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REVIEW ARTICLE

Reducing the hospital burden associated with the treatment of pulmonary embolism

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Summary. Pulmonary embolism (PE) is the most feared clinical presentation of venous thromboembolism (VTE). Patients with PE have traditionally been treated in hospital; however, many are at low risk of adverse outcomes and current guidelines suggest outpatient treatment as an option. Outpatient treatment of PE offers several advantages, including reduced risk of hospital-acquired conditions and potential cost savings. Despite this, patients with low-risk PE are still frequently hospitalized for treatment. This narrative review summarizes current guideline recommendations for the identification of patients with low-risk PE who are potentially suitable for outpatient treatment, using prognostic assessment tools (e.g. the Pulmonary Embolism Severity Index [PESI] and simplified PESI) and clinical exclusion criteria (e.g. Hestia criteria) alone or in combination with additional cardiac assessments. Treatment options are discussed along with recommendations for the follow-up of patients managed in the non-hospital environment. The available data on outpatient treatment of PE are summarized, including details on patient selection, anticoagulant choice, and short-term outcomes in each study. Accumulating evidence suggests that outcomes in patients with low-risk PE treated as outpatients are at least as good as, if not better than, those of patients treated in the hospital. With mounting pressures on health care systems worldwide, increasing the proportion of patients with PE treated as outpatients has the potential to reduce health care burdens associated with VTE.

Keywords: ambulatory care; anticoagulants; pulmonary embolism; risk stratification; venous thromboembolism.

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Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major health care burden worldwide (estimated annual incidence of 0.75 to 2.69 cases per 1000 population), and is associated with considerable morbidity and health care resource utilization [1]. In patients with PE, almost half report reduced aerobic functional capacity 1 year after their PE diagnosis, which negatively impacts on patient quality of life [2,3].

The hospital burden of PE is particularly high for several reasons. First, approximately two-thirds of non-fatal PE and fatal VTE cases are associated with recent ($\leq$ 90 days) hospitalization for surgical procedures associated with a moderate to high risk of VTE or admission to a medical ward after acute medical illness, making them leading preventable causes of hospital-acquired morbidity and mortality [4–6]. Second, patients diagnosed with PE have traditionally been treated in hospital [7]. Last, data from the European PREFER in VTE registry indicated that 10% to 25% of patients with PE were rehospitalized within 1 year of diagnosis, and 20% of these readmissions were due to VTE-related events [8,9].

Current guidelines suggest that the approximately 30% to 55% of patients with PE who are at low mortality risk may be suitable for early discharge and outpatient treatment [10–16]. Nonetheless, clinical trial and real-world data suggest that 80% to 98% of patients diagnosed with PE are admitted to hospital [15–21]. The necessity of this strategy is unclear, because some centers have established outpatient treatment pathways that result in ~50% to 70% of patients with PE receiving outpatient therapy [22,23]. As well as clinical indicators of cardiopulmonary stability (e.g. blood pressure and oxygen saturation) and PE risk (e.g. high/intermediate vs. low risk), factors favoring hospitalization over outpatient treatment include first VTE (vs. recurrent VTE), provoked VTE (vs. unprovoked VTE), advancing age, and presence of comorbidities (e.g. renal impairment or cancer) [20,22,24–26]. Type of health care system, geographical location, level of medicolegal

risk, physician attitudes, and patient preferences also influence the proportion of patients with PE treated in the outpatient setting [22,27–29].

Increasing the number of patients with PE treated as outpatients could potentially reduce PE-related hospital burdens. Avoidance of hospitalization, or early hospital discharge, reduces hospital length of stay (with associated cost savings) [30] and offers additional benefits, facilitating improved outcomes (e.g. eliminating/reducing the risk of hospital-acquired infections) [31], potentially limiting the functional decline associated with hospitalization (typically observed in the elderly) [32], improving patient quality of life, and resulting in an earlier return to physical and professional activity [33]. This non-systematic narrative review aims to provide an overview of information that may be of help to physicians in selecting appropriate hemodynamically stable PE patient candidates for outpatient treatment. Current guideline recommendations will be discussed, along with a review of available evidence supporting outpatient treatment of PE with traditional anticoagulants and with direct oral anticoagulants (DOACs).

Identification of low-risk, hemodynamically stable patients with confirmed pulmonary embolism

The majority of patients diagnosed with acute PE (~95%) are hemodynamically stable at presentation and are considered non-high-risk [10,34,35]. Further prognostic assessment of these patients is recommended to determine those who may require close clinical monitoring versus those with a low mortality risk, thereby guiding the subsequent treatment strategy. Both the 2014 European Society of Cardiology (ESC) and 2016 American College of Chest Physicians (ACCP) guidelines suggest that selected low-risk patients may be suitable for early discharge/home treatment [10,11]. As a point of note, the ESC PE guidelines are scheduled for an update to be released in the second half of 2019.

Several prognostic risk scores, using baseline clinical parameters, can identify patients at low risk of adverse outcomes during the first one to three months of treatment; these include the GENEVA prognostic score, the Pulmonary Embolism Severity Index (PESI), and the simplified PESI (sPESI) (Table 1) [12,13,36]. More recently, prognostic scores have been developed to predict the risk of early complications (≤2 weeks) and facilitate outpatient treatment of PE (Table 1) [37–39]; however, these require further validation. Alternatively, clinical exclusion criteria, such as the Hestia criteria (Table 2), identify patients unsuitable for outpatient treatment [40]. Although not designed as a risk stratification tool per se, several analyses have shown patients meeting the Hestia criteria are at low risk of adverse outcomes in the first month post PE diagnosis [41–43].

Because PESI outperforms the GENEVA score at identifying patients with a low mortality risk [44], and both the PESI and sPESI are extensively externally validated, the 2014 ESC guidelines suggest the use of the PESI or sPESI to stratify non-high-risk patients into intermediate-risk or low-risk categories [10]. According to a recent meta-analysis pooling data from studies constructing or validating PE prognostic risk scores, the 30-day mortality rates for patients identified as low risk using the PESI or sPESI were 2.3% (9 studies, 19 451 patients) and 1.5% (11 studies, 28 237 patients), respectively; the corresponding rates for non-low-risk patients were 11.4% and 10.7%, respectively [14]. However, the bulk of studies validating these prognostic scores have used all-cause mortality (30-day or 90-day) as their primary outcome, whereas patients with PE frequently do not die of the PE itself, but instead die from the comorbidities (e.g. cancer) [39]. Furthermore, because these studies do not always distinguish between death occurring in hospital and post discharge, they may not be informative as to whether prolonged hospitalization or premature discharge might have contributed to death. Furthermore, they do not account for other non-mortality outcomes associated with clinical deterioration, such as hypoxia or hypotension, that may influence the decision to admit to hospital [39]. Finally, 30-day mortality in patients with low PESI/sPESI scores is similar to rates observed for some intermediate-risk to low-risk patients [45], suggesting that observation period beyond 30 days should be considered by physicians.

