REVIEW ARTICLE

Comprehensive Outpatient Management of Low-Risk Pulmonary Embolism: Can Primary Care Do This? A Narrative Review

David R Vinson, MD[1-3]; Drahomir Aujesky, MD, MS[4]; Geert-Jan Geersing, MD, PhD[5]; Pierre-Marie Roy, MD, PhD[6]

Perm J 2020;24:19.163

E-pub: 03/13/2020

https://doi.org/10.7812/TPP/19.163

ABSTRACT

Introduction: The evidence for outpatient management of hemodynamically stable, low-risk patients with acute symptomatic pulmonary embolism (PE) is mounting. Guidance in identifying patients who are eligible for outpatient (ambulatory) care is available in the literature and society guidelines. Less is known about who can identify patients eligible for outpatient management and in what clinical practice settings.

Objective: To answer the question, "Can primary care do this?" (provide comprehensive outpatient management of low-risk PE).

Methods: We undertook a narrative review of the literature on the outpatient management of acute PE focusing on site of care. We searched the English-language literature in PubMed and Embase from January 1, 1950, through July 15, 2019.

Results: We identified 26 eligible studies. We found no studies that evaluated comprehensive PE management in a primary care clinic or general practice setting. In 19 studies, the site-of-care decision making occurred in the Emergency Department (or after a short period of supplemental observation) and in 7 studies the decision occurred in a specialty clinic. We discuss the components of care involved in the diagnosis, outpatient eligibility assessment, treatment, and follow-up of ambulatory patients with acute PE.

Discussion: We see no formal reason why a trained primary care physician could not provide comprehensive care for select patients with low-risk PE. Leading obstacles include lack of ready access to advanced pulmonary imaging and the time constraints of a busy outpatient clinic.

Conclusion: Until studies establish safe parameters of such a practice, the question "Can primary care do this?" must remain open.

INTRODUCTION

The initial site of care of patients with newly diagnosed, acute, symptomatic pulmonary embolism (PE) is undergoing a transition away from routine hospitalization for select low-risk patients.[1-3] The supporting evidence for outpatient management (without hospitalization) continues to mount and has involved multiple countries and different types of health care systems, including, for example, a multinational randomized controlled trial in academic medical centers and a recent controlled pragmatic trial in community hospitals in the US.[4,5] Outpatient (ambulatory) care for eligible low-risk patients is endorsed by specialty societies around the world.[6-9] The practice improves the health care community's resource stewardship and spares patients the costs, inconveniences, and risks associated with unnecessary hospitalization.[10,11]

However, little is known about who can identify patients eligible for outpatient management and in what clinical settings. A stable, ambulatory patient with PE-related complaints may present to a variety of venues, including the primary care clinic, specialty (or secondary care) clinic, or the Emergency Department (ED). Comprehensive outpatient PE care requires diagnostic confirmation, determination of outpatient eligibility, anticoagulation, patient and family education, and arrangement for close follow-up. This level of care necessitates that the clinician coordinate laboratory, radiology, pharmaceutical, and educational resources (Table 1).

Which of the above settings can provide such care? What is the evidence that primary care clinics can marshal the resources needed for outpatient management of acute PE? Or that they have the time and staffing to do so? To address these questions, we undertook a narrative review of the literature.

METHODS

One of us (PMR) recently published a narrative review of outpatient PE management[1] that we in this current review have adopted, modified, and expanded. The original search was a systematic review from January 1950 to December 2016 using PubMed and Embase, with a manual search of references used in the main studies. We used the search terms *pulmonary embol** or *pulmonary thromboembol** and *outpatient** or *ambulatory care* or *home care* or *home treatment*. Studies were included only if they were published in English and explicitly mentioned the outpatient treatment setting or early hospital discharge of patients with acute, symptomatic, objectively proven PE. We excluded abstracts, editorials, and reviews.[1]

For this current narrative review, we ran a second search from January 1, 2017, through July 15, 2019, using the same sources, search terms, and eligibility criteria. From the expanded collection of studies, we excluded those not reporting outpatient management (defined here as discharge to home from the ambulatory clinic, the ED or specialty unit, or within 48 hours [≤ 2 nights] of hospitalization for observation), not reporting PE-specific clinical outcomes for patients with nonincidental PE, not specifying venues of care (ED vs clinic), discharging patients to a patient hotel, and those with secondary analyses of datasets already included in the review.

Author Affiliations

[1] The Permanente Medical Group, Oakland, CA

[2] Kaiser Permanente Division of Research, Oakland, CA

[3] Department of Emergency Medicine, Kaiser Permanente Sacramento Medical Center, CA

[4] Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland

[5] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands

[6] Emergency Department, Centre Hospitalier Universitaire, UMR (CNRS 6015 - INSERM 1083) Institut Mitovasc, Université d'Angers, France

Corresponding Author

David R Vinson, MD (drvinson@ucdavis.edu)

Keywords: ambulatory care, primary health care, pulmonary embolism, risk assessment, systematic review

RESULTS

We identified 26 eligible studies.[4,5,11-34] As of July 15, 2019, we found no studies of comprehensive PE management provided in a primary care or general practice clinic. In 19 studies the site-of-care decision making occurred in the hospital-based ED (or ambulatory care unit) or after a short period of supplemental outpatient or inpatient observation.[4,5,11-27] In 7 studies, site-of-care decision making occurred in a specialty clinic.[28-34] The research on this topic has been recently accelerating, because 10 of the 19 ED studies were published since January 1, 2017.[5,11-19] We report findings from the included studies in Table 2 (studies published on or after January 1, 2017) and Table 3[a] (studies published before January 1, 2017). Both Tables 2 and 3[a] are organized by patient care setting (ED/ambulatory care unit and specialty clinic). Seventeen studies are prospective in nature, and 16 include more than 100 outpatients (range = 30-544 outpatients). The research on outpatient PE management is an international endeavor, because the 26 studies were conducted in 16 countries.

