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## Sex disparities in cardiogenic shock: Insights from the FRENDSHOCK registry

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**Abbreviations:** ACS, acute coronary syndrome;; AMI, acute myocardial infarction;; AMICS, acute myocardial infarction associated cardiogenic shock;; CAG, coronary artery angiogram;; CS, cardiogenic shock;; ECLS, extracorporeal life support;; ICU, intensive care unit;; ICCU, intensive cardiac care unit;; LVEF, left ventricular ejection fraction;; MCS, mechanical circulatory support;; PCI, Percutaneous Coronary Intervention,; VAD, ventricular assist device..

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## ABSTRACT

**Background:** Cardiogenic shock (CS) is the most severe form of acute heart failure. Discrepancies have been reported between sexes regarding delays, pathways and invasive strategies in CS complicating acute myocardial infarction. However, effect of sex on the prognosis of unselected CS remains controversial.

**Objectives:** The aim was to analyze the impact of sex on aetiology, management and prognosis of CS.

**Methods:** The FRENSHOCK registry included all CS admitted in 49 French Intensive Care Units (ICU) and Intensive Cardiac Care Units (ICCU) between April and October 2016.

**Results:** Among the 772 CS patients included, 220 were women (28.5%). Women were older, less smokers, with less history of ischemic cardiac disease (20.5% vs 33.6%) than men. At admission, women presented less cardiac arrest (5.5 vs 12.2%), less mottling (32.5 vs 41.4%) and higher LVEF ( $30 \pm 14$  vs  $25 \pm 13$ ). Women were more often managed via emergency department while men were directly admitted at ICU/ICCU. Ischemia was the most frequent trigger irrespective of sex (36.4% in women vs 38.2%) but women had less coronary angiogram and PCI (45.9% vs 54% and 24.1 vs 31.3%, respectively). We found no major difference in medication and organ support. Thirty-day mortality (26.4 vs 26.5%), transplant or permanent assist device were similar in both sexes.

**Conclusion:** Despite some more favorable parameters in initial presentation and no significant difference in medication and support, women shared similar poor prognosis than men. Further analysis is required to cover the lasting gap in knowledge regarding sex specificities to distinguish between differences and inequalities. NCT02703038

## 1. Background

Cardiogenic shock (CS) is characterized by its diversity in terms of etiologies and severity, and prognosis seems to be linked to aetiology [1]. Impact of sex on CS prognosis remains controversial [2-5]. Addressing sex disparity appears crucial as differences in the impact of risk factors, the role of specific risk factors and biological specificities have been reported in heart failure pathophysiology [6]. Likewise, such differences have been acknowledged in ischemic cardiac disease regarding presentation, diagnosis, and management [7]. Noteworthy, despite higher rate of non-obstructive coronary disease, women presented the paradox of higher rate of symptoms and higher morbidity and mortality [8]. In the setting of acute coronary syndrome, significant disparities between sexes have been reported regarding delays of care and treatment, pathways and the use of invasive strategies [9-12]. In women, clinical presentation may be more diverse and less typical, care pathway may be impacted by sex specificities and management of heart disease jeopardized by less obvious aetiology. Short-term mortality depends mainly on the main trigger and admission site. Ischemic CS have been reported to have the worse in-hospital mortality rate as high as 50% [13] but prevalence of non-ischemic CS accounted for >60% of all cases of CS as recently reported in our FRENSHOCK cohort [14]. In order to improve our understanding of the impact of sex in the CS we proposed a comprehensive analysis of the large observational FRENSHOCK cohort including unselected CS based on CS aetiologies, baseline characteristics, management and follow-up at 30 days and 1 year [15].

## 2. Methods

### 2.1. Patient population

This study is post-hoc cohort analysis of the prospective multicenter observational FRENSHOCK registry, conducted in metropolitan France between April and October 2016 in 49 Intensive Care Units (ICU) and Intensive Cardiac Care Units (ICCU) (NCT02703038), whose primary objective was to describe the characteristics, management and outcome of patients with CS [14,15].

All adult patients ( $\geq 18$  years old) with CS were prospectively included if they met at least one criterion of each of the following three

components: (i) hemodynamic 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<sup>2</sup>; (ii) left and/or right heart pressure elevation, defined by clinical signs, radiology, blood tests, echocardiography, or signs of invasive hemodynamic 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 inability to consent and a diagnosis of CS refuted in favor of alternative diagnoses (septic shock, refractory cardiac arrest, post cardiomy CS).

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).

### 2.2. Data collection

Data on baseline characteristics, including demographics (age, sex, body mass index and employment status), risk factors, medical history and previous medication were collected in the FRENSHOCK registry as well as pre-ICU/ICCU course, clinical, biological and echocardiographic data within the first 24 h after admission. CS triggers, cardiac procedures, organ replacement therapies, in hospital complications, 30-day and 1-year follow up (treatments, back to work) and mortality were collected [15].

### 2.3. Statistical analysis

Continuous data were reported as mean (+/- standard deviations) or medians (and interquartile range) when appropriate. Categorical data were reported in numbers and percentages. Univariable comparisons between groups (women vs men) were performed using Student's *t*-tests (or Mann & Whitney non parametric tests when skewed) for continuous data; and using chi square or Fisher's exact tests for categorical data. Factors independently associated with female sex were identified using stepwise descending logistic regression, taking into account variables

found associated with female sex at  $p < 0.20$  in univariable analyses. The logistic regression analysis aimed to estimate the differences between men and women in terms of clinical presentation (at admission), independently of the effects of potential confounding factors. Gender was used as the dependent variable and the different terms relating to the clinical presentation at admission that had been found to be unbalanced between men and women in the univariable analyses were introduced into the model as explanatory variables.

