Risk stratification of outpatient management in acute venous thromboembolism

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Home treatment of acute pulmonary embolism: state of the art in 2018.

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ABSTRACT

Purpose of review: Historically, because of the necessity of parenteral anticoagulation, patients with acute pulmonary embolism (PE) are hospitalized until stable oral anticoagulation is achieved. Despite improvements in prognostic risk stratification and the introduction of the direct oral anticoagulants, home treatment is still not widely applied. Main advantages of home treatment involve improvement of quality of life and significant healthcare cost reduction. In this review, we summarized recent published data on home treatment of patients with acute PE.

Recent findings: Although a significant decrease in mean duration of hospital admission for PE has been demonstrated over the last decade in Europe, most PE patients are currently hospitalized while they might be treated in an outpatient setting. In recent years, five major studies have been performed, in which the decision to initiate home treatment was based on the Hestia criteria in most patients. Over 98% of patients treated at home had an uncomplicated course.

Summary: Home treatment of acute PE is suggested to be feasible and safe in 30% to 55% of all patients. Results of ongoing trials will provide more insight in the optimal strategy to select patients with PE who are eligible for home treatment and likely will result in more widespread application of this practice.

INTRODUCTION

Pulmonary embolism (PE) is a common and serious condition that often leads to hospitalization because of a potential risk of early adverse events and historical indication for parenteral anticoagulation. These adverse events particularly include thromboembolic recurrence or major bleeding potentially leading to death.[1,2] However, this risk of adverse events differs among patients, depending on the presence of a variety of clinical characteristics during diagnosis, including -and most importantly- hemodynamic status.[3,4]

Over the last decade, there has been trend towards identifying PE patients at low-risk of early adverse events who may be treated in an outpatient setting instead of initial hospitalization. This is partially due to introduction of low-molecular weight heparins (LMWH), fondaparinux and more recently, direct oral anticoagulants (DOACs) since these agents do not require laboratory monitoring and can be administered according to either weight based doses (for LMWH) or fixed doses (for DOACs). 'Home' or 'outpatient' treatment has many advantages, such as improvement of quality of life compared to hospitalisation, prevention of hospital overcrowding and significant reduction in healthcare costs.[5-7] It has been estimated that 30% to 55% of acute PE patients could be selected for home treatment which could lead to a decrease in yearly US health care costs of $1 billion.[8,9] However, despite improvements in prognostic risk stratification, home treatment is still not widely applied.[10] The aim of this review is to summarise recent published data on home treatment of patients with acute PE.

CURRENT DURATION OF HOSPITAL ADMISSION FOR ACUTE PE IN EUROPE

The median duration of hospital admission for acute PE has decreased over the past decade in Europe. According to a recent large study comprising mainly European hospitals, the mean duration of admission was 13.6 days (standard deviation (SD) 4.7) in 2001 and 9.3 (SD 0.9) days in 2013[10]**. Data for individual European countries show large regional differences (**Table 1**). A nationwide population-based cohort study in Spain of 165.229 patients found a mean hospitalization length of 14 (SD 13) days between 2001 and 2010 [11], and a nationwide retrospective study in France including 34,179 PE patients reported this length to be 10 days (SD 7.7) in 2010.

Length of hospital stay strongly depends on clinical characteristics and PE-related findings of the study population, e.g. age, blood pressure, heart rate, oxygen supplementation and comorbidities. Several clinical prediction rules have been developed that contain a mixture of these characteristics and can help to identify patients with low risk of adverse outcome[12-16]. In addition to the risk of recurrent PE and bleeding, obvious criteria such as hypoxaemia requiring supplemental oxygen, pain requiring intravenous analgesia and home circumstances that ensures adequate therapy compliance in an outpatient setting also influence the length of hospitalization.

The decision to choose for home treatment thus greatly depends on local case mix as well as the organization of outpatient care by general practitioners and/or in the outpatient clinics.

