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CURRENT VIEW ON ANTICOAGULANT AND THROMBOLYTIC TREATMENT OF ACUTE PULMONARY EMBOLISM

Abstract

The presented review concerns contemporary views on specific aspects of anticoagulant and thrombolytic treatment of venous thromboembolism and mostly of acute pulmonary embolism. Modern classifications of patients with acute pulmonary embolism, based on early mortality risk and severity of thromboembolic event, are represented. The importance of multidisciplinary approach to the management of patients with pulmonary embolism with the assistance of cardiologist, intensive care specialist, pulmonologist, thoracic and cardiovascular surgeon, aimed at the management of pulmonary embolism at all stages: from clinical suspicion to the selection and performing of any medical intervention, is emphasized. Anticoagulant treatment with the demonstration of results of major trials, devoted to efficacy and safety evaluation of anticoagulants, is highlighted in details. Moreover, characteristics, basic dosage and dosage scheme of direct (new) oral anticoagulants, including apixaban, rivaroxaban, dabigatran, edoxaban and betrixaban are described in the article. In particular, the management of patients with bleeding complications of anticoagulant treatment and its application in cancer patients, who often have venous thromboembolism, is described. Additionally, modern approaches to systemic thrombolysis with intravenous streptokinase, urokinase and tissue plasminogen activators are presented in this review. The indications, contraindications, results of clinical trials devoted to various regimens of thrombolytic therapy, including treatment of pulmonary embolism with lower doses of fibrinolytic agents, are described.

Key words: *pulmonary embolism, venous thromboembolism, thromboembolism of pulmonary artery, treatment, risk stratification, anticoagulant therapy, direct oral anticoagulants, systemic thrombolysis, fibrinolysis, bleeding complications*

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ESC — European Society of Cardiology, FDA — Food and Drugs Administration, MOPPET — moderate pulmonary embolism treated with thrombolysis, PEITHO — pulmonary embolism thrombolysis study, PERT — Pulmonary Embolism Response Team, PESI — Pulmonary Embolism Severity Index, tPA — tissue plasminogen activator, VKA — vitamin K antagonists, ACD — anticoagulant drug, ACT — anticoagulant therapy, APTT — activated partial thromboplastin

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time, VTE — venous thromboembolism, CI — confidence interval, PE — pulmonary embolism, INR — international normalized ratio, LMWH — low molecular weight heparin, UFH — unfractionated heparin, HR — hazard ratio, DOAC — direct oral anticoagulants, PTT — prothrombin time, PTS — post-thrombotic syndrome, RCT — randomized clinical trial, STL — systemic thrombolysis, DVT — deep vein thrombosis, CTEPH — chronic thromboembolic pulmonary hypertension

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially fatal disease [1, 2]. The incidence of the first acute event of VTE is 0.7–1.4 per 1 thousand people/years, and is most common in people aged over 55 years [2, 3]. In persons, aged 70 years and older, VTE rate reaches 7 cases per 1 thousand people [4]. At the same time, though DVT rate remains constant over time, the hospitalization for PE in the United States increased more than twofold in recent decades, mainly due to the widespread introduction of sensitive imaging that can determine small emboli [5].

With the obvious success of modern diagnostic methods, the management of patients with PE presents significant challenges. This is due to the diverse clinical presentation and different hemodynamic response to the embolization of pulmonary vasculature, which in turn is associated with the massiveness of the emboli, the state and compensatory capabilities of the heart, the presence and severity of concomitant diseases. Therapeutic measures include the use of anticoagulant drugs (ACD), thrombolytics, interventional approaches described earlier [6], surgical embolectomy and maintenance therapy. In addition, if the use of endovascular therapeutic methods, unfortunately, is limited to large medical centers, the basic therapy of VTE, including anticoagulant therapy (ACT) and systemic thrombolysis (STL), as a rule, is available in almost all specialized hospitals. The purpose of this review was to discuss modern approaches to the treatment of patients with acute PE with ACT and STL.

Clinical classification of pulmonary embolism severity

Assessment of the massiveness of PE or calculation of the mortality risk in this event is a crucial step in determining the principles and sequence of treatment strategy stages. The clinical classification of PE severity is based on the calculated risk of early (up to 30 days) mortality due to thromboembolic event [1]. This distribution (or stratification), which is important both diagnostically and therapeutically, is based on an assessment of the patient's clinical status at the time of presentation. High-risk PE is assumed or confirmed in the presence of shock or persistent hypotension, and non-high-risk PE (intermediate or low) — in their absence (Table 1) [1].

Classification of PE severity based on massiveness (scope) of the thromboembolism case was previously widely used. However, even in the recommendations of the European Society of Cardiology (ESC) 2008 it was noted that PE severity should be understood more as an individual assessment

Table 1. *Classification of patients with acute pulmonary embolism based on early mortality risk*

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III–V or sPESI > I	Sign of RV dysfunction on an imaging test	Cardiac laboratory biomarkers
High		+	(+)	+	(+)
Intermediate-	**High**	–	+	Both positive	
	Low	–	+	Either one (or none) positive	
Low		–	–	Assessment optional; if assessed, both negative	

Note: PESI — Pulmonary Embolism Severity Index; RV — right ventricular; sPESI — simplified Pulmonary Embolism Severity Index; sPESI ≥1 point(s) indicates high 30-day mortality risk. Adapted from S.V. Konstantinides et al. [1]

of early mortality due to PE [7], rather than the anatomical volume, shape and disposition of the intrapulmonary embolus assessment. Therefore, in ESC Guidelines for the diagnosis and treatment of acute PE 2008 it was proposed to replace the incorrect, according to experts, terms of massive, submassive and non-massive PE with the corresponding risk categories of early mortality presented in Table 1 [7]. However, in the literature, especially in North America, there are widespread definitions of massive, submassive PE, which correspond to cases of high and intermediate risk, respectively [8–11]. The assessment of the lesion massiveness should ideally take into account the angiographic control of the scale and distribution of the embolic material using the Miller index [12].

In addition to assessing the risk of early mortality (or massiveness) for PE after diagnosis, it is considered extremely important to calculate the prognosis of the disease using the clinical index of PESI (**P**ulmonary **E**mbolism **S**everity **I**ndex) in the original [13] and **s**implified versions — sPESI [14].

Interdisciplinary approach

Timely diagnosis, accurate risk stratification, and adequate use of reperfusion techniques are crucial measures to ensure the earliest possible favorable outcome in patients with high or intermediate-high risk PE [15]. Hospitalization of patients with suspected or already diagnosed PE outside the working hours of the main specialists (at night or on weekends) is combined with the worst prognosis due to the lack of timely, specialized medical care by experienced doctors. In recent years, in the United States and most recently in Europe, a new coordinated approach for the management of patients with PE — with the help of a multidisciplinary team of specialists called PERT (**P**ulmonary **E**mbolism **R**esponse **T**eam) [16], competent in the treatment of PE and including, at least, pulmonologist, interventional radiologist, cardiologist and thoracic surgeon, was developed [17]. PERT provides highly professional care focused on the treatment of PE at all its stages, from clinical suspicion of PE to selection and implementation of any medical intervention: ACT, STL, interventional methods of treatment, surgical embolectomy, etc. Therapeutic strategy should optimally integrate all of the available range of therapeutic techniques in compliance with, albeit multidisciplinary, a unified approach to the management of such patients [18].

