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Ultrasound-assisted thrombolysis for acute intermediate-high-risk pulmonary embolism

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ABSTRACT

Introduction: Ultrasound-assisted thrombolysis (USAT) was reported to be efficacious for treatment of intermediate-risk pulmonary embolism (PE) in a randomised controlled trial. This report presents the experiences from implementing USAT for intermediate-high-risk (IHR) PE at a tertiary hospital in Denmark.

Methods: Haemodynamically stable patients with CT with verified central PE were eligible for USAT if imaging showed signs of right-ventricular dysfunction and myocardial biomarkers were elevated. Patients without signs of improvement on initial unfractionated heparin treatment received USAT with 10 mg alteplase per catheter for 15 hours.

Results: In the course of a 25-month period, 75 patients were referred for treatment. A total of 50 patients were eligible for treatment of whom 32 patients underwent USAT. The remaining patients received unfractionated heparin (UFH) alone. Ninety-four percent of the USAT patients experienced a reduction of symptoms. At the 30-day follow-up, four patients had complications in the form of major bleeding and three patients had died, with no significant difference between USAT with UFH and UFH alone. Nine patients with USAT had follow-up CT angiographies showing a significant post-procedure reduction in right-to-left ventricular diameter ratio, mean ± standard deviation: 1.4 ± 0.3-1.1 ± 0.1.

Conclusions: USAT seems to be an efficacious treatment option for IHR-PE with persistent symptoms, but special care should be taken avoid access-site haematomas and bleeding complications. Future trials should further investigate catheter-based and/or reduced-dosage systemic thrombolysis for IHR-PE management.

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Trial registration: not relevant.

Pulmonary embolism (PE) is the third-most common cause of cardiovascular death and a major cause of morbidity and hospitalisation [1]. PE has an incidence of 44-56 per 100,000 persons annually and is associated with a 90-day all-cause mortality rate of 8.7-17% [2-4]. According to the European Society of Cardiology (ESC) Guidelines on the diagnosis and management of acute pulmonary embolism, intermediate-risk PE patients are recognised by having a Pulmonary Embolism Severity Index (PESI) class III-V or sPESI (simplified PESI) score ≥ 1, without any signs of cardiovascular shock or arterial hypotension. These patients have a 30-day all-cause mortality rate reaching 15% [5, 6]. Imaging tests showing signs of right ventricular (RV) dysfunction *and* increased cardiac biomarkers indicating RV overload or myocardial damage further distinguishes patients into the intermediate-high-risk (IHR) category. IHR-PE remains a clinical challenge as the decision on whether and how to restore pulmonary arterial blood flow remains essentially unanswered [1, 5].

Thrombolytic treatment of intermediate-risk pulmonary embolism has shown no definitive mortality benefits over anticoagulation therapy alone in large randomised controlled trials [7]. Meanwhile, catheter-directed treatments (CDT) for PE have yet to be implemented in guidelines as clinically relevant treatment alternatives for IHR-PE management [5].

Ultrasound-assisted thrombolysis (USAT) represents a recent CDT development, and has been shown to be efficacious in reducing RV overload faster than anticoagulation treatment

alone [8]. Several case series and a small randomised trial have been completed, showing low counts of major bleeding complications compared with standard high-dose thrombolytics [8-11]. It remains unclear whether the potential short-term and long-term benefits of USAT outweigh the overall bleeding risks of thrombolytic treatment.

We present our experience implementing USAT as an initial treatment for acute IHR-PE in a real-world clinical setting at a tertiary heart centre in Denmark.

METHODS

Diagnosis, risk stratification and initial management

Diagnosis of PE was conducted at the referring hospital according to national clinical guidelines and confirmed by a CT angiography showing PE proximal to segmental arteries. IHR status was indicated by echocardiography showing signs of RV dysfunction with either right-to-left ventricular diameter ratio (RV/LV ratio) > 1.0, paradoxical septal motion or a tricuspid regurgitation gradient > 30 mmHg [5]. According to ESC guidelines, patients with IHR-PE are defined as having:

PESI class III-V or sPESI score ≥ 1

Cardiac imaging showing signs of RV strain or dysfunction

Elevated cardiac biomarkers: troponin I or T, alternatively N-terminal pro-brain natriuretic peptide

Absence of sustained arterial hypotension: systolic blood pressure < 90 mmHg, and shock.

