Contemporary management and outcomes of patients with high-risk PE

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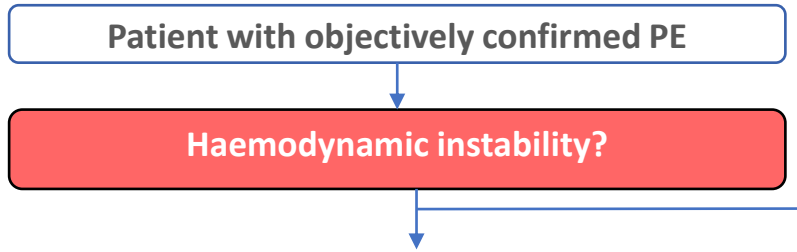
Conflict of interest disclosure

❑ **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
Honoraria or consultation fees:	Bayer, MSD, BMS, PFIZER, SANOFI-AVENTIS, Boston Scientifics, INARI, Viatris, GSK, Janssen
Participation in a company sponsored bureau:	No
Stock shareholder:	No
Spouse / partner:	No
Other support / potential conflict of interest:	No

Risk stratification based on early mortality risk: 2019 ESC / ERS guidelines



YES

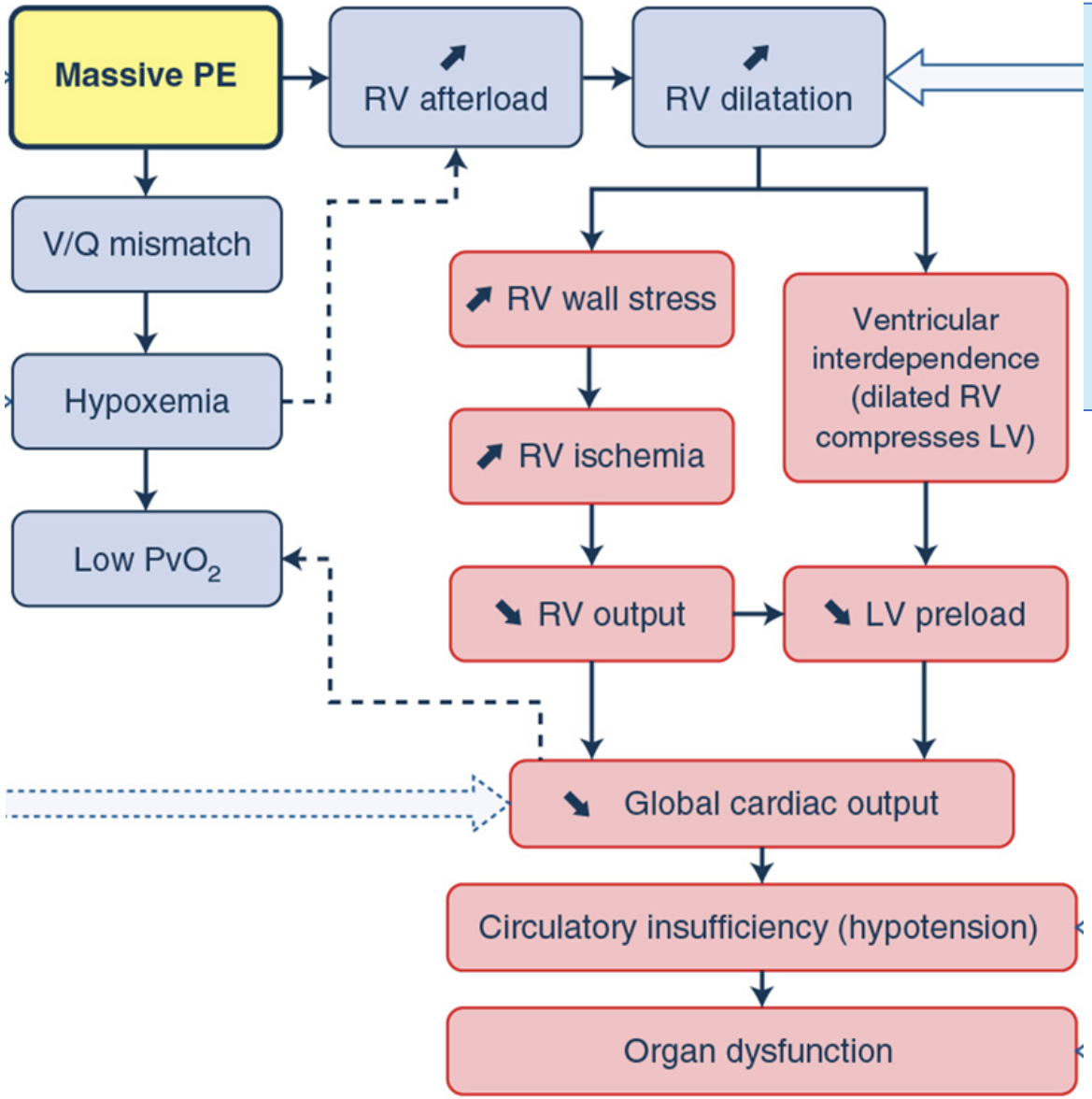
(1) Cardiac arrest	(2) Obstructive shock[68–70]	(3) Persistent hypotension
Need for cardiopulmonary resuscitation	Systolic BP < 90 mmHg or vasopressors required to achieve a BP ≥90 mmHg despite adequate filling status	Systolic BP < 90 mmHg or systolic BP drop ≥40 mmHg, lasting longer than 15 min and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

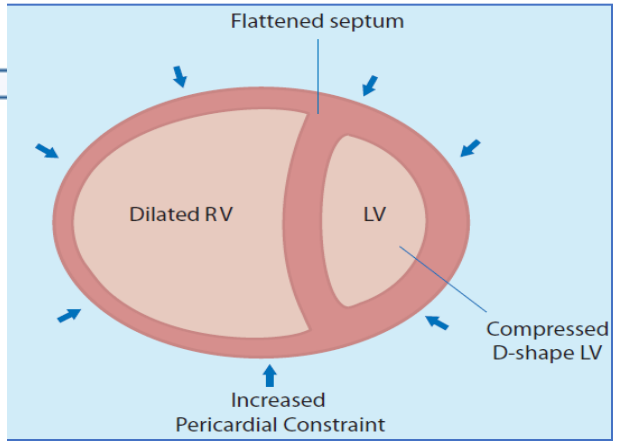
- **These patients are rares:**
  - ICOPER (1995-1996)[1]: **4,2%** (103/2454)
  - RIETE (2001-2016)[2] : **3,5%** (1207/34380)
  - German healthcare database (2005-2015) [3] : **3,5%** (30939/885806)
- **High mortality rate: 30-40%; 60-70% if cardiac arrest**