Table 2 and Table 3[a] illustrate the variety encompassed under the broad umbrella of outpatient PE management. Variation is evident across the spectrum of care: Who arrives for evaluation (walk-ins such as to the ED vs a referred population, as seen in many specialty clinics); how patients are identified as eligible for home care (physician discretion vs explicit criteria, which also vary widely; one study used a separate risk stratification score for patients with cancer-associated PE[23,35]); whether observation is required and, if so, for how long; pharmacotherapy (eg, low-molecular-weight heparin [LMWH], warfarin, or a direct oral anticoagulant [DOAC]); the nature of postdischarge follow-up care; and the timing of outcome metrics. Differences continue beyond the variables reported in Table 2 and Table 3[a], such as extent and content of patient education.

Despite the diversity of approaches to outpatient PE management illustrated here, the clinical outcomes are reassuring. The combination of careful patient selection, appropriate treatment, attentive patient and family education, and close follow-up (Table 1) facilitates favorable outcomes, as attested by the low incidence of adverse outcomes across the studies.

Table 1. Elements and resources involved in comprehensive outpatient pulmonary embolism care, regardless of clinical setting

Element	Resource[a]	Examples[a]
Diagnostic evaluation	Laboratory	D-dimer
	Radiology	Chest radiography, computed tomography pulmonary angiography (CTPA); compression ultrasonography
	Nuclear medicine	Ventilation-perfusion imaging
Determination of outpatient eligibility	Oxygen saturation	Peripheral cutaneous oxygen saturation
	Laboratory	Biomarkers of right ventricular dysfunction, eg, troponin
	Radiology	Compression ultrasonography, assessment of right ventricular dysfunction, eg, CTPA or echocardiography if deemed appropriate
	Consultant	Thrombosis specialist (ie, pulmonologist, hematologist, or internal medicine physician), emergency medicine physician
Anticoagulation	Laboratory	Complete blood cell count, creatinine clearance
	In-office medications	Initiate treatment before pulmonary imaging or discharge to pharmacy, depending on pretest risk assessment
	Pharmacy	Direct oral anticoagulants, low-molecular-weight heparins[b]
Education of patient and family	Information on the disease and the treatment, including what to expect and what to watch for	Physician or nurse: Conversation supplemented with printed or electronic discharge instructions; pharmacist: Proper medication use (including subcutaneous injections if low-molecular-weight heparins are indicated), adverse effects, complications
Arrangement for close follow-up	Appointment access	Primary or specialty care; telephone-based anticoagulation management services, if available

[a] Resources for the diagnostic evaluation and the determination of outpatient eligibility assume the performance of a thorough history and physical examination, including basic vital signs. Resource availability and clinical application vary greatly by patient, clinician, and practice setting. We report here only common examples, which may or may not be indicated in every case. See Table 2 and Table 3 (available from: www.thepermanentejournal.org/files/2020/19.163T3.pdf[4,20-34]) for illustrations of variation in practice.

[b] For some patients who are uninsured or have limited pharmacy coverage, additional personnel (eg, social workers) may be needed to help with medication procurement.

DISCUSSION

Two Sites of Outpatient Pulmonary Embolism Care Described in the Literature

1. Emergency Department (and Ambulatory Care Unit)

Much of the research on comprehensive outpatient PE management that we identified in our literature search has been undertaken in traditional hospital-based EDs (Table 2 and Table 3[a]). The ED is a natural venue for outpatient PE research because many patients with suspected or newly diagnosed PE present themselves (or are directed) to its doors, which are conveniently open 24/7. The acceptance of all-comers includes patients with PE arriving by ambulance, who are a higher-acuity population and can constitute in some settings approximately 20% of the entire PE population in the ED.[15] The ED has easy access to laboratory, radiology, and nuclear medicine studies to pursue and secure a PE diagnosis (Table 1).[36] Continuous cardiopulmonary monitoring is readily available if needed. If a 12-hour to 24-hour period of formal observation is indicated, some EDs just extend the patient stay, whereas others transfer care to an affiliated outpatient observation or clinical decision unit.[37] Some studies of outpatient PE management include up to a 24-hour observation period in their definition of outpatient care. The meaning of outpatient itself varies, as there is no established definition. In some PE studies, outpatient care includes a stay in the *inpatient* setting. We note those studies of expanded ED care in Table 2 and Table 3[a].

