

Supplementary Online Content

Cholley B, Caruba T, Grosjean S, et al. Effect of levosimendan on low cardiac output syndrome in patients with low ejection fraction undergoing coronary artery bypass grafting with cardiopulmonary bypass. the LICORN randomized trial. *JAMA*. doi: 10.1001/jama.2017.9973

eFigure 1: Forest plot of relative risk differences for the primary end point and its components.

eFigure 2: Forest plot of the absolute risk difference in the primary end point according to predefined subgroups.

eFigure 3: Kaplan-Meier estimates of the probability of survival at Day 180.

eFigure 4: Cumulative incidence of patients “out of ICU and alive” at Day 28.

eFigure 5: Cumulative incidence of patients “off ventilator” at Day 28.

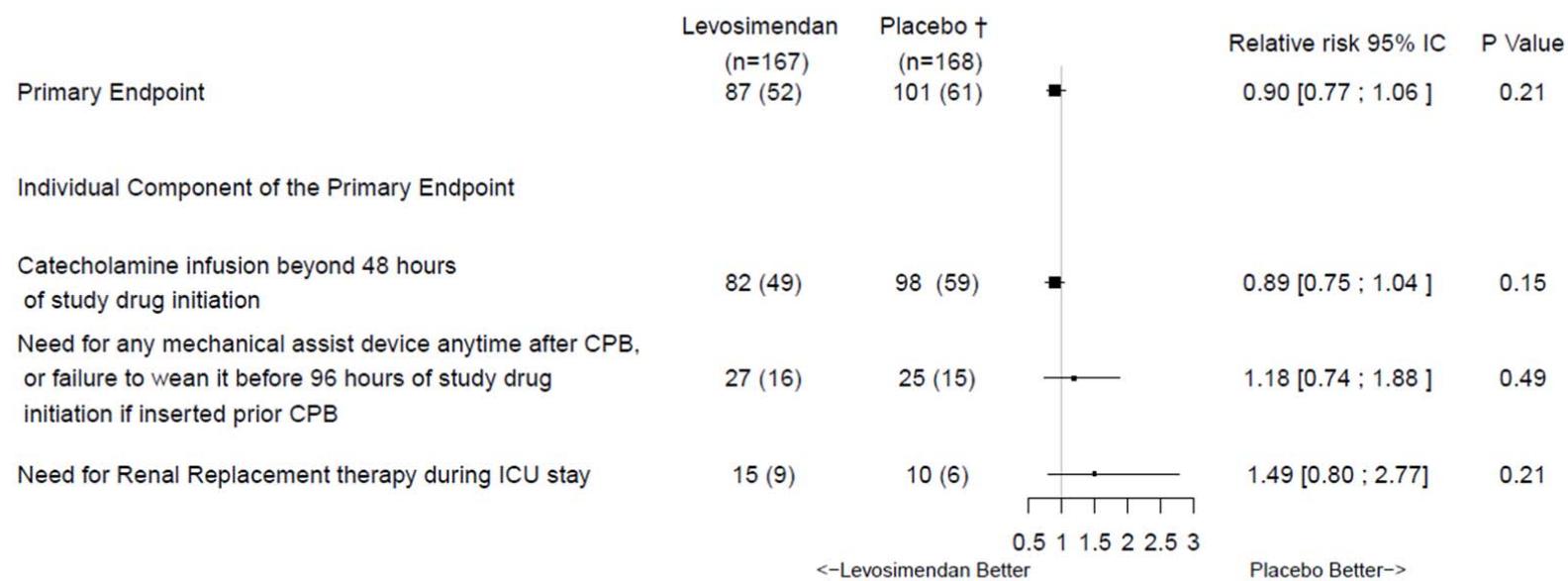
eTable 1 Euroscore II

eTable 2: Relative Risks for in-hospital mortality, mortality at Day 28 and Day 180

eTable 3: Complete list of serious adverse events in the levosimendan and placebo groups

This supplementary material has been provided by the authors to give readers additional information about their work.