Survival curves were plotted using the Kaplan-Meier's method, to estimate the differences in survival between men and women in terms of all-cause mortality, heart transplantation or use of ventricular assist device (VAD) within 30 days and one year. Differences in survival were approached using the Logrank test.

Two-sided  $p$ -values  $< 0.05$  were considered as statistically significant in all analyses. All analyses were performed using Stata SE version 17 (StataCorp. 2021. Stata: Release 17. Statistical Software. College Station, TX: StataCorp LLC).

### 3. Results

#### 3.1. Baseline characteristics

Among the 772 CS patients included in 49 centres (Supplemental Fig. 1), 220 were women (28.5%). Table 1 reported the clinical characteristics. Women were older ( $68 \pm 16$  vs  $65 \pm 14$ ,  $p = 0.03$ ), more

**Table 1**  
Clinical characteristics at admission according to sex in the FRENSHOCK registry.

	Overall (n = 772)		Women (n = 220)		Men (n = 552)		p
Age (years), mean +/- SD	65.7	+/- 14.9	67.5	+/- 16.1	65.0	+/- 14.3	0.033
BMI (kg/m <sup>2</sup> ), mean +/- SD	25.8	+/- 5.5	25.7	+/- 6.0	25.9	+/- 5.3	0.617
n	744		209		535		
Employment status, n (%)							0.001
Employed	128	(19.1)	24	(12.4)	104	(21.8)	
Unemployed	25	(3.7)	2	(1.0)	23	(4.8)	
Housekeeping	14	(2.1)	8	(4.1)	6	(1.3)	
Disability	56	(8.3)	17	(8.8)	39	(8.2)	
Retired	448	(66.8)	142	(73.6)	306	(64.0)	
Risk factors, n (%)							<
Current smoker	206	(27.8)	34	(16.5)	172	(32.2)	0.001
Diabetes mellitus	217	(28.2)	59	(26.8)	158	(28.7)	0.595
Arterial hypertension	364	(47.2)	110	(50.0)	254	(46.1)	0.327
Dyslipidaemia	277	(35.9)	73	(33.2)	204	(37.0)	0.315
Medical history, n (%)							
History of cardiac disease	433	(56.2)	103	(46.8)	330	(59.9)	0.001
Ischaemic	230	(29.8)	45	(20.5)	185	(33.6)	0.001
Hypertrophic	11	(1.4)	4	(1.8)	7	(1.3)	0.519
Idiopathic	78	(10.1)	17	(7.7)	61	(11.1)	0.164
Toxic	34	(4.4)	4	(1.8)	30	(5.4)	0.027
Multisite pacing	63	(8.2)	23	(10.5)	40	(7.3)	0.144
ICD	127	(16.5)	23	(10.5)	104	(18.9)	0.004
CABG	62	(8.0)	9	(4.1)	53	(9.6)	0.011
PCI	166	(21.5)	38	(17.3)	128	(23.2)	0.069
Peripheral artery disease	91	(11.8)	19	(8.6)	72	(13.1)	0.085
Ischemic stroke	62	(8.0)	17	(7.7)	45	(8.2)	0.839
Chronic renal failure	164	(21.3)	41	(18.6)	123	(22.3)	0.259
Dialysis	11	(1.4)	2	(0.9)	9	(1.6)	0.737
COPD	50	(6.5)	11	(5.0)	39	(7.1)	0.29
Active cancer	51	(6.6)	12	(5.5)	39	(7.1)	0.413

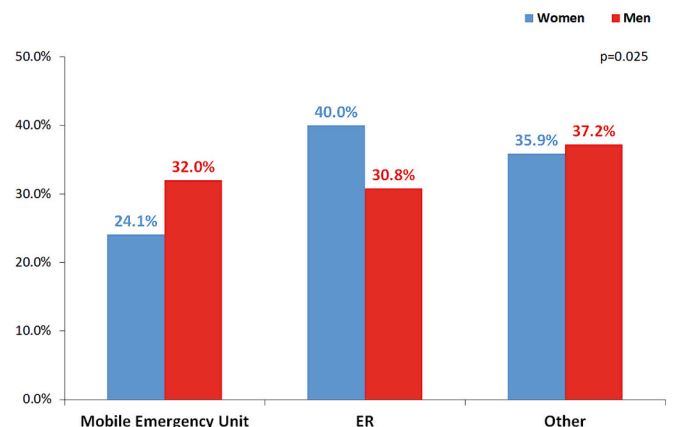
often housekeeping (4.1 vs 1.3%,  $p = 0.001$ ) or retired (73.6 vs 64%,  $p = 0.001$ ). Cardiovascular risk factors were similar between sex but men were twice likely current smokers (32.2% vs 16.5%,  $p < 0.001$ ). Women reported less previous ischemic cardiac disease (20.5% vs 33.6%,  $p < 0.001$ ) and less history of CABG (4.1 vs 9.6%,  $p = 0.011$ ). Toxic, including alcoholic, cardiac disease were less frequent in women (1.8 vs 5.4%,  $p = 0.027$ ). Women had less implantable cardioverter-defibrillator than men (10.5% vs 18.9%,  $p = 0.004$ ). At admission, aspirin, statin and amiodarone prescription were less frequent in women without any difference in oral anticoagulation (Supplemental Table S1). However, women were significantly more often prescribed beta blockers (47.5% vs 38.5%,  $p = 0.022$ ).