Adult patients meeting these criteria with symptom onset within 14 days were candidates for referral for further work-up at the Heart Centre, Rigshospitalet. Any absolute contraindication to thrombolysis would exclude USAT treatment.

Work up at the Heart Centre included administration of unfractionated heparin (UFH), targeting an activated partial thromboplastin time of 1.5-2.5 times the baseline value or an activated clotting time of 160-180 seconds [5]. Patients initially treated with low-molecular-weight heparin were switched to UFH. Patients were monitored by telemetry, cardiac biomarkers were re-assessed and oxygen was administered targeting an oxygen saturation of 95% or more.

Selection criteria for ultrasound-assisted thrombolysis

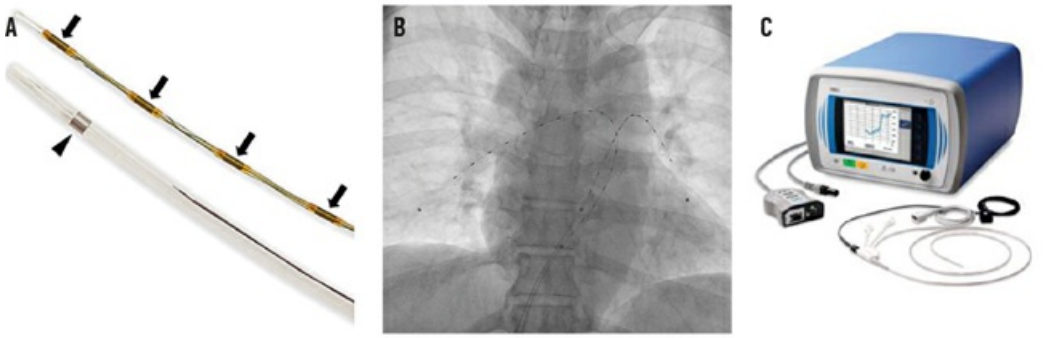
Patients were reassessed the following morning. Patients without signs of clinical improvement were considered candidates for USAT if a supplementary oxygen requirement persisted, and no signs were seen of clinical improvement with a resting heart rate above 80.

Patients' informed consent for the procedure was obtained.

The ultrasound-assisted thrombolysis procedure

The USAT procedure used the EkoSonic Endovascular System, see **Figure 1**A. An interventional cardiologist inserted each EKOS catheter via femoral-vein access through a 6 French sheath and positioned it in the lower pulmonary arteries near the emboli, see Figure 1B.

FIGURE 1 / Presentation of the ultrasound-assisted thrombolysis system used in the present case series. **A.** The bi-lumen catheter of the EkoSonic device (bottom). The thrombolytic drug is administered through the peripheral lumen and leaves the catheter through multiple small side holes while the ultrasonic core wire (top) and coolant run through the central lumen. **B.** A thoracic X-ray showing the placement of catheters bilaterally within the pulmonary arteries. Core wire transducers (A, arrows) are visible as black beads on a string with the catheter markers (A, arrowhead), also being radiopaque. **C.** The EkoSonic main unit which manages the ultrasonic therapy for a single catheter. Images from the EKOS Corporation, Washington, USA.



After catheter placement, the core ultrasound wires were inserted. Room-temperature isotonic saline was administered as a coolant throughout the treatment period. All patients received bilateral treatment after connecting the catheters to the EKOS console, see Figure 1C. Thrombolysis treatment followed the protocol for the ULTIMA randomised controlled trial [8]: Alteplase administered as 1 mg/hour for five hours, then 0.5 mg/hour for ten hours; a total dose of 10 mg per catheter for 15 hours [8]. The intravascular ultrasound delivery was initiated after the patient was admitted to the intensive care unit for close monitoring.