Anticoagulant therapy

The clinical study by D.W. Barritt and S.C. Jordan published in *The Lancet* [19] in 1960 was of fundamental importance in the development of modern guidelines for the management of patients with PE based on PE treatment with ACT [20]. ACT is the main method of treatment for the majority of patients with acute PE and, in addition, represents the basis of therapy for the prevention of acute and chronic complications, including relapses of PE (leading to hemodynamic insufficiency), lower limb DVT, which is often a source of PE and post-PE syndrome [15, 21]. The ACT is usually considered in the management of hemodynamically stable patients [22].

The ACT plays one of the key roles, if not the basis of the therapeutic strategy in VTE and, in particular, acute PE [23]. There are 3 phases of VTE treatment: initial (first 5–10 days), long-term (from the end of the initial phase to 3–6 months) and extended (>3–6 months) [2]. The duration of the ACT should not be less than 3 months. During this period, traditional modes of acute phase therapy are represented by parenteral administration of ACD (unfractionated heparin (UFH) i. v., subcutaneous injections of low molecular weight heparins (LMWH) or fondaparinux) in the first 5–10 days, layered on or replaced by vitamin K antagonists (VKA), which are selected until the therapeutic range of the international normalized ratio (INR) 2.0–3.0 is reached [4, 21, 24]. LMWH are preferable in comparison with UFH, as their use is associated with a lower rate of massive bleeding, a more reliable therapeutic effect and a lower probability of heparin-induced thrombocytopenia [23].

The benefits of ACT, including prevention of thrombus enlargement, reduction of VTE recurrence, hemodynamic collapse and death, should be carefully weighed against the risk of bleeding to determine the choice of ACT and the duration of

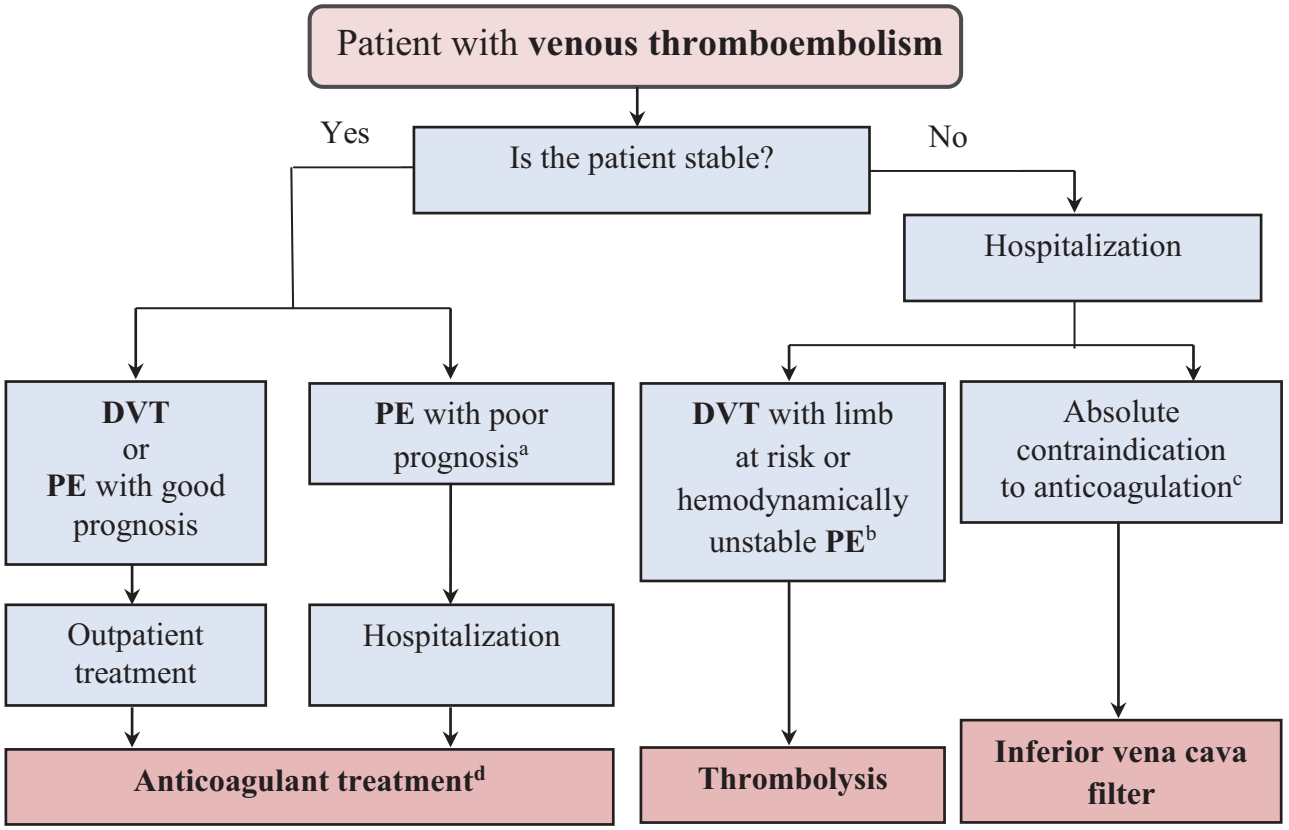

Figure 1. *Approach to initial treatment of venous thromboembolism*

Notes: DVT — deep vein thrombosis; PE — pulmonary embolism. a — assessment of 30-day mortality risk with the Pulmonary Embolism Severity Index score or its simplified version or the Hestia criteria. b — catheter-directed thrombolysis for DVT and systemic thrombolysis for PE. c — active bleeding, high risk of bleeding, or other contraindication to anticoagulant therapy. d — initiate treatment with direct oral anticoagulants (rivaroxaban or apixaban, or initial low molecular weight heparin followed by dabigatran or edoxaban). Modified from T. Tritscher et al. [2]

treatment (Fig. 1) [2]. In order to determine the risk of VTE recurrence and duration of the ACT, thromboembolic events are distinguished between provoked (transient, caused by any identifiable factors) and unprovoked (in the absence of any identifiable risk factor for the development of VTE) [23, 25].