#### 3.2. Presentation of cardiogenic shock

Initial CS diagnosis and management differ according to the sex with more first medical contact at the emergency department for women whereas men more often benefit from mobile intensive care unit or others ( $p = 0.025$ ) (Fig. 1). At admission, women presented half less cardiac arrest (5.5% vs 12.2%,  $p = 0.006$ ) and less mottling (31.5 vs 41.4%,  $p = 0.033$ ) (Table 2). LVEF was significantly higher among women ( $30 \pm 14$  vs  $25 \pm 13\%$ ,  $p < 0.001$ ) while the other echocardiographic findings especially RV function parameters or the presence of severe valvulopathy did not differ between sex (Supplemental Table S2). Ischemia was the first reported trigger observed in one third of the cohort regardless of sex. Supra-ventricular arrhythmias and inobservance were less frequently reported in women than in men (Fig. 2).

#### 3.3. Management of cardiogenic shock

Table 3 shows no difference in medical management between sex, except that a lower proportion of women received dobutamine (77.2% vs 84.3%,  $p = 0.019$ ) and when prescribed, dobutamine was administered at lower maximum doses. Less than half of the women benefit from a coronary artery angiogram (CAG) (45.9% vs 54%,  $p = 0.043$ ) with subsequently less frequent percutaneous intervention carried out (24.1% vs 31.3%,  $p = 0.046$ ). Moreover, when performed, CAG found more non-obstructive coronary disease (26.7% vs 15.8%,  $p = xx$ ) and less three vessels disease (7.9% vs 26.5%,  $p < 0.001$ ). Men and women benefited equally from respiratory supports, renal replacement therapy or mechanical circulatory support (MCS). After adjustment on age, CS identified trigger (ischemic or not) and initial LVEF ( $> 40\%$  or not), cardiac arrest at admission, women still receive less dobutamine and had less CAG with subsequent PCI.



**Fig. 1.** First admission department according to sex. ER, emergency room.

**Table 2**

Clinical and biological presentation at admission according to sex in the FRENDSHOCK registry.

	Overall (n = 772)		Women (n = 220)		Men (n = 552)		p
<b>Admission unit, n (%)</b>	0.59						
ICCU	414	(70.2)	111	(68.5)	303	(70.8)	
ICU	176	(29.8)	51	(31.5)	125	(29.2)	
<b>Clinical presentation at admission</b>							
<b>Heart rate</b>							
(bpm). mean	+/-		+/-		+/-		
+/- SD	95.6	29.6	96.2	29.7	95.4	29.5	0.758
n	769		220		549		
<b>SBP (mmHg).</b>							
mean +/- SD	+/-		+/-		+/-		
n	101	25	100	25	102	25	0.427
n	770		220		750		
<b>DBP (mmHg).</b>							
mean +/- SD	+/-		+/-		+/-		
n	63	17	62	18	64	17	0.102
n	769		220		549		
<b>Sinus rhythm. n (%)</b>							
n (%)	399	(52.0)	111	(50.5)	288	(52.6)	0.598
<b>Cardiac arrest.</b>							
n (%)	79	(10.3)	12	(5.5)	67	(12.2)	0.006
<b>Mottling. n (%)</b>							
n (%)	256	(38.8)	62	(32.5)	194	(41.4)	0.033
<b>LVEF ≤40%</b>							
n	85.6%		77.0%		89.0%		<0.001
n	763		217		546		
<b>Blood tests at admission</b>							
<b>Sodium (mmol/L). mean +/- SD</b>							
n	135	+/- 6	134	+/- 6	135	+/- 6	0.229
n	760		215		545		
<b>eGFR (mL/min/1.73 m<sup>2</sup>). mean +/- SD</b>							
n	49.6	26.6	49.1	27.8	49.7	26.2	0.787
n	751		211		540		
<b>Bilirubin (mg/L). median (IQR)</b>							
n	16 (9–29)		14 (9–28)		17 (10–29)		0.122
n	544		147		397		
<b>Haemoglobin (g/dL). mean +/- SD</b>							
n	12.5	2.3	11.8	2.1	12.8	2.4	< 0.001
n	754		213		541		
<b>Arterial blood lactates (mmol/L). median (IQR)</b>							
n	3.0 (2.0–4.7)		3.0 (2.0–4.9)		3.0 (2.0–4.6)		0.748
n	684		194		490		
<b>ASAT (IU/L). median (IQR)</b>							
n	90 (39–301)		78 (37–238)		92 (39–342)		0.205
n	547		150		397		
<b>ALAT (IU/L). median (IQR)</b>							
n	59 (27–183)		48 (24–176)		63 (28–184)		0.091
n	559		156		403		
<b>Nt proBNP (pg/mL). median (IQR)</b>							
n	9277	12,476	8910		(3791–20,520)		0.139
n	(4052–23,256)		(4411–34,206)		170		
n	224		54		170		
<b>BNP (pg/mL). median (IQR)</b>							
n	1150	1437	1101		(476–2566)		0.363
n	(477–2768)		(477–3030)		177		
n	264		87		177		
<b>CRP (mg/L). median (IQR)</b>							
n	28 (9–69)		32 (11–88)		27 (9–64)		0.265
n	406		111		295		

### 3.4. 24 h cardiogenic shock monitoring

At 24 h, hemodynamic status improved in women with higher systolic blood pressure and better increase in LVEF, compared to men. There was no further sex-related difference in recorded parameters (**Supplemental Table S3**).

