

AER 2019



25^{ème} AER : 19 & 20 novembre 2020



AP-HP.Centre
Université de Paris



Embolie pulmonaire grave

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AER 2019 - Lyon

Conflict of interest disclosure

I have the following real or perceived conflicts of interest that relate to this presentation:

Affiliation / Financial interest	Commercial Company
Grants/research support:	Bayer, MSD, BMS, Daiichi-Sankyo, Portola
Honoraria or consultation fees:	Bayer, MSD, BMS, PFIZER, SANOFI-AVENTIS, BTG, Boston Scientifics
Participation in a company sponsored bureau:	No
Stock shareholder:	No
Spouse / partner:	No
Other support / potential conflict of interest:	No

High-risk PE is defined by hemodynamic instability: new 2019 ESC-ERS PE guidelines

(1) Cardiac arrest	(2) Obstructive shock ^{68–70}	(3) Persistent hypotension
Need for cardiopulmonary resuscitation	Systolic BP < 90 mmHg or vasopressors required to achieve a BP \geq 90 mmHg despite adequate filling status And End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate)	Systolic BP < 90 mmHg or systolic BP drop $>$ 40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolaemia, or sepsis

- These patients are rare:
- ICOPER (1995-1996)¹: **4.2%** (103/2454)
- RIETE (2001-2016)²: **3.5%** (1207/34380)
- German healthcare database (2005-2015)³: **3.5%** (30939/885806)

1 Goldhaber et al. Lancet 1999;353:1386-1389

2 Jimenez et al. Int J Cardiol 2018;269:327-333

3 Keller et al. Eur Heart J 2019; doi:10.1093/eurheartj/ehz236

Management Strategies and Determinants of Outcome in Acute Major Pulmonary Embolism: Results of a Multicenter Registry

WOLFGANG KASPER, MD, STAVROS KONSTANTINIDES, MD,* ANNETTE GEIBEL, MD,*

(J Am Coll Cardiol 1997;30:1165–71)

- 1001 patients with « major » PE in 204 centres

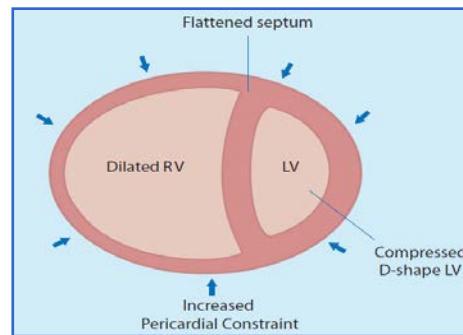
Event	RV dysfunction	Hypotension	Shock	Cardiac arrest
	Group 1 (n = 407)	Group 2 (n = 316)	Group 3 (n = 102)	Group 4 (n = 176)
Overall mortality	33 (8.1%)	48 (15%)	25 (25%)	114 (65%)
Death due to PE	29 (7.1%)	43 (14%)	23 (23%)	106 (60%)
Death due to underlying disease	3 (0.7%)	3 (1.0%)	1 (1.0%)	2 (1.1%)
Death due to complications of diagnostic procedures or treatment	1 (0.3%)	2 (0.6%)	1 (1.0%)	6 (3.4%)
Nonfatal events				
Recurrent PE	57 (14%)	61 (19%)	22 (22%)	32 (18%)
Arterial thromboembolism	5 (1.2%)	4 (1.3%)	0	5 (2.8%)
Cerebral bleeding	1 (0.3%)	3 (1.0%)	0	1 (0.6%)
Other major bleeding*	30 (7.4%)	24 (7.6%)	12 (12%)	21 (12%)

Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany

Karsten Keller ^{1†}, Lukas Hobohm^{1,2†}, Matthias Ebner³, Karl-Patrik Kresoja^{3,4,5}, European Heart Journal (2019) **0**, 1–8
Thomas Münzel^{2,6}, Stavros V. Konstantinides^{1,7‡}, and Mareike Lankeit^{1,3,5*‡} doi:10.1093/eurheartj/ehz236

	Haemodynamically unstable patients (n = 78 643; 8.9%)	Haemodynamically stable patients (n = 807 163; 91.1%)
CPR (with and without MV) (n = 60 519)	Shock (no CPR, no MV) (n = 9436)	No shock, no CPR (n = 807 163)
In-hospital death	50 940 (84.2%)	4423 (46.9%)
Treatment with systemic thrombolysis	15 517 (25.6%)	1375 (14.6%)
Odds ratios for in-hospital death in patients who underwent thrombolysis^a		
Univariate model [OR (95% CI)]	0.88 (0.84-0.92), P < 0.001	0.40 (0.36-0.46), P < 0.001
Multivariate model [OR (95% CI)]	0.92 (0.87-0.97), P = 0.002	0.42 (0.37-0.48), P < 0.001

