Clinical trial results:
Study Comparing the Efficacy and Tolerability of Epinephrine and Norepinephrine in Cardiogenic Shock. OPTIMA CC.

(French full title : Optimisation du traitement vasopresseur du choc cardiogénique postinfarctus du myocarde reperfusé. Etude comparant l'efficacité et la tolérance de l'adrénaline et la noradrénaline (Optima CC))

Summary

EudraCT number	2009-017081-23
Trial protocol	FR
Global end of trial date	10 February 2016

Results information

Result version number	v1 (current)
This version publication date	28 April 2022
First version publication date	28 April 2022

Trial information

Trial identification

Sponsor protocol code	CPRC2009/OPTIMA CC-LEVY/NK

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01367743
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHRU de NANCY
Sponsor organisation address	29 Avenue du Maréchal de Lattre de Tassigny, NANCY, France, 54035
Public contact	El Mehdi SIAGHY, CHRU de NANCY, 0033 383155286, dripromoteur@chru-nancy.fr
Scientific contact	El Mehdi SIAGHY, CHRU de NANCY, 0033 383155286, dripromoteur@chru-nancy.fr

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 February 2016
Global end of trial reached?	Yes
Global end of trial date	10 February 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Compare the efficiency and the tolerability of norepinephrine and epinephrine in cardiogenic shock after reperfused myocardial infarction.

Protection of trial subjects:

Patients was included in emergency situation.
For all patients included, all diagnostic, therapeutic and weaning procedures have be done according to the current standard of care at the discretion of the investigator.
There was no foreseeable risks associated with this study; the drugs was used in the usual therapeutic setting.
The doses were adapted according to the therapeutic objectives. The administration scheme was identical for both molecules, and corresponds to current practices in intensive care.

Background therapy:

For all patients included, all therapeutic and weaning procedures have be done according to the current standard of care at the discretion of the investigator.

Evidence for comparator:

Norepinephrine and epinephrine are currently the most commonly used vasopressor agents in clinical practice (PMID: 19781431 ; 28131429 ; 22920912). Studies comparing epinephrine and norepinephrine in patients with septic shock found no significant differences in outcome (PMID: 24686400). Nevertheless, these drugs may have certain specific effects in patients with cardiogenic shock (CS) that could influence outcome. Norepinephrine is likely less thermogenic than epinephrine and therefore may have a more desirable effect on myocardial oxygen consumption (PMID : 22920912). During acute ischemic CS, norepinephrine induces favorable effects on myocardial function (PMID: 26849625, PMID: 24509521). Conversely, epinephrine may induce a higher cardiac index and deliver available nutrients very rapidly to the heart through lactate production (PMID: 17242933).
Two retrospective studies further suggested that epinephrine may have deleterious effects associated with greater circulating cardiovascular biomarkers in patients with CS (PMID: 27374027, PMID: 12458064). Moreover, despite these potential negative warnings, epinephrine is still used to treat the most severe forms of CS after myocardial infarction. However, none of these findings has been assessed prospectively in this specific clinical setting. The recent scientific statement from the American Heart Association recommends performing RCTs to identify the optimal vasopressor regimen in these patients (PMID: 28923988).

Actual start date of recruitment	06 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 57
Worldwide total number of subjects	57
EEA total number of subjects	57

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	22
From 65 to 84 years	31
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

This multicenter study was conducted between 6 Sept 2011 (first inclusion) and 10 Feb 2016 (last patient last visit) in 9 French intensive care units (ICUs). The cardiogenic shock patients admitted in ICUs was included in emergency situation with inclusion/exclusion criteria verification.

Pre-assignment

Screening details:

Nb of subjects screened for inclusion : 163.Reasons for excluding subjects: Moribund (34);Poor neurologic prognosis (30);Immediate ECLS(22);Declined to participate(7);No medical insurance(5); Other reasons(8).Nb of patients included:58 (57 patients with written informed consent (27 EPI vs 30 NOREPI). No written consent obtained for one patient).