EKOS catheters were removed after completion of the thrombolytic therapy. The sheaths were removed two hours later to reduce the risk of groin haematoma, and manual compression was applied on the puncture site until haemostasis was achieved. Treatment with UFH continued during and after the USAT procedure. Mandatory ultrasound guidance for venipuncture was introduced in the middle of the study period as groin haematomas were found to occur more frequently than expected.

Analyses and statistics

The data for this report were extracted from patients' medical charts as part of the assessment of the efficacy and safety of the USAT procedure programme. Access to medical charts was permitted by local authorities that waived consent as the study formed part of the hospital quality control efforts. No patients were lost to follow-up.

Assessment of symptom improvement and groin haematoma was done by the attending physician. CT RV/LV ratios were measured unblinded by a single investigator. Major bleeding was assessed from the patient charts using the GUSTO criteria [12] for severe or moderate bleeding.

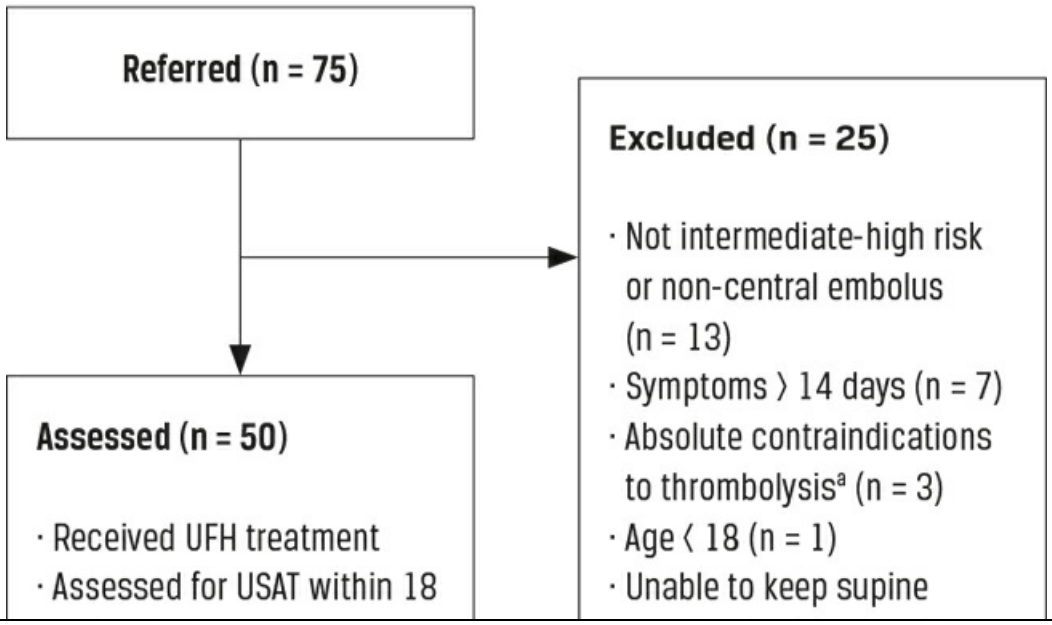
Analyses were performed in R 3.3.2. All values are given as a count with percentage, median with range or mean ± the standard deviation, as applicable. The Clopper–Pearson method was used for 95% confidence intervals of binomial proportions when given.

