Design and preliminary results of FRENSHOCK 2016: A prospective nationwide multicentre registry on cardiogenic shock

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Abbreviated title: Design and preliminary results of FRENSHOCK 2016

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Summary

Background. – Most data on the epidemiology of cardiogenic shock (CS) have come from patients with acute myocardial infarction admitted to intensive cardiac care units (ICCUs). However, CS can have other aetiologies, and could be managed in intensive care units (ICUs), especially the most severe forms of CS.

Aim. – To gather data on the characteristics, management and outcomes of patients hospitalized in ICCUs and ICUs for CS, whatever the aetiology, in France in 2016.

Methods. – We included all adult patients with CS between April and October 2016 in metropolitan France. CS was defined (at admission or during hospitalization) by: low cardiac output, defined by systolic blood pressure < 90 mmHg and/or the need for amines to maintain systolic blood pressure > 90 mmHg and/or cardiac index < 2.2 L/min/m²; elevation of the left and/or right heart pressures, defined by clinical, radiological, biological, echocardiographic or invasive haemodynamic overload signs; and clinical and/or biological signs of malperfusion (lactate > 2 mmol/L, hepatic insufficiency, renal failure).

Results. – Over a 6-month period, 772 patients were included in the survey (mean age 65.7 ± 14.9 years; 71.5% men) from 49 participating centres (91.8% were public, and 77.8% of these were university hospitals). Ischaemic trigger was the most common cause (36.3%).

Conclusions. – To date, FRENSHOCK is the largest CS survey; it will provide a detailed and comprehensive global description of the spectrum and management of patients with CS in a high-income country.

Résumé

Contexte. – La majorité des données disponibles sur le choc cardiogénique (CC) concernent des patients présentant un syndrome coronarien aigu hospitalisés en soins intensifs de cardiologie. Or, les patients en CC peuvent avoir d'autres étiologies et être pris en charge en réanimation, avec souvent une défaillance multi viscérale et possiblement un profil clinique et un pronostic différent.

But. – Faire un état des lieux des caractéristiques, de la prise en charge et du pronostic des patients pris en charge pour un CC quelle qu'en soit son étiologie, en France en 2016

Méthodes. – Les patients présentant un CC entre Avril et Octobre 2016 en France ont été prospectivement inclus. Le CC était défini par l'association d'un critère : de bas débit cardiaque défini

par une pression artérielle systolique < 90 mmHg ou la nécessité d'amines vasopressives et/ou inotropes, et/ou par un index cardiaque < 2,2 L/min/m^2 ; une élévation clinique, biologique, échographique ou invasive des pressions de remplissage droites et/ou gauches ; et des signes de malperfusion clinique et/ou biologique (lactate > 2 mmol/L, insuffisance rénale et/ou hépatique).

Résultats. – Sur une période de 6 mois, 772 patients ont été inclus (âge moyen de 65,7 ± 14,9 ans ; 71,5 % d'hommes) dans 49 centres (91,2 % publics dont 71,4 % universitaires). Le facteur déclenchant ischémique était majoritaire (36,3 %).

Conclusions. – FRENSHOCK est à ce jour le plus vaste registre de CC toutes causes, permettant de faire une description précise et détaillée de la typologie et la prise en charge de ces patients dans un pays à haut niveau de revenu.

KEYWORDS

Cardiogenic shock;

Registry;

Design;

Abbreviations: AMI, acute myocardial infarction; BNP, brain natriuretic peptide; CS, cardiogenic shock; IABP, intra-aortic balloon pump; ICU, intensive care unit; ICCU, intensive cardiac care unit.

Background

Cardiogenic shock (CS) is usually defined as a state of organ malperfusion in a context of low cardiac output without hypovolaemia, signalling primary cardiac failure. However, various definitions have been proposed [1], indicating a wide spectrum of clinical presentations and outcomes, ranging from mild haemodynamic perturbations considered as “pre-shock” to much more severe haemodynamic compromise leading to multiorgan failure [2].