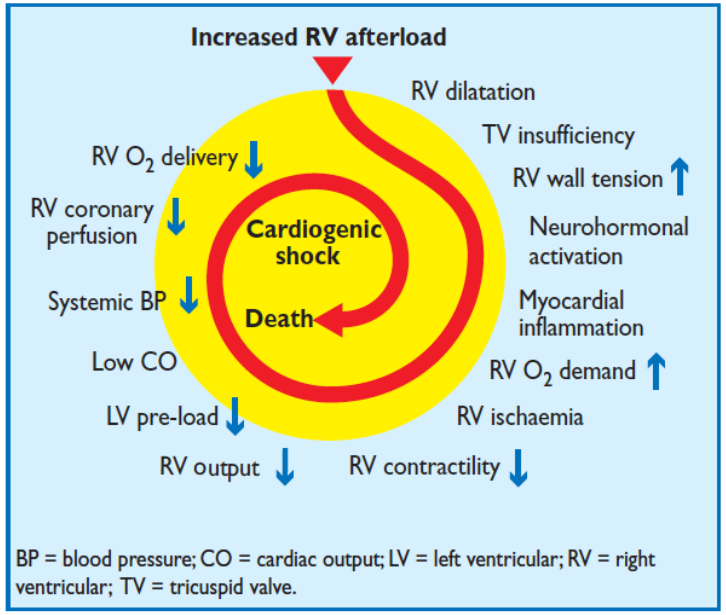
HIGH

Konstantinides SV *et al*, *Eur Heart J* 2019: doi:10.1093/eurheartj/ehz405

Key factors contributing to haemodynamic collapse in acute PE







BP = blood pressure; CO = cardiac output; LV = left ventricular; RV = right ventricular; TV = tricuspid valve.

Millington et al ICM 2023

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

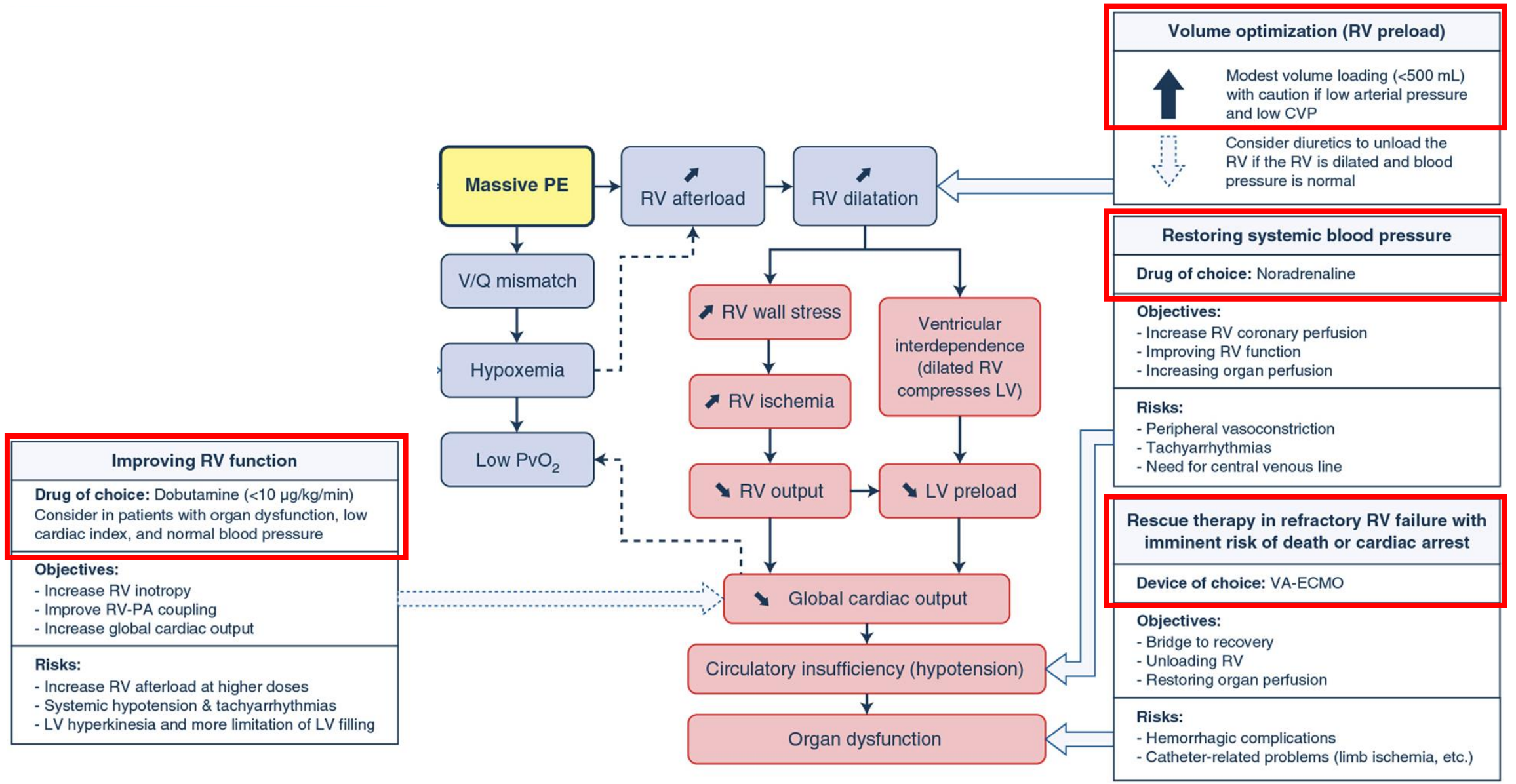
→ Primary reperfusion treatment

Fibrinolysis or embolectomy (surgical/per-cutaneous)