Key factors contributing to haemodynamic collapse in acute PE



↑ RV afterload

Catecholamine-driven tachycardia
RV dilatation ↑RV wall tension

Ventricular interdependence
↑ Pericardial constraints

RV dysfunction

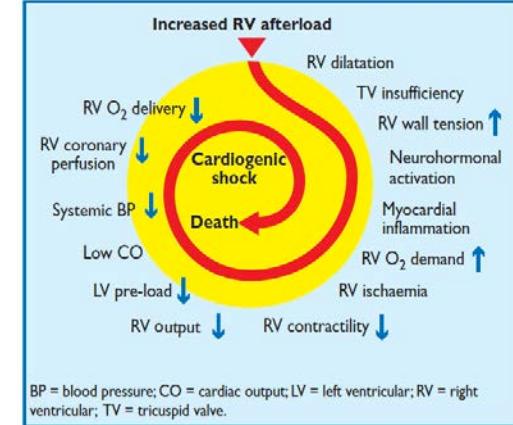
RV ischemia

↓RV output

↓LV pre-load

↓RV coronary perfusion

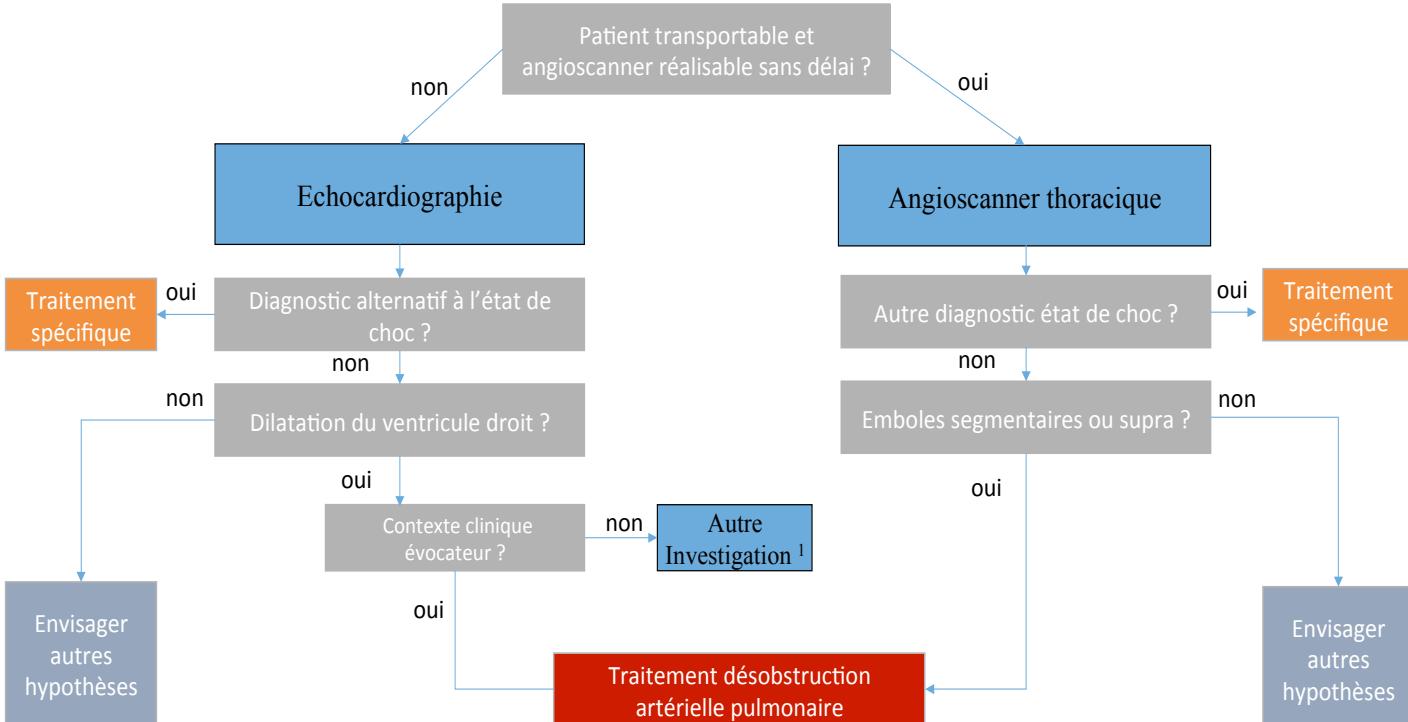
Hypotension



Conséquences diagnostiques

- Vite
- Efficace
 - D-dimères inutiles
 - Echo veineuse peu efficace
- Le moins invasif possible
 - Angiographie pulmonaire désuète

Recommandations SPLF 2019



1. Lorsque le contexte clinique n'est pas évocateur, une autre hypothèse pouvant expliquer le tableau clinique comme chez un patient insuffisant respiratoire chronique, il est suggéré de réaliser d'autres investigations (échographie veineuse, angioscanner thoracique si l'état hémodynamique le permet...) afin de confirmer le diagnostic

Therapeutic goals of high-risk PE

- Rapid haemodynamic stabilisation
 - Improve RV function
 - Volume expansion
 - Positive inotropics agents
 - Increase systolic blood pressure and RV coronary perfusion
 - vasopressors
- Restoration of pulmonary blood flow : decrease RV afterload
 - Primary reperfusion treatment
 - Fibrinolysis or embolectomy (surgical/per-cutaneous)
 - Avoid recurrent PE
 - Anticoagulant treatment: UFH / LMWH

Volume expansion



- RV preload increase through Frank Starling mechanism, but...
 - ↑ RV wall stress and ↑ paradoxical septal motion
 - ↓ LV preload
- Mercat et al Crit Care Med 1999;27:540-4
 - 13 patients with massive PE

	Base	FL 250	FL 500
RAP, mmHg	9 ± 1	$14 \pm 1^*$	$17 \pm 1^*$
mPAP, mmHg	31 ± 2	$34 \pm 2^*$	$35 \pm 2^*$
CI, L/mn/m ²	$1,6 \pm 0,1$	$1,7 \pm 0,1^*$	$2 \pm 0,1^*$
mBP, mmHg	101 ± 4	103 ± 4	103 ± 4

Improve RV function and cardiac output



- Positive inotropic agents
 - Dopamine, dobutamine
 - ↑ CO with dobutamine in patients with severe PE (*Jardin et al Crit Care Med 1985*)
 - Levosimendan
 - ↑ the sensitivity of the cardiac myofilaments to Ca²⁺ during systole without affecting diastole
 - Dilatation of pulmonary, systemic and coronary circulations
 - Improvement of RV function (*Morelli Crit Care Med 2006*)
- Vasopressors
 - Norepinephrine: α-adrenergic agonist
 - ↑ right coronary artery perfusion and RV function
 - In case of persistent shock

2019 ESC-ERS PE guidelines

Strategy	Properties and use	Caveats
Volume optimization		
Cautious volume loading, saline, or Ringer's lactate, ≤ 500 mL over 15–30 min	Consider in patients with normal–low central venous pressure (due, for example, to concomitant hypovolaemia)	Volume loading can over-distend the RV, worsen ventricular interdependence, and reduce CO ²³⁹
Vasopressors and inotropes		
Norepinephrine, 0.2–1.0 µg/kg/min ^a ²⁴⁰	Increases RV inotropy and systemic BP, promotes positive ventricular interactions, and restores coronary perfusion gradient	Excessive vasoconstriction may worsen tissue perfusion
Dobutamine, 2–20 µg/kg/min ²⁴¹	Increases RV inotropy, lowers filling pressures	May aggravate arterial hypotension if used alone, without a vasopressor; may trigger or aggravate arrhythmias

Norepinephrine and/or dobutamine should be considered in patients with high-risk PE.