When the time for disposition arrives, the ED can easily risk-stratify their patients with PE to identify those eligible for discharge to home (more on this later in this section).[38] On the treatment side, the ED can initiate anticoagulation therapy and begin patient education, which can continue when the patient is introduced to the pharmacy before or just after discharge. Thrombosis specialists are often available at all hours for consultation. Facilitating

postdischarge follow-up care is the 1 element of comprehensive PE care that can be difficult for some EDs to achieve.[39,40] Post-ED follow-up can include more than just general practitioner or specialty clinic appointments; some health care organizations also provide a pharmacy-led, telephone-based outpatient anticoagulation team (anticoagulation management services) that follows-up with these patients, whatever their anticoagulant.[39,41,42]

A variation of the traditional ED care delivery model is the UK's hospital-based ambulatory emergency care unit.[43] Patients are accepted into the unit by clinician referral only and are limited to those who are likely manageable as outpatients,[12] including patients transferred in via ambulance. Most of these units are not open around-the-clock. Proximity to the affiliated medical center gives these ambulatory care units ready access to the laboratory and advanced imaging resources needed for the diagnosis and risk stratification of patients with acute PE.

2. Specialty Clinic Setting

In some countries outside the US, such as Canada, it is not the ED to which patients with diagnosed or suspected PE are referred. Specialty-run thrombosis clinics have featured prominently in the literature on outpatient PE management (Table 3[a]). The specialty that manages these "clot clinics" varies and includes internal medicine, pulmonology, hematology, and vascular medicine. Oncology clinics can also provide comprehensive care for their stable, outpatient care-eligible patients with PE, and sometimes share tasks with pharmacists.[44] These secondary care thrombosis clinics, like the ED, have the skill set and resources to provide care from diagnosis to treatment, risk stratification, and discharge, and, contrary to the ED, specialty clinics can provide their own follow-up care. The disadvantages compared with the ED is that these clinics often do not receive ambulance traffic, nor are they always open around-the-clock. Another difference is that specialty-run clinics are not usually equipped with continuous cardiopulmonary monitoring, although the importance of this component of care in assessing outpatient eligibility is not known. For many hemodynamically stable patients with low-risk PE, 1 or 2 sets of vital signs may be sufficient to confirm stability.

Several society guidelines address criteria for outpatient PE site-of-care decision making without specifying the training and experience of the decision maker.[6,9] The British Thoracic Society, however, is more explicit: If PE is diagnosed by a general practitioner in the outpatient setting in the UK, the patient should be transferred to the ED or an ambulatory care unit,[12,45,46] as explained earlier, where they can be evaluated by a consultant or a clinician "designated to undertake this role within the department with consultant advice available."[7]

Paving the Way for Comprehensive Primary Care-based Pulmonary Embolism Management

The growing literature on the safety and effectiveness of outpatient management of PE in the ED and specialty clinic setting have set the stage for management of select patients with low-risk PE in the primary care setting. Two other factors have helped pave the way for primary care physicians to expand their role in PE management: Decentralization of management of deep vein thrombosis (DVT) and simplification of pharmacotherapy.

Decentralizing Deep Vein Thrombosis Management

For select patients with DVT, a similar shift in site of care—from the ED to the primary care clinic—began years ago in the US and is now well established in some countries, such as France. After the advent of LMWH, one of our medical centers in the US, part of a large integrated health care system, developed an outpatient clinical care pathway for select patients with DVT.[47] Initially, all patients with newly diagnosed DVT were directed to the hospital-based ED for risk stratification to inform site-of-care decision making. Over time, it was realized that for some low-risk patients the temporary transfer of care to the ED was superfluous—the referring primary care clinician was just as capable of identifying which patients were eligible for outpatient treatment and managing these patients without recourse to the ED. Our medical center then pulled together a multidisciplinary team to design, implement, and monitor a clinical care pathway to enable general practitioners to provide comprehensive outpatient DVT management.[48] Today such practice has become more common in multiple settings around the world.[49] Perhaps such a change is on the horizon for select patients in the right practice settings with acute symptomatic PE.

Simplifying Pharmacotherapy

A more recent shift in pharmacotherapy away from vitamin K antagonists, such as warfarin, might facilitate the provision of comprehensive PE care in the primary care setting.[50] Recent society guidelines recommend DOACs, also known as nonvitamin K (or novel) oral anticoagulants, as the preferred agents for most patients with acute PE.[6,7,9,51] The DOACs avoid some of the complexities associated with vitamin K antagonists, such as regular laboratory monitoring and dose adjustments, as well as many food and drug interactions.[52] Even greater ease of administration is achieved with DOACs that are approved as monotherapy for PE (eg, rivaroxaban and apixaban), obviating the need for a 5- to 10-day lead-in period of subcutaneous LMWH therapy required with some DOACs (eg, dabigatran and edoxaban). The acquisition costs of DOACs, however, are an ongoing concern, particularly among socioeconomically disadvantaged populations, for whom out-of-pocket costs might be prohibitive.[53] The efficacy and safety of DOACs in patients with cancer-associated PE are currently under investigation.[54-56] Because DOACs have been associated with an increased risk of gastrointestinal and possible genitourinary tract bleeding, they should be used with caution in patients with malignancies in these regions.[57] The 2019 European Society of Cardiology guidelines recommend that in "patients with an anticipated low risk of bleeding and without gastrointestinal tumours, the choice between LMWH and edoxaban or rivaroxaban is left to the discretion of the physician, and the patient's preference."[9] Access to DOACs alone, however, is insufficient to facilitate outpatient PE care without concurrent implementation of the structural processes of care needed to support ambulatory PE management.[58]

Exploring the Primary Care Setting for Comprehensive Pulmonary Embolism Management

In this review of the literature we failed to identify any studies meeting our eligibility criteria that describe PE management

contained entirely in the primary care clinic setting, that is, comprehensive primary care clinic-based management. The lack of literature on this model of care delivery does not mean that such care is not being provided—we know anecdotally that it is. Lack of a published description of this care model, however, prevents a critical understanding and analysis of its execution by the medical community at large and impedes its expansion and adaptation to other clinics. In advance of such literature, we introduce the 4 key elements required for comprehensive care of patients with acute PE in the primary care setting: 1) outpatient diagnosis, 2) identification of patients eligible for outpatient care, 3) patient education, and 4) timely follow-up.