Prior to the introduction of direct (or new) oral anticoagulants (DOAC), urgent therapy of PE began with parenteral administration of anticoagulants, usually LMWH, as transitional treatment with VKA, reaching full activity only after 5-7 days [15, 24]. In the latest ESC Guidelines 2014 for the diagnosis and treatment of acute PE, immediate intravenous administration of UFH to high-risk patients (with shock or hypotension, class I, level of evidence C) is recommended [1]. The mode of transitional treatment with VKA is quite effective and safe in patients with PE and DVT: the 3-month rate of VTE relapses during VKA therapy is 3.4 % (up to 20 % in patients not receiving treatment) with massive bleeding rate of 1.6 % [26]. However, the practical application of therapy with VKA is problematic, since it requires frequent determination of INR and fractional selection of the optimal dosage to ensure the presence of the drug in the effective therapeutic range. Moreover, there are many interactions between VKA and other drugs, including allopurinol, amiodarone, selective serotonin reuptake inhibitors, antibiotics and antiepileptic agents, as well as various vitamin K-rich products, such as broccoli, grapefruit, cauliflower, etc. [15].

Despite treatment with ACT, a substantial portion of survivors after DVT or PE is at risk of consequences, such as post-thrombotic syndrome (PTS), recurrent DVT or chronic thromboembolic pulmonary hypertension (CTEPH). In the fall of 2018, the American Society of Hematology published recommendations for the management of VTE using ACT, which are of undisputed interest

to practitioners [27]. Recommendations, suggesting that the choice of anticoagulant by doctors has already been made, mainly relate to the selection of the initial dosage of ACD; drug-drug interactions; evaluation of INR in close proximity to the patient; revision of the term for re-determination of INR; switch to another ACD; organized training of patients; improving compliance with the ACT regimen, etc. [27].

Patients with provoked events, having a removable or treatable cause (e. g., immobilization after injury or surgery), should receive anticoagulants for a period of 3 months [2, 23]. Patients who experienced the first unprovoked episode of VTE are at high risk of relapse (10 % after 1 year and 30 % — 5 years) and should thus receive the ACT indefinitely, until a high risk of hemorrhagic complications is reached [28].

Direct oral anticoagulants

The introduction of DOAC in 2012 greatly simplified the conduct of ACT in patients with VTE. DOAC can be prescribed in fixed dosages without the need for regular determination of INR and, in addition, have fewer interactions with other drugs [29]. Currently, there are 4 drugs for the treatment of PE: dabigatran (specific thrombin inhibitor) and three Xa factor blockers: apixaban, rivaroxaban and edoxaban (Table 2) [4]. In addition, the US FDA approved betrixaban,

Table 2. *Direct oral anticoagulant agents in the treatment and secondary prevention of VTE*

	Dosage and Interval			Not recommended or contraindicated
	Initial Phase	**Long-Term Phase**	**Extended Phase**	
Rivaroxaban	15 mg twice a day with food for 21 days	20 mg once daily with food		• CrCl <30 ml/min • Moderate or severe hepatic impairment (Child-Pugh B and C), or hepatic disease associated with coagulopathy • Concomitant use of combined P-gp and strong CYP3A4 inhibitors or inducers
Dabigatran etexilate	Initial therapy with parenteral anticoagulation for 5–10 days should precede administration of dabigatran etexilate	150 mg twice daily		• CrCl <30 ml/min • Concomitant treatment with P-gp inhibitors in patients with CrCl <50 ml/min • Concomitant treatment with P-gp inducers (i. e., rifampin)
Apixaban	10 mg twice a day for 7 days	5 mg twice daily	2.5 mg twice daily after at least 6 months of treatment	• CrCl <15 ml/min Severe hepatic impairment (Child-Pugh C), or hepatic disease associated with coagulopathy • Strong dual inhibitors or inducers of CYP3A4 and P-gp
Edoxaban	Initial therapy with parenteral anticoagulation for 5–10 days should precede administration of edoxaban	60 mg once daily 30 mg once daily can be considered in patients with ≥1 of the following factors: CrCl 15–50 ml/min; body weight ≤60 kg; concomitant use of P-gp inhibitors, cyclosporin, dronedarone, erythromycin, or ketoconazole		• CrCl <15 ml/min • Moderate or severe hepatic impairment (Child-Pugh B and C), or hepatic disease associated with coagulopathy • Concomitant treatment with rifampin

Note: CrCl — creatinine clearance; CYP3A4 — cytochrome P450-3A4; P-gp — P-glycoprotein; VTE — venous thromboembolism. Adapted from S.V. Konstantinides et al. [4]

another Xa factor inhibitor with a very low dependence on renal clearance (7–14 %), but it has not yet been studied in the treatment of PE [15]. To date, there has been one large, international, double-blind, randomized clinical trial (RCT) to investigate the efficacy and safety of betrixaban in patients for the prevention of VTE [30]. Prolonged use of betrixaban (35–42 days) was accompanied by a decrease in events caused by VTE, including PE, without increasing massive bleeding rate based on a modified analysis of all patients who underwent randomization.

Permission to use DOAC in the treatment of PE was based on the results of phase III studies of initial therapy, as well as prolonged treatment, which showed that DOACs are as effective as traditional drugs, but unlike the latter, treatment with them is associated with a lower rate of massive bleeding (Table 3) [31]. In the first meta-analysis, the rate of recurrent VTE and VTE-related deaths after 6 months was 2.0 % in patients receiving DOAC and 2.2 % in the group of patients treated with VKA. Massive bleeding was reported in 1.1 % of patients in the DOAC group and in 1.7 % of patients in the VKA group.

Table 3. *Overview of phase 3 trials using DOACs for the treatment of acute VTE*

Trial	Intervention	Study duration; number of patients	Study design	Efficacy outcome	Safety outcome
			Dabigatran		
RE-COVER [35]	Dabigatran[a] versus warfarin[a]	6 months; 2,539 patients with acute VTE	Double blind	Recurrent VTE or fatal PE: 2.4 % for dabigatran versus 2.1 % for warfarin	Massive bleeding: 1.6 % for dabigatran versus 1.9 % for warfarin
RE-COVER II [36]	Dabigatran[a] versus warfarin[a]	6 months; 2,589 patients with acute VTE	Double blind	Recurrent VTE or fatal PE: 2.3 % for dabigatran versus 2.2 % for warfarin	Massive bleeding: 1.2 % for dabigatran versus 1.7 % for warfarin
			Rivaroxaban		
EINSTEIN-DVT [37]	Rivaroxaban versus warfarin[a]	3–12 months; 3,449 patients with acute DVT	Open label	Recurrent VTE or fatal PE: 2.1 % for rivaroxaban versus 3.0 % for warfarin	Massive bleeding or CRNM bleeding: 8.1 % for rivaroxaban versus 8.1 % for warfarin
EINSTEIN-PE [38]	Rivaroxaban versus warfarin[a]	3–12 months; 4,832 patients with acute PE with or without DVT	Open label	Recurrent VTE or fatal PE: 2.1 % for rivaroxaban versus 1.8 % for warfarin	Massive bleeding or CRNM bleeding: 10.3 % for rivaroxaban versus 11.4 % for warfarin
			Apixaban		
AMPLIFY [39]	Apixaban versus warfarin[a]	6 months; 5,395 patients with acute DVT and/or PE	Double blind	Recurrent VTE or fatal PE: 2.3 % for apixaban versus 2.7 % for warfarin	Massive bleeding: 0.6 % for apixaban versus 1.8 % for warfarin
			Edoxaban		
Hokusai-VTE [40]	Edoxaban combined with LMWH versus UFH or LMWH with warfarin	3–12 months; 8,240 patients with acute DVT and/or PE	Double blind	Recurrent VTE or fatal PE: 3.2 % for edoxaban versus 3.5 % for warfarin	Massive bleeding or CRNM bleeding: 8.5 % for edoxaban versus 10.3 % for warfarin