### 3.5. Factors associated with a significant interaction with female sex

All factors associated with a significant interaction with female sex are summarized in the **Central Illustration** and **Supplemental Table S4**. After regression, the only parameters independently associated with female sex were baseline characteristics and admission pathway.

### 3.6. In-hospital outcome

During hospitalization, we noted non-significant higher rate of heart transplant list registration in men than in women (47.6 vs 3.5%,  $p = 0.059$ ). Women presented a greater LVEF improvement during hospitalization ( $+10.7 \pm 15.9\%$  vs  $+7.6 \pm 13.5\%$ ,  $p = 0.04$ ) with a better LVEF at discharge ( $40 \pm 15$  vs  $33 \pm 14$ ,  $p < 0.001$ ). No difference in in-ICU or in-hospital mortality or discharge mode was observed between sex (**Table 4**).

### 3.7. 30-days and 1-year outcome

There was no difference between sex in 30-day mortality, at 26% ( $p = 0.932$ ) (**Fig. 3A**), heart transplantation, VAD or all-cause death (**Fig. 3B**). Interestingly we noted a trend of more permanent VAD in men than in women (2.7 vs 0.5%,  $p = 0.05$ ) (**Table 4**). The 30-day mortality of ischemic CS, defined by the performance of any PCI during CS hospitalization, also showed no significant difference between sexes: 15.1% in women vs 23.7% in men,  $p = 0.18$ . During the 12-month follow up, women and men presented similar rate of major cardiac events such as death, or cardiac transplantation (**Table 4**). Regarding the age difference between sex at admission, multiple specific analyzes were performed and found no correlation between age and sex, and no interaction with all-cause mortality between sex at 30 days and 1 year (**Table S5**).

Regarding medication at one year, (**Supplemental Table S6**) follow up reported less prescription of aspirin, P2Y12 inhibitor and statin for women, but also less use of beta-blockers and ACE inhibitor.

## 4. Discussion

This large national registry of unselected patients with CS highlights that sex differences in CS are related to clinical presentation and care pathway rather than management or outcomes. The main result of the FRENDSHOCK Sex analysis is that despite some initial more favorable parameters in initial presentation in women including greater LVEF and less cardiac arrest, CS severity defined by use of vasopressive drugs, presence of organ failure and lactates level, and prognosis remain as poor in women as in men.

The literature has been recently enriched mostly by sex analysis in patients with acute myocardial infarction associated CS (AMICS). In the study by Sambola et al., women were less often admitted to revascularization capable hospitals than men (79.6% vs. 85.3%  $P = 0.01$ ), and to ICCU center (25.7% vs 29.2%,  $P = 0.001$ ) [16]. However, in contemporary CS cohorts, AMI represents only 40% of CS, while other 60% are caused by non-acute ischemic causes [1]. In our cohort, an ischemic trigger was reported in the same proportion in women and men (36% vs 38%,  $p = 0.63$ ) but there was a significant difference in the prevalence of other causes which account for 20% in women but only 10% in men ( $p < 0.001$ ). This is of major relevance since non-ischemic causes gathering a very heterogeneous group of aetiologies (decompensation of chronic heart failure, genetic, toxic, idiopathic, valvular, restrictive, pulmonary embolism, stress cardiomyopathy, myocarditis, tamponade, mix septic and CS) require a specific treatment approach and are associated with a worse prognosis [17].

Data are controversial regarding disparities in CS management between sex. In a cohort of unselected CS, Yan et al. showed that women were more likely to be treated with catecholamines or vasopressors but were less likely to undergo temporary MCS than men [5]. In our study, we found no major differences in CS medication, temporary MCS, or

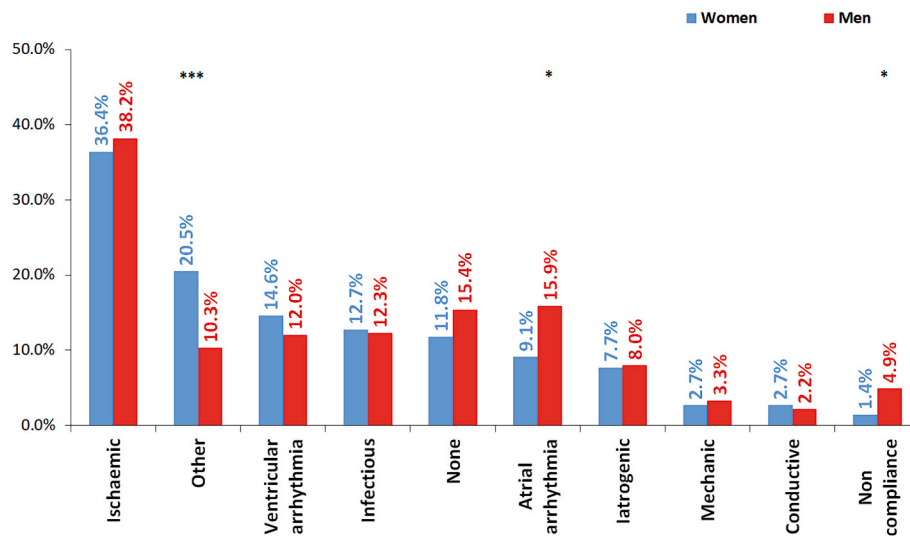


Fig. 2. CS trigger according to sex in the FRENDSHOCK registry.