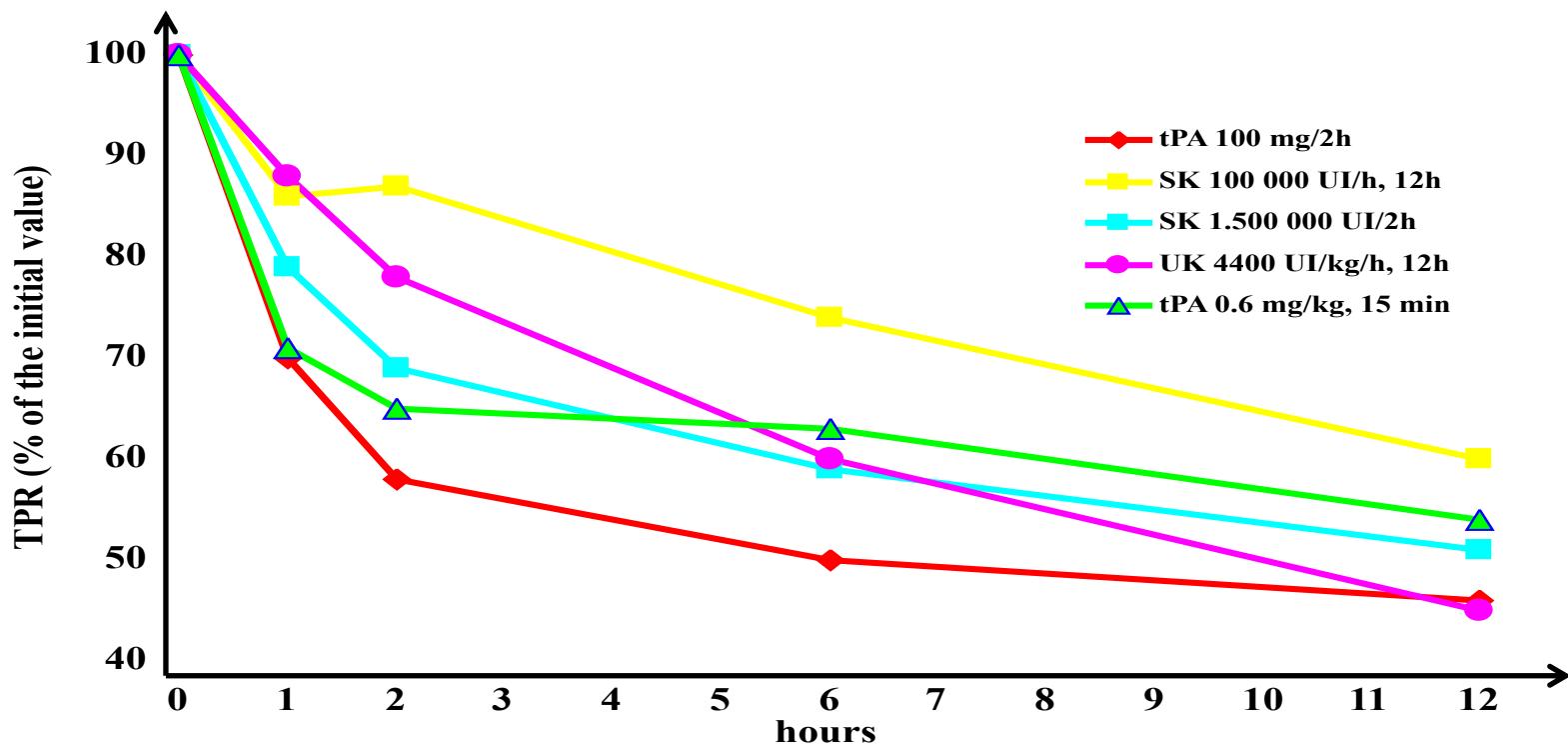
IIa

C

Traitement anticoagulant

- Dès que le diagnostic est suspecté +++
- Héparine non fractionnée
 - Si choc
- Héparine de bas poids moléculaire – fondaparinux
 - Si EP de gravité intermédiaire

Decrease RV afterload: systemic fibrinolysis



Meyer 92, Sors 94, Meneveau 97, Meneveau 98

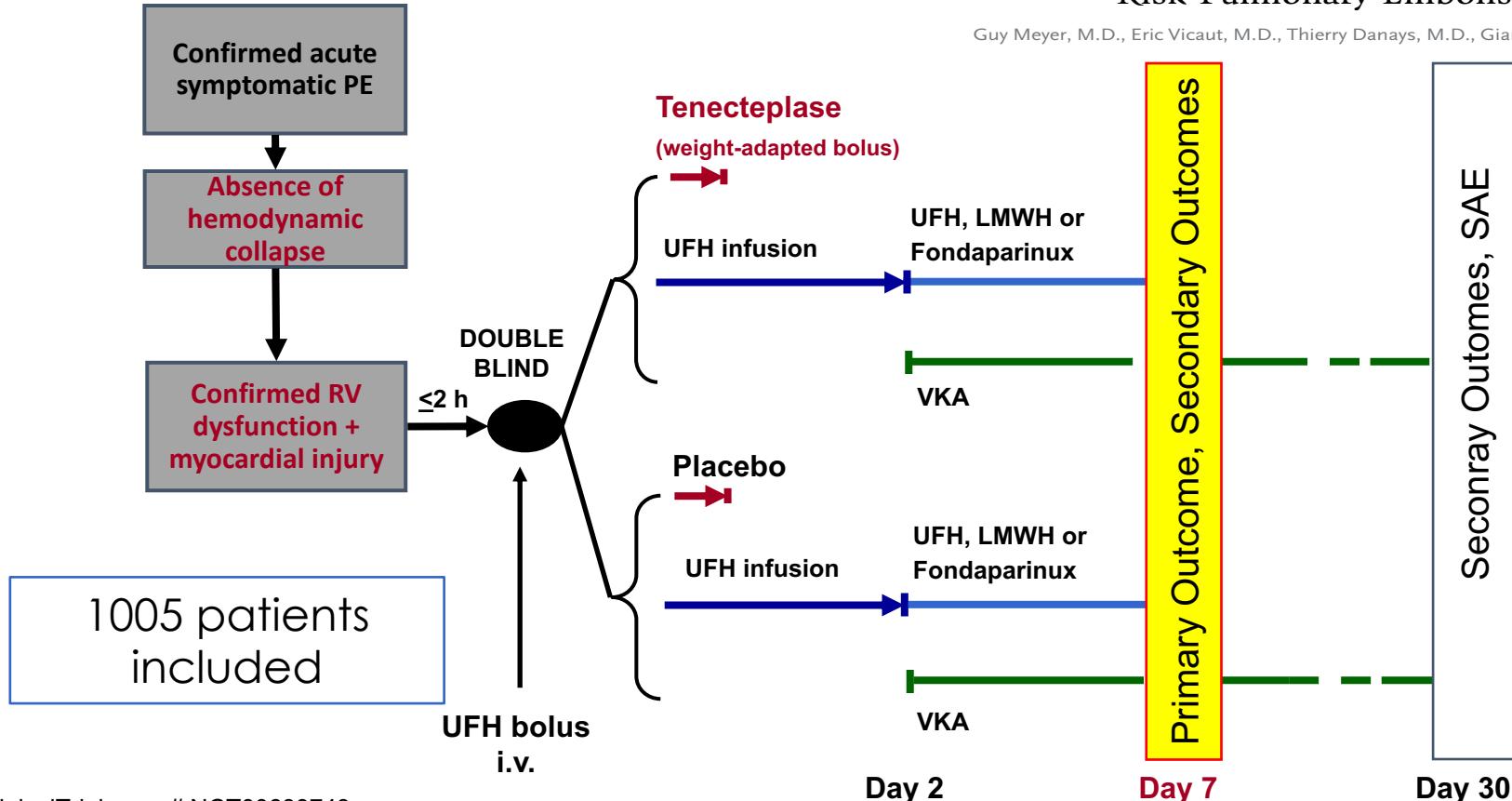
Effects of fibrinolysis on pulmonary vascular obstruction