Note: In the trials, dabigatran (twice a day) and edoxaban (once a day) in intensive regimen were started after a minimum 5-day period of therapeutic dose of LMWH, which was followed by a direct oral anticoagulant (DOAC) in a fixed dose for both drugs, whereas apixaban (twice a day) and rivaroxaban (once a day) were given in a higher loading dose (for 7 days for apixaban and for 21 days for rivaroxaban) followed by a lower fixed dose. CRNM — clinical-relevant non-massive; DVT — deep vein thrombosis; LMWH — low molecular weight heparin; PE — pulmonary embolism; UFH — unfractionated heparin; VTE — venous thromboembolism. [a] — combined with enoxaparin. Adapted from M.V. Huisman et al. [15].

Compared with patients treated with VKA, patients taking DOAC showed a significant decrease (62 %) in massive bleeding in a critical area (e. g., brain or pericardium), as well as intracranial bleeding (61 %), overall — fatal hemorrhages (64 %) [32]. Based on the results and practical advantages of DOAC (fixed dosage, oral administration, no need for monitoring), recent recommendations of the American College of Thoracic Physicians included the use of DOAC, not VKA, in patients with PE who do not have an active cancer [28]. The use of Xa factor antagonists and direct thrombin inhibitors is likely to increase as they are added to the general guidelines as a first-line therapy.

Despite the advantages of DOAC over VKA, there are subgroups of patients with PE, for whom VKA administration is preferred [33]. First, these are patients suffering from end-stage renal failure or with creatinine clearance of <30 ml/l, since the majority of DOAC and LMWH are eliminated mainly through the kidneys [2, 23]. Secondly, for some patients who do not comply with the drug regimen, the need for serial measurement of INR acts as a kind of "guarantor" in terms of VKA intake. Thirdly, some patients' insecurity with insurance coverages when taking DOAC, as VKAs mainly are cheap products and are covered by insurance programs. Finally, VKAs are preferred in patients with antiphospholipid syndrome [23, 33].

At this time, there are practically no data on direct comparative analysis of individual drugs in the DOAC group and the choice of one of them is based on the difference in therapeutic regimens, characteristics of the patient and his/her preferences [23]. Although in early 2019, there were results of comparative analysis of apixaban and rivaroxaban prescribed for the prevention of repeated VTE episodes [34]. The total VTE recurrence rate in the group treated with apixaban was 3 per 100 person-years, and in the group of rivaroxaban — 7 per 100 person-years. The rate of massive bleeding was 3 per 100 person-years in the apixaban group and 6 per 100 person-years in the rivaroxaban group. When using the multivariate Cox regression model, apixaban compared to rivaroxaban was associated with a reduced risk of repeated VTE episodes (HR 0.37, 95 %, CI 0.24-0.55; p<0.0001) and massive hemorrhagic events (0.54 [0.37–0.82]; p=0.0031) [34].

DOACs should be avoided in case of simultaneous use of cytochrome P450 3A4 inhibitors or inducers (Table 2), including azole antifungals (e. g., ketoconazole), some protease inhibitors used in the treatment of HIV (e. g., ritonavir) and antiepileptic agents (in particular, phenytoin and carbamazepine), since these drugs can affect serum concentrations of DOAC [2].

The choice — whether or not to start DOAC therapy in a patient with PE in the acute phase — is determined by the clinical situation and the presence of comorbidity. Patients at high risk with hemodynamic instability usually receive UFH or LMWH, and it is also allowed to start treatment with DOAC prior to the stabilization of hemodynamic parameters [1]. Only patients with severe kidney injury, determined by creatinine clearance <15 ml/min^{-1} for apixaban, rivaroxaban, edoxaban and <30 ml/min^{-1} for dabigatran, as well as with severe liver dysfunction should not be prescribed with DOAC. Moreover, DOACs are contraindicated in pregnant and lactating women due to the fact that all drugs of this group penetrate the placenta and breast milk, and safety data in these categories of patients are not available [15]. Given the lack of data on the safety of DOACs in patients with antiphospholipid syndrome and arterial thrombosis, these drugs should also not be used in the above groups of patients. Finally, patients weighing >120 kg should be excluded from treatment with DOACs due to insufficient information about their efficacy in people with increased weight [41]. Analyzing prospectively the experience of DOAC administration according multicenter registry in France (2012–2017), R. Chopard et al. [21] noted the widespread use of this group of anticoagulants (in 70 % of patients with acute PE), especially after DOACs became available on the market. Among the factors limiting administration of DOACs, researchers note active cancer and impaired renal function in patients.

Prevention and treatment of hemorrhagic complications during anticoagulant therapy

Patients with VTE receiving ACT differ from other categories of patients on treatment with ACD (in particular, with atrial fibrillation) by rare simultaneous administration of antiplatelet drugs, a higher frequency of concomitant cancer, as well as an intensive mode of ACT at the beginning of treatment [42].

Prior to the administration of ACD all available information about the patient should be carefully collected, in particular: 1. Does patient currently receive ACD? 2. When was the last time the drug was used and in what dosage? 3. Does the patient take aspirin or another drug that inhibits platelet function? 4. Does the patient have kidney disease?

The main therapeutic measures in the development of anticoagulant-associated hemorrhagic complications match the same principles on which the management of patients with bleeding of other etiology is based (Fig. 2).

Immediate measures to stop or slow bleeding include local hemostasis (compression of the available bleeding artery, tamponade of the nasal cavity, installation of an intraesophageal Sengstaken-Blakemore tube to stop bleeding from esophageal veins, etc.) and mitigation of blood loss consequences (oxygen, intravenous fluids, hemodynamic support, blood transfusion) [42].