Despite renewed interest and effort in recent years, with some large-scale randomized studies [3-5] in CS complicating acute myocardial infarction (AMI-CS), data on CS are scarce compared with other shock aetiologies. Most recommendations for CS management are low level in European guidelines [6]. Few strong recommendations exist, based on evidence from randomized studies, and which advocate urgent revascularization [3] and discourage the systematic use of an intra-aortic balloon pump (IABP) for AMI-CS [4, 5]. These contrast with weak recommendations regarding the use of catecholamines in the management of CS, in the absence of large dedicated randomized studies [7-9]. Consequently, there is a need for good quality and large-scale observational data [10]. Most data have been provided by health insurance (National Institutes of Health) database analyses in the USA [11-13] and acute coronary syndrome registries in the USA [14-16] and Europe [17-20]; these registries focused mainly on AMI-CS. Fewer data are available on all-cause CS, and results are discordant. The main registry is the recent prospective multicentre CARDSHOCK registry, which included 219 patients in nine European centres and reported a clear preponderance of AMI-CS (80%) [21]. In contrast, recent analyses of databases from France and the USA have suggested a clear increase in non-ischaemic aetiologies (up to 60% of CS cases). Furthermore, this study showed an increase in the prevalence of CS in intensive care (from 4.1% to 7.7% between 1997 and 2012) [22], and persistence of a high mortality rate, advocating further specific research [13, 16, 22]. Moreover, little is known about networks dedicated to CS, despite the fact that they could play a major role in the management of these patients [23].

The FRENSHOCK registry was a multicentre national registry that aimed to capture all instances of CS during a specific time window. The registry was designed to describe population characteristics, aetiologies, pathways, management and outcomes in everyday practice. The main objectives were to provide a precise overview of all-cause CS in France in 2016, and to assess 30-day and 1-year

outcomes of patients with CS. In this report, we present the design of the FRENSHOCK registry, and compared it with previous CS registries.

Methods

Study design

FRENSHOCK was a prospective multicentre observational survey conducted in metropolitan France during a 6-month period between April and October 2016 (Clinicaltrials.gov Identifier: NCT02703038). The general organization of the FRENSHOCK registry is presented in Appendix A.

Population

The study inclusion criteria are described in Table 1. Patients aged > 18 years were included prospectively, regardless of the CS aetiology, if they met at least one criterion in each of the following three components: (1) low cardiac output, defined by systolic blood pressure < 90 mmHg and/or the need for amines to maintain systolic blood pressure > 90 mmHg and/or cardiac index < 2.2 L/min/m² on echocardiography or right heart catheterization; (2) elevation of left and/or right heart pressures, defined by clinical signs, radiology (overload signs on chest X-ray or computed tomography scan), biological tests (natriuretic peptide elevation), echocardiography (usual signs of left ventricular filling pressure elevation) or invasive haemodynamic overload signs (elevation of mean pulmonary artery pressure or pulmonary capillary wedge pressure); and (3) signs of malperfusion, which could be clinical (oliguria, mottling, confusion) and/or biological (lactate > 2 mmol/L, hepatic insufficiency, renal failure).

Patients admitted after resuscitation of a cardiac arrest were included if they fulfilled previously defined CS criteria. Patients could be included regardless of whether CS was initial or secondary.

Exclusion criteria were refusal or inability to consent and diagnosis of CS refuted in favour of alternative diagnoses, such as septic shock, refractory cardiac arrest and postcardiotomy CS.

Organization and funding

Participating centres

At the end of 2015, participation in the study was offered to all types of institutions (academic hospitals, general hospitals and private clinics), and to all types of units that manage patients with CS in France (intensive cardiac care units [ICCUs], surgical intensive care units [ICUs], medical ICUs and general ICUs).

Data collected

Patient demographic data and information about socioprofessional situation (active, retired, disabled or unemployed) were recorded. Cardiovascular history, coexisting medical conditions (chronic kidney disease, pulmonary or neurological disease, cancer, etc.), risk factors (smoking status, hypertension, dyslipidaemia and diabetes mellitus), treatment at admission and clinical presentation were recorded.

Up to three CS triggers among the following were considered for each patient: ischaemic (type 1 or type 2 AMI according to European guidelines), mechanical complications, ventricular and supraventricular arrhythmia, severe bradycardia, iatrogenic events, infections and/or non-observance of previous medication. Investigators could also note if other factors or aetiologies existed – these triggering factors were marked as "others".

The care path and the time of care were specified: type of first medical contact, initial place of care, possible transfer to a tertiary centre and the corresponding deadlines.