Table 1. Current hospital stay after PE in Europe.

Article	Country, centres	Design	N	Hospital stay (days)
Guijarro et al. (2016) (11)	Spain, nationwide	Prospective registry	165,229	Mean 14 ± 13
Balahura et al. (2017) (25)	Romania, 1	Retrospective cohort	221	Mean 10 ± 5
Paczynska et al. (2016) (26)	Poland, 1	Prospective cohort	215	Median 7 (range 2-22)
Motte et al. (2016) (27)	Belgium, 10	Retrospective cohort	621	Mean 10 ± 6
Zanova et al. (2015) (28)	Czech Republic, 1	Retrospective cohort	188	Median 7*
Werth et al. (2015) (29)	Germany, 1	Retrospective cohort	439	Median 9 (IQR 2-16)
Olie et al. (2013) (30)	France, nationwide	Retrospective cohort	34,179	Mean 10*
Casazza et al. (2012) (31)	Italy, 47	Prospective cohort	1716	Mean 10 ± 7
Sharma et al. (2009) (32)	Croatia, 1	Retrospective cohort	165	Mean 15 ± 9

*No range could be retrieved from report.

WHAT IS HOME TREATMENT OF ACUTE PE?

In the literature, outpatient management of acute PE has been referred to as 'home treatment', 'early discharge' and 'outpatient treatment', although a clear definition is lacking. In recent years, five major prospective studies on home treatment of acute PE were performed; three RCTs and two prospective cohorts (**Table 2**). Two RCTs compared either discharge within 24 hours or within three days with 'full' hospitalization, whereas one RCT and two large prospective cohorts only evaluated patients who were discharged within 24 hours. While some patients in these studies were discharged from the emergency room, others were admitted on an observational unit or even to the hospital within this timeframe. Based on these definitions, home treatment does not only apply to patients who are not admitted at all, but comprises a more heterogeneous group of patients who are managed outside the hospital after a short period of hospitalization during which they are monitored and evaluated for the risks for adverse events before discharge. Notably, even when the broadest definition (discharge within 3 days after diagnosis) would be applied, this duration of admission is still much shorter that current European practice.

HOW TO IDENTIFY PATIENTS WHO ARE ELIGIBLE FOR HOME TREATMENT?

When considering home treatment of patients with acute PE, the first challenge is to identify patients who are at low risk for adverse events. This identification process can be facilitated by using validated risk stratification tools. The recommended approach by the ESC guidelines refers

to the Pulmonary Embolism Severity Index (PESI) score or its simplified version (sPESI).[12,17] The sPESI comprises six variables that are listed in **Table 3.** More recently, the BOVA and modified FAST risk scores have been derived.[13,14] The BOVA and FAST risk scores include various clinical features and biochemical markers, such as NT-proBNP, Troponin, D-dimer or a heart-type fatty acid binding protein (H-FABP), but suffer from a lack of external validation and evaluation in outcome studies.

Table 2. Definition and outcomes of five large studies.

Study	Design	Definition of home treatment	Selection method for outpatients	Treatment	Number of patients enrolled	% home treatment	3-month outcome incidences
Aujeski et al. (2011) (12)	RCT	Within 24 hours	sPESI score	LMWH followed by VKA	344	50	*Outpatient:* VTE: 0.6% Major Bleeding: 1.8% Mortality: 0.6% *Hospitalized:* VTE: 0% Major Bleeding: 0% Mortality: 0.6%
Zondag et al. (2011) (16)	Cohort	Within 24 hours	Hestia rule	LMWH followed by VKA	297	100	VTE: 2% Major bleeding: 0.7% Mortality: 1%
Agterof et al. (2010) (18)	Cohort	Within 24 hours	NT-proBNP	LMWH followed by VKA	152	100	VTE recurrence: 0% Major Bleeding: 0% Mortality: 0%
Den Exter et al. (2016) (19)	RCT	Within 24 hours	Hestia rule	LMWH followed by VKA	550	94	VTE: 1% Major bleeding: 0.8% Mortality: 1.3%
Otero et al. (2010) (20)	RCT	Within five days	Uresandi score	LMWH followed by VKA on day 10	132	55	*Outpatient:* VTE: 2.8% Major Bleeding: 5.5% Mortality: 4.2% *Hospitalized:* VTE: 3.3% Major Bleeding: 5.0% Mortality: 8.3%