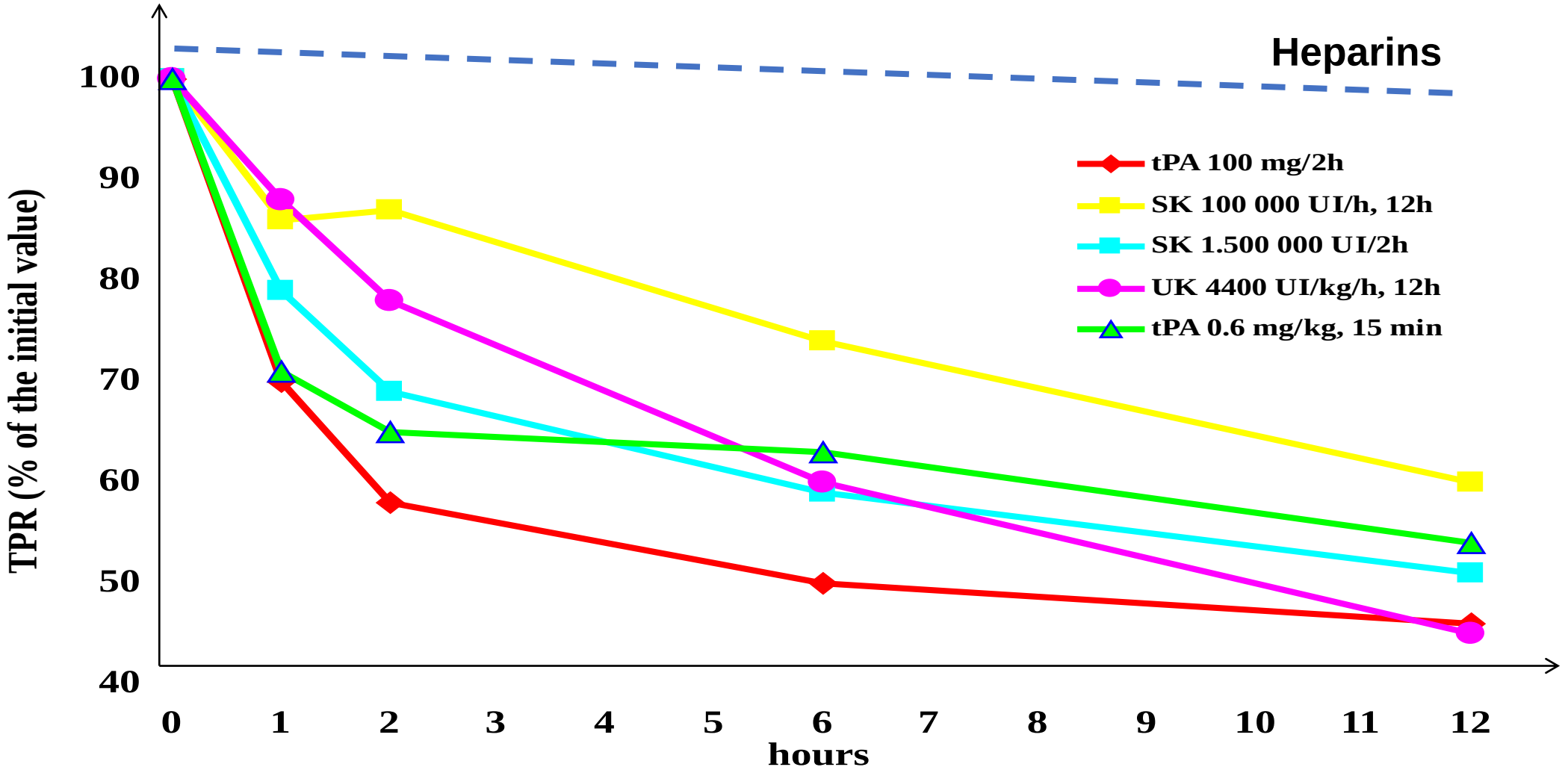
→ Avoid recurrent PE

Anticoagulant treatment: UFH / LMWH

Rapid haemodynamic stabilisation



Decrease RV afterload: systemic fibrinolysis



Meyer 92, Sors 94, Meneveau 97, Meneveau 98

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

European Heart Journal (2015) **36**, 605–614

Christophe Marti[1]*, Gregor John[1], Stavros Konstantinides[2], Christophe Combescure[3], Olivier Sanchez[4], Mareike Lankeit[2], Guy Meyer[4], and Arnaud Perrier[1]

15 RCT

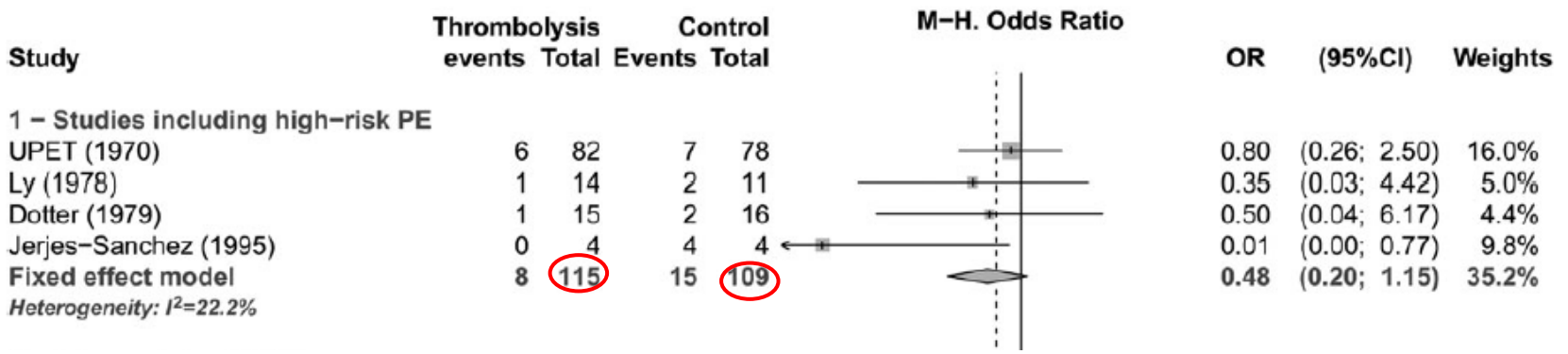
- 4 included (not exclusively) high-risk PE

2057 patients

All studies reported early all-cause mortality and primary endpoint was based on clinical events in 3 RCT including 1344 patients

First author and year of publication	Number of patients	Eligibility	Severity criteria	High-risk PE included	Thrombolysis	Control	Age limit (years)	Follow-up[a]	Invasive angiography	Primary endpoint
Becattini (2010)	58	Acute PE<10 days	RVD	No	Tenecteplase 30–50 mg plus heparin	Heparin	85	30 days	No	24 h RVD[b]
Dalla Volta (1992)	36	Acute PE<10 days	Miller score >11	No	Alteplase 100 mg/2 h plus heparin	Heparin	80	30 days	100%	Pulmonary perfusion[c]
Dotter (1979)	31	Acute PE	No	Yes	Streptokinase 2–11 MIU 18–72 h	Heparin	No	7 days	100%	Pulmonary perfusion[c]
Fasullo (2011)	72	Acute PE<6 h	RVD	No	Alteplase 100 mg/2 h plus heparin	Heparin	75	10 days	No	RVD[b]
Goldhaber (1993)	101	Acute PE<14 days	No	No	Alteplase 100 mg/2 h plus heparin	Heparin	No	14 days	21%	RVD[b]
Jerjes-Sanchez (1995)	8	Acute PE<14 days	Massive	Yes	Streptokinase 1.5 MIU/2 h	Heparin	No	In-hospital	No	RVD, pulmonary perfusion[d]
Kline (TOPCOAT) (2013)	83	Acute PE	RVD or hypoxaemia	No	Tenecteplase 30–50 mg/2 h plus enoxaparin	LMWH	No	5 days	NA	Composite clinical outcome
Konstantinides (MAPPET) (2002)	256	Acute PE<4 days	RVD or pHTA	No	Alteplase 100 mg/2 h plus heparin	Heparin	80	30 days/ in-hospital	16%	Death or treatment escalation
Levine (1990)	58	Acute PE<14 days	No	No	Alteplase 0.6 mg/kg/2 min	Heparin	No	10 days	67%	Pulmonary perfusion[d]
Ly (1978)	20	Acute PE<5 days	>1 lobe[d]	Yes	Streptokinase 72 h	Heparin	70	10 days	100%	Pulmonary perfusion[c]
Marini (1988)	30	Acute PE<7 days	>9 segments[d]	No	Urokinase 2.4–3.3 MIU /12–72 h	Heparin	72	7 days	100%	Pulmonary perfusion[d]
Meyer (PEITHO) (2014)	1005	Acute PE<15 days	RVD and elevated troponin	No	Tenecteplase 30–50 mg plus heparin	Heparin	No	7 days	1.4%	Death or haemodynamic collapse
Sharifi (2013)	121	Acute PE<10 days	≥2 lobes[d]	No	Alteplase 50 mg/ 2 h + heparin	Heparin or LMWH	No	In-hospital	No	Pulmonary hypertension[b]
Stein (PIOPED) (1990)	13	Acute PE<7 days	≥ 1 lobe or ≥ 2 segments[d]	No	Alteplase 40–80 mg/ 40–90 min + heparin	Heparin	No	7 days	100%	Pulmonary perfusionc
UPET (1970)	160	Acute PE<5 days	No	Yes	Urokinase 12 h	Heparin	No	14 days	100%	Pulmonary perfusion[c,d]

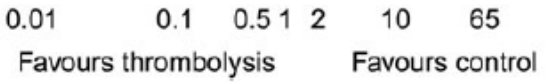
Thrombolysis vs anticoagulant alone in High risk PE



	Studies including[a] High-risk PE
	OR (95% CI)
Mortality	0.48 (0.20 to 1.15)
PE mortality	0.15 (0.03 to 0.78)
Death or treatment escalation	0.18 (0.04 to 0.79)
PE recurrence	0.97 (0.31 to 2.98)

[a]Not exclusively.