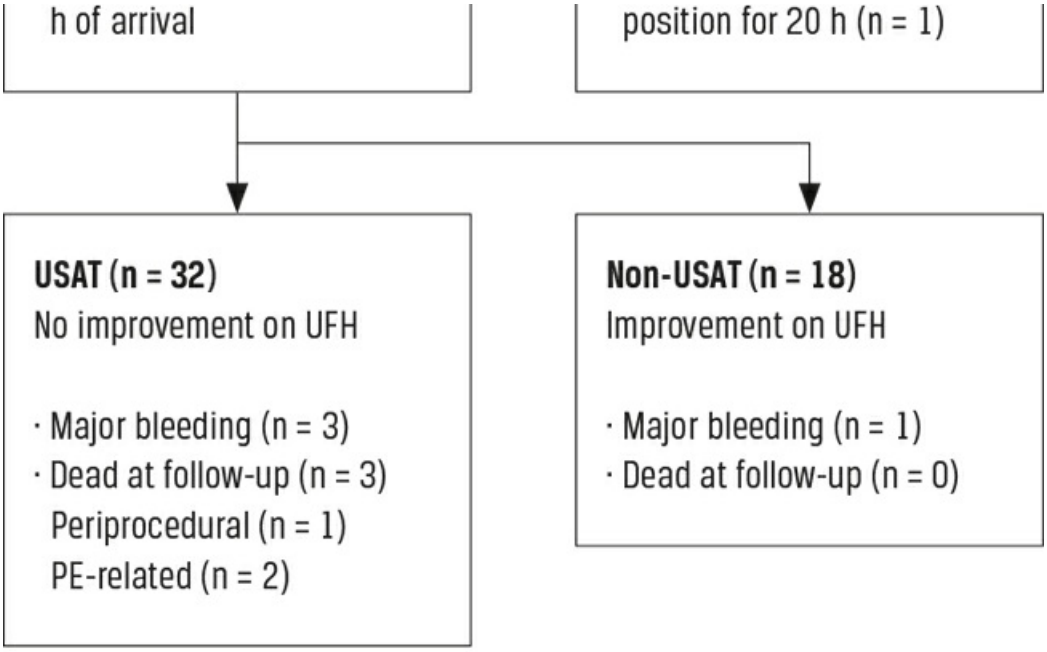
Trial registration: not relevant.

RESULTS

From October 2015 to November 2017, a total of 75 patients with CT-verified PE were referred to the Heart Centre for USAT. Twenty-five patients were excluded after initial assessment, see **Figure 2**, leaving 50 IHR-PE patients for analysis in the present case series. Thirty-two patients underwent USAT, whereas 18 improved on UFH treatment alone and were thereby considered to have a limited gain from the procedure. Clinical presentation and initial parameters showed no significant difference between the USAT and non-USAT patients, see **Table 1**.

FIGURE 2 / Patient procedure selection.





NOAC = novel anticoagulants; UFH = unfractionated heparin; USAT = ultrasound-assisted thrombolysis.
a) Absolute contraindications to thrombolysis included a history with cerebral haemorrhage, recent ischaemic stroke (< 6 mo.s), recent major surgery, trauma or intracranial surgery (< 3 wks), recent gastrointestinal bleed (< 1 mo.), known haemorrhagic risk or brain tumour. Patients with relative contraindications were evaluated on an individual basis, including patients with an increased prothrombin ratio or undergoing anticoagulation or (NOAC) treatment.

In the USAT group, all patients had catheters successfully placed bilaterally. See **Table 2** for outcome comparisons for both patient groups.

The 30-day major bleeding rate for all patients was 8.0% (95% confidence interval (CI): 2.2-19), with no occurrences of intracranial haemorrhage. Three USAT patients had a major bleeding event at follow-up: one periprocedural pericardial haemorrhage during thrombolysis treatment leading to tamponade and death in a patient who later proved to have high-grade ovarian carcinoma and pericardial carcinomatosis, one death five days post procedure suspected to be caused by internal haemorrhage from an unknown source, and one upper gastrointestinal haemorrhage 11 hours after completion of thrombolysis in a patient with disseminated uterine carcinoma.

TABLE 1 / Clinical presentation and baseline tests of patients treated with ultrasound-assisted thrombolysis vs non-ultrasound-assisted thrombolysis.