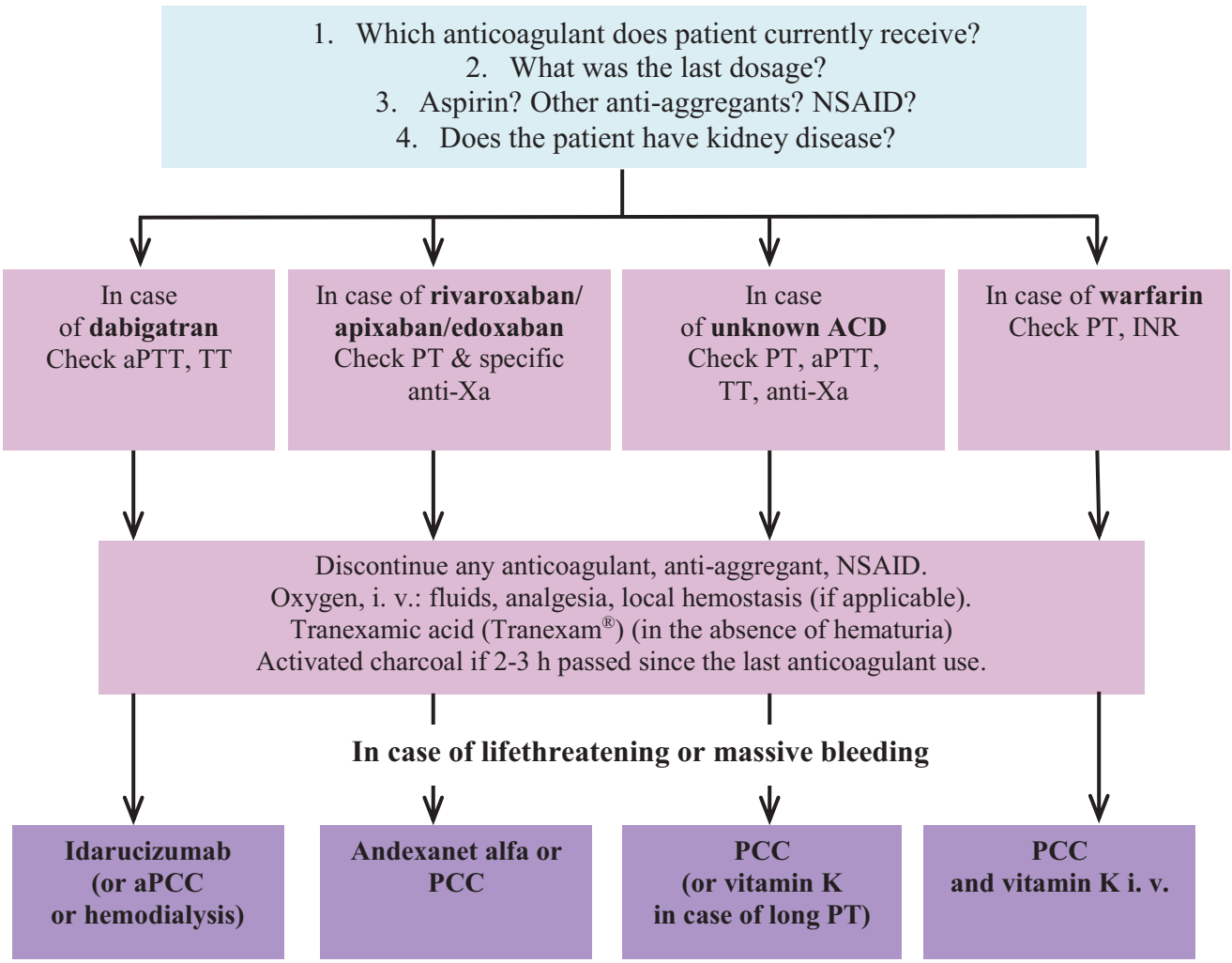

Figure 2. *Algorithm for management of anticoagulant associated massive bleeding*

Note: NSAID — nonsteroid anti-inflammatory drug; aPTT — activated partial thromboplastin time; TT — thrombin time; PT — prothrombin time; aPCC — activated prothrombin complex concentrate; PCC — prothrombin (plasma) complex concentrate; i. v. — intravenous. Adapted from S. Piran and S. Schulman [42]

Table 4. *Reversal strategies for different anticoagulants*

Anticoagulant type	Half-life, h	Route of elimination	Reversal strategy
VKA	20–60 (warfarin)	Liver metabolism; metabolites are primarily eliminated in the urine (warfarin)	Vitamin K, PCC, plasma
UFH	1–2	Therapeutic dose: hepatic elimination; very high doses: possible renal contribution	Protamine sulfate
LMWH	3–7	Renal	Protamine sulfate: partial reversal; rFVIIa: life-threatening bleeding
Fondaparinux	17–21	Renal	rFVIIa (high dose, 90 mcg/kg): life-threatening bleeding
Dabigatran	12–17	Renal (80 %)	Idarucizumab, aPCC
Apixaban	8–15	Renal (25 %)	4F-PCC, andexanet alfa
Betrixaban	19–27	Renal (11 %)	4F-PCC, andexanet alfa
Edoxaban	9–11	Renal (35 %)	4F-PCC, andexanet alfa
Rivaroxaban	9–13	Renal (66 %)	4F-PCC, andexanet alfa

Note: PCC — prothrombin complex concentrate; rFVIIa — recombinant activated factor VII; aPCC — activated prothrombin complex concentrate; 4F-PCC — four-factor prothrombin complex concentrate. Adapted from S. Piran and S. Schulman [42]

Tranexamic acid (in Russia: Tranexam®) should be used for bleeding caused by trauma or surgery [43]. This effective hemostatic drug is contraindicated in hematuria due to the risk of blood clots in the ureter and the development of hydronephrosis. Treatment with any antiplatelet, nonsteroidal anti-inflammatory drugs or ACD should be interrupted [42]. Charcoal enhances the elimination of DOAC and thus can be used for several hours if bleeding is caused by an overdose of anticoagulants or their accidental intake.

Evaluation of the level of anticoagulant effect is a useful and necessary method for optimal management of patients with hemorrhagic complications. In some cases, therapy may be interrupted for a few days until the anticoagulant effect disappears and the treatment should be aimed at stopping bleeding from the source. When waiting for the end of the anticoagulant effect, it is necessary to remember the values of the half-life periods of the main ACD (Table 4) [42].

On the other hand, if the patient developed acute kidney damage, there is a significant delay in the elimination of any DOAC. If the patient took VKA, a quick and accurate assessment is possible due to the measurement of INR in the immediate proximity of the patient. For patients taking DOAC, a global assessment of parameters such as thrombin time (TT), prothrombin time (PTT), or activated partial thromboplastin time (APTT) may, at best, provide a rough estimate of the effect, but less for apixaban and edoxaban than for dabigatran (with TT or APTT) or rivaroxaban (with PTT), as recently demonstrated in the review [44].

While TT is a fairly sensitive marker and will be able to determine the content of dabigatran in low concentrations, this indicator is not able to distinguish the content of anticoagulant in clinically acceptable or toxic levels. The APTT values for dabigatran and PTT for rivaroxaban in therapeutic doses are usually increased, but their sensitivity usually varies depending on the reagents used.

Clinical data on anticoagulant therapy in cancer

It is believed that patients with malignant tumors who have had at least one episode of VTE in their history should receive the ACT as long as the underlying disease is in the active stage or active antitumor therapy is being carried out [23].