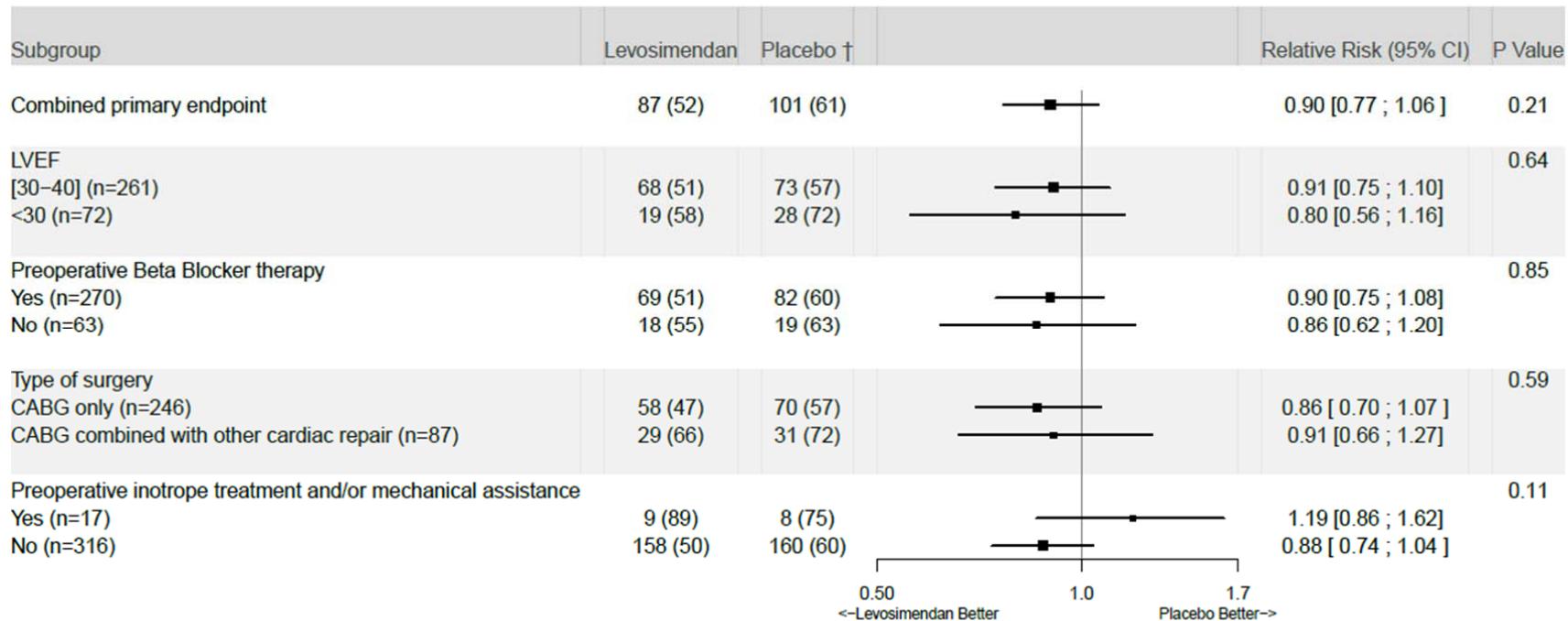
eFigure 1: Forest plot of relative risk differences for the primary end point and its components



CPB indicates cardiopulmonary bypass; ICU, intensive care unit. The size of data markers reflects the precision of estimation. The error bars indicate, 95% CIs.

†Two patients in the placebo group who refused participation after randomization could not be assessed for the primary endpoint and were excluded from the intention-to-treat analysis.

eFigure 2: Forest plot of the absolute risk difference in the primary end point according to predefined subgroups