Clinical, biological and echocardiographical data during the first 24 hours after admission were collected. Clinical data included blood pressure, heart rate, presence of signs of left and right heart failure (including Killip class), presence of mottling and presence of sinus rhythm. Biological data included serum electrolytes, renal and hepatic function and haemostasis, arterial and venous ($ScVO_2$) blood gases and arterial lactate, C-reactive protein, troponin and B-type natriuretic peptide (BNP) or N-terminal prohormone of BNP concentrations. Each concentration was measured in each investigating centre with its own dosage and reference value. Echocardiograms were done by the doctor in charge of the patient (cardiologist or intensivist), regardless of their level of expertise [24]. Mandatory echocardiographic data included left ventricular ejection fraction (visual evaluation or Simpson’s biplane), presence of pericardial effusion and presence of severe valvulopathy (defined as grade IV). Additional echocardiographic variables were favoured, but not mandatory (right ventricular function and overload variables based on the usual expert recommendations) [25].

The in-hospital CS management data recorded included use of inotropes and vasopressors (type, dose and duration), diuretics (type and dose), organ replacement therapies as ventilation (mechanical or non-invasive, and duration), temporary mechanical circulatory support (type of IABP; extracorporeal membrane oxygenation or Impella® (Abiomed, Danvers, MA, USA); and duration) and renal replacement therapy (continuous or intermittent type, indication and duration). End-stage heart failure treatment was recorded as urgent heart transplant list registration, bridge to a left ventricular assist device, total artificial heart or heart transplantation. If carried out, data from right heart catheterization, coronary angiography, revascularization by coronary artery bypass graft and/or percutaneous coronary intervention, but also any surgery, were collected. Information on in-hospital complications, such as stroke, bleedings and transfusions, haemolysis, thrombocytopoenia, infection, vascular complications and death, were collected.

Follow-up

Several follow-up points were considered, and are described in Table 2: at hospital discharge and 30 days by the local investigator; and at 1 year by dedicated research technicians based at the French Society of Cardiology.

At 1 year, follow-up was performed using the following sequential procedure: first, consult the registry office of the patient's birthplace for death certificates; then, contact the patient's general practitioner and/or cardiologist; and finally, contact the patient or their direct relatives. In many instances, written contact was followed by a telephone interview with the patient or their family to clarify mode of living, presence of left ventricular or biventricular assist device or heart transplantation, ongoing treatment and eventual return to work

Data quality

Data quality was ensured using numerous automated checks when the electronic case record forms were completed, and by the fact that some data entered were verified, and modified if necessary, by external research assistants from the French Society of Cardiology after verification with the patient's referring investigators. Completeness of the data was adequate for most variables (e.g. rates of missing values were 3.5% for height, 2.2% for weight, < 0.5% for admission blood pressure and heart rate and < 0.3% for previous cardiomyopathy). Once entered into the electronic case record form, data

were stored in a central database at the French Society of Cardiology in Paris. Data management is ensured, in conjunction with the French Society of Cardiology and Toulouse University.

Legal issues

Written informed consent was provided by each patient. Patients who died early after admission were not screened, and were not included as informed consent could not be obtained. The study was conducted in compliance with Good Clinical Practice, French law and the French data protection law. The data that were recorded and their handling and storage were reviewed and approved by the Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé (CCTIRS) (n° 15.897) and the Commission Nationale Informatique et Liberté (CNIL) (n° DR-2016-109). The study is registered with ClinicalTrials.gov (Identifier: NCT02703038).

Funding and data property

This was a French Society of Cardiology registry, carried out by its Emergency and Intensive Cardiac Care Unit group. The study was sponsored by the Fédération Française de Cardiologie, and was funded by unrestricted grants from Daiichi-Sankyo and Maquet SAS. Complementary grants will be sought for dedicated research projects within the main study.

Statistical analysis

Quantitative data are reported using means ± standard deviations, or medians (interquartile ranges) when skewed. Qualitative data are presented as numbers and percentages.

Planned analyses will compare different groups of patients with CS: patients with ischaemic and non-ischaemic CS or with and without clinical hypotension or with and without right failure. Univariate analyses for comparisons between groups will be performed using classical statistical tests: the χ^2 test or Fisher's exact test for categorical data, and Student's *t* test or analysis of variance for quantitative data. Non-parametric tests will be used when needed. Multivariable analyses will be conducted using appropriate methods (multiple logistic regression).

Global mortality after 30 days and after 1 year will be studied using Kaplan−Meier survival analyses. Relationships between patient characteristics and 30-day or 1-year mortality will be tested

using log-rank tests, and multivariable analyses will be performed using a Cox proportional hazards regression model.