	Total	USAT	non-USAT	p-value[a]
Patients, generally				
n (%)	50 (100)	32 (64)	18 (36)	-
Male, n (%)	32 (61)	22 (69)	9 (50)	0.18
Age, yrs, median (range)	66.5 (33-86)	65.5 (33-86)	69.5 (50-85)	0.43
History of, n (%)				
Venous thromboembolism	9 (18)	4 (13)	5 (28)	0.17
Active cancer	4 (8)	2 (6)	2 (11)	0.54
Major surgery within 3 mo.s	2 (4)	0	2 (11)	0.05
Diabetes Type 2	7 (14)	5 (16)	2 (11)	0.66
Factor V_{Leiden}, heterozygote	1 (2)	1 (3)	0	0.48
Embolus: saddle/proximal, n (%)	29 (58)/21 (42)	20 (63)/12 (37)	9 (50)/9 (50)	0.39
Duration of symptoms, days, median (range)	3 (0-14)	3 (1-14)	3 (0-10)	0.79
Chest pain, n (%)	20 (40)	12 (38)	8 (44)	0.69
DVT suspected[b], n (%)	13 (26)	8 (25)	5 (28)	0.88
Syncope, n (%)	10 (20)	6 (19)	4 (22)	0.76
Systolic blood pressure[c], mmHg, mean ± SD	135 ± 17.1	133 ± 15.2	137 ± 20.1	0.41
Heart rate[c], mean ± SD	98 ± 14	100 ± 13	94 ± 16	0.16
Tachycardiac: HR > 100, n (%)	22 (44)	16 (50)	6 (33)	0.25
O_2 supplement[c], l, median (range)	3 (0-30)	3 (0-30)	2 (0-10)	0.15
Troponin T level, ng/l, mean ± SD	130 ± 123	135 ± 132	122 ± 108	0.71
Creatine phosphokinase-MB[d] level , µg/l, mean ± SD	4.6 ± 4.2	4.7 ± 4.8	4.3 ± 2.7	0.84
CT RV/LV ratio, mean ± SD	1.4 ± 0.3	1.4 ± 0.3	1.3 ± 0.3	0.28

CT RV/LV ratio = CT-measured right-to-left ventricular diameter ratio; DVT = deep-vein thrombosis; HR = heart rate; SD = standard deviation; USAT = ultrasound-assisted thrombolysis.

a) Pearson's χ^2 test.

b) Clinical signs of deep-vein thrombosis, including unilateral lower extremity oedema, muscle pain or erythema.

c) Measured on admission to the Heart Centre.

d) Data not available in 12 (24%) patients, 6 patients in each group.

One non-USAT patient experienced a major haemothorax bleeding complication requiring infusion of two units of red blood cells. The 30-day all-cause mortality for all patients was 6.0% (95% CI: 1.2-17). Three USAT patients were deceased on follow-up: The two mentioned above and one patient with a history of stroke passed into cardiogenic shock two days post procedure, leading to cardiac arrest and death. There were no deaths at follow-up among the non-USAT patients.

TABLE 2 / Clinical outcome of patients treated with ultrasound-assisted thrombolysis vs non-ultrasound-assisted thrombolysis.

	USAT	Non-USAT
Baseline compared to 24 h		
Symptom improvement, %	94	100[a]
Groin haematoma, n (%)	5 (16)	-
Reduction in O_2 supplement, l, mean ± SD	4.2 ± 5.8[b]	2.3 ± 3.4[b]
Reduction in CT RV/LV ratio, mean ± SD[c]	0.27 ± 0.32[b]	-
30-day follow-up		
GUSTO criteria for severe/moderate bleeding, n (%)	3 (9.4)	1 (5.6)
Death, n (%):		
Periprocedural	1	-
PE-related[d]	2	0
Subtotal	3 (9.4)	0

CT RV/LV ratio = CT-measured right-to-left ventricular diameter ratio; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial; PE = pulmonary embolism; SD = standard deviation; UFH = unfractionated heparin; USAT = ultrasound-assisted thrombolysis.
a) Non-USAT were excluded from USAT by improvement of symptoms following UFH therapy.
b) Difference significant from 0 using a paired t-test with equal variances assumed.
c) 9 USAT patients had a post-procedure CT-angiography within 24-h.
d) Non-periprocedural deaths which were unexpected.