LMWH is considered to be the standard in the treatment of VTE associated with tumor process [45]. Supporting data on the benefits of LMWH over

VKA were obtained in two large RCTs. In the initial study of 676 cancer patients with acute episodes of VTE, 6-month treatment with dalteparin significantly reduced the incidence (by 52 %) of VTE recurrences without affecting massive bleeding or mortality rate compared to VKA [46]. A while later, it was noted in 900 cancer patients with acute VTE that treatment with tinzaparin in comparison with warfarin was accompanied by a slight decrease in the risk of recurrent VTE events (7.6 % and 10.5 %; p=0.07), did not affect massive bleeding or mortality rates and significantly reduced non-massive bleeding rate (10.9 % and 15.3 %; p=0.004) [47].

The results of a direct comparative study of DOAC and LMWH were published. The Hokusai-VTE-Cancer study was an open-label RCT devoted to the study the efficacy of daily intake of oral Xa inhibitor edoxaban compared with dalteparin in symptomatic or accidental episodes of VTE in 1,050 cancer patients over a period of 6 and 12 months [48]. Edoxaban turned out to be just as effective as dalteparin with respect to total relapses of VTE and massive bleeding rate (12.8 % and 13.5 %). The rate of VTE relapses decreased with edoxaban compared with dalteparin (7.9 % and 11.3 %), but the number of cases of massive bleeding (6.9 % and 4.0 %) increased due to a higher level of hemorrhagic complications in patients with tumors of the gastrointestinal tract (13.2 % and 2.4 %) [48]. In an open-label RCT of 406 patients with cancer, treatment of VTE for 6 months showed that rivaroxaban reduced the risk of VTE relapses compared to dalteparin (4 % and 11 %), but increased the risk of clinically significant non-massive bleeding (13 % and 2 %) [49].

The data obtained, including Hokusai-VTE-Cancer trial, suggest that DOACs may be more effective than LMWH for preventing recurrence of VTE in patients with malignant tumors, although due to an increased risk of massive bleeding, in comparison with patients receiving LMWH [50, 51]. Therefore, the recommendations of the International Society for Thrombosis and Hemostasis 2018 proposed to use DOACs for the treatment of cancer patients with VTE and low risk of bleeding with the consideration of LMWH as an effective alternative. In patients with high risk of hemorrhagic complications, the use of LMWH remains the preferred therapy [52].

Clinical studies on the comparative evaluation of DOAC and LMWH in the treatment of VTE are ongoing, and they should provide additional data on the complex efficacy and safety of the drug-specific and class-specific effects of DOAC used in cancer patients.

Reperfusion therapy

Despite the fact that the basic therapy of acute PE is ACT, in patients with massive or submassive PE more aggressive treatment, including thrombolysis (or fibrinolysis), catheter or surgical embolectomy, should be considered [53]. Reperfusion therapy of acute PE involves induction of STL with intravenous thrombolytic agents to restore blood flow [15].

Systemic thrombolysis

The decision on the use of thrombolytic therapy in acute PE should be based on the results of a careful calculation of the "risk-benefit" for each patient [53]. Modern guidelines recommend the immediate start of reperfusion therapy in patients with high-risk PE (massive embolism, class I, level of evidence B), if there are no absolute and relative contraindications for its implementation [1, 8, 28, 54]. These recommendations are mainly based on minor studies that demonstrated rapid improvement of surrogate hemodynamic parameters (the ratio of right and left ventricular end-diastolic sizes) after thrombolysis [55] and are supported by epidemiological data [56].

Fibrinolytic drugs are enzymes that convert native, circulating plasminogen into plasmin, and are represented by three main classes: tissue plasminogen activators (tPA), streptokinase and urokinase [57]. In turn, tissue plasminogen activators include alteplase, reteplase and tenecteplase. In addition, if heparin causes a passive reduction in the size of the thrombus, thrombolytics accelerate the process of hydrolysis of fibrin molecules [8, 57].

Thrombolytic therapy of acute PE restores pulmonary perfusion faster than isolated ACT [1, 58].

Early elimination of pulmonary obstruction leads to rapid decrease of pressure and resistance in the pulmonary artery with simultaneous improvement of right ventricular function [59]. However, hemodynamic benefits of thrombolysis are limited to a few days; survivors do not have a significant difference at the end of the first week [60].

In a minor prospective study of the outcome in patients with massive PE, the use of STL (streptokinase) demonstrated a decrease in mortality compared with the group receiving heparin only [61]. In addition, it is noted that STL reduces the risk of CTEPH and improves quality of life [62]. The meta-analysis showed that systemic thrombolytic therapy also reduces mortality in patients with submassive PE (HR 0.48; 95 % CI 0.25–0.92) [63]. However, such results are achieved with the risk of significant hemorrhagic complications (HR 2.91; 95 % CI 1.95–4.36), including intracranial hemorrhages (HR 3.18; 95 % CI 1.25–8.11). It is noteworthy that the use of STL in patients with sudden cardiac arrest due to PE and not subjected to shock therapy, admitted to clinics before cardiac arrest, was also associated with improved survival [64]. The most favorable effect is observed if the treatment is started in the first 48 hours after the symptoms onset. However, STL may be acceptable among patients with a duration of symptoms of 6–14 days [1]. According to a study by M. Zuin et al. [65], STL used during the first 8.5 hours after the onset of symptoms was associated with a decrease in 30-day mortality among patients with high-risk PE compared with patients who received thrombolytic therapy after 8.5 hours. Dosages of the main thrombolytic agents used for the treatment of PE are presented in Table 5 [66].

Meta-analysis of 15 studies with a total of 2,057 patients showed that fibrinolysis reduced overall mortality (HR 0.59; 95 % CI: 0.36–0.96) and contributed to a significant reduction in the composite end-point of death or treatment intensification (HR 0.34; 95 % CI: 0.22–0.53), mortality due to PE (HR 0.29; 95 % CI: 0.14–0.60), and relapse of PE (HR 0.50; 95 % CI: 0.27–0.94) [55]. However, the favorable effects of STL are noted along with an increased risk of massive hemorrhagic events (HR 2.91; 95 % CI: 1.95–4.36), intracranial and fatal bleeding (HR 3.18; 95 % CI: 1.25–8.11).

It should be noted that the interpretation of the results of meta-analyses should be carried out with extreme caution, given the pronounced heterogeneity of: 1. Scope of study and criteria for selection of patients (assessment of PE severity); 2. Fibrinolytic drugs, their dosages, modes of testing, and 3. Modes of treatment with fibrinolytics and duration of treatment [4]. These differences can become even more pronounced and even critical if studies with complete and reduced doses of fibrinolytics, as well as the method of administration (systemically or locally administered) are analyzed [63]. Table 6 presents the main studies on the results of the use of thrombolytic drugs in patients with acute PE [15].