Eur Heart J 2015;36:605-14



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

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Safety

Thrombolysis
Major bleeding: 9.9%
Fatal or intracranial haemorrhage: 1.7%

	All studies			Alteplase	Tenecteplase	Other thrombolytics	Group difference
	OR (95% CI)	*P*-value	I^2 (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	*P*-value
Major bleeding	2.91 (1.95 to 4.36)	<0.001	25	1.07 (0.43 to 2.62)	5.02 (2.72 to 9.26)	2.16 (1.03 to 4.54)	0.02
Fatal/intracranial haemorrhage	3.18 (1.25 to 8.11)	0.008	0	1.09 (0.27 to 4.40)	7.32 (1.64 to 32.63)	NA	0.07

Approved regimen and contraindications of thrombolysis in PE: ESC 2019

Streptokinase	250 000 IU as a loading dose over 30 minutes, followed by 100 000 IU/h over 12–24 hours
	Accelerated regimen: 1.5 million IU over 2 hours
Urokinase	4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg per hour over 12–24 hours
	Accelerated regimen: 3 million IU over 2 hours
rtPA	100 mg over 2 hours; or
	0.6 mg/kg over 15 minutes (maximum dose 50 mg)

Absolute contraindications:[a]

- Haemorrhagic stroke or stroke of unknown origin at any time
- Ischaemic stroke in the preceding 6 months
- Central nervous system damage or neoplasms
- Recent major trauma/surgery/head injury in the preceding 3 weeks
- Gastrointestinal bleeding within the last month
- Known bleeding risk

Relative contraindications

- Transient ischaemic attack in the preceding 6 months
- Oral anticoagulant therapy
- Pregnancy, or within one week postpartum
- Non-compressible puncture site
- Traumatic resuscitation
- Refractory hypertension (systolic blood pressure >180 mm Hg)
- Advanced liver disease
- Infective endocarditis
- Active peptic ulcer

Konstantinides SV *et al*, *Eur Heart J* 2019: doi:10.1093/eurheartj/ehz405

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

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

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

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 ???