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Randomization was computer generated, based on random blocks of 4, and stratified according to participating ICU. Treatment assignments and patient
reference number were placed in sealed, opaque envelopes, which were opened by an independent pharmacist in charge of the preparation of the study drugs. Norepinephrine or epinephrine syringes were prepared extemporaneously by the pharmacist. Each syringe was subsequently labeled with the patient's number only and was indistinguishable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Epinephrine

Arm description:

continuous infusion of commercial epinephrine prepared in syringes in order to obtain a MAP of 65-70 mmHg

Arm type	Active comparator
Investigational medicinal product name	Epinephrine
Investigational medicinal product code	ATC code : C01CA24
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IMP doses are expressed in micrograms per kilogram per minute. The dosages of epinephrine or norepinephrine will be the same (whatever the drug) as those used in same as those used in standard practice for the management of cardiogenic shock, with dosages ranging from 0.1 to 3 µg/kg/min being the usual dosages used in this in this pathology. The administration will be administrated with a syringe pump in continuous infusion. Doses were increased by 0.02 mg/kg/min (or higher in emergency cases). The targeted MAP was 65 to 70 mm Hg. A patient was considered to be weaned from vasopressor therapy after 24 h of hemodynamic stability without vasopressor support.

Arm title	Norepinephrine

Arm description:

continuous infusion of commercial norepinephrine prepared in syringes in order to obtain a MAP of 65-70 mmHg

Arm type	Active comparator

Investigational medicinal product name	Norepinephrine
Investigational medicinal product code	code ATC : C01CA03
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IMP doses are expressed in micrograms per kilogram per minute. The dosages of epinephrine or norepinephrine will be the same (whatever the drug) as those used in same as those used in standard practice for the management of cardiogenic shock, with dosages ranging from 0.1 to 3 µg/kg/min being the usual dosages used in this in this pathology. The administration will be administrated with a syringe pump in coninuous infusion. Doses were increased by 0.02 mg/kg/min (or higher in emergency cases). The targeted MAP was 65 to 70 mm Hg. A patient was considered to be weaned from vasopressor therapy after 24 h of hemodynamic stability without vasopressor support.

Number of subjects in period 1	Epinephrine	Norepinephrine
Started	27	30
Completed	27	30

Baseline characteristics

Reporting groups	
Reporting group title	Epinephrine
Reporting group description:	
continuous infusion of commercial epinephrine prepared in syringes in order to obtain a MAP of 65-70 mmHg	
Reporting group title	Norepinephrine
Reporting group description:	
continuous infusion of commercial norepinephrine prepared in syringes in order to obtain a MAP of 65-70 mmHg	

Reporting group values	Epinephrine	Norepinephrine	Total
Number of subjects	27	30	57
Age categorical Units: Subjects			
Adults (18-64 years)	9	13	22
From 65-84 years	15	16	31
85 years and over	3	1	4
Age continuous Units: years			
median	68	66	
inter-quartile range (Q1-Q3)	55 to 79	55 to 77	-
Gender categorical Units: Subjects			
Female	13	6	19
Male	14	24	38

End points

End points reporting groups

Reporting group title	Epinephrine
Reporting group description:	
continuous infusion of commercial epinephrine prepared in syringes in order to obtain a MAP of 65-70 mmHg	
Reporting group title	Norepinephrine
Reporting group description:	
continuous infusion of commercial norepinephrine prepared in syringes in order to obtain a MAP of 65-70 mmHg	

Primary: Change in cardiac index between H0 and H72

End point title	Change in cardiac index between H0 and H72
End point description:	
Baseline cardiac index was described in each group as median (Q1 - Q3).	
End point type	Primary
End point timeframe:	
Cardiac index was measured at randomization (H0) and at H2, H4, H6, H12, H24, H48, and H72.	

End point values	Epinephrine	Norepinephrine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: L/min/m2				
median (inter-quartile range (Q1-Q3))	1.8 (1.6 to 2.7)	2.1 (1.8 to 2.5)		

Attachments (see zip file)	FIg/Change in cardiac index.PNG

Statistical analyses

Statistical analysis title	Primary endpoint
Statistical analysis description:	
The evolution of cardiac index between H0 and H72 was compared in the 2 groups by using repeated-measures ANOVA based on the ranks of the values with the rank of baseline value as adjustment covariate. Because the post-baseline values were constrained by the clinical events observed during the follow-up, each value was ranked from lowest to highest at each time point, with the worst rank attributed for deceased patients and the second worst rank for patients who underwent ECLS.	
Comparison groups	Epinephrine v Norepinephrine

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.43 [1]
Method	Repeated-measures ANOVA
Confidence interval	
level	95 %
sides	2-sided

Notes:

[1] - Cardiac index evolution did not significantly differ between the epinephrine and norepinephrine groups.