**% of resolution of pulmonary vascular obstruction
(V/Q lung scan)**

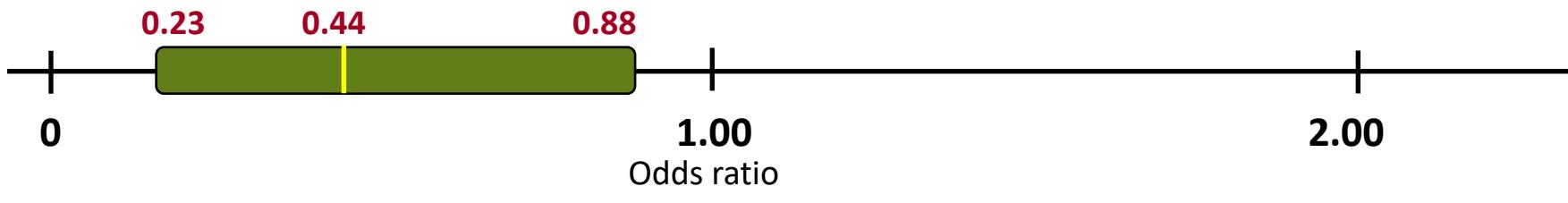
	Heparin (n = 70)	Urokinase (n = 72)
24h	7.4% (\pm 28.2)	23.7% (\pm 26.2)
D 2	16.2% (\pm 30.2)	27.4% (\pm 27.3)
D 7	41.9% (\pm 31.5)	44.9% (\pm 28.9)

PEITHO: Overview of study design



PEITHO: Primary efficacy outcome

	Tenecteplase (n=506)		Placebo (n=499)		<i>P</i> value
	n	(%)	n	(%)	
All-cause mortality or hemodynamic collapse within 7 days of randomization	13	(2.6)	28	(5.6)	0.015



Thrombolysis superior

PEITHO: Secondary efficacy outcomes

	Tenecteplase (n=506)		Placebo (n=499)		<i>P</i> value
	n	(%)	n	(%)	
All-cause mortality within 7 days	6	(1.2)	9	(1.8)	0.43
Hemodynamic collapse within 7 days	8	(1.6)	25	(5.0)	0.002
Need for CPR	1		5		
Hypotension / blood pressure drop	8		18		
Catecholamines	3		14		
Resulted in death	1		6		

PEITHO: Safety outcomes (within 7 days of randomization)

	Tenecteplase (n=506)		Placebo (n=499)		<i>P</i> value
	n	(%)	n	(%)	
Non-intracranial bleeding					
Major	32	(6.3)	6	(1.5)	<0.001
Minor	165	(32.6)	43	(8.6)	<0.001
<hr/>					
Strokes by day 7		12 (2.4)	1 (0.2)	0.003	
Hemorrhagic	10		1		
Ischemic	2		0		

Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis

Eur Heart J 2015;36:605-14

Christophe Marti^{1*}, Gregor John¹, Stavros Konstantinides², Christophe Combesure³, Olivier Sanchez⁴, Mareike Lankeit², Guy Meyer⁴, and Arnaud Perrier¹

2057 patients with PE included in 15 RCT comparing thrombolysis + anticoagulant vs anticoagulant alone

Efficacy

Intermediate risk PE	Odds Ratio (95% CI)
Mortality	0.42 (0.17 – 1.03)
PE mortality	0.17 (0.05 – 0.67)
Death or treatment escalation	0.37 (0.20 – 0.69)
PE recurrence	0.25 (0.06 – 1.03)

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Safety

	Odds Ratio (95% CI)	P-value	I ² (%)
Major bleeding	2.91 (1.95 – 4.36)	< 0.001	25
Fatal/intracranial bleeding	3.18 (1.25 – 8.11)	0.008	0

2019 ESC-ERS PE guidelines

Recommendations	Class ^b	Level ^c
It is recommended that anticoagulation with UFH, including a weight-adjusted bolus injection, be initiated without delay in patients with high-risk PE.	I	C
Systemic thrombolytic therapy is recommended for high-risk PE. ²⁸²	I	B