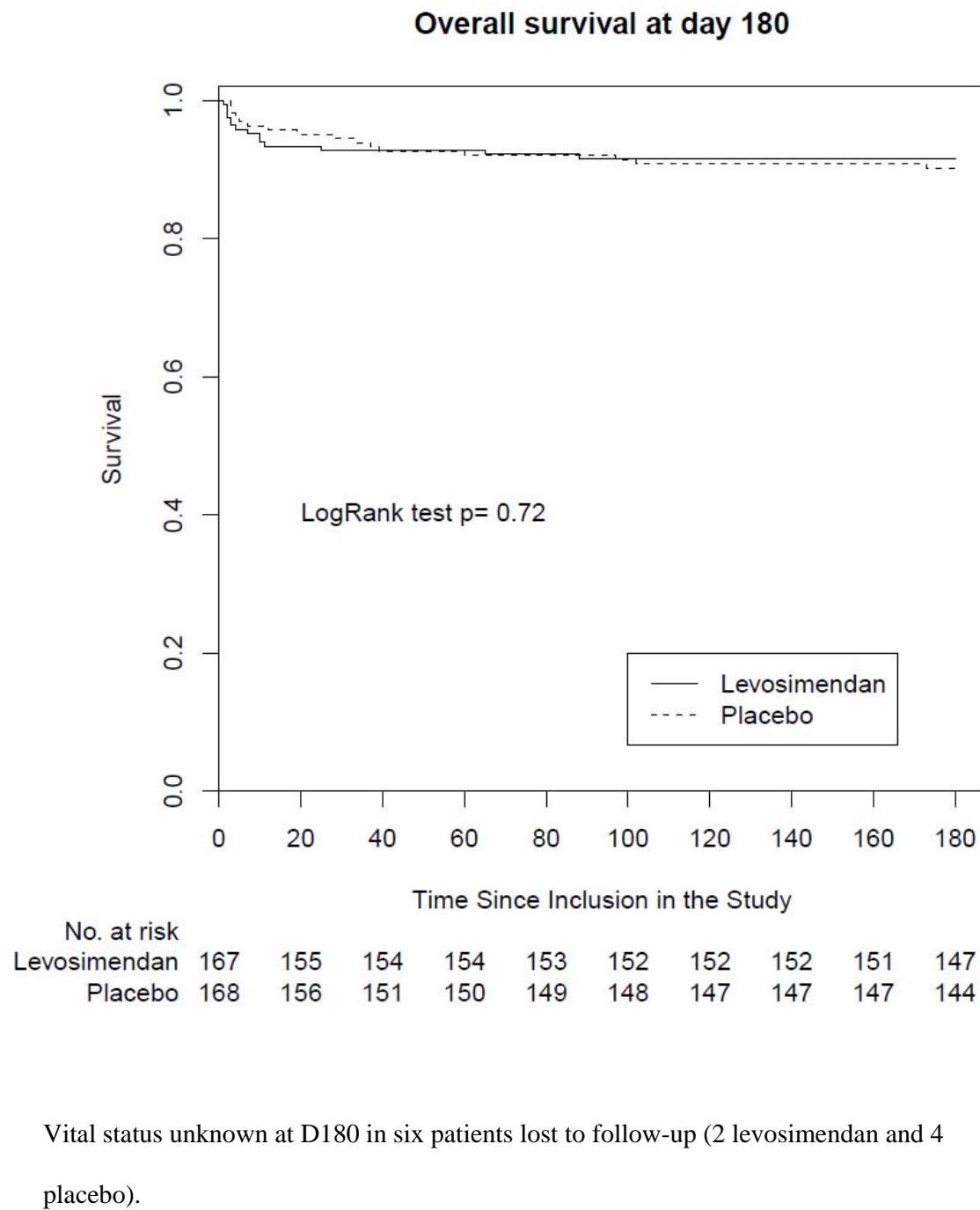


CABG indicates coronary artery bypass graft; LVEF, left ventricular ejection fraction. The size of the data markers reflects the precision of estimation.

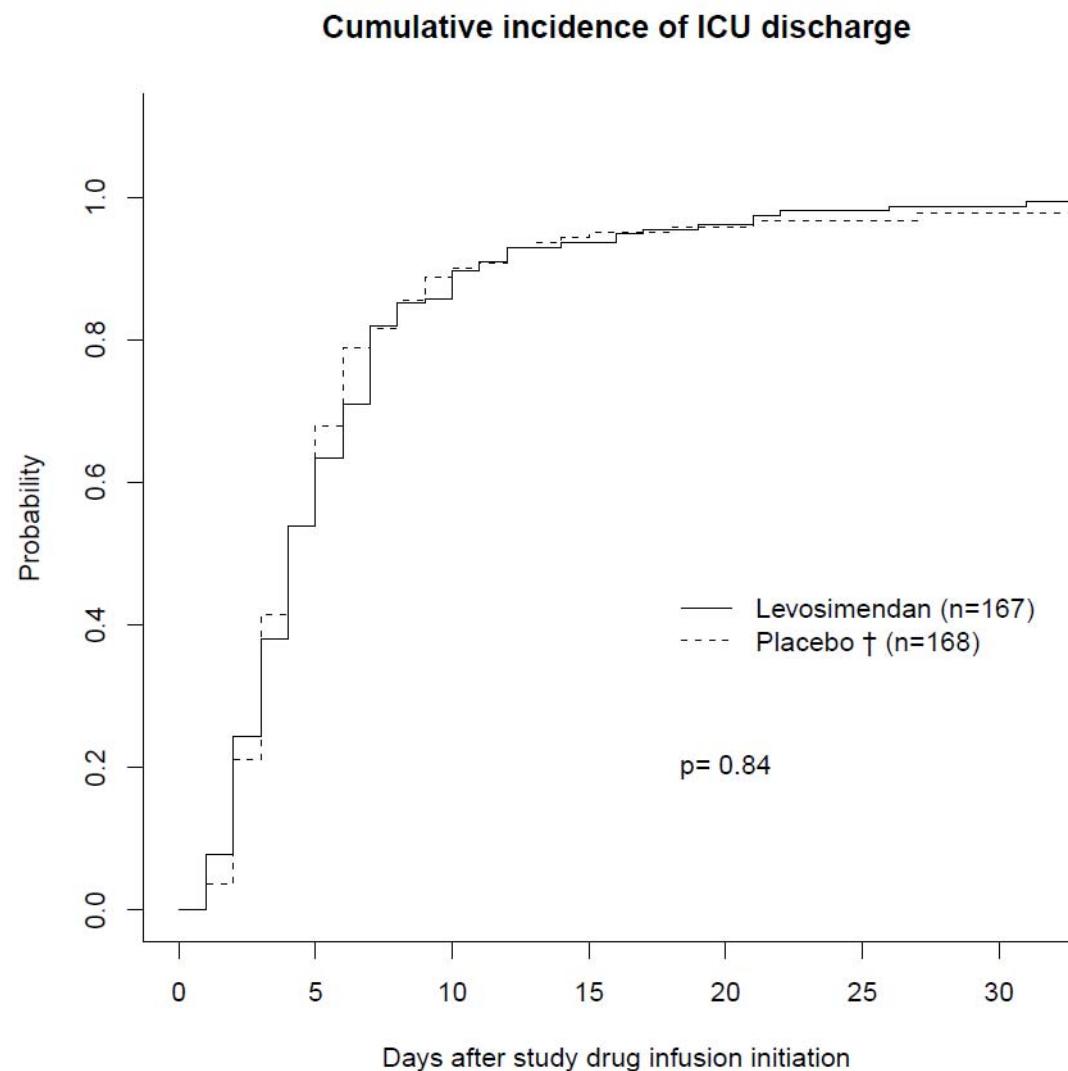
The error bars indicate 95% CIs. P values correspond to test for interaction.

†Two patients in the placebo group who refused participation after randomization could not be assessed for the primary endpoint and were excluded from the intention-to-treat analysis.

eFigure 3: Kaplan-Meier estimates of the probability of survival at Day 180.