CS, cardiogenic shock.

\* <0.05; \*\* < 0.01; \*\*\* < 0.001.

Table 3

In-hospital management according to sex in the FRENDSHOCK registry.

	Overall (n = 772)		Women (n = 220)		Men (n = 552)		p	Adjusted p*
<b>CS medication, yes, n (%)</b>								
Diuretics	633	(82.4)	175	(79.9)	458	(83.4)	0.248	0.528
Fluid expansion during the first 24 h	321	(41.9)	98	(44.8)	223	(40.7)	0.304	0.528
Dobutamine	632	(82.3)	169	(77.2)	463	(84.3)	0.019	0.140
If yes, Maximum dose (µg/kg/min):							0.032 **	0.015 **
5–10	405	(63.7)	124	(72.9)	281	(60.3)		
10–15	136	(21.4)	28	(16.5)	108	(23.2)		
>15	47	(7.4)	9	(5.3)	38	(8.2)		
Norepinephrine	410	(53.4)	122	(55.7)	288	(52.5)	0.415	0.730
Epinephrine	95	12.4	20	(9.1)	75	(13.7)	0.085	0.109
Norepinephrine + dobutamine combination	352	(45.8)	100	(45.7)	252	(45.9)	0.952	0.959
Levosimendan	57	(7.4)	14	(6.4)	43	(7.8)	0.492	0.880
Dopamine	2	(0.3)	0	(0.0)	2	(0.4)	1.000	
Isoprenaline	32	(4.2)	13	(5.9)	19	(3.5)	0.121	0.227
Antiarrhythmic	298	(38.8)	81	(37.0)	217	(39.5)	0.514	0.724
Transfusion	128	(16.7)	39	(17.8)	89	(16.2)	0.599	0.497
Fibrinolysis	13	(1.7)	5	(2.3)	8	(1.5)	0.535	0.936
<b>Organ replacement therapies, n (%)</b>								
Respiratory support								
Invasive	291	(37.9)	77	(35.2)	214	(39.0)	0.324	0.390
Non invasive	199	(25.9)	140	(25.5)	59	(26.4)	0.681	0.576
Mechanical circulatory support	143	(18.6)	35	(16.0)	108	(19.6)	0.244	0.756
IABP	48	(34.0)	15	(42.9)	33	(31.1)	0.204	0.629
Impella	26	(18.4)	5	(14.3)	21	(19.8)	0.465	0.924
ECLS	85	59.9	19	(54.3)	66	(61.7)	0.438	0.669
Renal replacement therapy	122	(15.8)	39	(17.7)	83	(15.1)	0.360	0.223
<b>Invasive cardiology, n (%)</b>								
CAG	399	(51.7)	101	(45.9)	298	(54.0)	0.043	0.075
CAG result							< 0.001	0.033
Normal	74	(18.6)	27	(26.7)	47	(15.8)		
1 - vessel disease	80	20.1	26	(25.7)	54	(18.1)		
2 - vessel disease	91	22.8	24	(23.8)	67	(22.5)		
3 - vessel disease	87	(21.8)	8	(7.9)	79	(26.5)		
Unknown	67	(16.8)	16	(15.8)	51	(17.1)		
Culprit lesion	256	(80.5)	60	(84.5)	196	(79.4)	0.334	0.844
Any PCI	217	(28.1)	53	(24.1)	164	(29.7)	0.117	0.045
Any PCI (even in a second time)	226	(29.3)	53	(24.1)	173	(31.3)	0.046	0.016
Right heart catheterisation	121	(15.8)	37	(16.9)	84	(15.3)	0.584	0.263
Pace-maker implantation	35	(4.8)	9	(4.3)	26	(5.0)	0.681	0.381
Defibrillator implantation	37	(5.1)	7	(3.3)	30	(5.8)	0.174	0.291
Radiofrequency ablation	17	(2.3)	3	(1.4)	14	(2.7)	0.420	0.328