1. Pursuing the Outpatient Diagnosis of Pulmonary Embolism

The most difficult and challenging aspect for securing the diagnosis of PE in primary care is identifying which patients with PE-related complaints warrant diagnostic evaluation. Both underimaging and overimaging may cause harm; the former contributes to a delay in diagnosing a potentially fatal condition, and the latter, in the case of computed tomography pulmonary angiography (CTPA), can lead to needless complications from intravenous contrast medium (eg, allergic reaction and contrast agent-induced acute kidney injury) and exposure to radiation (eg, breast cancer), not to mention poor resource utilization. Nevertheless, once a suspicion is clear and ruling out PE becomes imperative, the management of patients with suspected PE typically relies on the combination of pretest probability (ie, the clinical assessment based on historical and examination findings) and selective D-dimer testing, both readily available in primary care.[36] We will address these separately.

Assessing pretest probability: Owing to the frequency and lack of specificity of the signs and symptoms of PE, the clinical decision to investigate appears to be mainly subjective. A promising starting point in the evaluation of a patient with possible PE is the PE rule-out criteria.[59-61] When applied to patients with a low pretest probability of PE as judged by physician gestalt, these criteria can exclude PE solely on clinical grounds, without the need for laboratory or radiology testing. A randomized trial found that *ED patients* with very low pretest probability who had none of the specified 8 criteria could safely forgo additional diagnostic evaluation, including a D-dimer test, with reassuring outcomes.[62,63] The PE rule-out criteria are advocated by the American College of Physicians for use by *outpatient physicians*,[36] but they may not be ready for broad application in primary care until they are validated in this setting.

Patients who have 1 or more of the PE rule-out criteria or for whom the criteria are not applicable (because patients are not low risk by gestalt) need additional pretest probability stratification using one of several evidence-based clinical prediction rules widely endorsed by society guidelines.[6,8,9,36] Five of these prediction tools for PE diagnosis have been validated in primary care and are easily applied in this setting: The original Wells, modified Wells, simplified Wells, revised Geneva, and simplified revised Geneva models.[64] Whereas efficiency was comparable for all 5, the Wells rules demonstrated the best performance in terms of lower failure rates, that is, the lowest risk of missed PE when imaging was withheld.[64] Performance of these rules can vary considerably depending on differences in disease prevalence and practice environment, where both case mix and physician experience vary.[65,66]

Using D-dimer in the assessment: Patients with low to moderate pretest probability of PE should receive D-dimer testing. A low D-dimer value in this population safely excludes PE. Specifically for primary care, a meta-analysis found this to be true also for the use of rapid point-of-care D-dimer assays.[67] Results of a prospective study in Dutch primary care settings confirmed that the combination of the Wells score with a qualitative point-of-care D-dimer assay safely excluded the diagnosis in patients with suspected PE, comparing favorably with similar studies performed in secondary and tertiary care settings.[68] D-dimer values show improved efficiency when interpreted in light of age as well as pretest clinical probability.[69-71] A structured diagnostic approach that is built around a simplified Wells rule is the YEARS algorithm, which has demonstrated good performance in the ED and inpatient settings.[70] A large prospective study of the YEARS algorithm is under way to validate a risk-stratified use of D-dimer (rather than a 1-size-fits-all approach) in the primary care setting.[72]

Obtaining advanced pulmonary imaging: The probability assessment crosses the threshold for advanced imaging if the patient has a high pretest probability for PE or a low to moderate pretest probability with an elevated D-dimer value.[36] Research findings have established the effectiveness and safety of validated strategies for the diagnosis of acute PE in the ambulatory care setting.[64,68,73] Multidetector CTPA is the imaging method of choice in most patients with suspected PE. A ventilation-perfusion scan is preferred for patients with severe renal failure.[9] Which physician specialty orders advanced imaging, however, varies considerably across practice settings and may be subject to established local (or national) patterns of care as well as physician schedule, staffing, and time of day. In some practice settings, the primary care physician has ready access to timely pulmonary imaging and radiology interpretation and can proceed with imaging if indicated. We see this in action in one of our own practice settings (DRV). For example, in a real-world study of outpatient PE management in the US, 14.5% of 1703 ED patients arrived with a diagnosis in hand, thanks to a pulmonary imaging study ordered by an outpatient clinician, most commonly primary care physicians.[5] However, timely and convenient advanced imaging services are not available to all primary care clinics. In these cases, patients may need to be referred to the ED, ambulatory care unit, or specialty clinic for reassessment and ordering of diagnostic imaging if indicated. In some countries, such as the Netherlands and the UK, primary care physicians who identify patients in need of advanced PE imaging customarily transfer them to a higher level of care to confirm the diagnosis.[7,73]

2. Identifying Patients with Pulmonary Embolism Who are Eligible for Ambulatory Care

If a primary care physician sought to provide comprehensive care for select patients with newly diagnosed acute PE, the next step would be determining eligibility for outpatient management. The broader topic of outpatient PE care has been much studied, as the results in Table 2 and Table 3[a] attest, although none of these studies speak directly to the primary care setting.