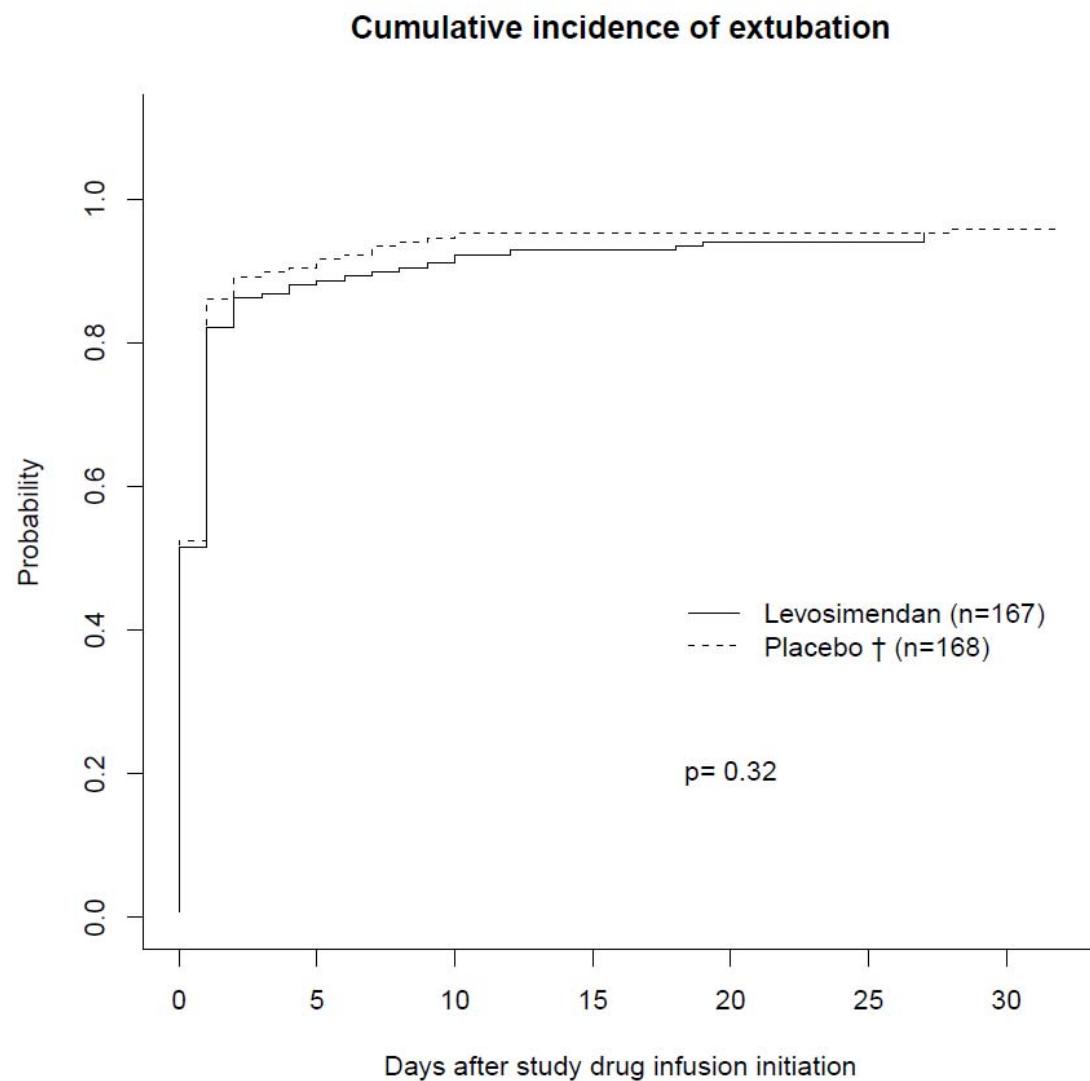
eFigure 4: Cumulative incidence of patients “out of ICU and alive” at Day 28.



Comparisons were made using Gray's test

†Two patients in the placebo group who refused participation after randomization could not be assessed for the primary endpoint and were excluded from the intention-to-treat analysis.

eFigure 5: Cumulative incidence of patients “off ventilator” at Day 28.



Comparisons were made using Gray's test.

†Two patients in the placebo group who refused participation after randomization could not be assessed for the primary endpoint and were excluded from the intention-to-treat analysis