Cardiac evaluation

Other evaluations used in prognostic risk stratification include assessment of right ventricle (RV) function (by echocardiography or computed tomography [CT] angiography), measurement of brain natriuretic peptide (BNP) or N-terminal (NT)-proBNP (biomarkers for RV overload), and measurement of biomarkers indicative of myocardial injury (e.g. cardiac troponin and heart-type fatty acid-binding protein [10]. Although the negative predictive values of the PESI/sPESI can be improved when combined with negative cardiac biomarker results (PESI with negative heart-type fatty acid-binding protein or sPESI with negative high-sensitivity troponin/BNP/NT-proBNP) [46–49], routine performance of laboratory tests in patients identified as low risk by PESI/sPESI is not considered necessary for prognostic risk stratification by current guidelines [10]. However, hemodynamically stable patients identified as intermediate risk using the PESI/sPESI are a heterogeneous population; consequently, the 2014 ESC guidelines suggest that RV function and myocardial damage should be assessed to aid further risk stratification. Patients with both abnormal RV function and a positive cardiac troponin are classified as intermediate risk to high risk and should be closely monitored for signs of hemodynamic decompensation, with "rescue" reperfusion initiated if clinically indicated. Patients with normal RV function and/or normal cardiac biomarkers are intermediate risk to low risk [10]. Although none of the guidelines advocate routine

Table 1 Clinical risk prediction scores for patients with PE

	PESI [12] (points)	sPESI [13] (points)	GENEVA prognostic score [36] (points)	RIETE prognostic score [38] (points)	simplified Ottawa prognostic score [37] (points)
Age	+ Age in years	+1 (if >80 years)	–	–	+1 (if >65 years)
Male sex	+10	–	–	–	–
History of cancer	+30	+1	+2	–	+1 (history of cancer or active cancer)
Active cancer	–	–	–	+1 (no metastases) +2 (metastases)	
Chronic heart failure	+10	+1	+1	+1	–
Chronic pulmonary disease	+10	+1	–	–	–
Pulse rate ≥110 bpm	+20	+1	–	+1	–
Systolic blood pressure <100 mmHg	+30	+1	+2	+1	+1 (<90 mmHg)
Respiratory rate >30 breaths min^{-1}	+20	–	–	–	–
Arterial O_2 saturation <90% (or PaO_2 <60 mmHg)	+20	+1	+1	+1	+1(O_2 saturation <93%)
Moderate renal impairment (CrCl 30–60 mL min^{-1})	–	–	–	+1	–
Severe renal impairment (CrCl <30 mL min^{-1})	–	–	–	+3	–
Temperature <36 °C	+20	–	–	–	–
Altered mental status	+60	–	–	–	–
Confirmed DVT	–	–	+1	–	–
Recent major bleeding	–	–	–	+2	–
Recent immobilization (≥4 days)	–	–	–	+1	–
Platelet count <100 000 μL^{-1} or >450 000 μL^{-1}	–	–	–	+1	–
Requirement for i.v. medication (e.g. analgesia or UFH)	–	–	–	–	+1
Points-based risk classification					
Low risk	≤65 (Class I) 66–85 (Class II)	0	≤2	0	0
Not low risk	86–105 (Class III) 106–125 (Class IV) >125 (Class V)	≥1	≥3	≥1	≥1
Outcomes in original derivation/validation cohorts	30-day mortality	30-day mortality	Composite of death, VTE, and major bleeding at 90 days	Composite of death, VTE, and major bleeding at 10 days	Composite of death, VTE, and major bleeding at 14 days
Low risk, %	0–3.5	1.0–1.1	2.2	0.6	<1
Not low risk, %	3.2–24.5	8.9–10.9	26.1	4.6	NR
Area under receiver operating characteristic curve	0.77–0.79	0.75	0.82	0.77	0.77–0.80

bpm, beats per minute; CrCl, creatinine clearance; DVT, deep vein thrombosis; i.v., intravenous; NR, not reported; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; sPESI, simplified Pulmonary Embolism Severity Index; UFH, unfractionated heparin; VTE, venous thromboembolism.

cardiac evaluation (i.e. RV imaging and biomarker assessment), the 2014 ESC and 2016 ACCP guidelines both advise that patients with signs of RV dilation or myocardial injury should be treated in hospital [10,11,50]. In contrast, the 2018 British Thoracic Society (BTS) guidelines suggest that patients with RV dilation may still be considered low risk providing cardiac biomarkers (i.e. one or more of BNP, NT-proBNP, or high-sensitivity troponin) are normal (Fig. 1) [50].

A recent meta-analysis of patients identified as low risk by the PESI, sPESI, and Hestia criteria investigated the prognostic significance of RV dysfunction diagnosed on the basis of echocardiography or CT pulmonary angiography [51]. In addition, the prognostic significance of elevations in troponin or natriuretic peptide levels was evaluated. The investigators found that, in low-risk patients with acute PE, early mortality was associated with the presence of RV dysfunction at admission. The

Table 2 Hestia exclusion criteria and exclusion criteria to be used in combination with PESI/sPESI to identify patients with PE unsuitable for outpatient treatment

Clinical criteria	Hestia study [40]	2018 BTS guidelines [50]
PE-related factors		
Does the patient have a PESI III–IV or sPESI ≥1?	–	Yes/no
Is the patient hemodynamically unstable?	Yes/no*	Yes/no†
Is thrombolysis or embolectomy necessary?	Yes/no	Yes/no
Has the patient required supplemental O_2 to maintain an O_2 saturation >90%?	Yes/no (>24 h O_2)	Yes/no
Was the patient already receiving anticoagulant treatment when diagnosed with PE?	Yes/no	Yes/no
Is the patient in severe pain, requiring i.v. pain medication?	Yes/no (>24 h i.v. analgesia)	Yes/no
Treatment-related factors		
Does the patient have active bleeding or a high risk of bleeding?	Yes/no‡	Yes/no§
Does the patient have renal impairment?	Yes/no (CrCl <30 mL min^{-1})	Yes/no (eGFR <30 mL min^{-1})
Does the patient have severe liver impairment?	Yes/no	Yes/no
Does the patient have a history of heparin-induced thrombocytopenia?	Yes/no	Yes/no¶
Does the patient have a social reason for treatment in hospital?	Yes/no** (>24 h treatment in hospital)	Yes/no††
Concomitant conditions/comorbidities		
Does the patient have a medical reason for treatment in hospital (e.g. infection, malignancy)?	Yes/no (>24 h treatment in hospital)	Yes/no
Is the patient pregnant?	Yes/no	–
Interpretation	"No" to all questions = consider outpatient treatment "Yes" to any question = admit to hospital	

bpm, beats per minute; BTS, British Thoracic Society; CrCl, creatinine clearance; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; HR, heart rate; i.v., intravenous; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; SBP, systolic blood pressure; sPESI, simplified Pulmonary Embolism Severity Index. *Including the following criteria but left to physician discretion: SBP <100 mmHg with heart rate >100 bpm; admission to intensive care unit. †Defined as HR >110 bpm; SBP <100 mmHg; requirement for inotropes or critical care; requirement for thrombolysis or embolectomy. ‡Recent GI bleeding (≤14 days), recent stroke (<4 weeks), recent operation (<2 weeks), bleeding disorder or thrombocytopenia (platelet count <75 000 μL−1), uncontrolled hypertension (SBP >180 mmHg or DBP >110 mmHg). §e.g. recent GI bleed or surgery, previous intracranial hemorrhage, or uncontrolled hypertension. ¶Within the last year when there is no alternative to repeating heparin treatment. **e.g. no support system. ††e.g. inability to return home, inadequate care at home, lack of telephone communication, or concerns over compliance.

findings of this study may, therefore, have implications for the management of patients who are identified as low risk based solely on clinical criteria, but who also present with RV dysfunction based on imaging or laboratory markers.