Secondary: Change in heart rate between H0 and H72

End point title	Change in heart rate between H0 and H72

End point description:

Baseline heart rate was described in each group as median (Q1 - Q3).

End point type	Secondary

End point timeframe:

Heart rate was measured at randomization (H0) and at H2, H4, H6, H12, H24, H48, and H72.

End point values	Epinephrine	Norepinephrine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: bpm				
median (inter-quartile range (Q1-Q3))	96 (85 to 116)	97 (78 to 111)		

Attachments (see zip file)	Change in heart rate/Change in heart rate.PNG

Statistical analyses

Statistical analysis title	Change in heart rate between H0 and H72

Statistical analysis description:

The evolution of heart rate between H0 and H72 was compared in the 2 groups by using repeated-measures ANOVA based on the ranks of the values with the rank of baseline value as adjustment covariate. Because the post-baseline values were constrained by the clinical events observed during the follow-up, each value was ranked from lowest to highest at each time point, with the worst rank attributed for deceased patients and the second worst rank for patients who underwent ECLS.

Comparison groups	Epinephrine v Norepinephrine
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031 [2]
Method	Repeated-measures ANOVA

Notes:

[2] - Mean heart rate increased significantly in the epinephrine group, whereas it did not change significantly in the norepinephrine group.

Secondary: Change in mean arterial pressure

End point title	Change in mean arterial pressure

End point description:

Baseline mean arterial pressure was described in each group as median (Q1 - Q3).

End point type	Secondary

End point timeframe:

Mean arterial pressure was measured at randomization (H0) and at H2, H4, H6, H12, H24, H48, and H72.

End point values	Epinephrine	Norepinephrine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: mmHg				
median (inter-quartile range (Q1-Q3))	72 (69 to 79)	71 (66 to 83)		

Attachments (see zip file)	Change in MAP/Change in MAP.PNG

Statistical analyses

Statistical analysis title	Change in MAP between H0 and H72

Statistical analysis description:

The evolution of MAP between H0 and H72 was compared in the 2 groups by using repeated-measures ANOVA based on the ranks of the values with the rank of baseline value as adjustment covariate. Because the post-baseline values were constrained by the clinical events observed during the follow-up, each value was ranked from lowest to highest at each time point, with the worst rank attributed for deceased patients and the second worst rank for patients who underwent ECLS.

Comparison groups	Epinephrine v Norepinephrine
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25 [3]
Method	Repeated-measures ANOVA

Notes:

[3] - The evolution of MAP during the first 3 days of the study was similar between groups.

Secondary: Change in stroke volume index between H0 and H72

End point title	Change in stroke volume index between H0 and H72

End point description:

Baseline stroke volume index was described in each group as median (Q1 - Q3).

End point type	Secondary

End point timeframe:

Stroke volume index was measured at randomization (H0) and at H2, H4, H6, H12, H24, H48, and H72.

End point values	Epinephrine	Norepinephrine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: mL/beat/m²				
median (inter-quartile range (Q1-Q3))	20.2 (15.2 to 29.8)	21.5 (17.5 to 27.6)		

Attachments (see zip file)	Change in SVi/Change in SVi.PNG

Statistical analyses

Statistical analysis title	Change in SVi between H0 and H72

Statistical analysis description:

The evolution of SVi between H0 and H72 was compared in the 2 groups by using repeated-measures ANOVA based on the ranks of the values with the rank of baseline value as adjustment covariate. Because the post-baseline values were constrained by the clinical events observed during the follow-up, each value was ranked from lowest to highest at each time point, with the worst rank attributed for deceased patients and the second worst rank for patients who underwent ECLS.

Comparison groups	Epinephrine v Norepinephrine
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25 [4]
Method	Repeated-measures ANOVA

Notes:

[4] - The evolution of SVi was similar between groups.

Secondary: Change in cardiac double product between H0 and H72

End point title	Change in cardiac double product between H0 and H72

End point description:

Baseline cardiac double product was described in each group as median (Q1 - Q3).

End point type	Secondary

End point timeframe:

Cardiac double product was measured at randomization (H0) and at H2, H4, H6, H12, H24, H48, and H72.