All analyses will be performed using Stata statistical software, version 10 (StataCorp, College Station, TX, USA)

Results

Population description

A total of 777 patients were included initially, but five were excluded because they had been enrolled twice; 772 patients were therefore included in the final analysis.

Among the 52 centres that agreed to participate, 49 were active (Fig. 1): 35 academic hospitals, 10 general hospitals and four private clinics. Inclusion per centre varied from 1 to 72 patients, predominantly in public hospitals (*n* = 731; 94.7%), and particularly university hospitals (*n* = 670; 86.8%) (Appendix B).

The first preliminary results from the FRENSHOCK registry are presented in Table 3. Patients were mostly men (71.5%), with a mean age of 65.7 ± 14.9 years. More than half had previous cardiomyopathy, especially of ischaemic origin. Patients had comorbidities – frequently previous myocardial revascularization, peripheral vascular disease, stroke, chronic obstructive pulmonary disease and chronic organ failure. More than one-third of the population had no cardiovascular risk factors. The CS aetiology often had several triggers, but ischaemic was most common (36.3%), although type 1 AMI concerned only 17.2% of the population. Patients were managed and included in ICCUs (70.2%) or ICUs (general, medical or surgical) (29.8%).

Discussion

To our knowledge, FRENSHOCK is the largest published multicentre prospective study on CS of all aetiologies to date, with 772 patients included in 49 centres. FRENSHOCK will offer unique insights into real-life practice, though the participation of university and non-university hospitals as well as public and private centres.

This study derives its originality from the inclusion of patients who would usually have been excluded from previous studies because of restrictive inclusion/exclusion criteria. Patients could be included if they were aged > 18 years, because of administrative regulations, but without an upper age

restriction; patients aged up to 98 years could therefore be included for the first time. In ageing societies, elderly people represent a growing proportion of hospitalizations in ICUs and ICCUs (42.1% aged > 75 years and 15.5% aged > 85 years in ICCUs in 2014 in France [26]), but have largely been underconsidered in other studies; here, our methods enabled us to describe CS in elderly patients, in terms of characteristics, care and prognosis. Furthermore, our innovative inclusion criteria took into account the limitations of CS definitions, which is a strength of the study.

Our CS definition is pragmatic and practical, based on simple criteria available at the patient's bedside in any centre, regardless of its level of expertise, allowing rapid recognition and inclusion of patients in primary, secondary and tertiary care centres. Our definition is easy to use, to remember and to apply in daily practice. Indeed, to be considered as having CS, patients had to fulfil only three criteria: one low flow criterion, one overload criterion and one organ malperfusion criterion.

Contrary to previous definitions [1], typical daily non-invasive paraclinical approaches could be used to define low cardiac output (echocardiography) and overload variables (natriuretic peptides elevation, echocardiography, computed tomography and/or chest X-ray). Invasive haemodynamic evaluation by right heart catheterization was possible, but not mandatory, unlike in some previous trials (including the SHOCK study [3]).

To date, classical CS definitions have been based on and created for AMI-CS; in the SHOCK and IABP SHOCK II study definitions [3, 5], patients had to present signs of left heart failure, defined by clinical signs (pulmonary congestion) and/or haemodynamic signs (pulmonary capillary wedge pressure elevation > 15 mmHg), restricting the CS definition to ischaemic CS (predominantly left). Here, inclusions were not restricted to ischaemic CS or AMI-CS in centres capable of percutaneous coronary intervention, enabling us to address the lack of data in non-ischaemic CS. Thus, the inclusion of a majority of patients without an ischaemic trigger should provide interesting data in this population.

In addition, the FRENSHOCK definition of CS allows us to include patients with isolated or predominantly right heart failure, as right heart failure signs are part of the definition of the overload component of the registry. Importantly, these patients were discarded in previous studies and registries dedicated to patients with AMI-CS, despite a high prevalence (30–45%) [27] and a poor prognosis for right heart failure in patients with CS [28].

Further, patients with low cardiac output, congestion and malperfusion, but without “strictly” hypotension, were also taken into account, which is original and may provide useful data in this population, as their prognosis seems similar to that for patients with classical definitions of shock [29].

Altogether, this large study paints an accurate picture of contemporary clinical practice, and hence provides a better description of understudied populations.