LMWH=Low-Molecular-Weight Heparin, VKA=Vitamin K Antagonist VTE=Venous Thromboembolism

Table 3. Uresandi score (15)

Clinical variable	Score
Recent major bleeding episode	4 points
Cancer with metastasis	4 points
Creatinine levels of over 2 mg/dL	3 points
Cancer without metastasis	2 points
Immobility due to a recent medical condition	2 points
Absence of surgery in the past 2 months	1 point
Age of over 60 years	1 point

Risk of complications:
Low: ≤2
High: 2

PESI and sPESI have been shown to appropriately predict the 30-day rate of adverse events in patients with acute PE. However, the decision for home treatment is not only confined to risk of 30-day outcome measures. The 'Hestia' clinical decision rule contains pragmatic parameters of both risk of mortality and bleeding, but also of hypoxemia, pain requiring analgesia and bleeding risk (**Table 4**).[16] Currently, the Hestia rule is the best-validated clinical decision tool in the English literature for selecting PE patients eligible for home treatment, while prospective studies evaluating clinical outcome of home treatment based on the sPESI, BOVA or modified FAST score are not available.

Table 4. sPESI score (12)

Criteria	Score
Age>80	1
Cancer	1
Chronic cardiopulmonary disease	1
Pulse > 110 bpm	1
SBP <100mmHg	1
Arterial blood oxygen saturation <90%	1

Mortality risk:
Low: 0
High: ≥1

HOME TREATMENT VERSUS HOSPITALIZATION

The five largest prospective studies published to date are listed in **Table 2.**[12,16,18-20] These studies are not easily comparable because of heterogeneous selection criteria and various definitions of home treatment. In all studies, patients were initially treated with LMWH with overlapping vitamin-K antagonist (VKA) therapy, with most of studies using a minimum of five days LMWH treatment until the international normalized ratio was in the therapeutic range of 2.0–3.0. Two

studies also included patients with active malignancies who received monotherapy with LMWH treatment.[16,19]

The first randomized controlled trial by Otero *et al.* [20] compared the 3-month rate of VTE recurrences and bleeding events of discharge within three days versus standard hospitalization in 132 low-risk PE patients. Low-risk patients were identified according to the (non-validated) Uresandi clinical score **(Table 3).**[15] This study found no significant differences between the rates of recurrent VTE (2.8%, 95% confidence interval (CI) 1.1-6.6, versus (vs.) 3.3%, 95%CI 1.3-8) and bleeding (1.4% vs. 1.6%) between home treatment and hospitalization respectively. The study became suspended after the first 132 patient were enrolled, due to an unexpected high mortality rate in both arms of the study (4.2%, 95%CI 0.5-8.9, early discharge vs. 8.3%, 95%CI 1.1-15, hospitalization; relative risk (RR): 0.5, 95%CI 0.12-2.01). Inherent to early termination of the trial, the confidence intervals of this mortality rate were wide.

In the second trial [12], 1557 acute PE patients were assessed for eligibility, of whom only 344 low-risk PE patients were randomized to discharge from the emergency department within 24 hours or hospitalization. After initial screening based on ad hoc criteria necessitating hospitalisation, the Pulmonary Embolism Severity Index (PESI) score was used to identify patients with low mortality risk (categories I and II; **Table 4**). Non-inferiority was shown in the incidence of recurrent VTE (0.6% vs. 0%, 95% upper confidence limit (UCL) of difference 2.7) and death (0.6% vs. 0.6%, 95% UCL 2.1) at 90 days for home treatment and hospitalization, respectively. Although the major bleeding incidence at 90 days exceeded the non-inferiority threshold in the home treatment group (1.8% vs. 0%, 95% UCL 4.5), the authors concluded that outpatient was non-inferior to inpatient treatment in terms of efficacy and safety.