DISCUSSION

When managing IHR-PE, treatment strategies must balance the risk of deterioration and haemodynamic collapse against the risk of bleeding complications from thrombolytic therapy [1, 5]. USAT is a recent development in catheter-based thrombolysis promising to provide low-risk therapy for acute PE management. To the best of our knowledge, the ULTIMA trial by Kutcher et al [11] remains the only randomised trial comparing CDT to standard therapy for PE completed to date [8]. Randomising 59 CT-confirmed acute intermediate-risk PE patients, they found that USAT was superior to UFH alone in reducing RV/LV ratio at 24 hours. USAT was reported as safe, with no occurrences in either group of haemodynamic decompensation, major bleeding, or stroke at 90 days and a single death in the UFH group. Our report follows the USAT regimen described in the ULTIMA trail while assessing only IHR patients and selecting only patients lacking improvement on UFH treatment for the procedure. The higher rate of major bleeding events and death seen among our patients is likely explained by their increased risk and the restrictive exclusion criteria used in the ULTIMA trail. The SEATLE II observational study further explored the safety of USAT in 150 massive and sub-massive PE patients. They found that USAT reduced RV/LV ratio, thrombotic burden and mean pulmonary artery systolic pressure at 48 hours post procedure without any occurrences of stroke and with one major bleeding event and 15

moderate bleeding events [10].

The present cases series raises some concerns regarding the relatively high incidence of bleeding episodes and groin haematoma. Even if access-site complication can be reduced, e.g. by ultrasound-guided puncture, the risks associated with USAT should be discussed carefully, and protocolised implementation and studies are warranted. Cancer patients seemed to have an even higher bleeding risk and should be managed with caution.

Our report shows that USAT provides improved simple haemodynamic parameters in IHR-PE patients who do not respond to initial UFH therapy, offering an alternative to systemic thrombolysis. Earlier observational studies have shown that CDT, including USAT, provide early improvement of symptoms and haemodynamic parameters when treating acute PE [9, 11]. The ultrasonic component of USAT aims to increase penetration of the thrombolytic drug into the thrombus using high-frequency ultrasound, accelerating the fibrinolytic process [8, 13]. It remains unclear whether this benefit contributes clinically to clearing the embolus or whether traditional CDT offers equivalent outcomes [11].

The choice of whether, when and how to use thrombolytics for intermediate-risk PE remains controversial despite the completion of large international trials. The PEITHO trail randomised 1,005 acute intermediate-risk PE patients at 76 sites to receive either tenecteplase in combination with parenteral anticoagulation or parenteral anticoagulation alone. They found that thrombolytics prevented haemodynamic decompensation or death while increasing the risk of major bleeding and stroke. As a result, no difference in the overall mortality rate was found at either the 30-day or the 48-month follow-up [14]. An earlier study found a similar result from 256 randomised patients [15]. At least 12 systematic reviews of thrombolytic treatment for intermediate-risk PE have been published following the completion of the PEITHO trial [16]. These reviews show consensus on some mortality rate benefit from using thrombolytics, but the risks of major bleeding and the benefit-to-harm ratio are discordant between the systematic reviews conducted.

Several studies have hinted that low-dose thrombolytics, catheter-based or not, have the potential to become a go-to-treatment option for IHR-PE [17]. The MOPETT trial, completed by Sharifi et al in 2013, randomised 121 patients with “moderate” PE (comparable-to-intermediate-risk PE) to receive either ≤ 50% of normal dose thrombolysis with anticoagulation therapy or anticoagulation alone [18]. They showed that low-dose thrombolytics were safe in effectively reducing symptoms and length of hospital stay without increasing the risk of bleeding. Wang et al compared alteplase 100 mg for two hours versus 50 mg for two hours in 118 randomised high-risk PE patients. They found that both regimes had a similar efficacy with the lower dosage decreasing bleeding risk in non-overweight patients [19]. Results from the OPTALYSE PE trial show that shortened and very-low-dosage USAT, with as little as 4 mg alteplase per catheter for two hours, reduced the RV/LV ratio to a degree similar to the one observed in the regime followed in the ULTIMA

study, whereas reductions in thrombotic burden were dose-dependent [20].