To date, data on CS diagnosis, epidemiology, outcomes and management are scarce compared with other types of shock. For example, there were 32,749 references in PubMed and 519 ClinicalTrial identifiers for septic shock in September 2018 compared with 13,144 and 66, respectively, for CS. Furthermore, only 29 were prospective observational or interventional studies, and only nine had more than two investigating centres (Table 4). Through the FRENSHOCK database, we have many opportunities to acquire knowledge about CS. Thus, subgroup analyses are planned, including dichotomic variables, such as right failure non-ischaemic CS, and continuous variables, such as age. The aim is to better understand the pathophysiological and prognostic differences in these previously poorly described populations. Various therapeutic strategies are used, and their link with outcomes will be detailed and analysed.

Study limitations

First, inclusions were not exhaustive, and probably were not consecutive in all centres, because some centres with a known high volume of patients with CS included fewer than five patients during the 6-month inclusion period. Moreover, non-inclusions and reasons for not including patients were not counted. Therefore, we can approach the wide spectrum of CS in real-life practice in France, but not its incidence, even if FRENSHOCK is the largest survey to date on patients with CS, facilitating future appealing analyses.

Second, almost three-quarters of the inclusions were in academic centres, which prevents extrapolation of the results to all centres. However, in practice in France, we can expect that patients with CS are transferred to expert centres with a technical platform to support them, which limits this selective bias.

Third, this was an observational survey, with its intrinsic biases, and some data should be interpreted with caution. As a real-life survey, no previous level of expertise was required to perform or interpret imaging. Echocardiograms were performed in each centre by the physician in charge of the

patient, who could be a cardiologist or an intensivist, depending on the type of structure and place (emergency room, ICCU or ICU). The absence of imaging standardization and centralization (core laboratory) could be a source of bias in the definition of CS and its type. However, as quoted in an expert consensus statement, echocardiographic markers of CS, defined as the basic competence in critical care echocardiography, should be easily recognized by operators with minimal training [24]. Moreover as a non-interventional survey, the impact of different medications and management strategies should be assessed with caution [30].

Finally, data from patients who died early (i.e. before informed consent was obtained) were not collected and recorded in the database because of administrative regulations; this could be a source of bias, leading to an underestimation of mortality in our cohort.

Conclusions

As a result of its broad inclusion criteria and limited exclusion criteria, the FRENSHOCK survey will provide a large and original dataset on contemporary CS; it will facilitate important subgroup analysis of aetiologies excluded from previous registries and trials. This is the largest prospective multicentre survey of CS of all causes, allowing a contemporary description of CS in everyday clinical practice in France.

Acknowledgements

We are indebted to all patients who agreed to participate in the registry, and to all cardiologists, intensivists and surgeons who took part. Our thanks to all the devoted personnel of Société Française de Cardiologie who actively participated in conducting the registry, especially N. Naccache and E. Drouet.

Sources of funding

This study was supported by a grant from the Fédération Française de Cardiologie, and by unrestricted grants from the Daiichi-Sankyo-Eli-Lilly alliance and Maquet SAS.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Figure legend