End point values	Epinephrine	Norepinephrine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: mmHg.bpm				
median (inter-quartile range (Q1-Q3))	10300 (8755 to 12549)	9672 (8040 to 11858)		

Attachments (see zip file)	Change in CDP/Change in CDP.PNG

Statistical analyses

Statistical analysis title	Change in CDP between H0 and H72

Statistical analysis description:

The evolution of CDP between H0 and H72 was compared in the 2 groups by using repeated-measures ANOVA based on the ranks of the values with the rank of baseline value as adjustment covariate. Because the post-baseline values were constrained by the clinical events observed during the follow-up, each value was ranked from lowest to highest at each time point, with the worst rank attributed for deceased patients and the second worst rank for patients who underwent ECLS.

Comparison groups	Norepinephrine v Epinephrine
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Repeated-measures ANOVA

Notes:

[5] - Cardiac double product, a surrogate of myocardial oxygen consumption, increased in the epinephrine group, whereas it did not change in the norepinephrine group.

Secondary: Change in cardiac power index between H0 and H72

End point title	Change in cardiac power index between H0 and H72

End point description:

Baseline cardiac power index was described in each group as median (Q1 - Q3).

End point type	Secondary

End point timeframe:

Cardiac power index was measured at randomization (H0) and at H2, H4, H6, H12, H24, H48, and H72.

End point values	Epinephrine	Norepinephrine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: W/m²				
median (inter-quartile range (Q1-Q3))	0.29 (0.24 to 0.43)	0.33 (0.26 to 0.41)		

Attachments (see zip file)	Change in CPI/Change in CPI.PNG

Statistical analyses

Statistical analysis title	Change in cardiac power index between H0 and H72

Statistical analysis description:

The evolution of cardiac power index between H0 and H72 was compared in the 2 groups by using repeated-measures ANOVA based on the ranks of the values with the rank of baseline value as adjustment covariate. Because the post-baseline values were constrained by the clinical events observed during the follow-up, each value was ranked from lowest to highest at each time point, with the worst rank attributed for deceased patients and the second worst rank for patients who underwent ECLS.

Comparison groups	Epinephrine v Norepinephrine
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44 [6]
Method	Repeated-measures ANOVA

Notes:

[6] - The evolution of cardiac power index was similar between groups.

Secondary: Change in SvO2 between H0 and H72

End point title	Change in SvO2 between H0 and H72

End point description:

Baseline SvO2 was described in each group as median (Q1 - Q3).

End point type	Secondary

End point timeframe:

SvO2 was measured at randomization (H0) and at H2, H4, H6, H12, H24, H48, and H72.

End point values	Epinephrine	Norepinephrine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	29		
Units: pct				
median (inter-quartile range (Q1-Q3))	72 (59 to 79)	71 (65 to 78)		

Attachments (see zip file)	Change in SvO2/Change in SvO2.PNG

Statistical analyses

Statistical analysis title	Change in SvO2 between H0 and H72

Statistical analysis description:

The evolution of SvO2 between H0 and H72 was compared in the 2 groups by using repeated-measures ANOVA based on the ranks of the values with the rank of baseline value as adjustment covariate. Because the post-baseline values were constrained by the clinical events observed during the follow-up, each value was ranked from lowest to highest at each time point, with the worst rank attributed for deceased patients and the second worst rank for patients who underwent ECLS.

Comparison groups	Epinephrine v Norepinephrine
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18 [7]
Method	Repeated-measures ANOVA

Notes:

[7] - The evolution of SvO2 during the study period was similar between the 2 groups.

Secondary: Change in arterial lactate between H0 and H72

End point title	Change in arterial lactate between H0 and H72

End point description:

Baseline arterial lactate was described in each group as median (Q1 - Q3).

End point type	Secondary

End point timeframe:

Arterial lactate was measured at randomization (H0) and at H2, H4, H6, H12, H24, H48, and H72.

End point values	Epinephrine	Norepinephrine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: mmol/L				
median (inter-quartile range (Q1-Q3))	5.0 (2.7 to 6.1)	2.9 (1.9 to 4.8)		

Attachments (see zip file)	Change in arterial lactate/Change in arterial lactate.PNG

Statistical analyses

Statistical analysis title	Change in arterial lactate between H0 and H72

Statistical analysis description:

The evolution of arterial lactate between H0 and H72 was compared in the 2 groups by using repeated-measures ANOVA based on the ranks of the values with the rank of baseline value as adjustment covariate. Because the post-baseline values were constrained by the clinical events observed during the follow-up, each value was ranked from lowest to highest at each time point, with the worst rank attributed for deceased patients and the second worst rank for patients who underwent ECLS.