**Table 4**  
Cardiogenic shock prognosis according to sex in the FRENSHOCK registry.

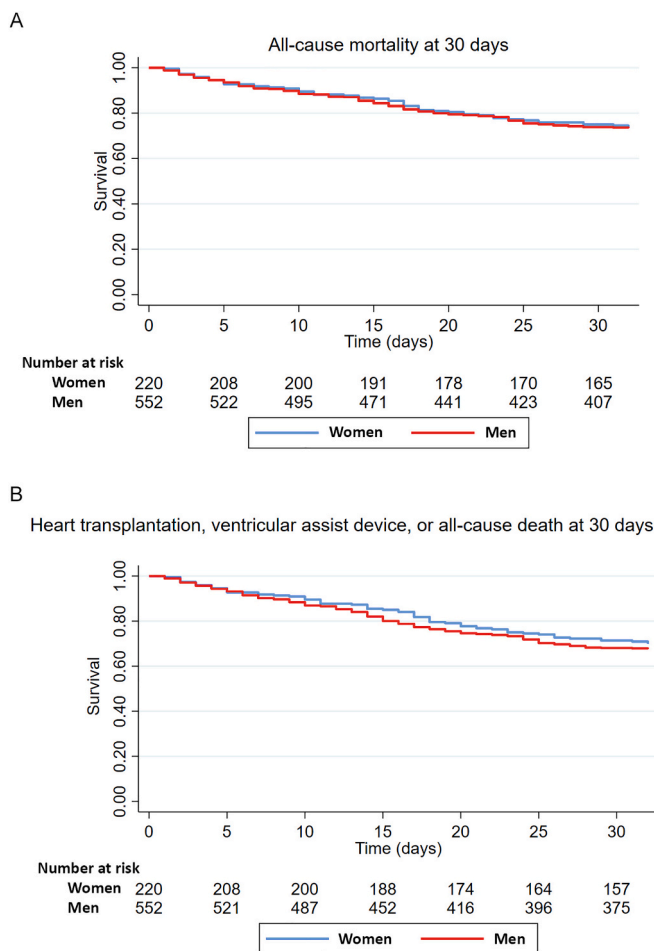
	Overall (n = 772)		Women (n = 220)		Men (n = 552)		p-value	Adjusted p *
<b>Characteristics at discharge</b>								
LVEF (%), mean +/- SD	35.0	+/- 14.5	40.1	+/- 15.0	33.0	+/- 13.8	< 0.001	< 0.001
n	439		120		319			
LVEF variation **, mean +/- SD	+ 8.5	+/- 14.2	+ 10.7	+/- 15.9	+ 7.6	+/- 13.5	0.041	0.009
n	436		120		316			
Discharge mode							0.896	0.175
Home	171	(26.4)	47	(25.4)	124	(26.7)		
Rehabilitation	44	(6.8)	10	(5.4)	34	(7.3)		
Transferred §	214	(33.0)	62	(33.5)	152	(32.8)		
Death	217	(33.4)	65	(35.1)	152	(32.8)		
Other	3	(0.5)	1	(0.5)	2	(0.4)		
<b>30-day outcomes</b>								
All-cause mortality	204	(26.4)	58	(26.4)	146	(26.5)	0.981	0.767
Heart transplantation	33	(4.4)	7	(3.2)	26	(4.7)	0.343	0.716
VAD	16	(2.1)	1	(0.5)	15	(2.7)	0.046	0.130
<b>1-year outcomes</b>								
All-cause mortality	349	(45.2)	105	(47.7)	244	(44.2)	0.374	0.560
Heart transplantation	47	(6.1)	9	(4.1)	38	(6.9)	0.143	0.417

LVEF, left ventricular ejection fraction; VAD, permanent ventricular assist device; SD, standard deviation.

\* adjusted for age, aetiology of CS (ischemic or not), LVEF ≤ 40% and resuscitated cardiac arrest at admission.

\*\* At discharge compared with admission.

§ transfer in other department or center.



**Fig. 3.** Kaplan-Meier curve showing cardiogenic shock prognosis at 30-day described by all-cause mortality (Fig. 3A) and need for heart transplantation and/or ventricular assist device requirement and/or all-cause death (Fig. 3B) according to sex in the FRENSHOCK registry.

Fig. 3A: Logrank  $p = 0.932$  and Fig. 3B: Logrank  $p = 0.473$ .

end-stage organ failure support, suggesting that severity of CS fortunately trumps all other considerations. We observed however that women received less often dobutamine and at lower doses while there was no difference in other catecholamines. Hypotheses could be a significantly higher LVEF at admission in women, or presence of underlying specific cardiomyopathy (hypertrophic, hypertensive, restrictive) with a part of diastolic dysfunction, or disparities in the etiologies of CS in women requiring specific management rather than cardiac inotropy. As previously demonstrated, women continue to have less cardiac catheterization and subsequent PCI [16] despite reporting similar rate of ischemic trigger 36.4% vs 38.2% ( $p = 0.63$ ). In our study, only 52% of women with CS were invasively explored, which is low, compared to previous investigations performed in ACS settings, reported around 85% [18]. This may reflect broad etiologies of CS captured in our cohort and the lower perceived ischemic risk in women, less likely to be smokers or having an history of CAD. Reassuringly, there was no difference between sex in PCI performed at the acute phase with 50/63 (88%) of the culprit lesions being treated in women, and 164/196 (84%) in men.

Few studies paid attention to potential disparities between sex in care pathway of unselected patients with CS. Despite fewer cardiac arrests, less mottling and higher LVEF at admission, women shared with men similar poor prognosis with a 30-day mortality rate at 26%. This may reflect the impact of the aetiology itself on the prognosis and/or suggest the presence of other factors or marker not recorded in the dataset that may capture this difference in prognosis. This corresponds well with the limits of the contribution of the initial value of LVEF in the early management of acute heart failure as has recently been highlighted. [19,20].

This sex-specific disconnect between severity, acuity, management and survival raises questions about differences in CS phenotypes and etiologies between sex and differences in the quality of care delivered including early recognition of non-ischemic CS.

Differences in prognosis depending on the CS aetiology are reported [21] but data comparing ischemic and non-ischemic CS prognosis are conflicting [17,22]. Possible explanations are the use of variable definitions of ischemic CS, but also on the constitution of the non-ischemic CS group (all-comers CS or HF related CS only for example), the place of recruitment/care and the severity of these CS [23,24].

Hypoperfusion and multiple organ failure are associated with poor prognosis in CS. Arterial lactate is a marker of hypoperfusion, especially

in women [25]. We observed that lactate level was as high in women than in men as other markers of shock severity. This underscores the discrepancy between reassuring clinical and echocardiographic presentation and the true severity of CS.