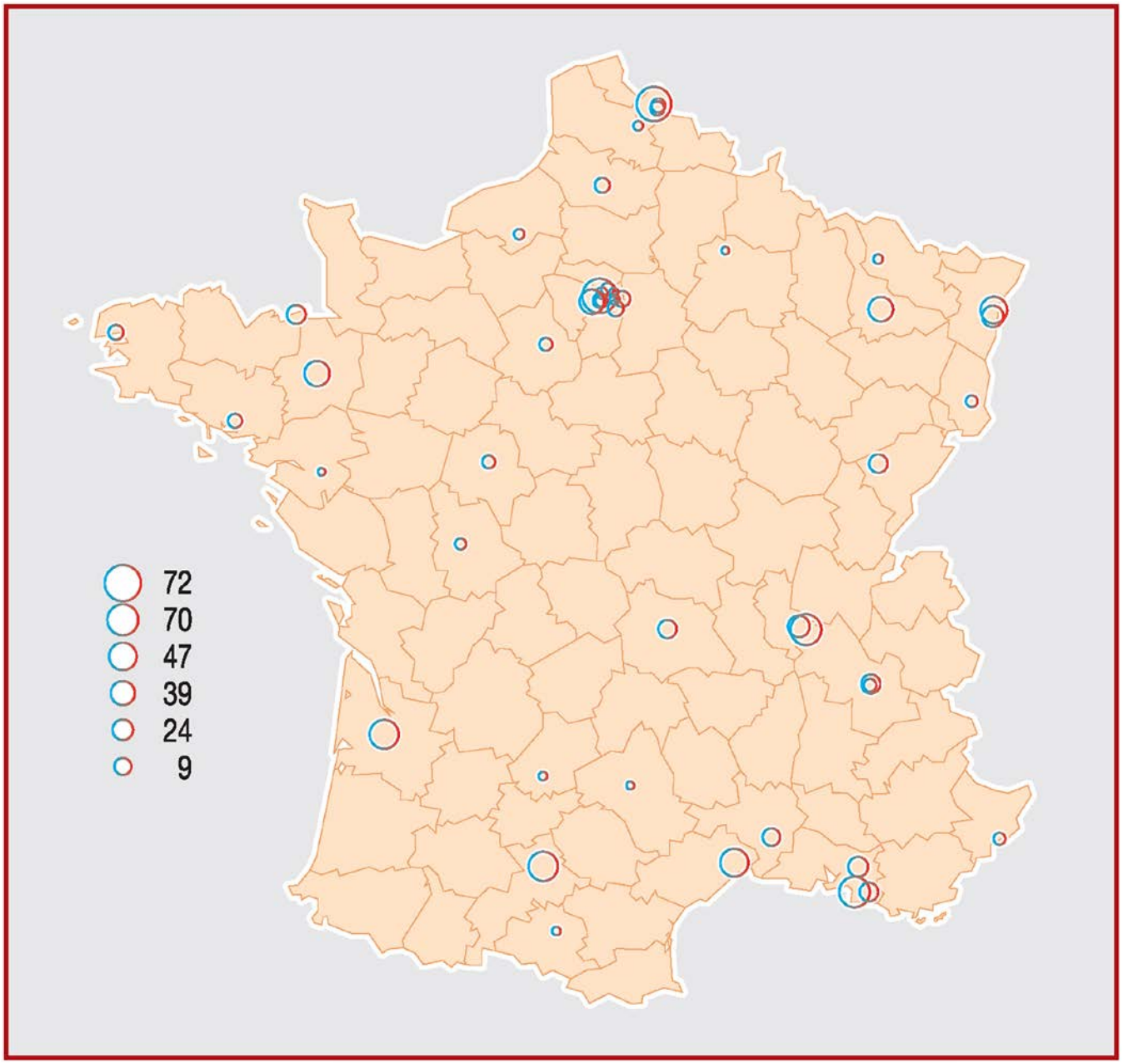

Figure 1. Geographic distribution of the centres participating in the FRENSHOCK registry.

Table 1 Inclusion criteria (FRENSHOCK definition of cardiogenic shock).

Component	Criteria
Low cardiac output	SBP < 90 mmHg or need for vasopressors/inotropes to maintain SBP > 90 mmHg
	CI < 2.2 L/min/m^2 (by echocardiography and/or invasive haemodynamic evaluation with right heart catheterization)
Right and/or left overload	Clinical assessments (dyspnoea, rales and crepitations, jugular venous distension and/or abdominojugular test, oedema)
	Biological tests (NT-proBNP > 900 pg/mL and/or BNP > 400 pg/mL)
	Radiology (overload signs on chest X-ray and/or chest tomodensitometry)
	Echocardiography (E/A > 2 if LVEF < 45% or E/Ea > 13 if LVEF normal; or sPAP > 35 mmHg and/or E deceleration time < 150 ms and/or Ap-Am > 30 ms and/or E/Vp ≥ 2.5)
	Invasive haemodynamic evaluation with right heart catheterization (PCWP > 15 mmHg and/or mPAP > 25 mmHg)
Organ malperfusion	Clinical (oliguria < 0.5mL/kg/h, confusion, cold/clammy skin and extremities and/or marbling)
	Biology (lactate > 2 mmol/L, metabolic acidosis, liver insufficiency and/or renal failure)

To be considered to have cardiogenic shock, patients had to fulfil at least one criterion from each of the three components: low cardiac output; left and/or right overload; and organ malperfusion. BNP: B-type natriuretic peptide; CI: cardiac index; LVEF: left ventricular ejection fraction; mPAP: mean pulmonary arterial pressure; NT-proBNP: N-terminal prohormone of B-type natriuretic peptide; PCWP: pulmonary capillary wedge pressure; SBP: systolic blood pressure.