Comparison groups	Epinephrine v Norepinephrine
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Repeated-measures ANOVA

Notes:

[8] - Regarding metabolic changes, during the first 24 h, epinephrine use was associated with increased lactate level, whereas lactate level decreased in the norepinephrine group.

Secondary: Change in SOFA score between H0 and H72

End point title	Change in SOFA score between H0 and H72

End point description:

Baseline SOFA score was described in each group as median (Q1 - Q3).

End point type	Secondary

End point timeframe:

SOFA score was calculated at randomization (H0) and at H24, H48, and H72.

End point values	Epinephrine	Norepinephrine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: pts				
median (inter-quartile range (Q1-Q3))	10 (9 to 12)	9 (8 to 12)		

Statistical analyses

Statistical analysis title	Change in SOFA score between H0 and H72

Statistical analysis description:

The evolution of SOFA score was compared in the 2 groups by using repeated measures ANOVA with baseline value as the adjustment covariate.

Comparison groups	Epinephrine v Norepinephrine
Number of subjects included in analysis	57
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.44 [9]
Method	Repeated-measures ANOVA

Notes:

[9] - Regarding organ dysfunction, the SOFA score and its components did not differ between the 2 groups, either at inclusion or during patient course.

Other pre-specified: Refractory cardiogenic shock (primary safety endpoint)

End point title	Refractory cardiogenic shock (primary safety endpoint)

End point description:

Refractory CS was defined as CS with major cardiac dysfunction assessed according to echocardiography, elevated lactate level, and acute deterioration of organ function (e.g., oliguria, liver failure) despite the use of >1 mg/kg/min of epinephrine/norepinephrine or dobutamine >10 mg/kg/min and/or intra-aortic balloon support and sustained hypotension (SAP <90 mm Hg or MAP <65 mm Hg) despite adequate intravascular volume. This event was defined by the independent safety monitoring board at the first meeting (September 2015) while reviewing adverse events.

End point type	Other pre-specified

End point timeframe:

Refractory cardiogenic shock were observed during study follow-up.

End point values	Epinephrine	Norepinephrine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	30		
Units: no unit				
No refractory shock	17	28		
Refractory shock	10	2		

Statistical analyses

Statistical analysis title	Incidence of refractory cardiogenic shock
Comparison groups	Epinephrine v Norepinephrine
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011 [10]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	8.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.61
upper limit	42.18

Notes:

[10] - Epinephrine was associated with a higher incidence of refractory cardiogenic shock.

Post-hoc: Change in use of inotropes between H0 and H72

End point title	Change in use of inotropes between H0 and H72

End point description:

Baseline dobutamine dose was described in each group as median (Q1 - Q3).

End point type	Post-hoc

End point timeframe:

Dobutamine dose was measured at randomization (H0) and at H2, H4, H6, H12, H24, H48, and H72.

End point values	Epinephrine	Norepinephrine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: µg/min/kg				
median (inter-quartile range (Q1-Q3))	6.1 (0.5 to 11.7)	4.8 (0.0 to 8.0)		

Statistical analyses

Statistical analysis title	Change in dobutamine dose between H0 and H72

Statistical analysis description:

The evolution of dobutamine dose was compared in the 2 groups by using repeated measures ANOVA with baseline value as the adjustment covariate.

Comparison groups	Epinephrine v Norepinephrine
Number of subjects included in analysis	38
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.78 [11]
Method	Repeated-measures ANOVA

Notes:
[11] - There was no statistically significant difference in dobutamine at the different time points.

Post-hoc: Change in NT-proBNP between H0 and H72

End point title	Change in NT-proBNP between H0 and H72

End point description:
Baseline NT-proBNP was described in each group as median (Q1 - Q3).

End point type	Post-hoc

End point timeframe:
NT-proBNP was measured at randomization (H0) and at H24, H48, and H72.

End point values	Epinephrine	Norepinephrine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	29		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	4499 (541 to 11668)	1739 (702 to 5956)		

Statistical analyses

Statistical analysis title	Change in NT-proBNP between H0 and H72

Statistical analysis description:
The evolution of NT-proBNP was compared in the 2 groups by using repeated measures ANOVA with baseline value as the adjustment covariate.

Comparison groups	Epinephrine v Norepinephrine
Number of subjects included in analysis	56
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.2 [12]
Method	Repeated-measures ANOVA

Notes:
[12] - No statistically significant difference was observed in levels of NT-proBNP during the first 72 h.