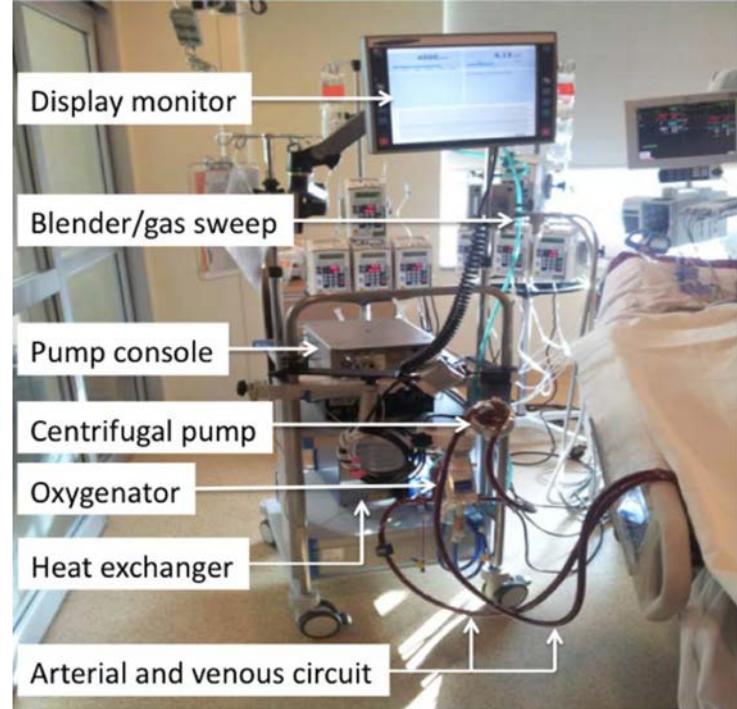
Other therapeutic options



- Extracorporeal Membrane Oxygenation (ECMO)
- Surgical thrombectomy
- Percutaneous catheter directed thrombectomy +/- local fibrinolysis
- For patients in whom thrombolysis has failed or is contraindicated
- ≈ 3% of high risk PE
- Multidisciplinary discussion is recommended +++
 - PE Response Team (PERT): interventionalist, cardiac surgeon, pulmonary / critical care medicine

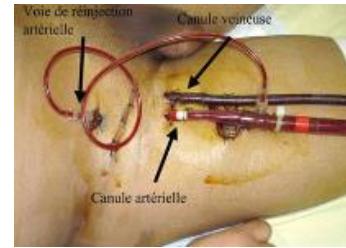
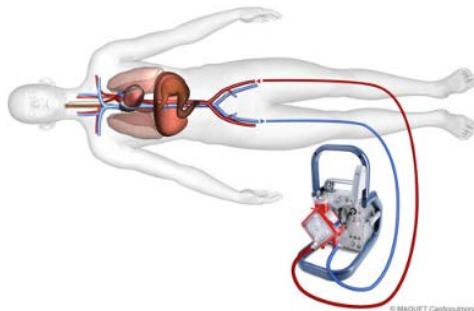
V/A-ECMO

- Lower RV overload
- Improve hemodynamic status
- Restore tissue oxygenation
- Rapidly efficacious
- Indicated in case of severe and refractory shock with or without multiple organ failure
- Requires a specific and trained team +++



VA-ECMO

2 strategies for its use in high-risk PE



As a bridge to a reperfusion therapy

Surgical embolectomy

Catheter-based thrombectomy

As a standalone therapy

Hemodynamic support while waiting for the action of endogenous fibrinolysis

VA-ECMO for patients with high-risk PE

Reference	Inclusion dates	Patients, n	Pre-ECMO Cardiac arrest (%)		Fibrinolytic therapy (%)	Mechanical PE removal on ECMO (n patients)	VA-ECMO-related complications (n patients)	Survival (%)
				Mechanical PE removal (n patients)				
Kawahito et al. [35]	1994–1998	7	71	0	100	3 surgical pulmonary embolectomies	0	57
Maggio et al. [4]	1992–2005	21 ^a	38	6 suction and 2 surgical pulmonary embolectomies	29	1 suction and 2 surgical pulmonary embolectomies	4 catastrophic neurological events; 1 dislodged arterial cannula	62
Sakuma et al. [36]	1983–2006	7	NR	0	86	1 suction and 1 surgical pulmonary embolectomy	NR	57
Malekan et al. [5]	2005–2011	4	NR	0	0	1 suction pulmonary emboectomy	None	100
Munakata et al. [30]	1992–2008	10	90	2 suction pulmonary embolectomies	100	7 suction pulmonary embolectomies	2 major bleeding	70
Omar et al. [37]	2007–2011	4	50	1 suction and 2 surgical pulmonary embolectomies	25	None	NR	25
Maj et al. [38]	NR	6	100	None	66	1 surgical pulmonary emboectomy	3 major bleeding	33
Swol et al. [39]	2008–2014	5	100	None	60	1 surgical pulmonary emboectomy	1 major bleeding	40
Cho et al. [40]	2000–2013	13	NR	None	15	11 surgical pulmonary embolectomies	NR	NR
This study	2006–2015	17	88	1 suction and 1 surgical pulmonary embolectomies	47	1 suction and 1 surgical pulmonary embolectomy	15 major bleeding	47 ^b