The CHEST criteria to determine outpatient eligibility are simple and sensible. The patient should be "clinically stable with good cardiopulmonary reserve; no contraindications such as recent bleeding, severe renal or liver disease, or severe thrombocytopenia (ie, <70,000/mm^3); expected to be compliant with treatment; and the patient feels well enough to be treated at home."[6] Treatment compliance requires a certain level of health literacy, motivation, and psychosocial stability, factors commonly included in the eligibility criteria of outpatient PE studies (Table 2 and Table 3[a]).[74]

Numerous prognostic models are available to aid the physician in identifying low-risk patients who may be eligible for outpatient management.[75] The validated instruments most well studied to guide the disposition decision are the PE Severity Index and its shortened counterpart, the simplified PE Severity Index (Table 4).[76,77] Both indexes provide estimates of 30-day all-cause mortality.[4,78,79] The simplified PE Severity Index identifies fewer patients who are eligible for outpatient care than the original.[75,80] It is, however, easier to remember than the original, a distinction less meaningful in this day of autopopulating electronic clinical decision-support tools.[80] The European Society of Cardiology has incorporated the PE Severity Index into its risk stratification system.[9] When used in site-of-care decision making, short-term mortality estimates are combined with commonsense contraindications to ambulatory care, as several studies have done (Table 2 and Table 3[a]).[5,81]

Index scores can be used in a strict fashion; for example, only patients with lower-risk class I or II scores on the PE Severity Index are considered for ambulatory care,[4,18] or in a looser, informative fashion, in which mortality estimates contribute to the decision-making process but do not categorically govern it.[5,12,82]

The American College of Chest Physicians endorses this more flexible use of the PE Severity Index in their recent PE guideline, stating, "We consider clinical prediction rules as aids to decision making and do not require patients to have a predefined score (eg, low-risk PE Severity Index score) to be considered for treatment at home."[6] This approach of using prognostic rules as an adjunct to clinical judgment has been adopted by other guideline committees in site-of-care recommendations for other clinical conditions. For example, the UK's National Institute for Health and Care Excellence (NICE) guideline for adult pneumonia recommends that physicians "use clinical judgement in conjunction with the CRB65 score[83] to inform decisions about whether patients need hospital assessment."[84] Clinicians are advised to "consider" hospitalization for patients with higher-risk scores.

A second, validated, commonly used approach to identify patients with PE who are eligible for home discharge focuses on outpatient management exclusion criteria (Table 5). The first such list originated in Canada, where it has been safely used for decades.[34,85,86] These were expanded to form the Hestia criteria (Table 5), which also perform well in varied settings (Table 2 and Table 3[a]).[20,24] A similar list of outpatient exclusion criteria was employed in a large multinational outpatient PE trial that identified home eligibility on the basis of low-risk classification by the PE Severity Index (Table 5).[4] How the 2 overall strategies (mortality estimates plus exclusion criteria vs exclusion criteria alone) compare in terms of safety and efficiency has not been well studied. An international randomized controlled trial of the 2 approaches recently completed enrollment (clinicaltrials.gov identifier: NCT02811237).[87] This and similar studies will help define the role these tools can play in assisting site-of-care decision making.

Most of the above patient identification strategies do not require routine evaluation of right ventricular function in hemodynamically stable, low-risk patients. Selective use of echocardiography and serum biomarkers, such as troponin, accords with the recommendation of leading society guidelines.[6,7] The 2019 PE guidelines of the European Society of Cardiology, however, are the exception, calling for routine imaging of the right ventricle, even in otherwise low-risk patients, using CTPA or echocardiography.[9] Some evidence suggests that such testing may add clinically useful prognostic value even in normotensive

Table 4. Pulmonary embolism severity indexes

Parameter	Original score[a77]	Simplified score[b76]
Demographic characteristics		
Age/y	+1	
Age > 80 y	—	+1
Male sex	+10	—
Comorbid illness		
Cancer (active or history of)	+30	+1
Heart failure (systolic or diastolic)	+10	+1[c]
Chronic lung disease (includes asthma)	+10	
Clinical findings[d]		
Pulse ≥ 110/min	+20	+1
Systolic blood pressure < 100 mmHg	+30	+1
Respiratory rate ≥ 30/min	+20	—
Temperature < 36°C	+20	—
Arterial oxygen saturation < 90%[e]	+20	+1
Altered mental status[f]	+60	—

[a] A total point score for a given patient is obtained by summing the patient's age in years and the points for each applicable prognostic variable. Point scores correspond with the following classes that estimate escalating risks of 30-day all-cause mortality: ≤ 65 points, class I; 66-85 points, class II; 86-105 points, class III; 106-125 points, class IV; > 125 points, class V. Patients with 85 points or less (classes I and II) are considered low risk and eligible for ambulatory care consideration.[4]

[b] A total point score for a given patient is obtained by summing the points for each applicable prognostic variable. Patients with 0 points are considered low risk.

[c] The 2 variables were combined into a single category of chronic cardiopulmonary disease, that is, a patient is awarded 1 point for having either heart failure or chronic lung disease.

[d] The most abnormal vital signs in the direction of interest were used. Some studies include prearrival findings from emergency medicine services or the referring clinic.[5,15]

[e] With or without supplemental oxygenation.