Finally, the 2016 VESTA study was designed to assess the incremental value of NT-proBNP testing in patients meeting the Hestia criteria, ~1 in 10 patients had elevated NT-proBNP levels; however, none of these patients with elevated NT-proBNP levels experienced a primary outcome event (30-day composite outcome of PE or major bleeding-related mortality, cardiopulmonary resuscitation, admission to the intensive care unit, or rescue reperfusion), leading the authors to conclude that NT-proBNP testing does not clearly provide incremental safety when selecting patients with acute PE for outpatient treatment [52].

Recommendations for anticoagulant treatment in patients with confirmed acute pulmonary embolism

Anticoagulation is recommended in all patients with acute PE to reduce the risk of early death and recurrent symptomatic or fatal VTE. Patients with high-risk PE should receive prompt intravenous anticoagulation with unfractionated heparin (UFH) prior to reperfusion [10]. Guideline-recommended options for anticoagulation in patients with confirmed non-high-risk PE include [10,11]:

- A DOAC approved as a single-drug therapy (apixaban or rivaroxaban)
- Acute-phase parenteral anticoagulation followed by a DOAC (e.g. apixaban, dabigatran, edoxaban, or rivaroxaban)
- Acute-phase parenteral anticoagulation overlapping with and followed by a vitamin K antagonist (VKA)
- Parenteral anticoagulation alone

From a patient and health care provider prospective, some of the DOACs offer several practical advantages over VKAs, including the lack of requirements for bridging anticoagulant injections, coagulation monitoring, limited dietary restrictions, and fewer drug–drug interactions [30]. By simplifying VTE treatment, DOACs make outpatient PE therapy more tolerable and feasible. In particular, apixaban and rivaroxaban, both approved as single-drug therapies, facilitate initial outpatient PE treatment because

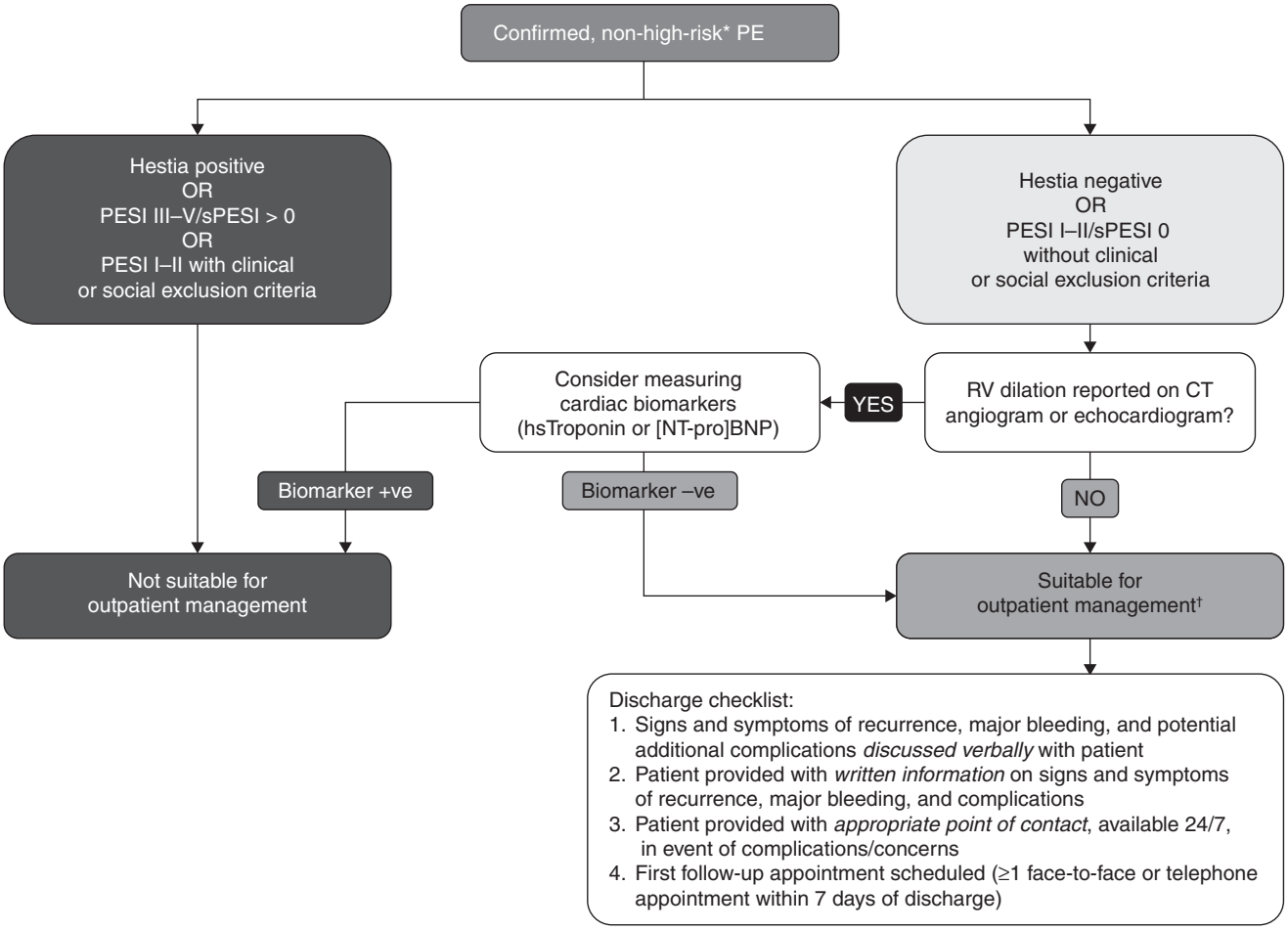

Fig. 1. Identification of patients with PE suitable for outpatient treatment and key considerations prior to discharge based on recommendations found in the 2018 BTS guidelines on the outpatient treatment of PE [50]. *i.e. no shock or hypotension at presentation. †All patients being considered for outpatient management should be reviewed by a senior clinician (e.g. a consultant) prior to discharge on an outpatient pathway. BNP, brain natriuretic peptide; BTS, British Thoracic Society; CT, computed tomography; hs, high-sensitivity; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; RV, right ventricle; sPESI, simplified Pulmonary Embolism Severity Index.

they eliminate the need for parenteral anticoagulants (i.e. bridging therapy) [32,33].

Moreover, meta-analyses of phase III DOAC trials indicate important safety benefits: DOACs are associated with a ~40% lower risk of major bleeding and a ~60% reduced risk of intracranial hemorrhage or fatal bleeding compared with VKAs [31]. Consequently, the 2016 ACCP guidelines suggest DOAC treatment over VKA for most patients with VTE [11]. Notable exceptions include pregnant women, who should be treated with low-molecular -weight heparin (LMWH), which does not cross the placental barrier [10]. For patients with cancer, the ACCP and ESC guidelines suggest parenteral therapy with LMWH over DOAC and VKA-based regimens [10,11]. However, emerging evidence (including data from the Hokusai-VTE-Cancer and selected studies of edoxaban and rivaroxaban, respectively, compared to LMWH [dalteparin]) suggest that DOACs may be more effective than LMWH for the prevention of recurrent VTE in patients with cancer [53,54], albeit at the expense of an increased risk of major bleeding versus those patients receiving LMWH [55]. Consequently, 2018 guidance from the International Society on Thrombosis and Haemostasis suggests the use of DOACs for cancer patients with VTE and a low risk of bleeding, with LMWH considered an effective alternative; in patients with a high risk of bleeding, LMWH remains the preferred treatment option [56].

