definition of CS has evolved over the years from persistent hypotension (starting with SBP < 80 mmHg, followed by SBP < 90 mmHg or use of pressors to maintain a SBP > 90 mmHg) to several haemodynamic parameters described in the SHOCK trial.[2] These haemodynamic parameters may not be universally applicable in clinical practice. In our registry, the first mean SBP was high for a CS population (101 ± 25 mmHg) with a high rate of patients with SBP ≥ 90 mmHg (507/772). Of these, 463 patients

(91.3%) had vasopressor or circulatory support. This indicates that patients were included at different times after CS.

The common definition of CS is binary (CS present or absent), while in fact CS should be considered as a continuum from mild haemodynamic perturbations observed in pre-shock or mild shock, progressing to shock, profound shock, and finally refractory shock which invariably results in death.[16] A new five-stage CS classification was recently proposed by the Society for Cardiovascular Angiography and Interventions (SCAI) (A: 'At risk'; B: 'Beginning'; C: 'Classic'; D: 'Deteriorating'; E: 'Extremis') to depict the entire spectrum of CS and predict the risk of death in ICCUs.[12,17] It may be difficult to use a posteriori in our registry and would therefore require adaptation as in the recent Cardiogenic Shock Working Group publication.[18] Our pragmatic and practical definition of CS is based on simple criteria available at the patient's bedside in any centre, regardless of the level of expertise, allowing rapid recognition of CS from among the different CS aetiologies and presentations without excluding non-ischaemic aetiologies or unusual presentations (low cardiac output without severe hypotension, right ventricular failure) which may concern almost 40 to 50% of CS cases.

Clinical characteristics compared with previous European observational studies

Clinical characteristics of the FRENSHOCK population show similarities with previous large European multinational observational studies (219 patients in 6 centres in the CardShock study, and 195 patients in 211 centres in 21 countries in the ESC Heart Failure Long-Term Registry).[19,20] *Table S6* compares main characteristics of these studies. Mean age (66 vs. 67 years), percentage of men (72% vs. 60 to 74%), risk factors, and medical history are similar. As in the CardShock study, our patients were included from emergency departments, ICCU, and ICU; although in other studies inclusions were only in cardiology departments.[11,12,20] But inclusion criteria were different and more restrictive in CardSHOCK with exclusion of CS caused by ongoing haemodynamically significant arrhythmias, although these are frequent in our registry (13.3% supra ventricular arrhythmias and 12.6% ventricular arrhythmias as CS triggers), and easily reversible causes potentially associated with a better prognosis. Moreover, in CardShock, patients were enrolled within 6 h of detection of CS, which explains the difference regarding biological and clinical presentation, especially haemodynamic parameters (e.g. SBP).

Cardiogenic shock triggers

Cardiogenic shock was long forgotten by cardiology research before being restricted to the form secondary to MI.[4–7] This can be explained by the fact that the underlying pathology and management differ from non-ischaemic cases. The rate of ischaemic CS (36% in our study) is variable according to the study, but classically stays the main aetiology (57.9 to 80.8%)[19,20] even if other studies have indicated more heterogeneous and non-ischaemic aetiologies (42.3 to 56.9%).[11–13] Non-ischaemic CS can be caused by a variety of diseases or triggers which lead to severe myocardial dysfunction (either through acute decompensation in chronic heart failure or de novo).[12,20] In our population, ventricular and supra-ventricular arrhythmias and infectious triggers were frequent and concerned respectively 12.6%, 13.3%, and 11.9% of our CS cases (CS precipitants in respectively 18.9%, 26.2%, and 24.6% in the ESC Heart Failure registry).[20] Unfortunately, the causes of non-ischaemic CS are rarely specified in the available studies and registers, and direct comparison is therefore impossible.[11–13]

Mortality and predictors of hospital death

The mortality rate observed in the FRENSHOCK registry (26%; range 16.7% to 48% according to the cause of CS) is lower than in previous studies where hospital mortality was between 30% and 40%.[13,18–21] The comparatively low short-term mortality observed in FRENSHOCK can be explained by several factors. First, it could be secondary to the FRENSHOCK definition used, but our 30 day mortality was quite similar regardless of the usual CS definitions used (respectively 26.8% and 28.3% for patients meeting the ESC-Heart failure and IABP-Shock2 definitions). Second, our inclusions were in 2016 and more recent than previous retrospective analyses which included patients for longer periods between 2005 and 2017.[11,12,20] Third, our lower mortality is related to differences in presentation, especially less severe baseline biological and haemodynamic parameters. This was in part related to the timing of inclusion relative to the time of shock onset, and to the variety of recruiting units (ICCU and ICU), as illustrated by the lower mortality in ICCU. In addition, our registry does not make it possible to differentiate isolated CS from mixed shocks, which may explain part of the observed differences in mortality compared with previous studies. The wider use of RHC could have helped to better classify these patients, but remains little carried out in France to date, even if recent US data found a possible link between its use and the short-term prognosis of CS patients.[22] Another factor might be that the in-hospital mortality rate for patients with non-acute coronary syndrome CS decreased between 2005 and 2014 from 42.4% to 23.3% as suggested in a large database (8 333 752 hospitalizations for heart failure) in the United States (P value for trend <0.001).[14]