eTable 1. Euroscore II*

	Levosimendan (n=167)	Placebo (n=168)	p-value
Patient related factors			
Age (years), mean (SD)	69 (10)	67 (10)	0.328
Gender, male sex	139 (83)	143 (85)	0.636
Renal impairment			
Normal CC>85 ml/min	60 (36)	58 (35)	0.66
Moderate (50<CC<85 ml/min)	71 (43)	79 (47)	
Severe (50 ml/min<CC)	36 (21)	31 (18)	
Dialysis (regardless of CC)	-	-	
Extra-cardiac arteriopathy	42 (25)	49 (29)	0.409
Poor mobility	9 (6)	5 (3)	0.27
Previous cardiac surgery	3 (2)	4 (2)	0.99
Chronic lung disease	6 (4)	15 (9)	0.044
Active endocarditis	0	0	-
Critical preoperative state	8 (5)	6 (4)	0.577
Diabetes on insulin	68 (41)	63 (38)	0.546
Cardiac related factors			
NYHA			
NYHA I	18 (11)	19 (11)	0.014
NYHA II	87 (52)	59 (35)	
NYHA III	57 (34)	84 (50)	
NYHA IV	5 (3)	6 (4)	
CCS class 4 angina	19 (11)	18 (11)	0.847
LV function†			
Good (LVEF>50%)	0	0	0.491
Moderate (LVEF 31-50%)	108 (65)	98 (58)	
Poor (LVEF 21-30%)	49 (29)	58 (35)	
Very poor (LVEF 20% or less)	10 (6)	12 (7)	
Recent myocardial infarction	33 (20)	50 (30)	0.034
Pulmonary hypertension			
No	123 (74)	114 (68)	0.281
Moderate (PA systolic 31-55 mmHg)	38 (23)	42 (25)	
Severe (PA systolic>55 mmHg)	6 (4)	12 (7)	
Operation related factors			
Urgency			
Elective	136 (81)	135 (80)	0.801
urgent	31 (19)	33 (20)	
Emergency	0	0	
Salvage	0	0	
Weight of the intervention			
Isolated CABG	128 (77)	131 (78)	0.9
2 procedures	36 (21)	35 (21)	
3 procedures	3 (2)	2 (1)	
Surgery on thoracic aorta	3 (2)	1 (1)	0.371
Euroscore II, median [quartiles] (range), %	3.1 [2;5.9] (0.7;31.1)	3.4 [2;6.4] (0.9;29.5)	0.597
Euroscore II in patients with LVEF<30% (n=72), median [quartiles] (range), %	4.5 [2.8;8.1] (1.2; 31.1)	4.4 [2.5;7.1] (1.5;29.5)	0.643

Abbreviations: CABG, coronary artery bypass graft; CC, creatinine clearance; CCS, Canadian Cardiovascular Society; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PA, pulmonary artery; SD, standard deviation.

*Values are expressed as number (percentage) unless otherwise indicated.

†Patients with LVEF>40% were not eligible for this study

Euroscore II is a risk model which provides the risk of death after cardiac surgery (range: 0.5% to 99.7%)

eTable 2. Relative risks for mortality*

	Levosimendan (n=167)	Placebo (n=168)	RR [95%CI]	p-value
In-hospital death	10 (6)	12 (7)	0.96 [0.43-2.15]	0.92
Mortality at Day 28	12 (7)	9 (5)	1.49 [0.64-3.42]	0.35
Mortality at Day 180	14 (8)	16 (10)	0.98 [0.49-1.97]	0.96

Abbreviations: CI, confidence interval; ICU, intensive care unit; RR, relative risk.

*Values are expressed as number (percentage) unless otherwise indicated.

eTable 3. Adjudicated serious adverse events (Intention-to-treat population)

All adjudicated *Serious Adverse Events* at the time of database lock are listed.

Serious Adverse Events include adverse events that result in death, require either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, result in a persistent or significant disability/incapacity or result in a congenital anomaly/birth defect.

Adjudication was made by the pharmacovigilance department of the sponsor (Assistance Publique – Hôpitaux de Paris), using the MedDRA (MEDical Dictionary for Regulatory Activities) standardized medical terminology (<https://www.meddra.org/>).

	LEVOSIMENDAN	PLACEBO
Atrial fibrillation	79 (14,2%)	76 (14,6%)
Arterial hypotension	49 (8,8%)	55 (10,6%)
Anemia	31 (5,6%)	32 (6,1%)
Ventricular fibrillation	25 (4,5%)	23 (4,4%)
Cardiogenic shock	15 (2,7%)	27 (5,2%)
Ventricular tachycardia	16 (2,9%)	14 (2,7%)
Drug overdose	13 (2,3%)	12 (2,3%)
Tachycardia	17 (3,1%)	8 (1,5%)
Drug administration duration too long	13 (2,3%)	11 (2,1%)
Acute renal insufficiency	9 (1,6%)	7 (1,3%)
Sinus tachycardia	9 (1,6%)	6 (1,2%)
Bradycardia	8 (1,4%)	7 (1,3%)
Mediastinitis	7 (1,3%)	8 (1,5%)
Ventricular extrasystoles	10 (1,8%)	3 (0,6%)
Renal failure	9 (1,6%)	2 (0,4%)
Cardiac failure	4 (0,7%)	6 (1,2%)
Hypokalemia	5 (0,9%)	5 (1,0%)
Drug administration duration too short	4 (0,7%)	5 (1,0%)
Pericardial effusion	5 (0,9%)	4 (0,8%)
Septic shock	5 (0,9%)	4 (0,8%)
Hemorrhage	4 (0,7%)	4 (0,8%)
Postoperative hemorrhage	4 (0,7%)	4 (0,8%)
Tachyarrhythmia	7 (1,3%)	1 (0,2%)
Urinary tract infection	7 (1,3%)	1 (0,2%)
Extrasystoles atrial	3 (0,5%)	4 (0,8%)
Underdose	3 (0,5%)	4 (0,8%)
Cardio-respiratory arrest	3 (0,5%)	3 (0,6%)
Decompensation cardiac	1 (0,2%)	5 (1,0%)
Multi organ failure	5 (0,9%)	1 (0,2%)
Pleural effusion	2 (0,4%)	4 (0,8%)
Pneumonia	5 (0,9%)	1 (0,2%)
Pneumothorax	2 (0,4%)	4 (0,8%)
Postoperative wound infection	3 (0,5%)	3 (0,6%)
Atrial flutter	3 (0,5%)	2 (0,4%)
Atrioventricular block third degree	1 (0,2%)	4 (0,8%)
Constipation	2 (0,4%)	3 (0,6%)
Hemorrhagic shock	0 (0,0%)	5 (1,0%)