Guideline recommendations for outpatient treatment

The 2014 ESC guidelines, the 2016 ACCP guidelines, and 2018 BTS guidelines suggest that patients with low-risk PE should be considered for outpatient treatment or early hospital discharge, providing a patient's circumstances and support network are adequate [10,11,50]. The 2018 BTS guidelines also emphasize that patients should only be treated as outpatients when a robust pathway for follow-up exists [50].

Although the 2014 ESC guidelines suggest the use of the PESI/sPESI (Table 1) to identify low-risk patients, the 2016 ACCP guidelines "consider clinical prediction

rules as aids to decision-making and do not require patients to have a PESI Class I–II/sPESI 0 to be considered for home treatment." Instead, it is suggested that patients meeting all the following criteria may be suitable for outpatient treatment: clinically stable, with good cardiopulmonary reserve; no contraindications (e.g. recent bleeding, severe liver or renal disease, or severe thrombocytopenia [platelet count <70 000 mm^{-3}]); expected to be compliant with treatment; and the patient feeling well enough to be treated at home [11]. The 2018 BTS guidelines suggest that patients suitable for home treatment include those who meet the Hestia criteria or those with a PESI Class I–II/sPESI 0 without additional exclusion criteria (Table 2 and Fig. 1) [50]. This suggestion to use the PESI/sPESI plus additional exclusion criteria stems from the fact that neither the PESI nor the sPESI was developed as a tool to identify patients for outpatient treatment, and additional exclusion criteria (with a high degree of overlap with the Hestia criteria) have been used in prospective studies evaluating the use of the PESI in the context of selecting patients for home treatment.

In addition to providing guidance on the initial outpatient treatment of low-risk patients with PE, the 2018 BTS guidelines also advise on the early discharge of patients initially ineligible for outpatient treatment – patients who are initially admitted with a PESI Class III (i.e. intermediate-risk PE), but have a PESI Class I–II or sPESI 0 at 48 h may be considered for early discharge [50].

Data supporting outpatient treatment of low-risk patients with pulmonary embolism

Efficacy and safety of outpatient treatment of pulmonary embolism

Available data on the efficacy and safety of early discharge/outpatient treatment of PE are summarized in Table 3.

Three randomized controlled trials have compared outcomes between patients with low-risk PE treated in the outpatient and inpatient settings and reported broadly similar rates for mortality, recurrent VTE, and major bleeding outcomes at 90 days [29,57,58]. In the OTPE trial, the incidence of outcome events at 90 days in outpatients was low (of 171 patients treated in the outpatient setting, 1 [0.6%] died, 1 [0.6%] experienced recurrent VTE, and 3 [1.8%] had a major bleeding event) [29]; in MERCURY PE, none of the 51 outpatients died or had a recurrent venous thromboembolic or major bleeding event [58]. In the study by Otero *et al*. that compared early discharge with standard hospitalization, mortality at 90 days was notably higher than in the OTPE and MERCURY PE studies, but similar between cohorts (4.2% and 8.3%, respectively) [57]. However, in the first 10 days of the Otero *et al*. study, two patients (2.8%) in the early discharge group died (vs. none in the standard hospitalization cohort), resulting in premature study discontinuation. Causes of death in these two patients were major bleeding and cardiac arrest associated with a large right heart thrombus, respectively [57]. These findings are important in the contexts of ensuring patient safety and medicolegal risk associated with potentially avoidable deaths. The results, therefore, suggest that it would be of benefit to conduct imaging assessments such as CTPA during diagnosis to exclude the presence of cardiac thrombi before committing to outpatient management of a patient with PE in order to maximize patient safety and minimize the potential for legal issues to arise. A fourth randomized controlled trial (the VESTA study) aimed to compare the safety of the Hestia criteria alone with the Hestia criteria combined with NT-proBNP testing for selecting patients with PE for outpatient treatment [52]. However, because only a low number of patients had elevated NT-proBNP levels (34/275 patients [12%]), the trial was unable to assess the incremental value of NT-proBNP testing in patients meeting the Hestia criteria. Nevertheless, the results did reinforce the findings of the original Hestia study, demonstrating a low risk of adverse events in outpatients selected by the Hestia criteria [52].

Reassuringly, prospective studies identifying patients with low-risk PE using a validated clinical prediction rule (PESI) with additional exclusion criteria or using the Hestia exclusion criteria reported low rates of adverse outcomes at 30 or 90 days – the incidences of mortality, recurrent VTE, and major bleeding at 90 days ranged from 0% to 1.5%, 0% to 2.0%, and 0% to 1.8%, respectively [29,40,52,58–61]. Several of the more recent studies have included a high proportion of patients with PE treated as outpatients with DOACs; consistently low rates of outcome events at 90–180 days were reported (Table 3) [27,58,60,62,63].

Despite current guidelines not advocating routine cardiac evaluation in patients with low-risk PE, a *post hoc* analysis of the original Hestia study assessed the utility of RV functional assessment in selecting patients with PE for outpatient treatment and exclusion criteria for three of the most recently completed prospective studies (i.e. the VESTA study, the LoPE study, and MERCURY PE) and the ongoing HotPE trial include evidence of RV functional impairment/damage [58,60,64,65]. Of the 275 patients treated as outpatients in the Hestia study, 95 (35%) had evidence of RV dysfunction on a CT angiogram (vs. 59% of the 221 patients treated in hospital) and would have, therefore, been classified as "intermediate risk" by ESC criteria. At the 30-day follow-up, two outpatients had died of non-PE-related causes one (0.6%) in the subgroup with normal RV function and one (1.1%) in the subgroup with RV dysfunction, suggesting some patients with modest RV dysfunction can be safely treated at home [64] (for comparison, in normotensive patients with Hestia exclusion criteria who were treated in hospital, 3/89 (3.4%) patients with normal RV function died during the same period versus 4/106 (3.8%) patients with RV dysfunction

Table 3 Summary of available data from studies including ≥50 patients with acute PE investigating early-discharge or outpatient treatment and reporting outcomes