The third study included 152 hemodynamically stable PE patients with normal N-terminal pro–brain natriuretic peptide (NT-proBNP) levels (18). Patients were discharged immediately from the emergency room or within a maximum of 24 hours after admission. The study reported no recurrent VTE, major bleeding or death occurrences during the 3-month follow-up period. It was therefore concluded that home treatment was safe in low-risk PE patients.

The Hestia study evaluated the efficacy and safety of home treatment in 297 PE patients using the Hestia criteria to identify eligibility for home treatment (**Table 5**).[16] Home treatment was started immediately or within 24 hours after PE diagnosis. Half of the patients diagnosed with PE were deemed eligible for home treatment. Of these patients, 2% (95%CI 0.8-4.3) suffered recurrent VTE, 0.7% (95%CI 0.08-2.4) experienced a major bleeding events and 1% (95%CI 0.2-2.9) died during the 3-month follow up period. The authors concluded that home treatment in patients with PE and none of the Hestia criteria is safe.

The safety of home treatment was further established by a third and largest RCT.[19]** This study compared the safety of the Hestia criteria alone with the Hestia criteria combined with NT-proBNP testing in 550 patients diagnosed with PE. Low incidences of VTE recurrence (1.1%, 95%CI 0.2-3.2), major bleeding (1.1%, 95%CI 0.2-3.2) and mortality (1.1%) were observed in patients selected for home treatment by the Hestia clinical decision rule alone. In the group

randomized to NT-proBNP testing, only 34 of the 257 patients (12.4%) had an elevated NT-proBNP level and thus were treated as inpatients. Adverse outcomes did not differ significantly between both groups. The most likely explanation for the low number of patients with elevated NTproBNP is that the Hestia rule preselects patients with normal NT-proBNP levels. This further strengthens the results of previous studies that applied the Hestia criteria. The authors concluded that the decision for home treatment can be safely based on these criteria alone.

Table 5. Hestia criteria (16)

Is the patient hemodynamically unstable? [a]	Yes/No
Is thrombolysis or embolectomy necessary?	Yes/No
Active bleeding or high risk of bleeding? [b]	Yes/No
More than 24 hour of oxygen supply to maintain oxygen saturation > 90%?	Yes/No
Is pulmonary embolism diagnosed during anticoagulant treatment?	Yes/No
Severe pain needing intravenous pain medication for more than 24 h?	Yes/No
Medical or social reason for treatment in the hospital for more than 24 h (infection, malignancy, no support system)?	Yes/No
Does the patient have a creatinine clearance of < 30 ml/min? [c]	Yes/No
Does the patient have severe liver impairment? [d]	Yes/No
Is the patient pregnant?	Yes/No
Does the patient have a documented history of heparin-induced thrombocytopenia?	Yes/No
If the answer to one of the questions is 'yes', the patient cannot be treated at home	

[a] Include the following criteria, but are left to the discretion of the investigator: systolic blood pressure <100mmHg with heart rate >100 beats per minute; condition requiring admission to an intensive care unit.

[b] Gastrointestinal bleeding in the preceding 14 days, recent stroke (less than 4 weeks ago), recent operation (less than 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count < 75 9 109/L), uncontrolled hypertension (systolic blood pressure > 180mm Hg or diastolic blood pressure > 110mm Hg).

[c] Calculated creatinine clearance according to the Cockroft-Gault formula.

[d] Left to the discretion of the physician.