Limitations

This series is based primarily on patients referred for evaluation in a tertiary heart centre, which introduced a source of bias. Non-USAT patients were selected based on symptomatic improvement during their initial UFH treatment, and comparing outcomes between the two groups should be interpreted accordingly. The USAT procedure was not initialised until after assessment of the preliminary UFH treatment effect, limiting direct comparison to the ULTIMA trial in which USAT was initiated within four hours. Post-procedure CTs were unblinded and only offered on clinical indications and thus not consecutively. Therefore, caution should be exercised when interpreting these results. The incidence of complications and events in both groups should be interpreted with caution.

CONCLUSIONS

USAT seems efficacious in relieving symptoms and reducing RV/LV ratios for patients with IHR-PE with persistent symptoms following initial unfractionated heparin treatment. The risk of access-site hematomas and procedure-related bleeding complications was not insignificant, and measures to reduce these should be considered as part of an implementation plan. The decision to offer USAT to patients should be carefully weighed against the potential risk.

USAT is a viable treatment option for IHR-PE, but more trials are needed on patient selection and the choice between catheter-based thrombolysis, reduced dosage systemic thrombolysis and anticoagulation therapy alone.

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LITERATURE

1. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet 2012;379:1835-46.
2. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999;353:1386-9.
3. Laporte S, Mismetti P, Decousus H et al. Clinical predictors for fatal pulmonary embolism in 15 520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. Circulation 2008;117:1711-6.
4. Naess IA, Christiansen SC, Romundstad P et al. Incidence and mortality of venous thrombosis: a population-

based study. J Thromb Haemost 2007;5:692-9.

5. Konstantinides SV, Torbicki A, Agnelli G et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35:3033-80.
6. Aujesky D, Obrosky DS, Stone RA et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005;172:1041-6.
7. Meyer G, Vicaut E, Danays T et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370:1402-11.
8. Kucher N, Boekstegers P, Müller OJ et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 2014;129:479-86.
9. Engelberger RP, Kucher N. Ultrasound-assisted thrombolysis for acute pulmonary embolism: a systematic review. Eur Heart J 2014;35:758-64.
10. Piazza G, Hohlfelder B, Jaff MR et al. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism. JACC Cardiovasc Interv 2015;8:1382-92.
11. Tafur AJ, Shamoun FE, Patel SI et al. Catheter-directed treatment of pulmonary embolism: a systematic review and meta-analysis of modern literature. Clin Appl Thromb. 2017;23:821-9.
12. GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673-82.
13. Braaten JV, Goss RA, Francis CW. Ultrasound reversibly disaggregates fibrin fibers. Thromb Haemost 1997;78:1063-8.
14. Konstantinides SV, Vicaut E, Danays T et al. Impact of thrombolytic therapy on the long-term outcome of intermediate-risk pulmonary embolism. J Am Coll Cardiol 2017;69:1536-44.
15. Konstantinides S, Geibel A, Heusel G et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 2002;347:1143-50.
16. Riva N, Puljak L, Moja L et al. Multiple overlapping systematic reviews facilitate the origin of disputes: the case of thrombolytic therapy for pulmonary embolism. J Clin Epidemiol 2018;97:1-13.
17. Sharifi M. Systemic full dose, half dose, and catheter directed thrombolysis for pulmonary embolism. When to use and how to choose? Curr Treat Options Cardiovasc Med 2016;18:31.
18. Sharifi M, Bay C, Skrocki L et al. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). Am J Cardiol 2013;111:273-7.
19. Wang C, Zhai Z, Yang Y et al. Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary thromboembolism. Chest 2010;137:254-62.
20. Tapson VF, Sterling K, Jones N et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism. JACC Cardiovasc Interv 2018;11:1401-10.