Table 2 Planned follow-up in the FRENSHOCK registry

	Hospital discharge	30 days	1 year
NYHA class	X		X
LVEF	X		
Ongoing medications	X		X
Mode of living	X		X
Return to work	X		X
Vital status	X	X	X
Terminal heart failure treatment	X	X	X
LVAD	X	X	X
BiVAD or TAH	X	X	X
HTx	X	X	X

BiVAD: biventricular assist device; HTx: heart transplantation; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association classification of dyspnoea; TAH: total artificial heart.

Table 3 Main characteristics of the FRENSHOCK population (*n* = 772).

Age (years)	65.7 ± 14.9
Men	552 (71.5)
BMI (kg/m^2)	25.8 ± 5.5
Cardiovascular risk factors	
Diabetes	217 (28.2)
Hypertension	343 (44.5)
Dyslipidaemia	241 (31.3)
Current smoker	206 (27.8)
Main medical history	
Peripheral artery disease	114 (14.8)
Previous myocardial revascularization	203 (26.3)
Chronic renal failure	164 (21.3)
Chronic dialysis	11 (1.4)
COPD	50 (6.5)
Chronic respiratory failure	8 (1.0)
Active neoplasia	51 (6.6)
Stroke	62 (8.0)
Previous known cardiopathy	
Ischaemic	230 (29.8)
Hypertrophic	11 (1.4)
Posthypertensive	24 (3.1)
Valvular	65 (8.4)
Dilated	110 (14.3)
Others	76 (9.9)
Previous MSP and/or IAD	162 (21.0)
Ischaemic trigger CS	280 (36.3)
Type 1 MI	133 (67.5)
Cardiac arrest before admission	79 (10.3)

Support unit	
ICCU	414/590 (70.2)
ICU	176/590 (29.8)

Data are expressed as mean ± standard deviation or number (%). BMI: body mass index; COPD: chronic obstructive pulmonary disease; CS: cardiogenic shock; IAD: internal automatic defibrillator; ICCU: intensive cardiac care unit; ICU: intensive care unit; MI: myocardial infarction; MSP: multisite pacing.

Table 4 Ongoing or scheduled prospective trials on cardiogenic shock.

Country	Clinical trial identifier	Title	Intervention	Primary endpoints	Start date (M/Y)	Centres (*n*)	Patients included (*n*)	CS aetiologies	Estimated completion date (M/Y)
France	NCT03528291	Transient Circulatory Support in CS (ALLOASSIST)	Observational	In-hospital mortality	05/2018	?	240	Miscellaneous	01/2018
Indonesia	NCT03635840	The Effects of IABP Prior to Revascularization on Mortality of ACS Patients Complicated With CS	RT; parallel assignment	30-day mortality	01/2018	1	92	ACS	12/2018
USA	NCT03141255	CS Intravascular Cooling Trial (CHILL-SHOCK)	RCT; pilot study	Safety (arrythmia, bleedings, hypokalaemia, bloodstream infection)	11/2017	1	20	Miscellaneous	/062019
USA	NCT03378739	Implementation of a CS Team and Clinical Outcomes (INOVA SHOCK Registry)	Observational	1-year mortality	01/2018	1	400	Miscellaneous	11/2018
France	NCT03340779	Norepinephrine vs Norepinephrine and	Interventional; crossover	Haemodynamic variables	01/2018	1	40	Miscellaneous	11/2019

		Dobutamine in CS (SHOCK-NORDOB)	assignment						
France	NCT03283995	Haemodynamic Assessment in CS Regarding the Etiology	Observational	Transpulmonary thermodilution at 48 hours	09/2017	1	64	Miscellaneous	09/2019
USA	NCT03431467	Impella CP With VA ECMO for CS (REVERSE)	RT; parallel assignment	Survival free from HTx, LVAD or inotropes at 30 days	03/2018	1	96	Miscellaneous	01/2021
Spain	NCT03437369	Efficacy and Safety on Heart Rate Control With Ivabradine on CS (ES-FISH)	RCT; pilot study	Change in cardiac output and heart rate at 24 hours	05/2018	1	22	Miscellaneous	10/2019
Italy	NCT02591771	Study of Multistep Pharmacological and Invasive Management for CS	Phase 2 trial with single group	60-day survival	10/2015	2	24	Miscellaneous	11/2018
Czech Republic	NCT02301819	ECMO in the Therapy of CS (ECMO-CS)	RT; parallel assignment	Death from any cause, resuscitated circulatory arrest and implantation of another MCSD at 30 days	09/2014	3	120	Miscellaneous	06/2019