Post-hoc: Change in Troponin T between H0 and H72

End point title	Change in Troponin T between H0 and H72

End point description:
Baseline Troponin T was described in each group as median (Q1 - Q3).

End point type	Post-hoc

End point timeframe:
Troponin T was measured at randomization (H0) and at H24, H48, and H72.

End point values	Epinephrine	Norepinephrine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	29		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	9.9 (3.1 to 33.0)	6.1 (2.1 to 19.7)		

Statistical analyses

Statistical analysis title	Change in Troponin T between H0 and H72

Statistical analysis description:

The evolution of Troponin T was compared in the 2 groups by using repeated measures ANOVA with baseline value as the adjustment covariate

Comparison groups	Epinephrine v Norepinephrine
Number of subjects included in analysis	56
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.21 [13]
Method	Repeated-measures ANOVA

Notes:

[13] - No statistically significant difference was observed in levels of Troponin T during the first 72 h.

Post-hoc: Change in GDF-15 between H0 and H72

End point title	Change in GDF-15 between H0 and H72

End point description:

Baseline GDF-15 was described in each group as median (Q1 - Q3).

End point type	Post-hoc

End point timeframe:

GDF-15 was measured at randomization (H0) and at H24, H48, and H72.

End point values	Epinephrine	Norepinephrine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	29		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	11182 (5108 to 22892)	17748 (9938 to 23586)		

Attachments (see zip file)	Change in GDF-15/Change in GDF-15.png

Statistical analyses

Statistical analysis title	Change in GDF-15 between H0 and H72

Statistical analysis description:

The evolution of GDF-15 was compared in the 2 groups by using repeated measures ANOVA with baseline value as the adjustment covariate.

Comparison groups	Epinephrine v Norepinephrine
Number of subjects included in analysis	56
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.002 [14]
Method	Repeated-measures ANOVA

Notes:

[14] - Levels of GDF-15 were markedly higher in the epinephrine versus norepinephrine group from H24 to H72.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE and SAE were collected and transmitted within 48 hours to sponsor from the enrollment until the end of hospital stay. After discharge, serious adverse events and deaths were collected until the end of study participation (6 months).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	norepinephrine
Reporting group description: -	
Reporting group title	epinephrine

Reporting group description: -

Serious adverse events	norepinephrine	epinephrine	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 30 (60.00%)	20 / 27 (74.07%)	
number of deaths (all causes)	11	14	
number of deaths resulting from adverse events	1	5	
Vascular disorders			
Shock			
subjects affected / exposed	3 / 30 (10.00%)	7 / 27 (25.93%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 2	0 / 7	
haemorrhagic shock			
subjects affected / exposed	0 / 30 (0.00%)	3 / 27 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Hypoperfusion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Peripheral ischaemia			

subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac disorders			
Ventricular fibrillation			
subjects affected / exposed	2 / 30 (6.67%)	2 / 27 (7.41%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Ventricular tachycardia			
subjects affected / exposed	4 / 30 (13.33%)	4 / 27 (14.81%)	
occurrences causally related to treatment / all	0 / 4	1 / 4	
deaths causally related to treatment / all	0 / 2	1 / 4	
Pericardial effusion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	4 / 30 (13.33%)	2 / 27 (7.41%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	3 / 30 (10.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Ventricular arrhythmia			

subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac failure chronic			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Torsade de pointes			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Atrial tachycardia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 30 (0.00%)	2 / 27 (7.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Ventricular failure			

subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Implantable defibrillator insertion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary revascularisation			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoxic-ischaemic encephalopathy			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 30 (3.33%)	2 / 27 (7.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Coma			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain hypoxia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 30 (3.33%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chest pain			

subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Effusion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Autoimmune heparin-induced thrombocytopenia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
pneumopathy			
subjects affected / exposed	2 / 30 (6.67%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			

subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Haemophilus infection			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	3 / 30 (10.00%)	2 / 27 (7.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Serratia bacteraemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
septicemia			

subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Product issues			
Device occlusion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	norepinephrine	epinephrine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 30 (66.67%)	16 / 27 (59.26%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 30 (6.67%)	2 / 27 (7.41%)	
occurrences (all)	2	2	
Hypertension			
subjects affected / exposed	1 / 30 (3.33%)	3 / 27 (11.11%)	
occurrences (all)	1	4	
Deep vein thrombosis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
hematoma			
subjects affected / exposed	1 / 30 (3.33%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Acute respiratory distress			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Hyperthermia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Catheter site haematoma			