[f] Acute or preexisting disorientation, lethargy, stupor, or coma.

patients with low-risk PE, although this is still being worked out.[88-91] Routine testing of right ventricular function has been incorporated into some clinical pathways to identify patients with PE who are eligible for outpatient care (Tables 2 and 3[a]).[18,92] However, adding N-terminal B-type natriuretic peptide to the Hestia rule does not appear to improve risk stratification for outpatient PE treatment.[20] What role the assessment of right ventricular function will play in the determination of primary care clinic-based outpatient eligibility is unclear.

If outpatient PE management is a viable option for the primary care patient with acute PE, the physician should work together with the patient to arrive at a mutually agreed-on site-of-care treatment plan (transfer of care vs home discharge).[93,94] Who better to take into account a patient's values and preferences in shared decision making than the physician who knows the patient best? Few studies have evaluated shared decision making in any aspect of venous thromboembolic disease management; site-of-care decision making from the primary care clinic is not among them.[95] Also given the paucity of literature on comprehensive primary care-based PE management, the evidence used in the shared decision-making discussion would have to be drawn from the broader outpatient PE literature performed in the ED and specialty clinic settings (Tables 2 and 3[a]).

3. Patient Education

Once the diagnosis of PE is established and eligibility for outpatient care is confirmed, additional responsibilities fall on the clinic that is entertaining comprehensive outpatient management (Table 1). The first among these is patient education. Topics here include at a minimum the risk factors, course, complications and prevention of PE; anticoagulation dosing, duration, medication interactions and adverse effects; and when and where to seek medical evaluation for new or worsening symptoms. Society guidelines in both Europe and the US recommend DOACs as the drugs of choice in the treatment of acute PE.[6,9] Some DOACs, however, such as dabigatran and edoxaban, require a 5- to 10-day lead-in with a LMWH, in which case instruction on subcutaneous medication administration will be necessary. In some practice settings, patient education of this sort lies principally with the nursing staff.

Currently, most society guidelines recommend at least 3 months of anticoagulation in the treatment of a first episode of acute PE, barring major contraindications.[6,9,51] The decision to extend anticoagulation therapy beyond 3 months depends on weighing the risks of venous thromboembolic recurrence with the risk of bleeding and can be a complex calculation in which patient preference and consultation with a thrombosis specialist factor prominently.[9]

4. Timely Follow-up

Timely follow-up after initial home discharge is important to assess symptom control; evaluate for the effectiveness of anticoagulation therapy and its adverse effects; and continue patient education on the disease, its treatment, and the prevention of recurrence and complications. The optimal timing and frequency of initial postdischarge follow-up has not been established, as the variation in Tables 2 and 3[a] attests. Most outpatient PE studies and clinical care pathways include an initial outpatient clinic appointment within 7 days.[39] Follow-up thereafter can

Table 5. Criteria used to exclude patients with acute pulmonary embolism (PE) from outpatient management

Categorization[a]	Criteria used in randomized controlled trial of PE Severity Index[4]	Criteria used in Hestia Study[b24]
PE factor		
Pain	Chest pain necessitating parenteral opioids	Severe pain needing intravenous pain medication > 24 h
Hemodynamics	SBP < 100 mmHg	(SBP < 100 mmHg + pulse > 100/min) or unstable by clinical judgment or requiring ICU care
O_2 saturation	Hypoxemia	> 24 h of O_2 supply needed to maintain O_2 saturation > 90%
Prearrival anticoagulation	Therapeutic oral anticoagulation	PE diagnosed during anticoagulation therapy
Treatment	Not included	Requiring thrombolysis or embolectomy for reasons other than hemodynamic instability
Comorbid condition		
Bleeding or risk thereof	Active bleeding or high risk of bleeding	Active bleeding or high risk of bleeding: GI bleeding or surgery ≤ 2 wk ago, stroke ≤ 1 mo ago, bleeding disorder or platelet count < 75 × 10^9/L, uncontrolled hypertension (SBP > 180 mmHg or DBP > 110 mmHg), or by clinician judgment
Renal function	Severe renal failure	Creatinine clearance < 30 mL/min according to Cockroft-Gault formula
Liver function	Not included	Severe liver impairment by physician judgment
Pregnancy	Pregnant	Pregnant
Heparin intolerance	Not included	Documented history of heparin-induced thrombocytopenia
Psychosocial factor		
Psychosocial factor	Barriers to adherence or follow-up; imprisonment	Medical or social reason for admission > 24 h (infection, malignancy, no support system)

[a] The tripartite categorization of PE factors, comorbid conditions, and psychosocial factors has been used elsewhere.[74]
[b] The 11 Hestia criteria were originally framed as questions; if any were answered in the affirmative, outpatient treatment was contraindicated.
DBP = diastolic blood pressure; GI = gastrointestinal; ICU = intensive care unit; O_2 = oxygen; SBP = systolic blood pressure.

be tailored to the patient's needs. An additional feature of long-term management of patients with a history of PE is to monitor for recurrence as well for the development of chronic thromboembolic pulmonary hypertension.[96] The aspects of long-term outpatient PE management that typically follow discharge from the ED or hospital are well within the established purview of primary care in the countries in which we practice.

Case Example

We include a hypothetical case example in the Sidebar: Case Example to illustrate the components of comprehensive primary care-based PE management that we have discussed in this narrative review (Table 1).