V/A-ECMO

Lower RV overload

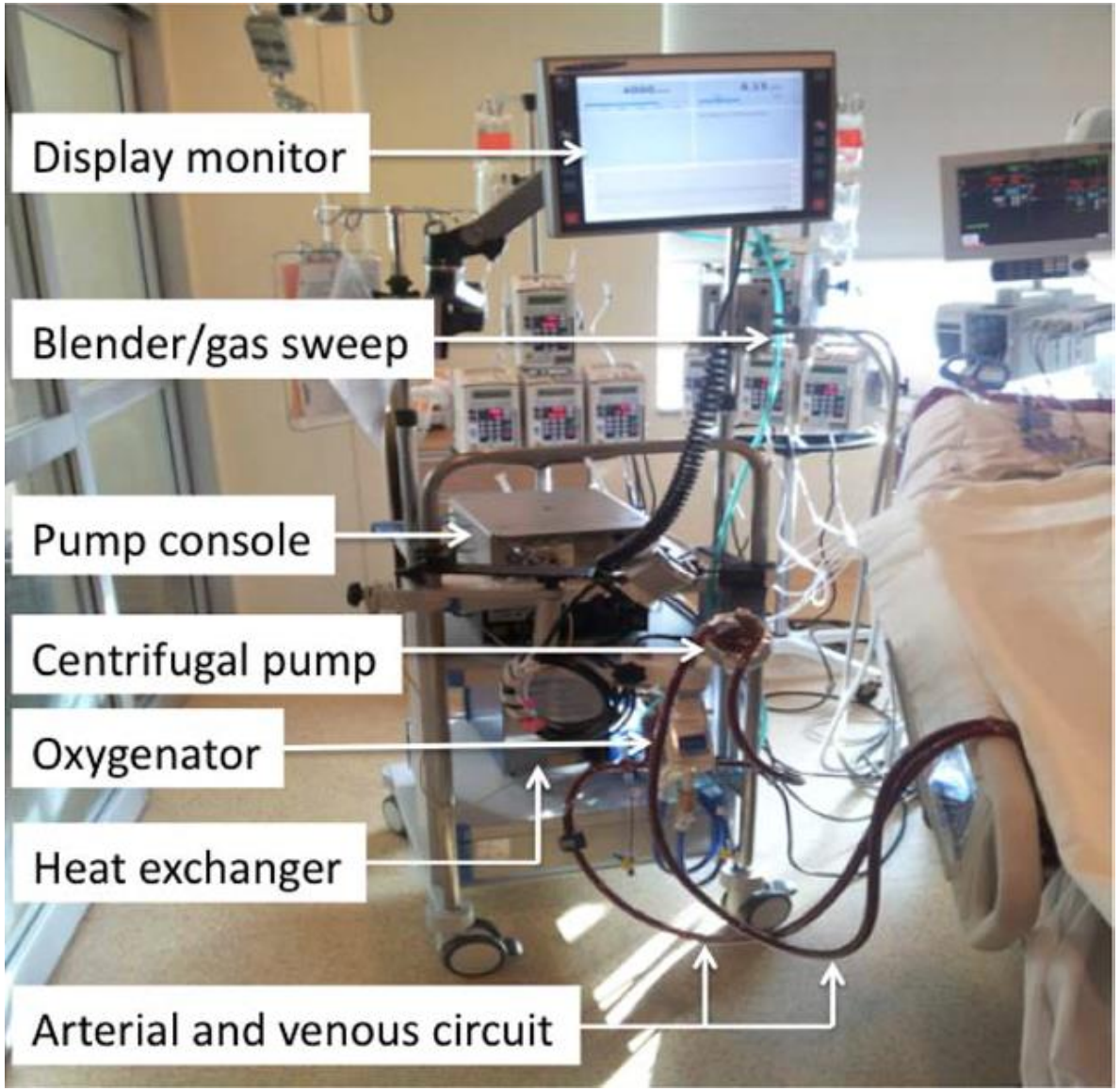
Improve hemodynamic status

Restore tissue oxygenation

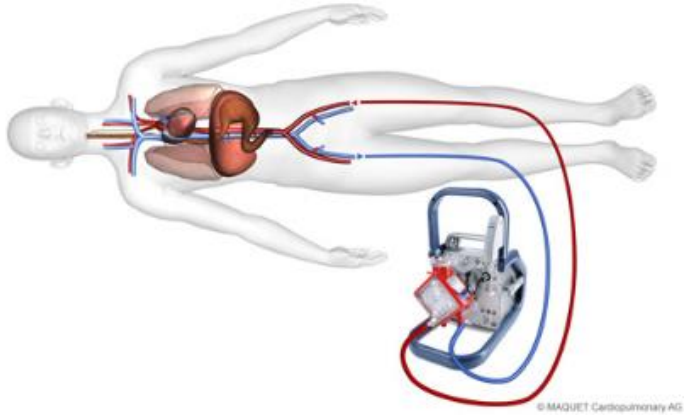
Rapidly efficacious

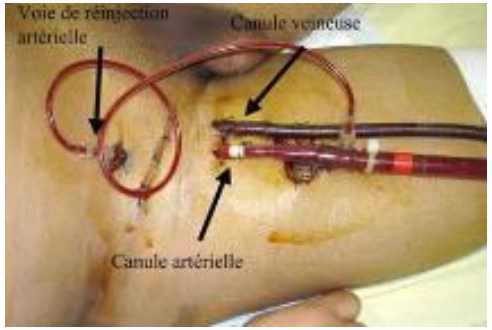
Indicated in case of severe and refractory shock with or without multiple organ failure

Requires a specific and trained team +++



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

Optimal reperfusion strategy in acute high-risk pulmonary embolism requiring extracorporeal membrane oxygenation support: a systematic review and meta-analysis

Chopard et al. Eur Respir J 2022

17 studies (327 PE patients) comparing mechanical embolectomy and other strategies (including systemic, catheter-directed thrombolysis, or ECMO as stand-alone therapy) with regard to mortality and bleeding outcomes

Mortality rate: 26.4% (mechanical reperfusion) vs 42.8% (other strategies)

- Mechanical reperfusion vs other strategies: OR 0.43 (95%CI, 0.23-0.997); p = 0.009; I2 = 35.2%
- Surgical embolectomy vs thrombolysis: OR 0.36 (95% CI, 0.18-0.73; p = 0.009; I2 = 32.9%

Bleeding rate: 24.5% (mechanical reperfusion) vs 19.6% (other strategies)

- OR 1.26; 95% CI, 0.54-2.92; I2 = 7.7%

Mechanical reperfusion, notably by surgical embolectomy, yields favorable results regardless of the timing of ECMO implantation in the reperfusion timeline, independent of thrombolysis administration or cardiac arrest presentation

2019 ESC-ERS PE guidelines

Recommendations	Class[b]	Level[c]
ECMO may be considered, in combination with surgical embolectomy or catheter-directed treatment, in patients with PE and refractory circulatory collapse or cardiac arrest.[d 252]	IIb	C

Konstantinides SV *et al*, *Eur Heart J* 2019: doi:10.1093/eurheartj/ehz405

Surgical embolectomy

Retrospective cohorts

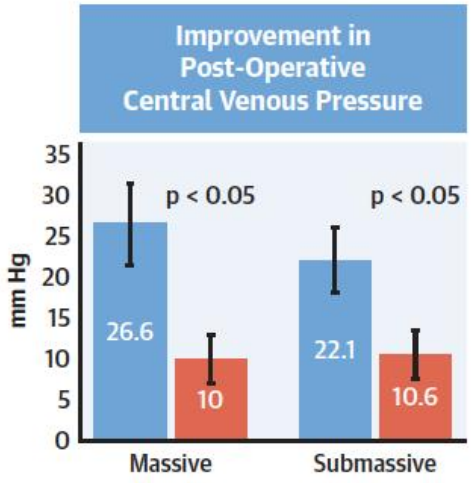
High mortality rates

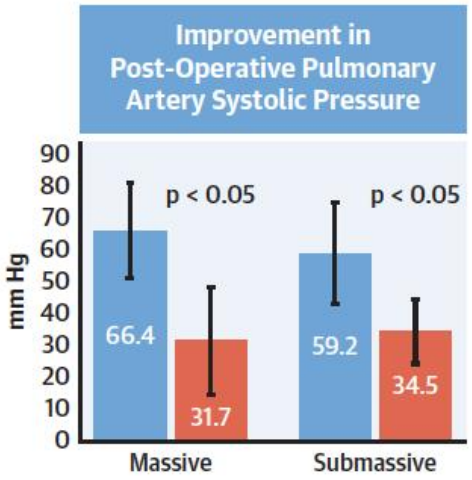
The unsatisfactory surgical results were often related to the compromised clinical status of the patients, especially those who had already undergone thrombolysis and entered the operation room with advanced cardiogenic shock in need of cardiopulmonary resuscitation.

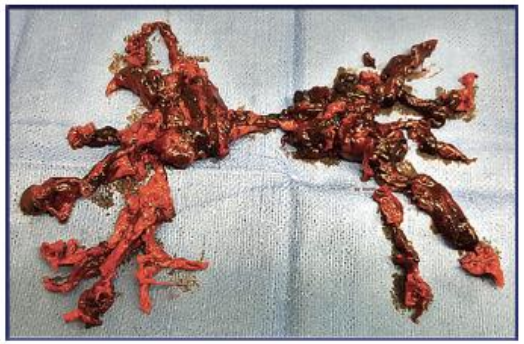
Period	Death n/N	Death %
1968-1989	184/526	35%
1990-1999	188/627	30%
2000-2008	41/215	19%

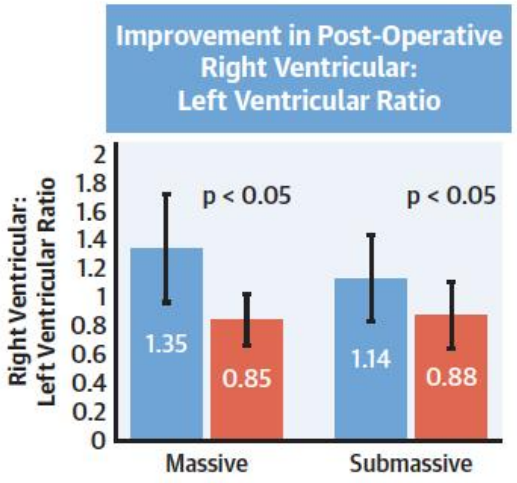
Samoukovic G. et al. *Interactive Cardiovasc Thorac Surg* 2010; 11: 265–270
Kalra et al. *Ann Thorac Surg* 2017;103:982-90

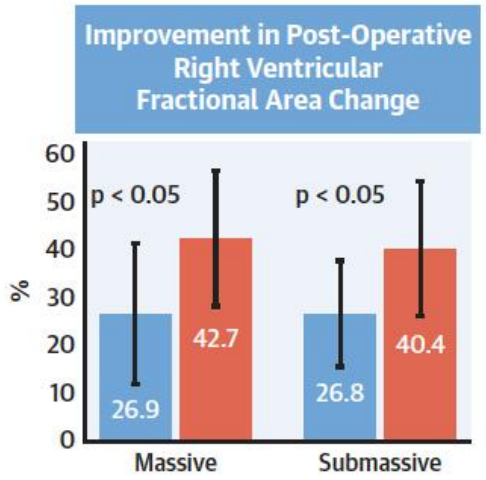
Surgical embolectomy











Pre-Operative Post-Operative

Goldberg, J.B. et al. J Am Coll Cardiol. 2020;76(8):903-11.