Study	Study design, inclusion criteria, treatment, and follow-up	Key exclusion criteria for outpatient treatment	Outcomes
Randomized controlled trials specifically designed to compare outcomes in outpatients and inpatients with PE matched for risk			
Otero *et al.* 2010 [57]	• Prospective RCT – early discharge (3–5 days post diagnosis) vs. inpatient treatment • Patients with acute PE identified as low risk using the clinical prediction rule of Uresandi *et al.* * • Early discharge (n = 72); inpatient (n = 60) • Treatment: >10 days LMWH, overlapping and followed by VKA (from day 10) for ≥90 days • Follow-up: daily up to 14 days; 30 and 90 days	• Hemodynamic instability • Troponin T ≥0.1 ng mL^{-1} • RV dysfunction on TEE • O_2 saturation <93% • Dyspnea (NYHA III/IV) • Other medical reason for hospitalization • Severe COPD/asthma • Active bleeding/high risk of bleeding • Recent surgery • BMI >30 kg m^{-2}	10-day mortality: 2.8% (early discharge) vs. 0% (inpatient) – study terminated early because of unexpected high mortality rate in early discharge group 90-day outcomes (early discharge vs. inpatient): • Mortality: 4.2% vs. 8.3% • Non-fatal recurrent VTE: 2.8% vs. 3.3% • Major bleeding: 1.4% vs. 1.6%
OTPE trial [29]	• Prospective RCT – outpatient treatment (discharge ≤24 h post diagnosis) vs. inpatient treatment • Patients with acute PE identified as low risk by PESI (PESI Class I–II) • Outpatient (n = 171); inpatient (n = 1680) • Treatment: ≥5 days enoxaparin overlapping with and followed by VKA for ≥ 90 days • Follow-up: daily for the first 7 days then 14, 30, 60, and 90 days post discharge	• O_2 saturation <90% (on room air) • SBP < 100 mmHg • Chest pain necessitating parenteral analgesia • Active or high risk of bleeding† • CrCl <30 mL min^{-1} • Extreme obesity (≥150 kg) • History of HIT or allergy to heparins • Therapeutic anticoagulation at PE diagnosis • Pregnancy • Barriers to treatment adherence/follow-up‡	90-day outcomes (outpatient vs. inpatient): • Mortality: 0.6% vs. 0.6% ($P_{\text{non-inferiority}}$ = .005) • Recurrent VTE: 0.6% vs. 0% ($P_{\text{non-inferiority}}$ = .011) • Major bleeding: 1.8% vs. 0% ($P_{\text{non-inferiority}}$ = .086) • Hospital (re)admission: 10.5% vs. 13.7% (P = .60)
MERCURY PE [58,81]	• Prospective RCT – outpatient treatment with rivaroxaban (ED discharge within 12–24 h of triage) vs. standard care (as per local protocol, which could include hospitalization) • Patients with acute PE identified as low risk by absence of Hestia exclusion criteria and normal troponin levels, randomized within 12 h of PE diagnosis • ED discharge on rivaroxaban (n = 51); standard care (n = 63) • Treatment: rivaroxaban vs. any FDA-approved anticoagulant¶ • Follow-up: 7, 14, 30, and 90 days	• Modified Hestia criteria§ • Cardiac troponin > institutional upper reference level • Barriers to treatment or follow-up • Life expectancy <6 months	Duration of initial hospitalization and subsequent hospitalizations for bleeding and/or venous thromboembolic events within 30 days of randomization: 4.8 (± 16.8) h (outpatient treatment with rivaroxaban) vs. 33.6 (± 48.0) h (standard care); P <.000190-day outcomes (outpatient treatment with rivaroxaban vs. standard care): • Mortality: 0% vs. 0% • Non-fatal recurrent VTE: 0% vs. 0% • Major bleeding: 0% vs. 0%
Other prospective studies reporting outcomes outpatients with PE			
VESTA study [52]	• Prospective RCT – safety of Hestia exclusion criteria alone (cohort 1) vs. Hestia exclusion criteria plus NT-proBNP testing (cohort 2) in selecting patients with acute PE for	• Hestia exclusion criteria • Life expectancy <3 months • NT-proBNP >500 ng L^{-1} (in patients randomized to the NT-proBNP cohort)	30-day composite outcome (cardiopulmonary resuscitation, admission to ICU, requirement for rescue reperfusion or mortality due to PE/major bleeding): 1.1%

Table 3 (Continued)

Study	Study design, inclusion criteria, treatment, and follow-up	Key exclusion criteria for outpatient treatment	Outcomes
	outpatient treatment -Patients in cohort 1 and patients in cohort 2 with a NT-proBNP $\leq$ 500 ng L^{-1} were treated as outpatients (discharge $\leq$ 24 h post diagnosis) • Cohort 1 (n = 275); cohort 2 (n = 275); cohort 2 treated as outpatients (n = 2410) • Treatment: ≥5 days LMWH overlapping with and followed by VKA for ≥90 days (or LMWH alone in patients with cancer) • Follow-up: 5–9, 28–42, and 90 days		(cohort 1) vs. 0% (cohort 2); P = .25 90-day outcomes (cohort 1 vs. cohort 2): • Mortality: 1.1% vs. 1.5% • Recurrent VTE: 1.1% vs. 0.73% • Major bleeding: 1.1% vs. 0.4%
Agterof *et al*. 2010 [59]	• Prospective single-arm study – outpatient treatment (discharge ≤24 h post diagnosis) • Patients with acute PE and NT-proBNP < 500 pg mL^{-1} • n = 152 • Treatment: LMWH overlapping and followed by VKA (or LMWH alone in case of malignancy) • Follow-up: 2, 4, 10, and 90 days	• Hemodynamic/respiratory instability (collapse, SBP <90 mmHg, HR > 100 bpm, O_2 saturation ≤90% on room air, or need for thrombolysis) • Other medical reason for hospitalization • Pain requiring i.v. analgesia • Active or high risk of bleeding • Pregnancy • Renal insufficiency (SCr >150 μM L^{-1}) • NT-proBNP ≥500 pg mL^{-1} • Likelihood of poor compliance • Lack of support system • Hestia exclusion criteria • Life expectancy < 3 months	10-day and 90-day outcomes: • Mortality: 0% • Recurrent VTE: 0% • Major bleeding: 0% 10-day hospitalization: 4.6%
Hestia study [40]	• Prospective single-arm study – outpatient treatment (discharge ≤24 h post diagnosis) • Patients with acute PE identified as low risk by absence of Hestia exclusion criteria • n = 297 • Treatment: ≥5 days LMWH overlapping with and followed by VKA for ≥90 days • Follow-up: 7, 42, and 90 days		90-day outcomes: • Mortality: 1.0% • Non-fatal recurrent VTE: 2.0% • Major bleeding: 0.67%
Beam *et al*. 2016 [63]; Kline *et al*. 2017 [27]	• Prospective single-arm study – outpatient treatment of patients with low-risk VTE • Patients with acute PE or DVT, identified as low risk by absence of modified Hestia exclusion criteria • PE (n = 67); DVT (n = 186) • Treatment: rivaroxaban • Follow-up: 1–2, 21 and 90–180 days	• Modified Hestia exclusion criteria** • Patients with cancer-associated VTE identified as non-low risk using POMPE-C tool	30-day outcomes: • Mortality: 0% • Recurrent VTE: 0.8% • Major bleeding: 0.8% • Rehospitalization: 1.6% (patients with recurrent VTE/major bleeding all had DVT at enrolment)

Table 3 (Continued)