Advantages and Risks of Comprehensive Primary Care-based Pulmonary Embolism Management

Advantages of comprehensive primary care-based outpatient PE management are expected at the patient level. These include maintaining continuity of care throughout the course of PE management by reducing the care transitions that can jeopardize

Case Example

A 32-year-old woman presents to your primary care office in the morning with a 3-day history of intermittent, mild, lateral right-sided pleuritic chest pain and mild dyspnea with moderate exertion. She says she has no fever, coryza, hemoptysis, or leg complaints. She returned home last week to San Francisco, CA, after a 10-day family vacation in Auckland, New Zealand. She has no abnormalities in her medical history. Her only medication is an oral estrogen-progestin contraceptive, which she began 3 months ago. Neither she nor her relatives have a history of thrombophilia nor venous thromboembolism. You are working in a multispecialty group that has an established outpatient pulmonary embolism (PE) diagnostic algorithm, based on the American College of Physicians Best Practice Advice,[1] and a disposition pathway, based on the American College of Chest Physicians CHEST guideline and expert panel report.[2]

Her vital signs are normal, including a cutaneous peripheral oxygen saturation. The results of her heart, lung, and limb examinations are also normal, as is a 12-lead electrocardiogram and chest radiograph. Using the original Wells criteria, you calculate that she has a moderate pretest probability for acute PE, so you send her to the on-site laboratory for a serum D-dimer, which returns a result at 1075 ng/dL (normal value for her age is < 500 ng/dL). Her complete blood cell count, renal function, and aspartate aminotransferase level are normal. Because of her moderate pretest probability, you administer an initial dose of a direct oral anticoagulant (DOAC) approved as monotherapy for PE and arrange for a computed tomography pulmonary angiography (CTPA) early that afternoon at the affiliated radiology suite across town. They call to inform you that she has a right-sided lobar embolism and no evidence of right ventricular enlargement or dysfunction.

She and her partner return to your office. Her second set of vital signs are relatively unchanged. You explain to them the diagnosis, the need to begin a 3-month course of a DOAC, and the options they have for when to discontinue oral contraceptive treatment.[3-5] In evaluating her site-of-care options, you calculate her PE Severity Index score.[6] Her 32-point score places her in the lowest mortality-risk category (class I) and, because of her lack of contraindications to outpatient care, including the Hestia criteria, she is eligible to safely forgo hospitalization.[2,7-9] She also meets the American College of Chest Physicians criteria for outpatient care.[2]

Using a shared decision-making model, you discuss the benefits and risks of the next site-of-care options. For the first option, they can drive to the local affiliated Emergency Department, which has access to her electronic health records, including your note and today's laboratory and radiology results. She then may be discharged home from the Emergency Department or observed overnight. Alternatively, they can go to the pharmacy down the hall, pick up her anticoagulation and analgesic medications, then go home. She and her partner prefer the second option. You write her a note for 1 week off work. While the clinic nurse completes the patient education that you began, the office staff schedules her for a telephone appointment with you in 2 days and an in-office visit in 1 week. The couple decides to continue oral contraception for the next 8 weeks with plans to switch to an intrauterine device 1 month before discontinuing anticoagulation.

Her 3-month PE treatment course is uneventful. No additional venous thromboembolism or other complications develop over the subsequent 2 years.

References

1. Raja AS, Greenberg JO, Qaseem A, Denberg TD, Fitterman N, Schuur JD; Clinical Guidelines Committee of the American College of Physicians. Evaluation of patients with suspected acute pulmonary embolism: Best practice advice from the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med 2015 Nov 3;163(9):701-11. DOI: https://doi.org/10.7326/M14-1772 PMID:26414967
2. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016 Feb;149(2):315-52. DOI: https://doi.org/10.1016/j.chest.2015.11.026 PMID:26867832 Erratum in: Correction to Grade in: Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016 Oct;150(4):988. DOI: https://doi.org/10.1016/j.chest.2016.08.1442
3. Baglin T, Bauer K, Douketis J, Buller H, Srivastava A, Johnson G; SSC of the ISTH. Duration of anticoagulant therapy after a first episode of an unprovoked pulmonary embolus or deep vein thrombosis: Guidance from the SSC of the ISTH. J Thromb Haemost 2012 Apr;10(4):698-702. DOI: https://doi.org/10.1111/j.1538-7836.2012.04662.x PMID:22332937
4. Martinelli I, Lensing AW, Middeldorp S, et al. Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use. Blood 2016 Mar 17;127(11):1417-25. DOI: https://doi.org/10.1182/blood-2015-08-665927 PMID:26696010
5. Schulman S. Less menorrhagia for women with VTE. Blood 2016 Mar 17;127(11):1378-9. DOI: https://doi.org/10.1182/blood-2016-01-692053 PMID:26989185
6. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005 Oct 15;172(8):1041-6. DOI: https://doi.org/10.1164/rccm.200506-862OC PMID:16020800
7. Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: An international, open-label, randomised, non-inferiority trial. Lancet 2011 Jul 2;378(9785):41-8. DOI: https://doi.org/10.1016/S0140-6736(11)60824-6 PMID:21703676
8. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J. 2019 Sep;54(3). DOI: https://doi.org/10.1093/eurheartj/ehz405 PMID:31504429
9. Kovacs MJ, Hawel JD, Rekman JF, Lazo-Langner A. Ambulatory management of pulmonary embolism: A pragmatic evaluation. J Thromb Haemost 2010 Nov;8(11):2406-11. DOI: https://doi.org/10.1111/j.1538-7836.2010.03981.x PMID:20626624

patient safety.[97] Maximizing home time (ie, time alive and out of a health care institution) and minimizing ED and hospital visits are additional important patient-centered outcomes.[98,99] In the US it also will save patients out-of-pocket costs, which can be substantial. These patient-level factors may contribute to improvements in patient satisfaction and quality of life. Benefits may also be seen at the public health level, with reductions in overall health care expenses and a better stewardship of hospital resources.[10,11,100]