Corsi et al.
Critical Care
2017;21:76

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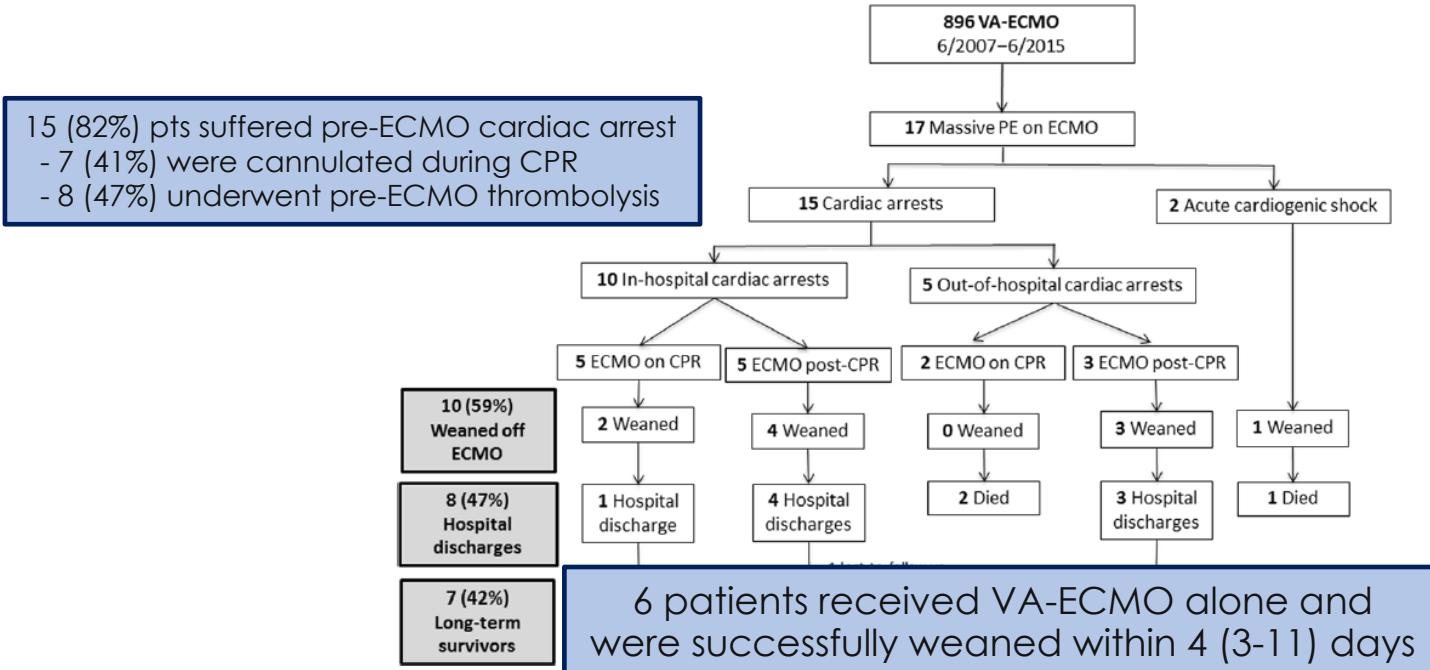
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Life-threatening massive pulmonary embolism rescued by venoarterial-extracorporeal membrane oxygenation

Corsi et al. *Critical Care* (2017) 21:76
DOI 10.1186/s13054-017-1655-8

Fillipo Corsi^{1,2}, Guillaume Lebreton³, Nicolas Bréchet², Guillaume Hekimian², Ania Nieszkowska², Jean-Louis Trouillet², Charles-Edouard Luyt², Pascal Leprince³, Jean Chastre², Alain Combes² and Matthieu Schmidt^{2,4*}

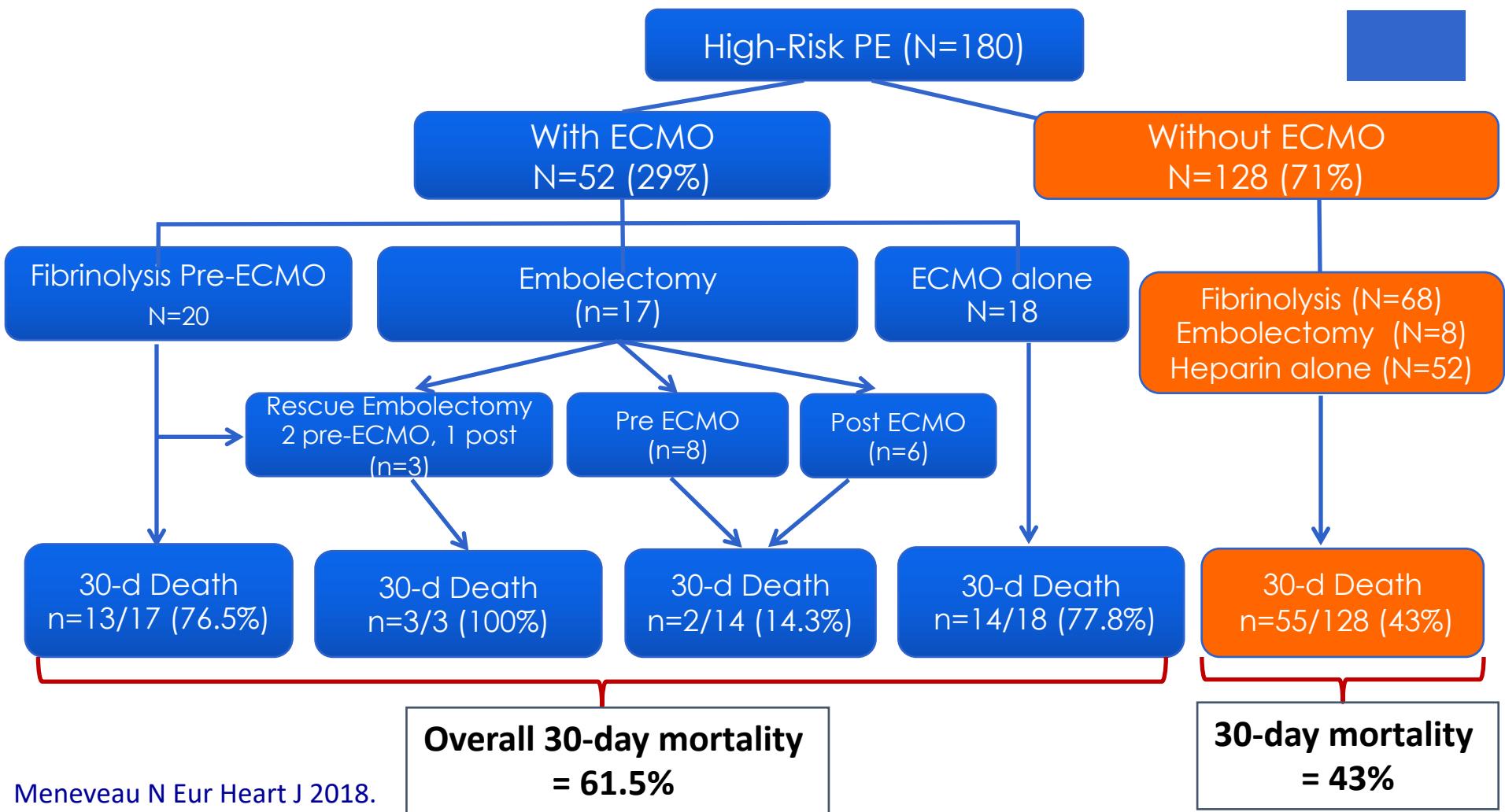


Outcomes after extracorporeal membrane oxygenation for the treatment of high-risk pulmonary embolism: a multicentre series of 52 cases