Study	Study design, inclusion criteria, treatment, and follow-up	Key exclusion criteria for outpatient treatment	Outcomes
Walen *et al.* 2017 [61]	• Prospective single-arm study – outpatient treatment • Patients with acute PE identified as low risk by PESI (PESI Class I–II) • $n = 250$ • Treatment: LMWH overlapping with and followed by VKA for ≥ 180 days • Follow-up: daily for 5 days, 28 and 180 days	• Hospitalization for > 24 h prior to PE diagnosis • Receiving treatment with anticoagulants at time of PE diagnosis • Place of residence > 30 km from hospital • Inability to fill in forms (e.g. due to dementia) • Pregnancy	30-day outcomes: • Mortality: 0.4% • Recurrent VTE: 0% • Relevant bleeding (defined by patient as severe): 3.2% • Hospital admission: 2.4%
LoPE study [60]	• Prospective, single-arm study – outpatient treatment (discharge after 12–24 h observation) • Patients with acute PE identified as low risk by PESI (PESI Class I–II), normal echocardiogram and negative CUS • $n = 200$ • Treatment: enoxaparin (0.5%), enoxaparin transitioned to warfarin (13%), apixaban (12%) or rivaroxaban (74.5%)	• High-risk PE (SBP < 95 mmHg or O_2 saturation on room air < 90%) • Abnormal RV function • DVT proximal to popliteal veins • Pregnancy • Renal or hepatic impairment • Other medical reason for hospitalization • Atrial or ventricular dysrhythmias • Barriers to treatment adherence/follow-up	90-day outcomes: • Composite of mortality, recurrent VTE and major bleeding: 0.5% • Mortality: 0% • Recurrent VTE: 0% • Major bleeding: 0.5%30-day hospital admission: 3%
Vanni *et al.* 2018 [82]	• Prospective cohort study – early discharge (≤48 h post triage) vs. inpatient treatment (Note: cohorts **not** matched for risk) • Early discharge ($n = 178$); inpatient ($n = 369$) • Treatment: any approved anticoagulant (UFH, LMWH, fondaparinux, warfarin, or a DOAC)	• At discretion of attending physician (but could include patient history, clinical evaluation, blood test results, including cardiac troponin if requested, evaluation of RV function, and patient's anticipated compliance)	30-day outcomes (early discharge vs. inpatient): • Mortality: 1.7% vs. 11.1% • Recurrent VTE: 1.1% vs. 1.4% • Major bleeding: 0% vs. 1.1%
Font *et al.* 2014 [83]	• Prospective cohort study in patients with cancer and PE – outpatient treatment (discharge ≥12 h post diagnosis) vs. inpatient treatment (Cohorts **not** matched for risk) • Outpatients ($n = 62$; 89% incidental PE); inpatients ($n = 76$; 14% incidental PE) • Treatment: LMWH • Follow-up: frequency not specified	• SBP < 100 mmHg • Oxygen saturation < 90% • Active bleeding • Platelet count ≤ 50 000 mm^{-3} • Renal failure • Lack of social support • Likelihood of poor treatment compliance • Other medical reason for hospitalization	30-day outcomes (outpatient vs. inpatient): • Mortality: 3.2% vs. 18.4% ($P = .006$) • Recurrent VTE: 0% vs. 2.6% ($P = NS$) • Major bleeding: 4.8% vs. 5.3% ($P = NS$)
EINSTEIN PE *post hoc* analysis [16]	• Outcomes by sPESI score in patients with PE treated as outpatients vs. inpatients • Outpatients ($n = 513$; sPESI 0 = 290; sPESI 1 = 178; sPESI ≥ 2 = 45); inpatients ($n = 4319$; sPESI 0 = 2299;	• Not specified	30-day outcomes (outpatient vs. inpatient): • Mortality: – sPESI 0: 0% vs. < 0.1% – sPESI 1: 1.1% vs. 0.8%

Table 3 (Continued)

Study	Study design, inclusion criteria, treatment, and follow-up	Key exclusion criteria for outpatient treatment	Outcomes
	sPESI 1 = 1597; sPESI ≥2 = 423) • Treatment: rivaroxaban or enoxaparin overlapping and followed by VKA		– sPESI ≥ 2: 6.7% vs. 3.3% • Recurrent VTE: – sPESI 0: 1.0% vs. 0.7% – sPESI 1: 1.7% vs. 0.9% – sPESI ≥2: 4.4% vs. 2.4% • Major bleeding: – sPESI 0: 0.7% vs. 0.6% – sPESI 1: 1.1% vs. 0.6% – sPESI ≥ 2: 0% vs. 2.1%
Hokusai-VTE subgroup analysis [18]	• Outcomes in patients with PE treated as outpatients • *n* = 231 • Treatment: ≥5 days enoxaparin (or UFH) either followed by edoxaban (*n* = 123) or overlapping with and followed by warfarin (*n* = 108) for ≥ 3–12 months • Follow-up: 5–12, 30, and 60 days (monthly thereafter if taking study drug)	• Not specified: treatment decisions were at the discretion of the attending physician	• Recurrent VTE at 12 months: 4.1% (edoxaban) vs. 4.6% (warfarin) • Major bleeding during on-treatment period: 3.3% (edoxaban) vs. 1.9% (warfarin)
Retrospective single-arm cohort studies of patients with PE treated as outpatients			
Fang *et al.* 2015 [19]	• Retrospective cohort study – outpatient treatment (discharge from ED) • Treatment: warfarin, LMWH, or fondaparinux • *n* = 494 (PESI Class I–II = 378; PESI class III–V = 116)	• Not specified	• 90-day mortality: 0.4% • 30-day bleeding leading to ED visit/hospitalization: 2.2% • 30-day hospitalization: 7.9%
Vinson *et al.* 2018 [25]	• Retrospective cohort study – outpatient treatment (discharged from ED) • Patients with acute PE presenting to ED • *n* = 179 (PESI Class I–II = 121; PESI Class III–IV = 58) • Treatment: enoxaparin overlapping with and followed by warfarin	• Exclusion criteria for outpatient treatment not specified (patient care left to discretion of treating emergency physicians)	30-day outcomes: • Mortality: 1.1% • Recurrent VTE: 1.7% • Major bleeding: 1.7%
Ghazvinian *et al.* 2018 [62]	• Retrospective analysis of Swedish AuriculA registry – outpatient treatment (ED visit ≤24 h) • Patients with acute PE identified as low risk by absence of defined exclusion criteria • *n* = 245 • Treatment: DOAC (92% rivaroxaban, 9% apixaban, 1% dabigatran)††	• Hemodynamic/cardiopulmonary instability (SBP < 100 mmHg; HR > 110 bpm; O_2 saturation < 93%) • PE affecting pulmonary trunk/main pulmonary artery (or > 40% obstruction with lung scintigraphy) • RV strain • Bleeding tendency • Social reasons necessitating hospital admission • Barriers to treatment adherence	6-month outcomes: • Mortality: 0.4% • Recurrent VTE: 0% • Major bleeding: 0.4%

Table 3 (Continued)

Study	Study design, inclusion criteria, treatment, and follow-up	Key exclusion criteria for outpatient treatment	Outcomes
Retrospective cohort studies comparing outcomes in outpatients and inpatients with PE			
Erkens *et al.* 2010 [84]	• Retrospective, cohort study – outpatient treatment vs. inpatient treatment (Note: cohorts **not** matched for risk) • Patients with acute PE without defined exclusion criteria • $n = 260$ • Treatment: 5 days LMWH overlapping with and followed by VKA for ≥90 days • Follow-up: 1–2, 7, and 90 days	• SBP < 100 mm Hg • O_2 saturation on air < 92% • High bleeding risk • Renal failure • Other medical reasons for hospitalization	90-day outcomes (outpatient vs. inpatient): • Mortality: 5% vs. 26.7% ($P = .000$) • Recurrent VTE: 3.8% vs. 4.7% ($P = .654$) • Major bleeding: 1.5% vs. 8.0% ($P = .001$)
Werth *et al.* 2015 [24]	• Retrospective cohort study – outpatient treatment (discharge < 24 h post triage) vs. early discharge (24–72 h post triage) vs. inpatient treatment (hospitalized ≥72 h) (Note: cohorts **not** matched for risk) • Patients with acute, confirmed PE presenting to the ED • Outpatient ($n = 49$); early discharge ($n = 62$); inpatient ($n = 328$) • Treatment: details not provided	• Exclusion criteria for outpatient treatment not specified (treatment decisions in patients with "low risk" PE based on clinical experience)	6-month outcomes (outpatient vs. early discharge vs. inpatient): • Mortality: 0% vs. 1.6% vs. 14.0% • Recurrent VTE: 6.1% vs. 4.8% vs. 3.4%
Roy *et al.* 2017 [22]	• Retrospective, propensity-matched‡‡ cohort study – outpatient treatment (discharged from ED or < 48 h post triage) vs. inpatient treatment • Patients with hemodynamically stable acute PE treated with anticoagulants • Outpatients ($n = 505$); inpatients ($n = 576$)	• SBP < 100 mm Hg • HR ≤120 bpm • O_2 saturation on air < 92% • High bleeding risk • Renal failure • Other medical reasons for hospitalization	14-day outcomes (outpatient vs. inpatient [matched cohorts]): • Mortality: 2.8% vs. 8.2% • Recurrent VTE: 0.6% vs. 1.7% • Major bleeding: 0% vs. 3.8%90-day outcomes (outpatient vs. inpatient [matched cohorts]): • Mortality: 3.2% vs. 16.3% – PESI I–II: 0.1% vs. 2.9% – PESI III–V: 4.4% vs. 22.8% • Recurrent VTE: – PESI I–II: 1.3% vs. 1.8% – PESI III–V: 4.5% vs. 6.3% • Major bleeding: 0.7% vs. 5.9% – PESI I–II: 0.2% vs. 4.1% – PESI III–V: 0.9% vs. 6.9%
Banala *et al.* 2017 [85]	• Retrospective cohort study in patients with cancer and incidental PE – outpatient treatment vs. inpatient treatment	• Exclusion criteria for outpatient treatment not specified (patients were admitted or discharged	• 30-day survival: 99% (outpatient) vs. 76% (inpatient) • 90-day survival: 90% (outpatient) vs. 69% (inpatient)