Single center retrospective single center study

2005-2019

136 patients who received surgical management

- **44 high-risk PE (shock)**
- 92 intermediate high-risk PE

TABLE 6 In-Hospital Outcomes

	All (N = 136)	SMPE (n = 92 [67.6%])	MPE (n = 44 [32.4%])	p Value
Mortality	6 (4.4)	1 (1.1)	5 (11.6)	0.015

TABLE 7 In-Hospital Morbidity and Mortality Stratified by Pre-Operative CPR

	CPR (n = 19 [14.0%])	No CPR (n = 117 [86%])	p Value
Mortality	4 (21.1)	2 (1.7)	0.03

Catheter-directed treatment options in PE

FIGURE 4 Penumbra Indigo Aspiration System

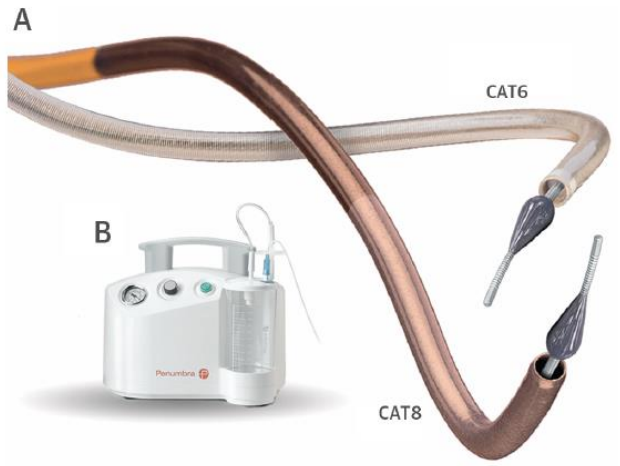


FIGURE 6 EkoSonic Endovascular Device

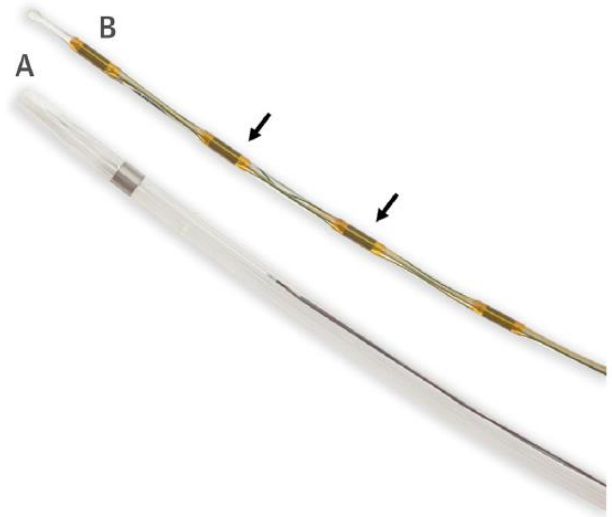


FIGURE 2 AngioVac Device

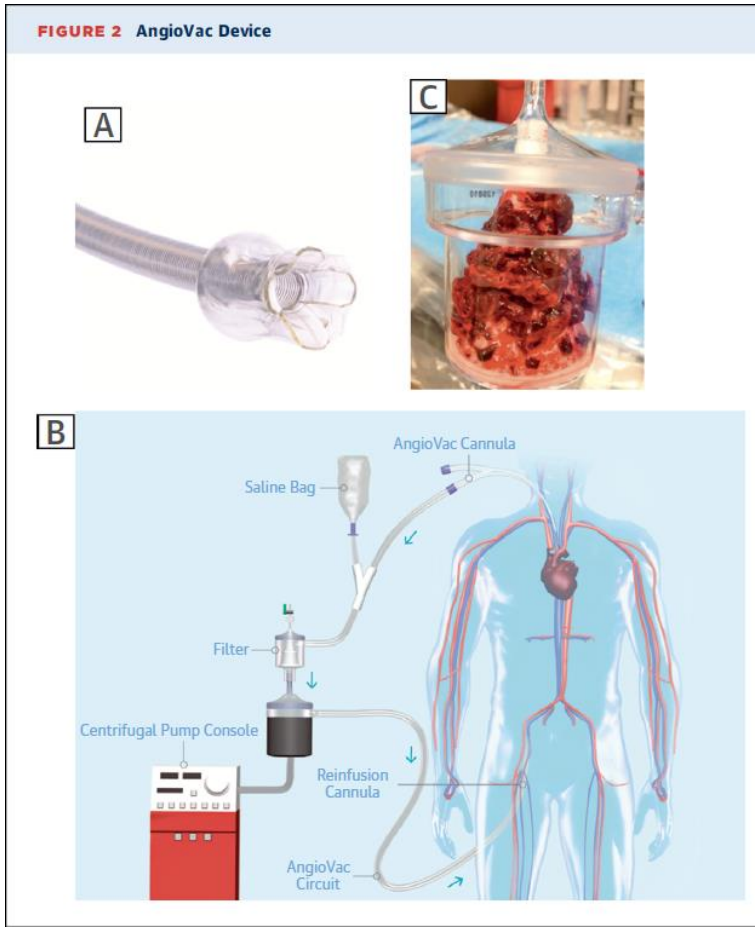
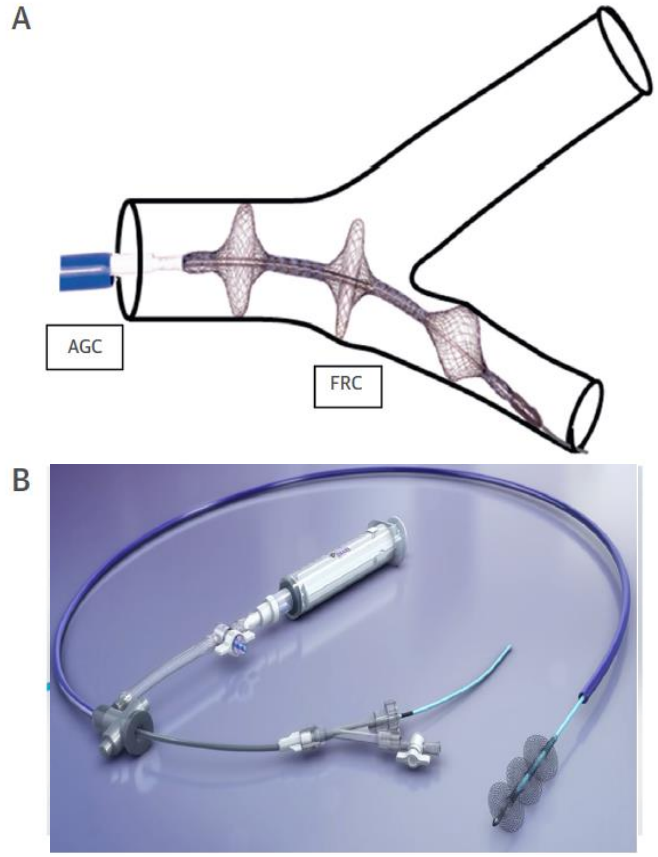
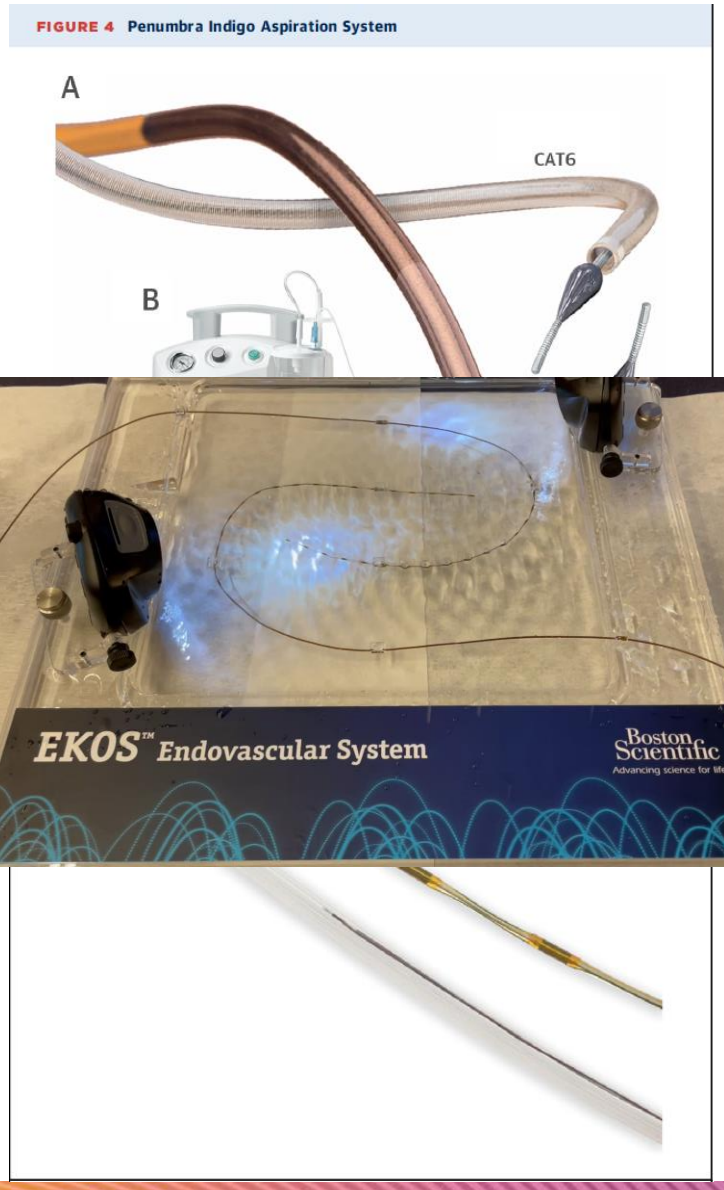
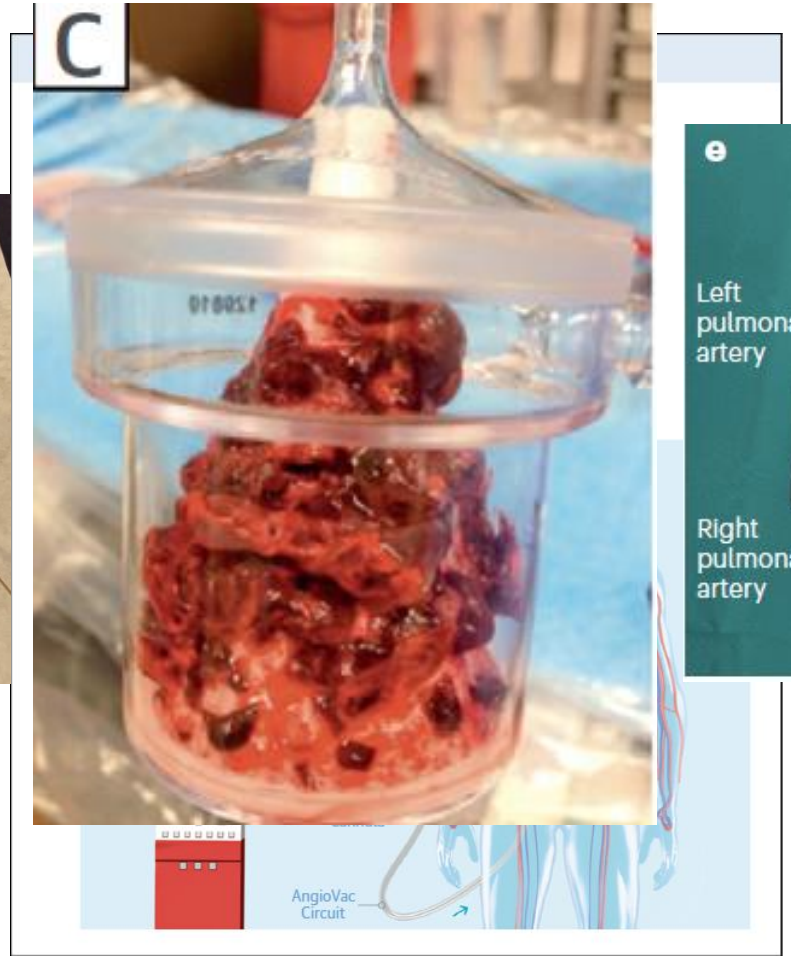