	LEVOSIMENDAN	PLACEBO
Paroxysmal atrial fibrillation	1 (0,2%)	4 (0,8%)
Renal impairment	2 (0,4%)	3 (0,6%)
Sternal dehiscence	4 (0,7%)	0 (0,0%)
Hypotension	2 (0,4%)	2 (0,4%)
Hypovolemia	2 (0,4%)	2 (0,4%)
Intraoperative hypotension	3 (0,5%)	1 (0,2%)
Ischemic stroke	0 (0,0%)	4 (0,8%)
Left ventricular insufficiency	3 (0,5%)	1 (0,2%)
Permanent atrial fibrillation	4 (0,7%)	0 (0,0%)
Pneumopathy	3 (0,5%)	1 (0,2%)
Sternitis	2 (0,4%)	2 (0,4%)
Vasoplegia syndrome	4 (0,7%)	0 (0,0%)
Cardiac arrest	3 (0,5%)	0 (0,0%)
Cardiac flutter	1 (0,2%)	2 (0,4%)
Circulatory collapse	1 (0,2%)	2 (0,4%)
Implantable defibrillator insertion	1 (0,2%)	2 (0,4%)
Left ventricular ejection fraction decreased	1 (0,2%)	2 (0,4%)
Leg ischemia	0 (0,0%)	2 (0,4%)
Osteitis	2 (0,4%)	1 (0,2%)
Pneumonia pseudomonas aeruginosa	2 (0,4%)	1 (0,2%)
Pulmonary embolism	1 (0,2%)	2 (0,4%)
Respiratory failure	0 (0,0%)	3 (0,6%)
Sepsis	1 (0,2%)	2 (0,4%)
Supraventricular tachycardia	1 (0,2%)	2 (0,4%)
Transfusion dependent anemia	3 (0,5%)	0 (0,0%)
Unknown cause of death	2 (0,4%)	1 (0,2%)
Acute pulmonary edema	1 (0,2%)	1 (0,2%)
Anemia postoperative	1 (0,2%)	1 (0,2%)
Anuria	0 (0,0%)	2 (0,4%)
Arrhythmia	2 (0,4%)	0 (0,0%)
Atrial fibrillation paroxysmal	2 (0,4%)	0 (0,0%)
Atrioventricular block	0 (0,0%)	2 (0,4%)
Bi-ventricular failure	2 (0,4%)	0 (0,0%)
Cardiac tamponade	2 (0,4%)	0 (0,0%)
Coma	0 (0,0%)	2 (0,4%)
Dilated cardiomyopathy	1 (0,2%)	1 (0,2%)
Drug administration rate too fast	1 (0,2%)	1 (0,2%)
Fever	2 (0,4%)	0 (0,0%)
Hemothorax	1 (0,2%)	1 (0,2%)
Hepatic failure	1 (0,2%)	1 (0,2%)
Hyperkalemia	2 (0,4%)	0 (0,0%)
Hypertension arterial	0 (0,0%)	2 (0,4%)
Intestinal obstruction	0 (0,0%)	2 (0,4%)
Ischemic cardiomyopathy	2 (0,4%)	0 (0,0%)
Left ventricular dysfunction	1 (0,2%)	1 (0,2%)
Lung infection	2 (0,4%)	0 (0,0%)
Myocardial infarction	0 (0,0%)	2 (0,4%)
<i>Obstructive arteriosclerosis of lower extremities</i>	2 (0,4%)	0 (0,0%)
Pneumonia bacterial	1 (0,2%)	1 (0,2%)

	LEVOSIMENDAN	PLACEBO
Pneumonia due to escherichia coli (e. Coli)	2 (0,4%)	0 (0,0%)
Prostatitis	1 (0,2%)	1 (0,2%)
Pulmonary sepsis	1 (0,2%)	1 (0,2%)
Reduced general condition	0 (0,0%)	2 (0,4%)
Respiratory distress	1 (0,2%)	1 (0,2%)
Right ventricular dysfunction	2 (0,4%)	0 (0,0%)
Sinus bradycardia	0 (0,0%)	2 (0,4%)
Staphylococcal septicemia	1 (0,2%)	1 (0,2%)
Surgical scar	1 (0,2%)	0 (0,0%)
Systemic inflammatory response syndrome	1 (0,2%)	1 (0,2%)
Thrombocytopenia	1 (0,2%)	1 (0,2%)
Ventilator associated pneumonia	1 (0,2%)	1 (0,2%)
Visual hallucinations	0 (0,0%)	2 (0,4%)
Abdominal aortic aneurysm	0 (0,0%)	1 (0,2%)
Acute pancreatitis	0 (0,0%)	1 (0,2%)
Acute prostatitis	1 (0,2%)	0 (0,0%)
Acute pulmonary oedema	1 (0,2%)	0 (0,0%)
Acute respiratory decompensation	0 (0,0%)	1 (0,2%)
Acute respiratory distress syndrome	1 (0,2%)	0 (0,0%)
Acute respiratory failure	0 (0,0%)	1 (0,2%)
Alcohol abuse	0 (0,0%)	1 (0,2%)
Anal abscess	1 (0,2%)	0 (0,0%)
Anasarca	1 (0,2%)	0 (0,0%)
Anticoagulation drug level above therapeutic	0 (0,0%)	1 (0,2%)
Anuric renal failure	1 (0,2%)	0 (0,0%)
Aortic aneurysm rupture	0 (0,0%)	1 (0,2%)
Arterial bypass operation	0 (0,0%)	1 (0,2%)
Arteritis	0 (0,0%)	1 (0,2%)
Asystole	1 (0,2%)	0 (0,0%)
Atrial arrhythmia	0 (0,0%)	1 (0,2%)
Atrial thrombosis	1 (0,2%)	0 (0,0%)
Atrioventricular block first degree	0 (0,0%)	1 (0,2%)
Bacteremia	0 (0,0%)	1 (0,2%)
Bacterial infection due to staphylococcus aureus	0 (0,0%)	1 (0,2%)
Balance disorder	0 (0,0%)	1 (0,2%)
Bleeding	1 (0,2%)	0 (0,0%)
Bronchial infection	1 (0,2%)	0 (0,0%)
C.difficile diarrhea	1 (0,2%)	0 (0,0%)
Candida pneumonia	0 (0,0%)	1 (0,2%)
Cardiac arrest transient	1 (0,2%)	0 (0,0%)
Cardiac arrhythmia	0 (0,0%)	1 (0,2%)
Cardiac valvulopathy	1 (0,2%)	0 (0,0%)
Cardioversion	1 (0,2%)	0 (0,0%)
Cerebral hemorrhage	1 (0,2%)	0 (0,0%)
Cerebrovascular accident	0 (0,0%)	1 (0,2%)
Cholecystectomy	0 (0,0%)	0 (0,0%)
Cholestasis	1 (0,2%)	0 (0,0%)
Cholesterol embolisation	0 (0,0%)	1 (0,2%)