Table 3 (Continued)

Study	Study design, inclusion criteria, treatment, and follow-up	Key exclusion criteria for outpatient treatment	Outcomes
	(Note: cohorts **not** matched for risk) • Outpatients (n = 135); inpatients (n = 58) • Treatment: LMWH (in 90% of patients) • Follow-up: ≤17 days, 30, and 90 days	according to clinical assessment)	

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; CUS, compressive ultrasound; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ED, emergency department; FDA, Food and Drug Administration; GI, gastrointestinal; HIT, heparin-induced thrombocytopenia; HR, heart rate; ICU, intensive care unit; i.v., intravenous; LMWH, low molecular weight heparin; NT-proBNP, N-terminal brain natriuretic peptide; NYHA, New York Heart Association; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; RCT, randomized controlled trial; RV, right ventricle; SBP, systolic blood pressure; sPESI, simplified Pulmonary Embolism Severity Index; SCr, serum creatinine; TEE, transesophageal echocardiography; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism. *Recent major bleeding (4 points); cancer with metastasis (4 points); creatinine > 2 mg dL−1 (3 points); non-metastatic cancer (2 points); recent immobilization due to medical condition (2 points); no recent surgery (1 point); age >60 years (1 point). Patients with a score ≤2 points are at low risk of developing PE-related complications. †Stroke ≤10 days or GI bleeding ≤14 days or platelet count <75 000 mm−3. ‡e.g. current alcohol abuse, illicit drug use, psychosis, dementia, or homelessness. §With removal of 24-h requirements. ¶In the standard care group, anticoagulant medications used for the longest duration after randomization were as follows: rivaroxaban (51%); apixaban (25%); warfarin (16%); UFH (3%); LMWH (3%); and dabigatran (2%). **SBP <100 mm Hg (in absence of history of low blood pressure); O_2 saturation on air < 95%; contraindications to anticoagulant treatment (active bleeding, high-risk postoperative status, CrCl <30 mL min−1, history of HIT or warfarin skin necrosis); other medical condition requiring hospital treatment (sepsis, new or decompensating existing organ failure, intractable pain requiring > doses i.v. narcotics); social reasons for hospital treatment (homelessness with history of non-adherence to treatment, suspected neglect or abuse, untreated psychosis, severe alcohol or drug dependency); coagulopathy or thrombocytopenia (platelet count <50 000 μL−1). ††> 100% due to patients switching DOACs (4 rivaroxaban-treated patients switched to apixaban or dabigatran). ‡‡Matched to balance out differences for 28 patient characteristics and known risk factors for adverse events (including clinical parameters indicative of cardiopulmonary stability; comorbidities associated with increased risk of mortality, VTE or major bleeding; extent of PE; RV dysfunction; PESI classification).

[64]). However, other investigators have argued that CT scans used to identify patients with RV dysfunction may overestimate RV strain. This would mean that the risk level is likely to be overestimated in many patients with modest RV dysfunction identified in this manner, and in reality they are actually low-risk patients [66]. In MERCURY PE and the LoPE study, patients with troponin elevation and signs of RV strain on echocardiography, respectively, were excluded. Of the 251 outpatients enrolled in both studies, none died or experienced a recurrent venous thromboembolic event by the 90-day follow-up (1 patient in the LoPE study experienced a trauma-related major bleeding event), demonstrating that low-risk patients without any evidence of RV damage/dysfunction can be safely treated without hospitalization.

Patient-reported outcomes in patients with pulmonary embolism treated as outpatients

As well as outcome data, several studies have analyzed patient-reported treatment satisfaction using validated (anticlot treatment scale or patient satisfaction questionnaire [PSQ]-18) and non-validated Likert-scale patient questionnaires. Overall, patients treated in the outpatient setting tend to report good levels of treatment satisfaction; however, treatment satisfaction is broadly similar between patients treated as outpatients and those admitted to hospital [29,58–60]. Notably, in the single-arm LoPE study, 89% of patients indicated a preference for home treatment if they experience a PE in the future [60].

Education and follow-up of patients with pulmonary embolism treated in the outpatient setting

Effective and safe treatment of patients with PE in the outpatient setting requires patient education and robust follow-up pathways. One recent US multicenter study demonstrated that the implementation of a treatment protocol that combined risk stratification, anticoagulation treatment with rivaroxaban, and well-defined procedures for follow-up of patients with DVT or PE increased the rates of patients treated as outpatients without increasing rates of adverse outcomes [67]. Another multicenter US study evaluated the use of an integrated electronic clinical decision support system for risk stratification and on-site decision making for identifying patients suitable for outpatient treatment of PE. This study also found that implementing such a system increased the rates of outpatient management of PE without compromising patient safety [68].

The 2018 BTS guidelines recommend that patients are provided with verbal and written information on the signs and symptoms of VTE recurrence, major bleeding, and additional complications, together with an appropriate point of contact (available 24 h) in the event of complications/concerns [50]. Patient follow-up is important to ensure treatment compliance, to assess any ongoing symptoms, and to provide the opportunity for patients to be reassured/raise any concerns – depending on the health care system, follow-up may occur at a dedicated thrombosis/anticoagulation clinic or with the patient's primary care provider [22,60,69]. To facilitate continuity of care, the first follow-up visit should be scheduled at the time of hospital discharge. Irrespective of anticoagulant treatment strategy (DOAC, VKA, or LMWH monotherapy), patients should have at least one face-to-face or telephone consultation during the first week after discharge [50]; centers with established protocols for outpatient treatment of PE typically schedule the first follow-up appointment within 24 to 48 h post discharge [22,69].