subjects affected / exposed	1 / 30 (3.33%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
medical site device haematoma			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	4	
Vascular stent stenosis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Pneumothorax			
subjects affected / exposed	0 / 30 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Acute pulmonary oedema			
subjects affected / exposed	1 / 30 (3.33%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
pneumopathy			
subjects affected / exposed	3 / 30 (10.00%)	1 / 27 (3.70%)	
occurrences (all)	3	1	
Pulmonary oedema			
subjects affected / exposed	1 / 30 (3.33%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Haemothorax			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	2 / 30 (6.67%)	3 / 27 (11.11%)	
occurrences (all)	2	3	
Anxiety			

subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Confusional state			
subjects affected / exposed	1 / 30 (3.33%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Atrial fibrillation			
subjects affected / exposed	4 / 30 (13.33%)	3 / 27 (11.11%)	
occurrences (all)	4	4	
Tachyarrhythmia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Cardiogenic shock			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Conduction disorder			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Ventricular tachycardia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Nervous system disorders			
neurological status deterioration			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Polyneuropathy			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	2 / 30 (6.67%)	3 / 27 (11.11%)	
occurrences (all)	6	3	
Thrombocytopenia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 30 (6.67%)	2 / 27 (7.41%)	
occurrences (all)	2	2	
Nausea			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Rectal haemorrhage			
subjects affected / exposed	2 / 30 (6.67%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Intestinal dilatation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	1 / 30 (3.33%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
redness			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	2 / 30 (6.67%)	2 / 27 (7.41%)	
occurrences (all)	2	2	
Renal failure			
subjects affected / exposed	1 / 30 (3.33%)	3 / 27 (11.11%)	
occurrences (all)	1	3	

Acute kidney injury			
subjects affected / exposed	2 / 30 (6.67%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Pneumonia aspiration			
subjects affected / exposed	3 / 30 (10.00%)	1 / 27 (3.70%)	
occurrences (all)	3	1	
Influenza			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	4 / 30 (13.33%)	4 / 27 (14.81%)	
occurrences (all)	4	4	
Respiratory tract infection			
subjects affected / exposed	1 / 30 (3.33%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
urinary infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 30 (3.33%)	5 / 27 (18.52%)	
occurrences (all)	1	5	
Hyperglycaemia			
subjects affected / exposed	1 / 30 (3.33%)	4 / 27 (14.81%)	
occurrences (all)	1	4	
Hyperkalaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Hypophosphataemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Diabetes mellitus			
subjects affected / exposed	0 / 30 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Hypoglycaemia			

subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 27 (3.70%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2011	Increase in the number of participating centers to increase the number of patients included; Increase in the number of patients after statistical re-evaluation; Simplification: some parameters that are complicated to obtain in all centers have been removed (gastric tonometry and indirect calorimetry).
02 December 2011	Different specialties of Adrenalin, with or without sulfites, and Noradrenalin can be used, according to the practice of each hospital. Suppression of near IR spectroscopy Modification of certain data to be collected Modification of the volume of the SST tube for biobanking from 7 to 5 ml Modification of the inclusion criteria, no need for the patient to be already intubated and ventilated, 8 hours instead of 6 Clarification of the discontinuation of vasopressors and the use of the Swan Ganz probe for the measurement of the cardiac index Added assessment of rhythm disturbances at each time interval Added the possibility to prepare a syringe at a concentration of 0.5mg/ml for weaning Clarification of the weaning day Clarification on the treatments to be reported in the CRF Addition of appendices with the echocardiography protocol and the use of the probe Addition of expected side effects
04 October 2012	Modification of the principal investigator of the Strasbourg center; Modification of the address of the Metz center (relocation of the service); Addition of a new center (Marseille); Clarification of concomitant treatments to be collected in the observation booklet; Collection of observational data concerning the anesthetic induction technique (if available) and the synacthen test (if available); Modification of the safety section (addition of an AR classification grid)
10 January 2014	Extension of the enrolment period by 2 years, clarifications regarding the administration of investigational drugs, addition of a new investigator center (CHU Toulouse)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The main limitation is that our study lasted 4 years and included only 57 patients during this period.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29976291