	LEVOSIMENDAN	PLACEBO
Chronic atrial fibrillation	1 (0,2%)	0 (0,0%)
Chronic renal failure	1 (0,2%)	0 (0,0%)
Chronic renal impairment	1 (0,2%)	0 (0,0%)
Clostridium difficile colitis	0 (0,0%)	1 (0,2%)
Coagulation disorder	1 (0,2%)	0 (0,0%)
Colon cancer	1 (0,2%)	0 (0,0%)
Conduction disorders	0 (0,0%)	1 (0,2%)
Convulsion	1 (0,2%)	0 (0,0%)
Coronary artery bypass	1 (0,2%)	0 (0,0%)
Deep vein thrombosis postoperative	1 (0,2%)	0 (0,0%)
Device breakage	0 (0,0%)	1 (0,2%)
Device complication	1 (0,2%)	0 (0,0%)
Diabetic foot	1 (0,2%)	0 (0,0%)
Diarrhea	0 (0,0%)	1 (0,2%)
Drug administration rate too slow	1 (0,2%)	0 (0,0%)
Drug prescribing error	0 (0,0%)	1 (0,2%)
Dyspnea	0 (0,0%)	1 (0,2%)
Enterobacter bacteremia	1 (0,2%)	0 (0,0%)
Enterobacter cloacae infection	0 (0,0%)	1 (0,2%)
Enterococcal septicemia	1 (0,2%)	0 (0,0%)
Enterococcus faecalis infection	0 (0,0%)	1 (0,2%)
Erythrocytes decreased	0 (0,0%)	1 (0,2%)
Escherichia coli infection	0 (0,0%)	1 (0,2%)
Extracorporeal membrane oxygenation	0 (0,0%)	1 (0,2%)
Extrasystoles supraventricular	1 (0,2%)	0 (0,0%)
Extrasystoles ventricular	1 (0,2%)	0 (0,0%)
Fainting	1 (0,2%)	0 (0,0%)
Femoropopliteal stenosis	0 (0,0%)	0 (0,0%)
Fibrillation ventricular	0 (0,0%)	1 (0,2%)
Gram-negative rod infection	1 (0,2%)	0 (0,0%)
Gram-positive cocci infection	1 (0,2%)	0 (0,0%)
Haemophilus influenza pneumonia	1 (0,2%)	0 (0,0%)
Haemophilus influenzae infection	1 (0,2%)	0 (0,0%)
Haemophilus pneumonia	1 (0,2%)	0 (0,0%)
Heart disorder	0 (0,0%)	1 (0,2%)
Heart injury	0 (0,0%)	1 (0,2%)
Hematoma	0 (0,0%)	1 (0,2%)
Hemiparesis (right)	1 (0,2%)	0 (0,0%)
Hemodynamic instability	1 (0,2%)	0 (0,0%)
Hemoglobin abnormal	1 (0,2%)	0 (0,0%)
Hemoglobin decreased	0 (0,0%)	1 (0,2%)
Hemolytic anemia	1 (0,2%)	0 (0,0%)
Hemolytic anemia drug-induced	0 (0,0%)	1 (0,2%)
Hemoptysis	0 (0,0%)	1 (0,2%)
Hemostasis	1 (0,2%)	0 (0,0%)
Heparin-induced thrombocytopenia	1 (0,2%)	0 (0,0%)
Hypercapnia	0 (0,0%)	1 (0,2%)
Hyperglycemia	0 (0,0%)	1 (0,2%)
Hyperlactatemia	1 (0,2%)	0 (0,0%)