Two meta-analyses have summarized these five studies and confirmed the safety of home treatment in selected PE patients.[9,21] The meta-analysis by Zondag *et al.* included 1657 PE patients who were treated at home and found low pooled incidences of recurrent VTE (1.7%, 95%CI 0.92-3.1), major bleeding (0.97%, 95%CI 0.58-1.59) and mortality (1.9%, 95%CI 0.79-4.8) which did not differ relevantly from these rates in hospitalized patients.[9] The meta-analysis of Piran *et al.* included 1258 patients and found these pooled incidences to be 1.47% (95%CI 0.47-3), 0.81% (95%CI 0.37-1.42) and 1.58 (95%CI 0.71-2.8), respectively (37). Consequently, since 2014, international guidelines indicate that home treatment for selected PE patients with adequate home circumstances should be considered (Grade 2B evidence).[22,23]

Only two studies addressed patient satisfaction of home treatment.[12,18] In the study performed by Aujeski *et al.* [12], a similar number of patients treated at home (92%) and hospitalized patients (95%) reported to be satisfied with their treatment. Agterof *et al.* [18] reported satisfac-

tion (PSQ-18) and anxiety (HADS-A) scores among the study patients. The HADS-A anxiety score did not change significantly between inclusion and after 10 days, whereas the PSQ-18 showed a high score for satisfaction with home treatment. However, evidence of improved patient satisfaction with home treatment is still limited and more research is required to evaluate patient experience of both in- and outpatient care.

DOACS

Anticoagulation is recommended in patients with acute PE to prevent both early death and recurrent symptomatic or fatal VTE.[22,23] In the last decades, the treatment of choice was LMWH with overlapping VKA until a stable therapeutic anticoagulant level was reached. The introduction of direct oral anticoagulants (DOACs) that specifically inhibit factor Xa or thrombin offer the advantage of oral treatment without overlapping treatment with parenteral anticoagulants, and monitoring of the anticoagulant effect is not necessary. Importantly, dabigatran and edoxaban need to be preceded with a short course of LWMH, while rivaroxaban and apixaban can be started at diagnosis. Because DOACs have been shown to be associated with less major, intracranial and fatal bleeding [24], international guidelines do now favour use of DOACs over VKA plus LMWH for the initial and long-term treatment of VTE.[22,23]

The availability of DOACs has further lowered the bar for treating patients with acute PE at home, although management studies applying DOACs in PE patients treated in the outpatient setting are currently not (yet) available.

FUTURE OUTLOOK

Four ongoing trials are currently enrolling patients. The HOME-PE study is a phase III, multicentre, non-inferiority study, which is randomizing 1975 normotensive PE patients to either using the Hestia rule or sPESI score to triage patients for home treatment (Clinicaltrials.gov identifier: NCT02811237). The main objective will be to demonstrate that a strategy based on the HESTIA rule compared to a strategy based on the sPESI score is at least as safe with regard to the 30-day rate of recurrent VTE, major bleeding and death. An important secondary objective is to demonstrate the superiority of Hestia with regard to the proportion of patients who are discharged within 24 hours after inclusion.

The three other trials aim to evaluate the use of DOACs in the setting of home treatment of PE. The Home Treatment of Pulmonary Embolism (HoT-PE) study will determine the feasibility, effectivity, and safety of rivaroxaban (EudraCT Nr. 2013–001657–28). This is a phase III, multicentre study with a planned sample size of 1050 patients with PE and none of the Hestia criteria. Moreover, patients can only enter the study if CT or echocardiographic assessed right

ventricular function is normal. The primary outcome is recurrent VTE or PE-related death within three months of enrolment. The third study is a multicentre prospective observational study to investigate the effectiveness of apixaban in a planned enrolment of 850 PE patients treated at home, who have none of the Hestia criteria or at discretion of the clinician in combination with an sPESI score of 0. Primary outcome will be the number of re-hospitalizations for VTE recurrence or bleeding within the first 30 days (Clinicaltrials.gov identifier: NCT03404635). Lastly, the MERCURY PE study is currently randomizing low-risk PE patients, as selected by the Hestia criteria, to home treatment or hospitalization, to compare the 30-day rates of recurrent VTE and major bleeding (ClinicalTrials.gov Identifier: NCT02584660). All patients randomized to home treatment are treated with rivaroxaban, while the initial hospitalization group will receive standard-of-care as per local protocol and defined by the medical team caring for the participant.