The intensity and timing of subsequent follow-up appointments are influenced, at least partly, by treatment strategy. Patients treated with parenteral anticoagulants overlapping with and followed by a VKA will require daily/alternate-day international normalized ratio (INR) testing until a therapeutic INR (2.0–3.0) is obtained (and parenteral anticoagulation can be stopped) and frequent INR testing thereafter. For patients initially treated with a parenteral anticoagulant for whom dabigatran or edoxaban is intended, we suggest scheduling a follow-up appointment at the time of DOAC initiation (i.e. after ≥5 days treatment with a parenteral anticoagulant) [70,71]. Likewise, for patients discharged on a DOAC approved as a single-drug therapy (i.e. apixaban and rivaroxaban), we advise that a follow-up appointment at the time of dose change may be considered to avoid potential for dosing errors – the recommended dose of apixaban for the treatment of VTE is 10 mg twice daily (bid) for the first seven days, followed by 5 mg bid thereafter; the recommended dose of rivaroxaban is 15 mg bid for three weeks followed by 20 mg once daily thereafter [72,73]. Patients with PE should be treated with anticoagulants for at least three months – a follow-up appointment at three months provides an opportunity for review and assessment whether extended anticoagulation is indicated [10,11].

Evidence gaps

Although guidelines suggest the use of the sPESI to identify low-risk patients suitable for outpatient treatment, there are currently no data from prospective studies evaluating the utility of the sPESI specifically for the outpatient treatment of PE. In an exploratory *post hoc* analysis of EINSTEIN PE, patients with an sPESI 0 treated as outpatients ($n = 290$) versus in-hospital ($n = 2\ 299$) had low 30-day rates of mortality (0% and < 0.1%, respectively), recurrent VTE (1.0% and 0.7%, respectively), and major bleeding (0.7% and 0.6%, respectively) [16]. A *post hoc* analysis of the Hestia study demonstrates that both the Hestia criteria and the sPESI are able to identify patients with PE at low risk of adverse clinical outcomes [74]. Of 247 patients meeting the Hestia criteria treated at home, 189 (77%) and 58 (23%) were low and high risk, respectively, by the sPESI (corresponding proportions in the 221 patients treated in hospital were 86 [39%] and 135 [61%], respectively). In patients who were low risk by the sPESI, the incidences of 30-day mortality were 0.5% (1/189) and 0% (0/86) for outpatients and inpatients, respectively; in patients who were high risk by the sPESI, the corresponding incidences were 1.7% (1/58) and 6.8% (9/132), respectively, suggesting that the Hestia criteria may identify a proportion of non-low-risk patients suitable for outpatient treatment [74].

Other studies also suggest that some patients with non-low- risk PE may be safely treated in the outpatient setting, including a retrospective, propensity-score-matched analysis of patients with PE from a single Canadian center (which used less stringent exclusion criteria than the Hestia criteria to select patients for outpatient treatment) (Table 3). In the matched cohorts, 30-day mortality was 0.1% and 2.9% in outpatients and inpatients classified as low risk by PESI class I–II, respectively, and 4.4% and 22.8% in patients classified as non-low risk by PESI class III–IV, respectively. However, in our view, these findings should be considered as hypothesis-generating because of limitations in the study design (potential for residual confounding) and should be further examined in prospective management studies and/or randomized controlled trials. Further insight may be provided by a large ongoing randomized controlled trial, HOME-PE (NCT02811237), which aims to enroll almost 2 000 patients and is comparing the Hestia criteria with the sPESI for the outpatient treatment of PE.

Patients with cancer and PE, who would be classified as intermediate risk on the basis of the sPESI [13], are an important subgroup in which more data on prognostic assessment and outpatient treatment are needed. Because the PESI has been shown to have limited clinical utility in patients with PE and cancer, cancer-specific prognostic assessment tools have been developed (e.g. POMPE-C, a score developed by the RIETE investigators, and the EPIPHANY index) [75–77]. A meta-analysis suggests the sensitivities of these tools are high (93%–97%), which indicate they are able to identify patients at risk of early death correctly, but their specificities are relatively low (22%–34%), which indicate they are less able to identify patients who survive correctly [78]. Emerging data suggesting how PE has been diagnosed in patients with cancer may give an indication of the risk of early adverse events. With the widespread utilization of CT imaging to monitor cancer progression, ~50% of patients with cancer diagnosed with

PE in specialist oncology centers have "incidental" or "unsuspected" PE (i.e. imaging performed for reasons other than PE suspicion) [79,80]. Analysis of data from the observational EPIPHANY study shows that patients with unsuspected PE who are truly asymptomatic (not hospitalized at the time of diagnosis and with no PE-related symptoms and normal vital signs) have a significantly lower 30-day mortality (3%) than both patients with unsuspected PE who were subsequently found to have symptoms of PE on clinical evaluation (20%) and patients with suspected PE (i.e. CT-imaging performed to confirm PE diagnosis; 21%) [80]. These findings are supported by data from two single-center studies (one prospective and one retrospective) showing good outcomes in patients with incidental PE treated at home (Table 3).

Pregnant women are another patient group in whom data are lacking regarding outpatient treatment of PE. Identification of low-risk PE in pregnancy is challenging because cardiopulmonary adaptations to pregnancy mean the PESI/sPESI is likely to overestimate the risk and the Hestia criteria exclude pregnant women from outpatient management [40,50]. Despite this, the 2018 BTS guidelines suggest that pregnant/postpartum women with PE should not be excluded from outpatient care pathways [50].

Additional data on the use of DOACs for outpatient treatment of PE can be expected in the future. The Home Treatment of Pulmonary Embolism (HotPE) study is an ongoing single-arm, multicenter prospective study investigating the feasibility, efficacy, and safety of home treatment (hospital discharge ≤48 h post presentation) of acute, low-risk PE using rivaroxaban. The study aims to enroll 1 050 patients identified as low risk by the absence of modified Hestia criteria (without 24-h requirements and exclusion of patients with estimated glomerular filtration rate <15 mL min^{-1} 1.73 m^{-2}) and absence of RV dysfunction or free-floating right heart thrombi on echocardiography or CT angiography [65].

Finally, although there is evidence to suggest that reductions in the rate of hospitalization will result in cost-saving benefits, there is currently a lack of specific evidence that outpatient PE management yields cost savings. Therefore, formal cost-effectiveness analyses in this setting would be of value.

Conclusions

Outpatient or early hospital discharge treatment of PE has the potential to reduce the patient and health care system burdens associated with treatment of PE. Mounting evidence suggests that outcomes in patients with low-risk PE treated as outpatients are at least as good as, if not better than, outcomes in those treated in hospital. The approval of the DOACs apixaban and rivaroxaban, as single-drug therapies for the treatment of PE, has increased the feasibility of early home treatment of PE, and available data suggest good outcomes in patients with PE treated with rivaroxaban in the outpatient setting. Patients with PE suitable for outpatient treatment are those with a low early mortality risk who are likely to be compliant with treatment. Physicians need to be confident in identifying these patients and available data suggest the PESI/sPESI and the Hestia exclusion criteria are useful tools that can be easily implemented in routine clinical practice. Although guidelines suggest limited added value of extra tests (such as RV functional assessment and cardiac biomarker measurement) for prognostic assessment, depending on physician attitude and/or the medicolegal environment, they may not be necessary when assessing patient suitability for outpatient treatment. Despite these additional tests being shown to reduce the proportion of patients classified as low risk, in some health care settings the extra reassurance and accountability provided by cardiac imaging showing normal RV function and/or normal levels of cardiac biomarkers may outweigh the extra time/resource use required for these assessments and, paradoxically, result in increased numbers of patients with PE treated as outpatients.

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