	LEVOSIMENDAN	PLACEBO
Hypertension	0 (0,0%)	1 (0,2%)
Hyperventilation	1 (0,2%)	0 (0,0%)
Hypothyroidism	0 (0,0%)	1 (0,2%)
Hypoxia	1 (0,2%)	0 (0,0%)
Incessant ventricular tachycardia	1 (0,2%)	0 (0,0%)
Infection pseudomonas aeruginosa	1 (0,2%)	0 (0,0%)
Influenza a virus infection	0 (0,0%)	1 (0,2%)
Intracardiac thrombus	0 (0,0%)	1 (0,2%)
Ischaemic stroke	0 (0,0%)	1 (0,2%)
Ischemia peripheral	0 (0,0%)	1 (0,2%)
Junctional arrhythmia	1 (0,2%)	0 (0,0%)
Klebsiella pneumonia	0 (0,0%)	1 (0,2%)
Lactic acidosis	1 (0,2%)	0 (0,0%)
Left bundle branch block	1 (0,2%)	0 (0,0%)
Left cardiac failure	0 (0,0%)	1 (0,2%)
Left ventricular assist device insertion	0 (0,0%)	1 (0,2%)
Left ventricular failure	0 (0,0%)	1 (0,2%)
Low cardiac output syndrome	0 (0,0%)	1 (0,2%)
Malignant tumor excision	1 (0,2%)	0 (0,0%)
Mediastinal bleeding	1 (0,2%)	0 (0,0%)
Mendelson's syndrome	1 (0,2%)	0 (0,0%)
Metabolic acidosis	0 (0,0%)	1 (0,2%)
Middle cerebral artery stroke	0 (0,0%)	1 (0,2%)
Monoplegia	0 (0,0%)	1 (0,2%)
Morganella morganii infection	0 (0,0%)	1 (0,2%)
Nausea	1 (0,2%)	0 (0,0%)
Non st segment elevation acute coronary syndrome	0 (0,0%)	1 (0,2%)
Nosocomial pneumonia	1 (0,2%)	0 (0,0%)
Oligoanuria	0 (0,0%)	1 (0,2%)
Paresthesia hand	1 (0,2%)	0 (0,0%)
Pericardial bleeding	0 (0,0%)	1 (0,2%)
Pericardial drainage	0 (0,0%)	1 (0,2%)
Peripheral arterial occlusive disease fontaine stage iv	1 (0,2%)	0 (0,0%)
Peripheral obliterative arteriopathy	1 (0,2%)	0 (0,0%)
Personality disorder	0 (0,0%)	1 (0,2%)
Pleural effusion recurrent	0 (0,0%)	1 (0,2%)
Pneumococcal pneumonia	0 (0,0%)	1 (0,2%)
Pneumonia staphylococcal	1 (0,2%)	0 (0,0%)
Proctocolitis	0 (0,0%)	1 (0,2%)
Prostatitis escherichia coli	1 (0,2%)	0 (0,0%)
Pulmonary edema	0 (0,0%)	1 (0,2%)
Refractory anemia	0 (0,0%)	1 (0,2%)
Refractory shock	1 (0,2%)	0 (0,0%)
Refusal of treatment by patient	0 (0,0%)	1 (0,2%)
Removal of foreign body	0 (0,0%)	1 (0,2%)
Renal insufficiency	0 (0,0%)	1 (0,2%)
Respiratory arrest	1 (0,2%)	0 (0,0%)

	LEVOSIMENDAN	PLACEBO
Retroperitoneal hematoma	0 (0,0%)	1 (0,2%)
Septic arthritis staphylococcal	1 (0,2%)	0 (0,0%)
Septicemia due to escherichia coli (e. Coli)	1 (0,2%)	0 (0,0%)
Serratia infection	1 (0,2%)	0 (0,0%)
Shock	1 (0,2%)	0 (0,0%)
Sinoatrial block	0 (0,0%)	1 (0,2%)
Staphylococcal bacteremia	0 (0,0%)	1 (0,2%)
Staphylococcus aureus septicemia	0 (0,0%)	1 (0,2%)
Stenotrophomonas infection	0 (0,0%)	1 (0,2%)
Sternal pain	1 (0,2%)	0 (0,0%)
Sternal stabilisation	1 (0,2%)	0 (0,0%)
Stone heart	1 (0,2%)	0 (0,0%)
Therapy cessation	0 (0,0%)	1 (0,2%)
Thoracic operation	1 (0,2%)	0 (0,0%)
Thoracic pain	1 (0,2%)	0 (0,0%)
Toe injury	0 (0,0%)	1 (0,2%)
Tonic-clonic convulsion	1 (0,2%)	0 (0,0%)
Tracheostomy	0 (0,0%)	1 (0,2%)
Transfusion	1 (0,2%)	0 (0,0%)
Transient ischaemic attack	1 (0,2%)	0 (0,0%)
Troponin increased	0 (0,0%)	1 (0,2%)
Urinary infection	0 (0,0%)	1 (0,2%)
Urinary tract infection bacterial	1 (0,2%)	0 (0,0%)
Vagal reaction	0 (0,0%)	1 (0,2%)
Ventricular bigeminy	1 (0,2%)	0 (0,0%)
Ventricular failure	0 (0,0%)	1 (0,2%)
Ventricular thrombosis	1 (0,2%)	0 (0,0%)
Vomiting	1 (0,2%)	0 (0,0%)
Wound desloughing	1 (0,2%)	0 (0,0%)
Total	555	521