These ongoing studies will provide more insight on PE management and the optimal identification strategy for patients who are able to be treated at home and likely results in more wide application of this practice.

CONCLUSION

Home treatment is feasible and safe in selected PE patients due to the low incidence of adverse events. Although most PE patients in Europe are currently hospitalized for almost two weeks, the availability of DOACS and the change in guideline recommendations will likely lead to a further decrease in the mean duration of hospitalization and an increase in the number of patients discharged within 24 or 48 hours of diagnosis. Results from ongoing trials are expected to further strengthen the current guideline recommendations on home therapy for acute PE.

REFERENCES

1. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, et al. Venous thromboembolism (VTE) in Europe - The number of VTE events and associated morbidity and mortality. Thrombosis and haemostasis. 2007;98(4):756-64.
2. Futterman LG, Lemberg L. A silent killer - Often preventable. Am J Crit Care. 2004;13(5):431-6.
3. Tapson VF. Acute pulmonary embolism. N Engl J Med. 2008;358(10):1037-52.
4. Carson JL, Kelley MA, Duff A, Weg JG, Fulkerson WJ, Palevsky HI, et al. The clinical course of pulmonary embolism. N Engl J Med. 1992;326(19):1240-5.
5. Kahler ZP, Beam DM, Kline JA. Cost of Treating Venous Thromboembolism With Heparin and Warfarin Versus Home Treatment With Rivaroxaban. Acad Emerg Med. 2015;22(7):796-802.
6. Misky GJ, Carlson T, Thompson E, Trujillo T, Nordenholz K. Implementation of an acute venous thromboembolism clinical pathway reduces healthcare utilization and mitigates health disparities. J Hosp Med. 2014;9(7):430-5.
7. Stein PD, Matta F, Hughes PG, Hourmouzis ZN, Hourmouzis NP, White RM, et al. Home Treatment of Pulmonary Embolism in the Era of Novel Oral Anticoagulants. Am J Med. 2016;129(9):974-7.
8. Dalen JE, Dalen JE, Jr. Unnecessary Hospitalizations for Pulmonary Embolism: Impact on US Health Care Costs. Am J Med. 2016;129(9):899-900.
9. Zondag W, Kooiman J, Klok FA, Dekkers OM, Huisman MV. Outpatient versus inpatient treatment in patients with pulmonary embolism: a meta-analysis. Eur Respir J. 2013;42(1):134-44.
10. Jimenez D, de Miguel-Diez J, Guijarro R, Trujillo-Santos J, Otero R, Barba R, et al. Trends in the Management and Outcomes of Acute Pulmonary Embolism: Analysis From the RIETE Registry. Journal of the American College of Cardiology. 2016;67(2):162-70.
11. Guijarro R, de Miguel-Diez J, Jimenez D, Trujillo-Santos J, Otero R, Barba R, et al. Pulmonary embolism, acute coronary syndrome and ischemic stroke in the Spanish National Discharge Database. European journal of internal medicine. 2016;28:65-9.
12. Aujesky D, Roy PM, Verschuren F, Righini M, Osterwalder J, Egloff M, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. Lancet. 2011;378(9785):41-8.
13. Bova C, Sanchez O, Prandoni P, Lankeit M, Konstantinides S, Vanni S, et al. Identification of intermediate-risk patients with acute symptomatic pulmonary embolism. Eur Respir J. 2014;44(3):694-703.
14. Dellas C, Tschepe M, Seeber V, Zwiener I, Kuhnert K, Schafer K, et al. A novel H-FABP assay and a fast prognostic score for risk assessment of normotensive pulmonary embolism. Thromb Haemost. 2014;111(5):996-1003.
15. Uresandi F, Otero R, Cayuela A, Cabezudo M, Jimenez D, Laserna E, et al. A clinical prediction rule for identifying short-term risk of adverse events in patients with pulmonary thromboembolism. Arch Bronconeumol. 2007;43(11):617-22.
16. Zondag W, Mos IC, Creemers-Schild D, Hoogerbrugge AD, Dekkers OM, Dolsma J, et al. Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study. J Thromb Haemost. 2011;9(8):1500-7.
17. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med. 2005;172(8):1041-6.
18. Agterof MJ, Schutgens RE, Snijder RJ, Epping G, Peltenburg HG, Posthuma EF, et al. Out of hospital treatment of acute pulmonary embolism in patients with a low NT-proBNP level. J Thromb Haemost. 2010;8(6):1235-41.