Table 5. *Thrombolytic agents and doses for high-risk pulmonary embolism*

Agent	Infusion treatment 12–24 h	Short infusion treatment
Urokinase (plasminogen activator)	4,400 IU/kg (bolus/30 min) + 4,400 IU/kg per hour 12–24 h	3 mln IU/2 h
Streptokinase (polypeptide derived from cultures of beta-hemolytic streptococci, binds to plasminogen and converts it to plasmin)	250,000 IU (bolus/15 min) + 100,000 IU/h 12–24 h	1.5 mln IU/2 h
Tenecteplase (binds to fibrin, increasing affinity for plasmin)	Not applicable	30–50 mg in bolus, adjusted by weight (5 mg for each 10 kg, from 60 to 90 kg)
Alteplase (binds to fibrin, increasing affinity for plasmin)	Not applicable	100 mg/2 h (10 mg in bolus, 50 mg in the first hour, and 40 mg in the second hour)

Note: IU — international unit. Modified from C. J. C. S. Fernandes et al. [66]

Table 6. *Prospective and cohort studies investigating thrombolytic agents and regimens in patients with acute PE*

Reference and/or trial	Population	Groups	Outcome	Time of outcome assessment	Thrombolysis group	Control group	P-value
PEITHO [8, 67]	Intermediate-risk PE (n=1,005)	Tenecteplase plus ACT versus ACT only	Death or hemodynamic collapse	7 days	2.6 %	5.6 %	0.02
			CTEPH	38 months	2.1 %	3.2 %	NS
			NYHA III–IV	38 months	12 %	10.9 %	NS
			Echo parameters of RV dysfunction	38 months	–	–	NS
			Death	38 months	20.3 %	18.0 %	NS
TOPCOAT [68]	Intermediate-risk PE (n=83)	Tenecteplase plus ACT versus ACT only	NYHA III–IV	90 days	5.4 %	20.5 %	NS
			RV dilatation or hypokinesis	90 days	33.3 %	37.8 %	NS
			6-minute walking distance <330 m	90 days	16 %	28 %	NS
TIPES [60]	Intermediate-risk PE (n=58)	Tenecteplase plus ACT versus ACT only	Reduction of RV/LV ratio, mean (s.e.)	24 hours	0.31	0.10	NS
			Hypokinesia of the RV free wall (s.e.)	7 days	0.47	0.34	NS
MAPPET-3 [69]	Intermediate-risk PE (n=256)	Alteplase plus ACT versus ACT only	Death or hemodynamic collapse	30 days	11 %	24.6 %	0.006
			Death	30 days	3.4 %	2.2 %	NS
MOPETT [70]	"Moderate PE" (n=121)	Half-dose of tPA versus ACT only	sPAP (mm Hg), mean (s.d.)	6 months	31	49	<0.001
			sPAP (mm Hg), mean (s.d.)	28 months	28	43	<0.001
			Death	28 months	1.6 %	5.0 %	NS

Note: LV — left ventricular; MAPPETT-3 — Management Strategies and Prognosis of Pulmonary Embolism-3 Trial; MOPETT — Moderate Pulmonary Embolism Treated with Thrombolysis; NS — not significant; NYHA — New York Heart Association; PEITHO — Pulmonary Embolism Thrombolysis; RV — right ventricular; RV/LV ratio — right-to-left ventricular diameter ratio; sPAP — systolic pulmonary artery pressure; TIPES — Tenecteplase Italian Pulmonary Embolism Study; TOPCOAT — Tenecteplase or Placebo: Cardiopulmonary Outcomes at Three Months. Adapted from M.V. Huisman et al. [15]

Patients at high risk with hemodynamic instability represent only a minority of all patients with PE (about 5 %). In turn, hemodynamically stable patients make up a much larger group (>95 %) [51, 66, 67], in which the use of STL in standard dosages is associated with the expectation of favorable hemodynamic and clinical effects [55, 71, 72]. In patients with high-risk acute PE the probability of death is high, which facilitates the decision in favor of STL, compared with patients who are hemodynamically stable [58]. Mortality among hemodynamically unstable patients varies from 35 to 58 % [12, 69].

Before carrying out STL, it is necessary to make sure that the patient does not have relative or absolute contraindications presented in the ESC Guidelines for diagnosis and treatment of acute PE 2014 [1] and modified by H.U. Virk et al. [58] (Table 7).

Absolute contraindications to STL may become relative in patients at the time of onset of the life-threatening condition of high-risk PE. In general, up to 2/3 of patients with acute PE do not receive thrombolytic therapy due to various contraindications [58]. Given the often decisive role of STL in the treatment of PE, which can save the life of the patient, balanced and individual approach to the assessment of absolute and relative contraindications is required.

The undesirable "risk-benefit" ratio in favor of the high probability of severe and potentially fatal hemorrhagic complications was the reason why

Table 7. *Contraindications to systemic thrombolysis in patients with acute pulmonary embolism*

Absolute contraindications	Hemorrhagic stroke or stroke of unknown origin at any time
	Ischemic stroke in the preceding 6 months
	Central nervous system damage or neoplasms
	Recent major trauma/surgery/brain injury in the preceding 3 months
	Gastrointestinal bleeding within the last month
	Active bleeding (excluding menses)
	Suspected aortic dissection Known malignant intracranial neoplasm
Relative contraindications	Transient ischemic attack in the preceding 6 months
	Oral ACT therapy
	Pregnancy, or period within one week postpartum
	Non-compressible puncture site
	Trauma or prolonged cardiopulmonary resuscitation >10 min
	Severe uncontrolled hypertension (systolic >180 mm Hg, diastolic >110 mm Hg)
	Advanced liver disease
	Infective endocarditis
	Active peptic ulcer
	Pericarditis
	Age >75 years
	Recent invasive procedure

Note: Adapted from S. V. Konstantinides et al. [1] and H. U. Virk et al. [58]

scientific societies removed the recommendation for routine use of STL in groups of patients with intermediate and intermediate-high risk [1, 8, 28]. Most scientific societies agree that immediate reperfusion therapy with systemic (intravenous) thrombolytics is indicated for a (small) group of patients with massive PE or high-risk PE, who have stable hypotension or shock (Table 8) [54]. On the other hand, from the point of view of the risk of potentially life-threatening bleeding associated with STL, its use in clearly "stable" patients with submassive PE or intermediate-risk PE is not recommended until hemodynamic decompensation or collapse developing during the ACT [54].

In 2014, the results of the largest to date study (PEITHO) conducted in 1,005 patients with intermediate-high risk PE [73] were published. The results indicate that intravenous use of tPA tenecteplase was accompanied by low levels of mortality or hemodynamic collapse (2.6 % compared to 5.6 % in the group of patients receiving heparin). However, treatment with tenecteplase was associated with significantly increased rates of hemorrhagic strokes and major extracranial bleeding. In particular, in the group of patients with tenecteplase treatment extracranial bleeding was noted in 6.3 % of cases (approximately in one of 16 patients), and among patients receiving anticoagulant — in 1.2 % of cases (in one of 83, $p<0.001$). Thus, the use of STL is indicated in patients who have a massive PE (or high risk), that is, have stable hypotension or shock [1, 8, 28]. This approach contradicts the ideas that existed until recent times regarding the possible clinical benefit of fibrinolysis in apparently stable patients with submassive PE (or intermediate risk) [4]. It should be noted that there are no combined data on the safety of other thrombolytic drugs to date, so the results of a study in 256 patients with intermediate-risk PE treated with alteplase, which did not reveal an increased risk of intracranial or fatal bleeding, are interesting [69]. Obviously, and this is noted by almost all experts, it is necessary to conduct additional studies to improve scientific understanding regarding the use of thrombolytic therapy in hemodynamically stable patients [74].