European Heart Journal (2018) 0, 1–9
doi:10.1093/eurheartj/ehy464

Nicolas Meneveau^{1,2*}, Benoit Guillon^{1,2}, Benjamin Planquette³, Gaël Piton^{2,4},
Antoine Kimmoun^{5,6}, Lucie Gaide-Chevronnay⁷, Nadia Aissaoui^{8,9}, Arthur
Neuschwander¹⁰, Elie Zogheib^{11,12}, Hervé Dupont^{11,12}, Sébastien Pili-Floury^{2,13},
Fiona Ecarnot^{1,2}, François Schiele^{1,2}, Nicolas Deye^{14,15}, Nicolas de Prost¹⁶,
Raphaël Favory¹⁷, Philippe Girard¹⁸, Mircea Cristinari¹⁹, Alexis Ferré²⁰, Guy Meyer³,
Gilles Capellier^{2,4}, and Olivier Sanchez³

- Multicenter retrospective study
- Jan 2014 – Dec 2015
- 180 patients with high-risk PE
 - Without ECMO
 - With ECMO
 - Fibrinolysis
 - Surgical embolectomy
- 30-day overall mortality

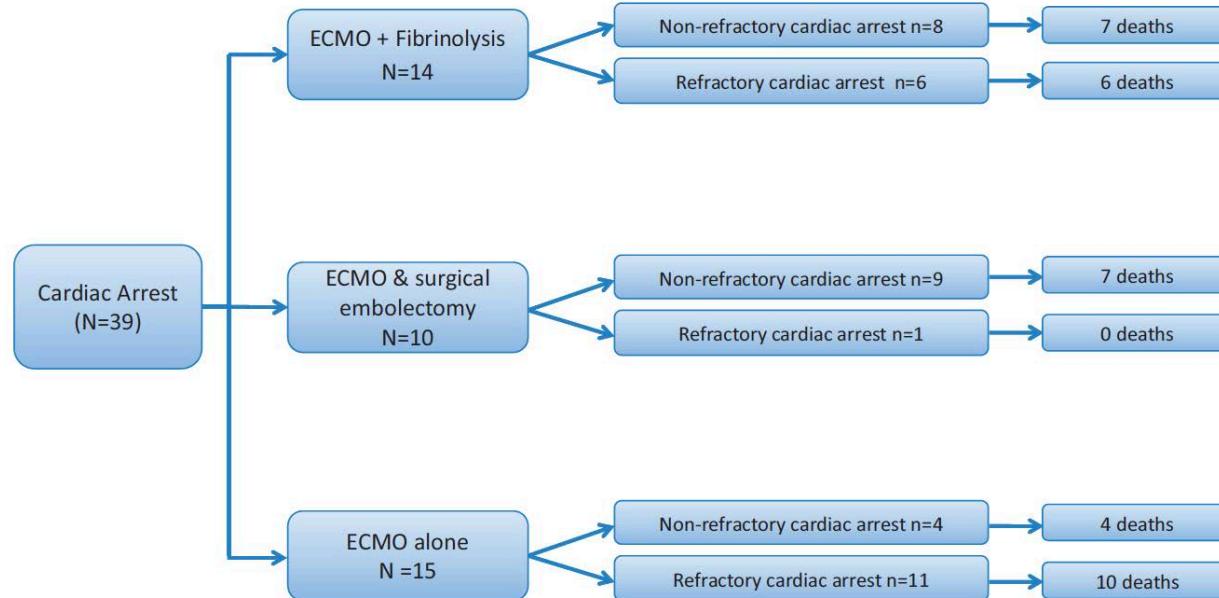


Outcomes according to initial treatment strategy

Signal for lower mortality & more successful weaning when ECMO is combined with surgical embolectomy

Outcome	ECMO + thrombolysis (N=17)	ECMO + surgical thrombectomy (N=17)	ECMO alone (N= 18)	P
30-day all-cause death	13 (76.5%)	5 (29.4%)	14 (77.8%)	0.004
90-day all-cause death	13 (76.5%)	7 (41.2%)	14 (77.8%)	0.037
90-day major bleeding	7 (41.2%)	9 (52.9%)	4 (22.2%)	0.14
90-day non-major bleeding	9 (52.9%)	9 (52.9%)	5 (29.4%)	0.32
Successful weaning from ECMO	5 (29.4%)	11 (64.7%)	3 (17.7%)	0.009
Length of ICU stay	2 [1; 9]	17 [2; 21]	2.5 [2; 10]	0.004

VA-ECMO implanted during cardiac arrest



Overall in-hospital mortality : 34/39 = 87%

No difference between pts with refractory CA & pts with resuscitated CA

No strategy appears to perform better than the others

Extracorporeal membrane oxygenation and surgical embolectomy for high-risk pulmonary embolism

Eur Respir J 2019; 53: 1801773

36 patients with high-risk PE needed v-a ECMO support

9 (25%) patients died while on ECMO support

CPR prior to ECMO n=5
In-hosp death: 100%

7 (19%) patients stabilised under ECMO and were weaned from ECMO support (two of these patients died thereafter)

CPR prior to ECMO n=2
In-hosp death: 29%

20 (56%) patients underwent surgical embolectomy

CPR prior to ECMO n=8

13 (65%) patients were found to have acute PE

7 (35%) patients were found to have acute-on-chronic PE

1 (5%) patient died

In-hosp death: 0%

13 patients survived until hospital discharge

6 patients survived until hospital discharge

2019 ESC-ERS PE guidelines



Recommendations	Class ^b	Level ^c
<p>ECMO <u>may be considered, in combination with</u> surgical embolectomy or catheter-directed treatment, in patients with PE and refractory circulatory collapse or cardiac arrest.^{d 252}</p>	IIb	C

Surgical embolectomy



- Retrospective cohorts
- High mortality rates
- The unsatisfactory surgical results were often related to the compromised clinical status of the patients, especially those who had already undergone thrombolysis and entered the operation room with advanced cardiogenic shock in need of cardiopulmonary resuscitation.