19. den Exter PL, Zondag W, Klok FA, Brouwer RE, Dolsma J, Eijsvogel M, et al. Efficacy and Safety of Outpatient Treatment Based on the Hestia Clinical Decision Rule with or without N-Terminal Pro-Brain Natriuretic Peptide Testing in Patients with Acute Pulmonary Embolism. A Randomized Clinical Trial. Am J Respir Crit Care Med. 2016;194(8):998-1006.
20. Otero R, Uresandi F, Jimenez D, Cabezudo MA, Oribe M, Nauffal D, et al. Home treatment in pulmonary embolism. Thromb Res. 2010;126(1):e1-5.
21. Piran S, Le Gal G, Wells PS, Gandara E, Righini M, Rodger MA, et al. Outpatient treatment of symptomatic pulmonary embolism: a systematic review and meta-analysis. Thromb Res. 2013;132(5):515-9.
22. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149(2):315-52.
23. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35(43):3033-69, 69a-69k.
24. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost. 2014;12(3):320-8.
25. Balahura AM, Guta A, Mihalcea V, Weiss E, Dorobantu M, Bartos D, et al. Pulmonary thromboembolism in an emergency hospital: Are our patients different? Rom J Intern Med. 2017;55(4):237-44.
26. Paczynska M, Kurnicka K, Lichodziejewska B, Goliszek S, Dzikowska-Diduch O, Sobieraj P, et al. Acute pulmonary embolism treatment with rivaroxaban results in a shorter duration of hospitalisation compared to standard therapy: an academic centre experience. Kardiologia polska. 2016;74(7):650-6.
27. Motte S, Melot C, Di Pierdomenico L, Martins D, Leclercq P, Pirson M. Predictors of costs from the hospital perspective of primary pulmonary embolism. The European respiratory journal. 2016;47(1):203-11.
28. Zanova M, Monhart Z. [Regional registry of pulmonary embolism]. Vnitrni lekarstvi. 2015;61(12):1010-4.
29. Werth S, Kamvissi V, Stange T, Kuhlisch E, Weiss N, Beyer-Westendorf J. Outpatient or inpatient treatment for acute pulmonary embolism: a retrospective cohort study of 439 consecutive patients. J Thromb Thrombolysis. 2015;40(1):26-36.
30. Olié V CF, Lamarche-Vadel A, De Peretti C. La maladie veineuse thromboembolique : patients hospitalisés et mortalité en France en 2010. Bull Epidémiol Hebd. 2013;33-34:417-24.
31. Casazza F, Becattini C, Bongarzoni A, Cuccia C, Roncon L, Favretto G, et al. Clinical features and short term outcomes of patients with acute pulmonary embolism. The Italian Pulmonary Embolism Registry (IPER). Thrombosis research. 2012;130(6):847-52.
32. Sharma M, Degoricija V, Legac A, Gradiser M, Vucicevic Z. The epidemiology and diagnostic approach to acute pulmonary embolism in the university hospital. Coll Antropol. 2009;33(1):57-63.