Interestingly, CS prognosis score published to date (CardShock score, IABP-SHOCK-II score CS4P score) not include the sex as a prognostic marker except the recent Cardiogenic Shock Score (CSS) [17] which accord 1-point (max 18) in case of female sex based on an HR of 1.09 [1.01–1.18] issued from a large multicentric derivation ( $n = 1308$ ) and validation ( $n = 934$ ) cohorts of unselected CS patients. But despite analysis showing a better predictive ability for the CSS than previous usual score for AMICS and non-AMI related CS, its diagnostic accuracy is modest with a C-statistic at 0.733 for AMICS and 0.717 for others CS.

In our registry, the absence of difference in prognosis between sexes could not be explained by the aetiology or severity of the CS, this indirectly implies the major part of the effect of sex itself. But it is unknown whether these disparities resulted from patient-related (sex-related differences in presenting symptoms or descriptions), or physician-related (sex-related differences in history taking, shock recognition or diagnostic testing) factors.

#### 4.1. Limitations

Our analysis of the FRENDSHOCK registry faced limitations inherent in any observational study namely the lack of granularity and subsequent potential bias. First, inclusions were not exhaustive and probably not consecutive in all centers. Second, 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. The written consent required to be included probably adds a second source of bias leading to an underestimation of mortality, because patients who died quickly without the possibility of consent could not be included. In effect, our analysis included only patients successfully resuscitated and sufficiently stable to provide written consent. Third, detailed aetiology of CS was not recorded in the electronic reported form, then limiting a more detailed analysis (Takotsubo, pulmonary embolism, acute decompensation of chronic heart failure, etiologies of infectious triggers, etc.). However, triggers of CS could be more precisely reported, with rational difficulties to separate aetiology and trigger. Potential differences in the impact of the aetiology or trigger on the prognosis according to sex could not be deeply investigated. We used these data in a descriptive way only as hypothesis-generating. Proper risk stratification with existing CS risk scores was not possible post hoc in our study due to missing variables, in particular the Cardiogenic Shock Score and calculation of risk score was not mandatory recorded to evaluate patient severity, particularly SCAI SHOCK Stage Classification was not used for the group classification, given that this score was not yet available at the time of the study. Besides, to serve our purpose to catch the broader endotypes of CS patients, inclusion criteria were deliberately wide in order to cover as much as possible the broad spectrum of CS. Data at admission were data collected at the time of enrollment, and not systematically at the time of CS onset. Finally, causes of death were not sufficiently detailed nor adjudicated to be reported or interpreted.

## 5. Conclusion

In this large unselected cohort of CS from all etiologies, women shared similar poor prognosis than men despite some more favorable parameters in initial presentation, less cardiac arrest, better LVEF and no significant difference in support and medication used, except for dobutamine use. These discrepancies deserve further analysis to cover the lasting gap in knowledge regarding sex specificities to distinguish between differences and inequalities.

## Ethics approval and consent to participate

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) ( $n^{\circ}$ 15.897) and the CNIL (French Data Protection Agency) ( $n^{\circ}$  DR-2016-109).

## Consent for publication

Not Applicable.

## Availability of data and material

Proposals for data access will be considered by the Frenshock Steering Committee in accordance with the data access policy of the study sponsor (French Cardiology Society).

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## Authors' contributions

All authors had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: SMS, ACM, FB, CHB and CD. Acquisition, analysis, or interpretation of data: SMS, ACM, FB, CHB, EP and CD. Drafting of the manuscript: SMS, ACM, FB, CHB and CD. Critical revision of the manuscript for important intellectual content: SMS, ACM, FB, CHB, NA, EP, VB and CD. Statistical analysis and data verification: VB, EP and CD. Obtained funding: EP and CD. Administrative, technical, or material support: Ep and CD. Supervision: SMS and CD.

## Declaration of competing interest

Manzo-Silberman S has received consulting fees from Bayer, Organon, Exeltis, lecture fees from Bayer, BMS, Exeltis and Organon, has served in the adjudication board for a study for Biotronik. Martin AC has received consulting fees from Alliance BMS-Pfizer, Bayer, grants from Alliance BMS-Pfizer, lecture fees from Alliance BMS-Pfizer, Abbott, Bayer, Novartis. Boissier.F has received travel and accommodation fees from AOP Orphan. Leurent.G reports proctoring activity, lecture and consultant fees from Abbott. Combaret N has received lecture fees from Pfizer and Medtronic. Gerbaud E has received consulting fees from Terumo, Abbott and Vifor pharma. Delmas C has received consulting fees from Abiomed, Abbott and Moderna; lecture fees from Abiomed, Abott, Astrazeneca, Bayer, Orion and Servier. All the other authors have nothing to disclaimed.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcc.2024.154785>.



org/10.1016/j.jcrc.2024.154785.