Table 8. *Recommendations of scientific societies and organizations regarding thrombolytic treatment of acute pulmonary embolism*

Guidelines	Populations	Recommendations	Strength/ class	Level of evidence
AHA, 2011 [8]	Massive PE	Thrombolysis reasonable for patients with acceptable risk of bleeding	IIa	B
	Submassive PE	Thrombolysis considered if there is a clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe right ventricular dysfunction, or major myocardial necrosis) and low risk of bleeding	IIb	C
	Candidates for thrombolysis	Catheter embolectomy and fragmentation or surgical embolectomy for patients with contraindications to fibrinolysis	IIa	C
		Catheter embolectomy and fragmentation or surgical embolectomy for patients who remain unstable after receiving fibrinolysis	IIa	C
ESC, 2014 [1]	High-risk PE	Intravenous anticoagulation with UFH to be initiated without delay	I	C
		Thrombolytic therapy	I	B
		Surgical embolectomy for patients in whom STL is contraindicated or has failed	I	C
		Percutaneous CDT as an alternative to surgical pulmonary embolectomy for patients in whom full-dose STL is contraindicated or has failed	IIa	C
	Intermediate-high risk PE	Routine primary STL not recommended	III	B
		Close monitoring to permit early detection of hemodynamic decompensation	I	B
		Thrombolytic therapy in presence of clinical signs of hemodynamic decompensation	IIa	B
		Surgical embolectomy or percutaneous CDT may be considered if the anticipated risk of bleeding under thrombolytic treatment is high	IIb	C
ACCP, 2016 [28]	With hypotension	In the absence of high bleeding risk: STL	2	B
		In the presence of high bleeding risk or if STL has failed: surgical embolectomy	2	C
	Without hypotension	STL not recommended	1	B
	Acutely deteriorating during ACT	STL	2	C
	Candidates for STL	STL via a peripheral vein or as CDT	2	C

Note: ACCP — American College of Chest Physicians; AHA — American Heart Association; CDT — catheter-directed thrombolysis; ESC — European Society of Cardiology. Green highlights indication for STL, and yellow — the recommendation to consider STL. Adapted from S.V. Konstantinides et al. [54]

The possible effects of STL on the long-term clinical outcome in patients after acute PE are not yet clear. It is believed that treatment with STL in the acute phase of PE can reduce residual or progressive thromboembolic obstruction in the lungs, thereby preventing the development of post-PE syndrome [75, 76]. A prospective cohort study that divided 121 patients with extensive PE (determined by detection of a large thrombus) into two groups: receiving reduced doses of systemic thrombolytic drugs or only anticoagulants, demonstrated that STL was accompanied by a lower rate of pulmonary hypertension after 28 months [70]. However, patients with intermediate-risk PE included in the PEITHO study were followed up for an average period of 38 months, and there were

no differences in long-term survival when comparing groups receiving thrombolytic therapy or only heparin [77].

Systemic thrombolysis with reduced doses of fibrinolytics

As we noted above, intravenous thrombolysis can be associated with life-threatening hemorrhagic complications, in particular intracranial hemorrhage [55]. Unfortunately, the rates of serious bleeding have not decreased over the past 40 years [73] and due to understandable fears there has been a sharp decline in the popularity of this method of treatment in clinical practice, even in patients with cardiogenic shock [54, 56, 78]. In order to improve the safety of fibrinolysis, efforts have been made to explore alternative methods, in particular whether reduced dosages of STL can be safe while maintaining normal perfusion of pulmonary vasculature. A randomized pilot study conducted in 118 patients with high- or intermediate-risk PE provided data that a half-dose of tPA resulted in fewer hemorrhagic complications than the full dose and was just as effective in terms of improving pulmonary vascular obstruction [79]. Unfortunately, the study was terminated prematurely for reasons not related to the protocol, and so the results are not conclusive.

In 2013, the results of the MOPETT trial [70], which studied the efficacy of a half dose ("safe dose") of alteplase (50 mg or 0.5 mg/kg i. v. for 2 h in patients less than 50 kg) in comparison with a group of 121 patients receiving only the ACT with symptomatic so-called "moderate" PE, were published. The authors found that a half dose of alteplase reduced the rate of pulmonary hypertension after 28 months ($P < 0.001$), duration of hospitalization ($P < 0.001$), rate of total mortality and relapses of PE ($P = 0.0489$) without hemorrhagic complications. However, study data again do not allow its complete interpretation due to the lack of study registration, the inclusion of eligibility criteria that do not meet the standard criteria, extremely high level of persistent pulmonary hypertension in the control group, which caused concern whether such a design can be representative based on non-selective selection of patients with really acute PE [54].

The results of a study by T.H. Kiser et al. recently became available [80], and they concern the comparative efficacy and safety of two dosages for the treatment of PE: half (50 mg) and full dose (100 mg) of alteplase. At baseline, patients receiving alteplase at half dose were less likely to require vasopressor therapy (23.3 % vs 39.4 %; $p < 0.01$) and invasive lung ventilation (14.3 % vs 28.5 %; $p < 0.01$) than patients in the group receiving a full dose of alteplase. Half-dose treatment was associated with a higher rate of intensification of therapy (53.8 % and 41.4 %; $p < 0.01$), mainly due to the need for repeated thrombolysis and catheter thrombus fragmentation. At the same time, hospital mortality was comparable (13 % vs 15 %). There was no difference in the level of cerebral hemorrhages, gastrointestinal bleeding, acute anemia due to blood loss [80]. It should be noted that in this study stratification of patients with high- and intermediate-risk PE was performed only on the basis of the need for vasopressors, which certainly increased the number of patients with high-risk PE [81].

In the treatment of 45 patients with PE of intermediate-high risk using reduced thrombolytic dosage (initially, infusion of 50 mg of alteplase for 2 h was performed followed by systemic administration of heparin for at least 24 h), excellent clinical outcome indicators were noted with a low rate of further hemodynamic deterioration, a short period of stay in the intensive care unit (4.2 days) and in hospital (7.4 days), excellent survival at the time of discharge (97.8 %) and on the 30th day of the disease (95.6 %) [82]. Unfortunately, despite the "half" thrombolytic therapy in the group of patients with low risk of hemorrhagic complications the authors often observed moderate or massive bleedings (in 5 patients, 11 %).

Although systemic fibrinolytic therapy in "half-dose" is more attractive for many doctors, the evidence in its favor should be considered preliminary at best, and such unapproved regimes cannot be recommended at the present stage [54, 81, 83]. Catheter techniques can be considered as an alternative option for patients with PE requiring active reperfusion treatment due to initial or developing hemodynamic decompensation, but in the presence of absolute or relative contraindications to systemic fibrinolysis [4, 6, 83].

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