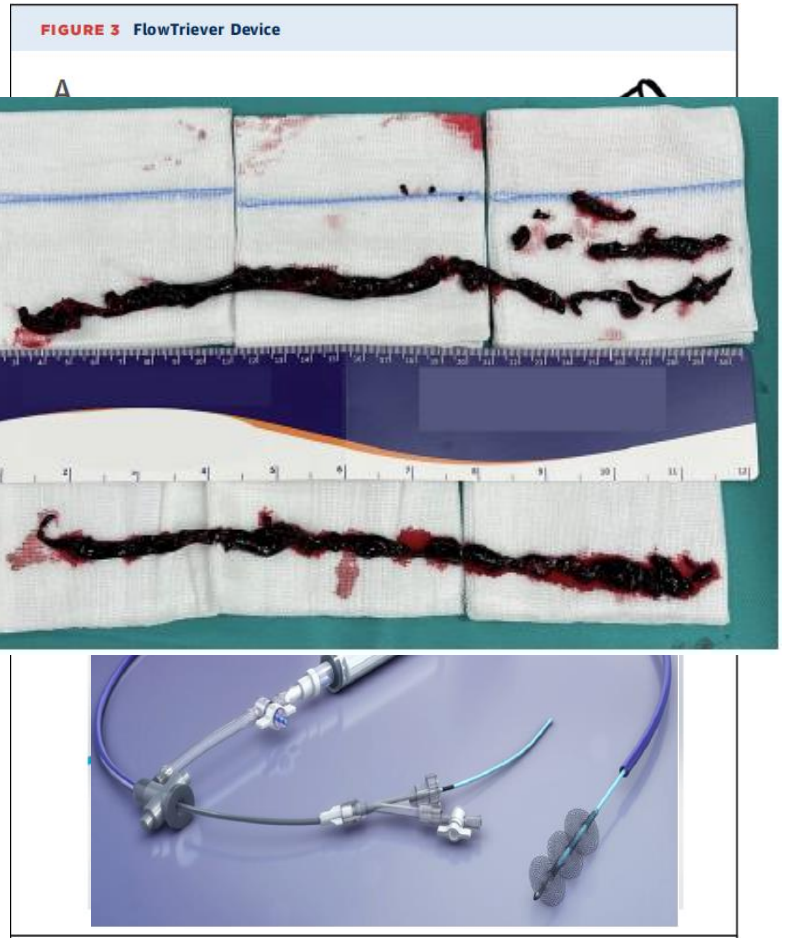
FIGURE 3 FlowTriever Device



Catheter-directed treatment in PE: impressive images of clot removal…





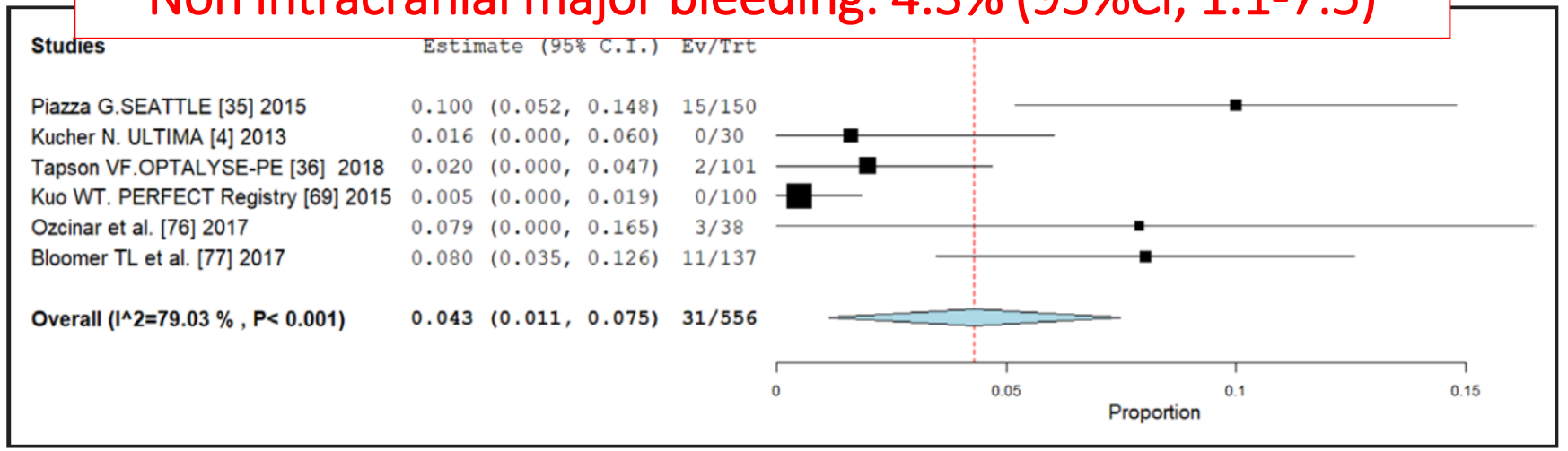


Catheter-directed treatment in PE: registries and RCT

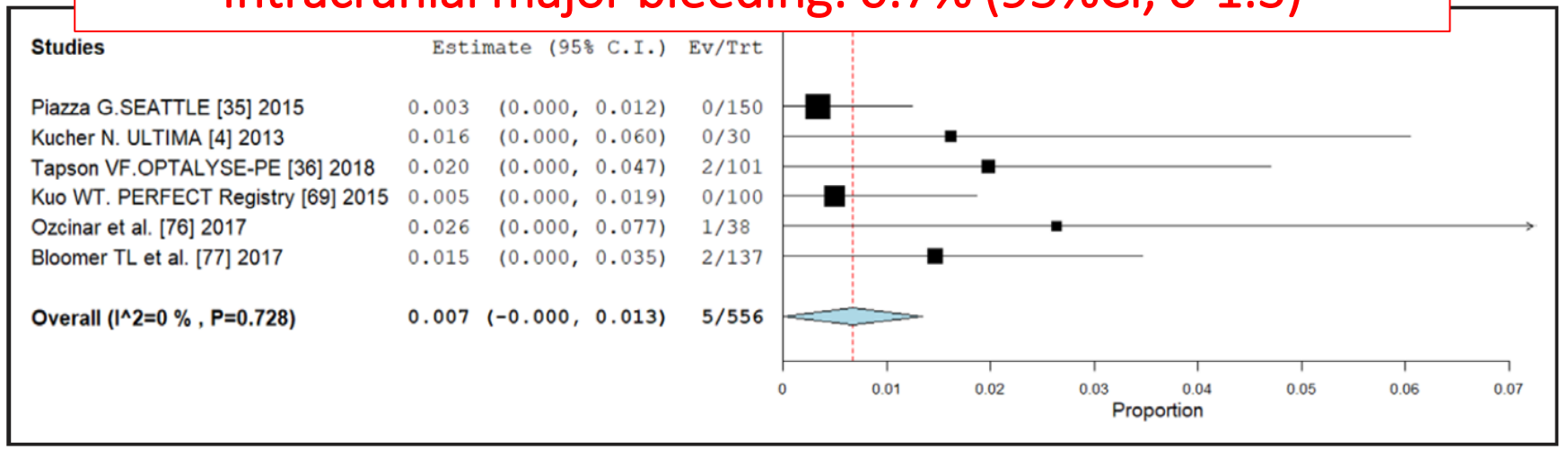
Study, year	Device	Comparator	Patients n	Inclusion criteria	Intermediate high-risk PE	High-risk PE	Primary outcome
SEATTLE 2, 2015	USAT (EKOS)	No	150	RV/LV > 0.9	79%	21%	RV/LV at H48
FLARE, 2019	FlowTriever	No	106	RV/LV > 0.9	56%	0%	RV/LV at H48
FLASH, 2023	FlowTriever	No	800	RV/LV > 0.9	77%	8%	Device related death, MB, intra-procedural adverse event
EXTRACT-PE, 2021	Indigo aspiration	No	119	RV/LV > 0.9	71%	0%	RV/LV at H48
ULTIMA, 2014	USAT (EKOS)	Anticoagulant	59	RV/LV > 1	80%	0%	RV/LV at H24
SUNSET sPE, 2021	USAT (EKOS)	Other CD Tlysis	82	RV/LV > 1 +/- ↑cTn/BNP	95%	0%	Miller score (CTPA) at H48
Kroupa et al, 2022	CD Tlysis	anticoagulant	23	RV/LV > 0,9	100%	0%	↑RV, ↓sPAP, ↓Qanadli: H48
CANARY, 2022	CD Tlysis	Anticoagulant	94	RV/LV > 0,9	100%	0%	RV/LV at M3

Major bleeding in prospective studies of catheter-directed thrombolysis

Non intracranial major bleeding: 4.3% (95%CI, 1.1-7.5)



Intracranial major bleeding: 0.7% (95%CI, 0-1.3)



Giri et al Circulation 2019;140:e774-801

Conclusion

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

Surgical embolectomy or catheter-directed treatment must be discussed if systemic thrombolysis is contraindicated or has failed

VA-ECMO is an effective therapeutic option for the most severe high-risk PE patients (i.e. cardiac arrest / refractory shock)

The best strategy (i.e. stand alone treatment vs bridge to surgical or catheter-directed reperfusion strategy) requires additional dedicated studies

Pulmonary Embolism Responsive Team (PERT) can help to decide on the most appropriate therapy.