## References

- [1] Chioncel O, Parissis J, Mebazaa A, Thiele H, Desch S, Bauersachs J, et al. Epidemiology, pathophysiology and contemporary management of cardiogenic shock - a position statement from the heart failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;22(8):1315–41.
- [2] Bukhari S, Fatima S, Elgendy IY. Cardiogenic shock in the setting of acute myocardial infarction: another area of sex disparity? *World J Cardiol* 2021;13(6):170–6.
- [3] Lam CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, et al. Sex differences in heart failure. *Eur Heart J* 2019;40(47):3859–68c.
- [4] Wang AS, Nemeth S, Kurlansky P, Brodie D, Takayama H, Naka Y, et al. Sex differences in patients with cardiogenic shock requiring extracorporeal membrane oxygenation. *J Thorac Cardiovasc Surg* 2022;164(3):960–9 e6.
- [5] Yan I, Schrage B, Weimann J, Dabboura S, Hilal R, Beer BN, et al. Sex differences in patients with cardiogenic shock. *ESC Heart Fail* 2021;8(3):1775–83.
- [6] Lala A, Tayal U, Hamo CE, Youmans Q, Al-Khatib SM, Bozkurt B, et al. Sex differences in heart failure. *J Card Fail* 2022;28(3):477–98.
- [7] Solola Nussbaum S, Henry S, Yong CM, Daugherty SL, Mehran R, Poppas A. Sex-specific considerations in the presentation, diagnosis, and Management of Ischemic Heart Disease: JACC focus seminar 2/7. *J Am Coll Cardiol* 2022;79(14):1398–406.
- [8] Bairey Merz CN. Women and ischemic heart disease paradox and pathophysiology. *JACC Cardiovasc Imaging* 2011;4(1):74–7.
- [9] Haider A, Bengs S, Luu J, Osto E, Siller-Matula JM, Muka T, et al. Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome. *Eur Heart J* 2020;41(13):1328–36.
- [10] Manzo-Silberman S, Couturaud F, Charpentier S, Auffret V, El Khoury C, Le Breton H, et al. Influence of gender on delays and early mortality in ST-segment elevation myocardial infarction: insight from the first French Metaregistry, 2005–2012 patient-level pooled analysis. *Int J Cardiol* 2018;262:1–8.
- [11] Mody P, Pandey A, Slutsky AS, Segar MW, Kiss A, Dorian P, et al. Gender-based differences in outcomes among resuscitated patients with out-of-hospital cardiac arrest. *Circulation*. 2021;143(7):641–9.
- [12] Stehli J, Martin C, Brennan A, Dinh DT, Lefkowitz J, Zaman S. Sex differences persist in time to presentation, revascularization, and mortality in myocardial infarction treated with percutaneous coronary intervention. *J Am Heart Assoc* 2019;8(10):e012161.
- [13] McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42(36):3599–726.
- [14] Delmas C, Roubille F, Lamblin N, Bonello L, Leurent G, Levy B, et al. Baseline characteristics, management, and predictors of early mortality in cardiogenic shock: insights from the FRENDSHOCK registry. *ESC Heart Fail* 2022;9(1):408–19.
- [15] Delmas C, Puymirat E, Leurent G, Elbaz M, Manzo-Silberman S, Bonello L, et al. Design and preliminary results of FRENDSHOCK 2016: a prospective nationwide multicentre registry on cardiogenic shock. *Arch Cardiovasc Dis* 2019;112(5):343–53.
- [16] Sambola A, Elola FJ, Buera I, Fernandez C, Bernal JL, Ariza A, et al. Sex bias in admission to tertiary-care centres for acute myocardial infarction and cardiogenic shock. *Eur J Clin Invest* 2021;51(7):e13526.
- [17] Beer BN, Jentzer JC, Weimann J, Dabboura S, Yan I, Sundermeyer J, et al. Early risk stratification in patients with cardiogenic shock irrespective of the underlying cause - the cardiogenic shock score. *Eur J Heart Fail* 2022;24(4):657–67.
- [18] Elgendy IY, Wegermann ZK, Li S, Mahtta D, Grau-Sepulveda M, Smilowitz NR, et al. Sex differences in management and outcomes of acute myocardial infarction patients presenting with cardiogenic shock. *JACC Cardiovasc Interv* 2022;15(6):642–52.
- [19] Baudry G, Lescroart M, Kimmoun A. Are left ventricular ejection fraction phenotypes meaningful in acute heart failure? *Eur J Heart Fail* 2023;25(6):829–31.
- [20] Farmakis D, Tromp J, Marinaki S, Ouwerkerk W, Angermann CE, Bistola V, et al. Impact of left ventricular ejection fraction phenotypes on healthcare resource utilization in hospitalized heart failure: a secondary analysis of REPORT-HF. *Eur J Heart Fail* 2023;25(6):818–28.
- [21] Puymirat E, Fagon JY, Aegerter P, Diehl JL, Monnier A, Hauw-Berlemont C, et al. Cardiogenic shock in intensive care units: evolution of prevalence, patient profile, management and outcomes, 1997–2012. *Eur J Heart Fail* 2017;19(2):192–200.
- [22] Thayer KL, Zweck E, Ayouty M, Garan AR, Hernandez-Montfort J, Mahr C, et al. Invasive hemodynamic assessment and classification of in-hospital mortality risk among patients with cardiogenic shock. *Circ Heart Fail* 2020;13(9):e007099.
- [23] Kapur NK, Kanwar M, Sinha SS, Thayer KL, Garan AR, Hernandez-Montfort J, et al. Criteria for defining stages of cardiogenic shock severity. *J Am Coll Cardiol* 2022;80(3):185–98.
- [24] Schrage B, Becher PM, Bernhardt A, Bezerra H, Blankenberg S, Brunner S, et al. Left ventricular unloading is associated with lower mortality in patients with cardiogenic shock treated with Venoarterial extracorporeal membrane oxygenation: results from an international, Multicenter Cohort Study. *Circulation* 2020;142(22):2095–106.
- [25] Collado-Lledo E, Llao I, Rivas-Lasarte M, Gonzalez-Fernandez V, Noriega FJ, Hernandez-Perez FJ, et al. Clinical picture, management and risk stratification in patients with cardiogenic shock: does gender matter? *BMC Cardiovasc Disord* 2020;20(1):189.