Data related to the prognosis of CS according to ischaemic or non-ischaemic trigger have shown conflicting results.[10,13,14,21] However, ischaemic CS is mainly associated

with lower in-hospital mortality except in the CardShock study.[19] An improvement in survival has been observed over the past two decades, attributed to the introduction of routine percutaneous revascularization in AMI and modern intensive care. But in our analyses, ischaemic cause was not associated with improved mortality and the impact of PCI on survival at 30 days was not significant as in the CardShock study.

In the multivariate analysis, four independent factors at admission (age, LVEF $<30\%$, lactate ≥ 4 mmol/L, infectious trigger) were associated with higher mortality at 30 days. In the CardShock study, the predictors of in-hospital death were different and included: prior coronary artery bypass surgery, ACS aetiology, confusion, previous MI, blood lactate, LVEF, age and SBP.[19] Other previously published studies have identified diverse factors associated with short-term mortality but these were related to CS aetiologies (mainly or only based on ischaemic CS) and the patient inclusion settings (mainly or exclusively in general ICUs).[19,23,24] Thus, faced with very similar initial characteristics on admission, it is difficult to predict on simple static elements, the prognosis of patients presenting for miscellaneous CS. In this sense, the use of the recent SCAI classification taking into account the evolution under treatment seems advantageous.[11,12]

Finally, the level of invasiveness of the treatment reflects the severity of the patient's presentation and the advanced shock state (norepinephrine, renal replacement therapy, and mechanical circulatory support) and is correlated with short-term prognosis without any significant difference depending on the type of support used (IABP, Impella or VA-ECMO for example).

Limitations

As in any observational study, there are limitations to our analysis. First, inclusions were not exhaustive and probably not consecutive in all centres. Moreover, non-inclusions and the reasons for non-inclusion were not presented. Second, patients were enrolled from ICU and ICCU (directly or after transfer from another centre) and we cannot exclude the possibility that severe comorbid, older, or most severe cases with multiple organ failure could have not been transferred for futility even if the older patient included was 98 years old. Moreover, data for patients who died early (before informed consent was obtained) were not collected and recorded in the database because of administrative regulations. This could be a source of bias resulting in an underestimation of mortality. Third, certain aetiologies or triggers of CS were not recorded in the electronic reported form and were therefore not collected (takotsubo, pulmonary embolism, acute decompensation of chronic heart failure, aetiologies of infectious triggers, etc.). Subsequently, a conclusion could not be drawn regarding them. In addition, causality between CS and 30 day mortality cannot be demonstrated. However, we adjusted our results based on well-recognized determinants of short-term outcome and sensitivity analyses confirmed our main findings. The period between admission and CS onset and from CS onset to enrolment in the registry were not recorded which may explain why some parameters described were not as high as expected (e.g. lactate levels could have been high at CS onset and not at inclusion). Finally, other previously identified risk indicators (e.g. confusion, medications, timing of revascularization, and organ support) were not recorded in our database.

Conclusions

Cardiogenic shock is characterized by its diversity in terms of aetiologies and severity. Ischaemic CS remains the main CS trigger but non-ischaemic causes accounted for more than 60% of all the cases. CS is still associated with significant but variable short-term mortality according to the cause and first place of admission, despite more frequent use of haemodynamic support and organ replacement therapies.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. FRENSHOCK definition of cardiogenic shock.
Table S2. Criteria used to define cardiogenic shock in the FRENSHOCK population.
Table S3. Vital parameters at 24 hours according to vital status at 30 days.
Table S4. In-hospital complications according to vital status at 30 days.
Table S5. Description of all odds ratios and 95% confidence intervals of all variables tested in multivariate analysis models in-hospital all-cause mortality: model 1 (based only variables available on admission) and model 2 (based on variables available at admission and on variables of in-hospital management).
Table S6. Comparison of major population characteristics and outcomes between the FRENSHOCK, the CardShock and the ESC Heart Failure Long-Term registries.

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