Germany	NCT02544594	Clinical Study of Extra-Corporal Life Support in CS Complicating AMI (ECLS-SHOCK)	RT; parallel assignment	LVEF at 30 days	11/2015	1	42	ACS	03/2019
China	NCT02870946	The Effect of Simultaneous Renal Replacement Therapy on ECMO Support for CS Patients	RT; parallel assignment	30-day mortality	08/2016	1	262	Miscellaneous	12/2018
Denmark/Germany	NCT01633502	Danish CS Trial	RT; parallel assignment	6-month mortality	12/2012	7	360	ACS/only STEMI	09/2022
USA	NCT02790242	Registry for CS: Utility and Efficacy of Device Therapy (RESCUE)	Observational	1-year survival after MCSD implantation	11/2013	7	200,000	Miscellaneous	08/2018
Germany/UE	NCT03637205	Extracorporeal Life Support in CS (ECLS-SHOCK)	RT; parallel assignment	30-day mortality	10/2018	?	420	ACS	01/2022
USA	NCT03387605	Effect of Ivabradine in Stage D HF/CS Patients on Dobutamine	RCT	Heart rate during first 72 hours	03/2018	1	40	Miscellaneous	01/2020
Czech Republic	NCT03551964	Dual Antiplatelet Therapy For Shock Patients With AMI (DAPT-SHOCK-AMI)	RCT	Death/MI/stroke at 30 days	08/2018	12	304	ACS	06/2020
China	NCT03549923	Evaluation of Early CRRT and	RCT	30-day mortality	06/2018	?	550	Miscellaneous	06/2022

		Beta-blocker Interventions in Patients With ECMO (ELITE)							
UK	NCT03532529	Evaluation of Speckle Tracking Parameters as Predictors of Successful VA ECMO Weaning Procedure.	Observational; pilot study	Death from any cause, HTx or new implantation of another MCSD at 30 days	09/2018	1	24	Miscellaneous	11/2019
France	NCT03327493	Impact of Adrenoreceptor Expressions on Inflammatory Pattern in Refractory CS Under VA ECMO (ADRECMO)	Interventional; single-arm assignment	Change in cytokine during ECMO support	10/2017	1	40	Miscellaneous	09/2019
France	NCT03436641	Microcirculation in CS (MicroShock)	Observational	Incidence of microcirculatory impairment in CS and 28-day mortality	05/2018	2	100	Miscellaneous	03/2020
Germany	NCT02697006	Synchronized Cardiac Assist for CS. The SynCor trial.	Observational	Safety and efficacy of i-cor device implantation	01/2016	1	48	ACS	05/2018
Korea	NCT02985008	Clinical Outcomes and Efficacy of LVAD for Korean Patients With CS: RESCUE	Observational	In-hospital mortality	04/2016	?	1000	Miscellaneous	12/2019

Canada	NCT03207165	Milrinone Versus Dobutamine in Critically Ill Patients	RT; parallel assignment	In-hospital mortality	08/2017	1	192	ACS	06/2020
France	NCT02754193	Effects of Induced Moderate HYPOthermia on Mortality in CS Patients Rescued by VA ECMO (HYPO-ECMO)	RT; parallel assignment	30-day mortality	07/2016	19	334	Miscellaneous	09/2019

Sixty-six studies were found to be registered on “clinicaltrials.gov” in September 2018 using the keyword “cardiogenic shock”; we deleted terminated or completed studies (n= 26), studies not exclusively concerning patients with CS (*n* = 7), studies that had been withdrawn or with status unknown (*n* = 4) and studies with a retrospective design (*n* = 4). Only trials including patients exclusively with CS are presented (e.g. patients benefiting from percutaneous coronary intervention at high risk are not presented). AMI: acute myocardial infarction; ACS: acute coronary syndrome; CRRT: continuous renal replacement therapy; CS: cardiogenic shock; ECMO: extracorporeal membrane oxygenation; HF: heart failure; HTx: heart transplantation; IABP: intra-aortic balloon pump; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; M: month; MCSD: mechanical circulatory support device; MI: myocardial infarction; RCT: randomized controlled trial; RT: randomized trial; STEMI: ST-segment elevation myocardial infarction; VA: venoarterial; Y: year.