Period	Death n/N	Death %
1968-1989	184/526	35%
1990-1999	188/627	30%
2000-2008	41/215	19%

Samoukovic G. et al. *Interactive Cardiovasc Thorac Surg* 2010; 11: 265-270
Kalra et al. *Ann Thorac Surg* 2017;103:982-90

Management of Unsuccessful Thrombolysis in Acute Massive Pulmonary Embolism*

(CHEST 2006; 129:1043–1050)

Nicolas Meneveau, MD, PhD; Marie-France Séronde, MD;
Marie-Cécile Blonde, MD; Pierre Legalery, MD; Katy Didier-Petit, MD;
Florent Briand, MD; Fiona Caulfield, MSc; François Schiele, MD, PhD;
Yvette Bernard, MD; and Jean-Pierre Bassand, MD

- January 1995 – january 2005
- 488 patients underwent thrombolysis for high-risk PE
- Unsuccessful thrombolysis
 - Persistent clinical instability (shock) AND residual echocardiographic RV dysfunction
 - Within 36h after thrombolysis
 - 40 patients (**8.2%**)
- Surgical embolectomy (n=14) or repeat thrombolysis (n=26) at the discretion of the treating physician

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Yvette Bernard, MD; and Jean-Pierre Bassand, MD

Variables	Rescue Embolectomy (n = 14)	Repeat Thrombolysis (n = 26)	OR	95% CI	p Value
Death	1 (7)	10 (38)	0.13	0.003–1.12	0.07
PE related-death	1 (7)	6 (23)	0.26	0.01–2.68	0.39
Recurrent PE	0	3 (11.5)			
Refractory shock	1 (7)	3 (11.5)			
Bleeding complications	2 (14)	6 (23)	0.56	0.05–3.86	0.82
Major bleeding episodes	2 (14) [0 fatal]	4 (15) [4 fatal]			
Intracranial hemorrhage	0	1 (4)			
Recurrent PE (fatal and nonfatal)	0	9 (35)	0.12	0–0.87	0.015
Uneventful evolution	11 (79)	8 (31)	8.25	1.49–51.71	0.004

*Values are given as No. (%), unless otherwise indicated.

- Rescue surgical embolectomy led to a better in-hospital course as compared to repeat thrombolysis
- => transfer the patients who do not respond to thrombolysis in a tertiary surgical cardiac center
- Role for VA-ECMO ???

Catheter-directed thrombolysis (CDT) ULTIMA study



- Multicenter randomized study
- 59 patients
 - Proximal PE
 - $RV/LV \geq 1$
 - No shock
- Ultrasound Assisted catheter directed thrombolysis (USAT)
 - rtPA 10 to 20 mg during 15h
 - UFH
- UFH

	USAT n = 30	Control n = 29
RV/LV before	1.28 ± 0.19	1.20 ± 0.14
RV/LV after (24h)	0.99 ± 0.17	1.17 ± 0.20
Major bleeding	0	0

CDT: SEATTLE II study

- Prospective multicenter registry
- EKOS
- rtPA 24 mg during 12h to 24h
- 150 patients with PE
 - With shock n=31
 - Intermediate high-risk n=119
- Primary efficacy outcome:
 - Change in the chest-CT RV/LV within 48h
- 1 lost of follow-up



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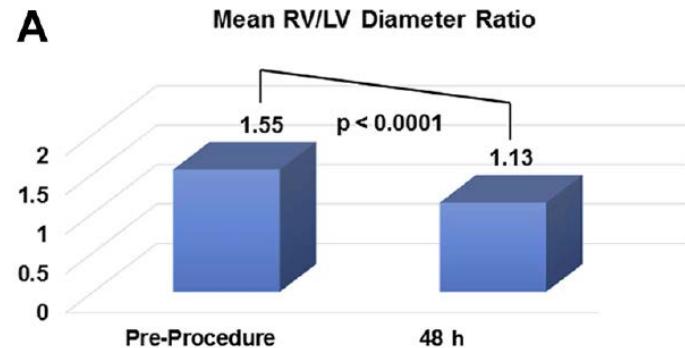


TABLE 5 Safety Outcomes (N = 150)

Length of stay, SD, days	8.8 ± 5
In-hospital death	3 (2)
30-day mortality*	4 (2.7)
Serious and severe adverse events potentially related to device	3 (2)
Serious and severe adverse events potentially related to t-PA	2 (1.3)
IVC filter placed	24 (16)
Major bleeding within 30 days*	15 (10)
GUSTO moderate*	14 (9.3)
GUSTO severe*	1 (0.7)
Intracranial hemorrhage	0 (0)

Catheter-directed embolectomy PERFECT registry



- Prospective multicenter registry
- 101 patients with acute PE
 - With shock n=28
 - « submassive » n=73
- Catheter-directed embolectomy
 - Mechanical
 - Catheter-directed thrombolysis: low dose hourly dose infusion of rtPA or UK during 24h
- Clinical success was defined as meeting all the following criteria:
 - Stabilization of hemodynamics, improvement of sPAP and/or RV/LV, survival of hospital discharge
 - Achieved in **24/28 (86%) massive PE / 71/73 (97%) submassive PE**
- No major procedure-related complications or major bleeding
- In-hospital mortality rate: 6%

Catheter-directed thrombolysis used concomitantly with VA-ECMO for high-risk PE

Study	N	CDT	30-day survival	ECMO duration
Munakata 2012	10	Pig-tail*	70%	48 ± 44 hours
Maj 2014	2	EKOS	50%	2-10 days
George 2018	15	EKOS	73%	—
Dumantepe 2019	21	EKOS	76%	5.5 [2-14] days
Overall			73%	

* fragmentation, thrombectomy, lysis infusion

Munakata R et al. Int Heart J 2012;53:370-374.
George B et al. Resuscitation 122 (2018) 1-5.

Maj G et al. Resuscitation 85 (2014) e175–e176.
Dumantepe M et al.

Conclusions

- Patients with high-risk PE are rare but have a high short-term mortality rate
- A majority of these patients can be treated successfully with inotropic agents and systemic fibrinolysis
- VA-ECMO is an effective therapeutic option for the most severe high-risk PE patients (i.e. cardiac arrest / refractory shock)
- The identification of patients who will yield the most benefit from VA-ECMO as well as the therapeutic strategy behind the use of ECMO is still challenging in daily clinical practice
- Pulmonary Embolism Responsive Team (PERT) can help to decide on the most appropriate therapy.
- ECMO in pts with failed fibrinolysis and in those with no reperfusion seems to be associated with unfavourable prognosis compared with ECMO in addition to surgical embolectomy or catheter-based therapy.
- These findings suggest that ECMO does not appear justified as a stand-alone treatment strategy in PE patients, but shows promise as a bridge to surgical or catheter-based reperfusion strategy.

SOS Embolie Pulmonaire Grave



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