How the risks of this newer model—in terms of unplanned ED visits and hospitalization, and short-term major hemorrhage, recurrent venous thromboembolism, and mortality—compare with transferring care to the ED or specialty care clinic, however, is unknown. As our literature review findings demonstrate, little research has been undertaken on comprehensive PE care in the primary care setting. To begin to address this deficit, one of us (DRV) has a retrospective cohort study under way that will shed some light on this new model of PE care delivery, at least as practiced in a community-based, integrated health care system in the US.[101] Far more research, however, will be needed before this novel approach to PE management is well understood in its varied settings and optimized in terms of operations and outcomes.

Limitations

We acknowledge several limitations of this narrative review. First, our search methods were limited by pragmatic constraints and excluded studies not in the English language, not cited in PubMed or Embase, and not referenced in the included studies or leading systematic reviews of outpatient PE management. Nevertheless, it is unlikely that our principal finding—that there is little research on comprehensive primary care-based PE—will be overturned by a more thorough search. Second, we did not address the management of acute PE in pregnancy, as it requires special considerations with diagnosis and treatment.[9] Third, the lack of research on primary care-based PE management precluded a more formal systematic review and left us to draw inferences about the requirements of primary care-based management from outpatient care in other settings, particularly hospital-based ED and specialty clinics. Pulmonary embolism research in these 2 settings may not be immediately translatable to the primary care clinic setting, given differences in case mix, disease prevalence, physician training and experience, and access to testing resources. Future studies emerging directly from the primary care setting will help fill the many gaps currently in the literature. Last, our limited experiences prevent us from speaking to the breadth of diversity encompassed under the banner of primary care, although we have published broadly on PE diagnostics and treatment and represent 3 specialties—primary care, internal medicine, and emergency medicine—and different practice settings in 4 countries. We look to other authors to supplement this initial foray into a what is sure to be a broad subject of investigation.

CONCLUSION

To the larger research question, "Can primary care do this?," that is, provide comprehensive outpatient management for low-risk patients with acute PE, we have 3 answers, which address the topic from skill-based, logistical, and evidence-based perspectives. The first answer arises from a general knowledge about the training, skills, and experience characteristic of primary care clinicians. (Two of the authors of this review are board-certified primary care physicians, in the US and the Netherlands, respectively.) General practitioners are skilled in risk stratification, frequently sorting out which patients with headache need cranial imaging, which patients with epigastric pain would benefit from laboratory testing, which patients with pneumonia can safely forgo hospitalization, and so on. With a little guidance, these clinicians could become just as adept at identifying which stable patients with acute PE may be eligible to bypass the hospital, and even forgo ED transfer. We anticipate that trained general practitioners, with direction from specialty guidelines, treatment pathways, or clinical decision-support systems, and ready access to on-call thrombosis specialists, can be capable of providing comprehensive outpatient PE management. Our first answer, then, is yes, absolutely; primary care physicians have the risk-stratification capabilities and informational resources to manage select low-risk patients with acute PE without needing to routinely transfer care.

The physician's knowledge base and diagnostic skills, however, are not the only variables in the equation, as there are several logistical considerations that must be addressed. For example, how accessible are the necessary laboratory and radiology services? Is advanced pulmonary imaging located nearby, and are timely appointments and radiology interpretations available? Are clinical staff available to assist with patient education? Does the physician have the extra time to coordinate this complex operation, time that is sure to exceed a routine appointment duration? Some care delivery systems may be more conducive to comprehensive outpatient PE management than others. Even if the primary care physician *can* provide comprehensive management of select low-risk patients with acute PE (answer 1), they cannot provide such care if their practice location, setting, staffing, or operational constraints do not accommodate the requirements of this new model of PE care delivery (answer 2). Primary care physicians who believe that their practice is already overburdened may not welcome a resource-intense expansion of responsibilities. The additional burden of PE care may be attenuated by designing clinical care pathways that lighten the cognitive load on physicians, share responsibilities, and streamline patient flow.

Our third approach to our research question is not as amenable to an answer as the first 2, for it looks to the literature for primary care specific evidence-based guidance. As we found in this narrative review, little has been published that describes and analyzes the practice of primary care-based comprehensive PE management. There is much we do not understand. What characteristics of primary care clinicians are associated with outpatient care? How are primary care clinicians selecting their patients for outpatient care? In what patients is screening for right ventricular dysfunction necessary? Should routine assessment of right ventricular dysfunction be required of the primary care risk stratification protocol? What are the risk profiles, treatment, and outcomes of patients managed exclusively in the primary care

setting? Is the practice safe? Is it efficient? How can it be improved? What is its impact on the patient care experience and the clinician's experience? On a comparative level, do the selection criteria need to be more conservative than those used in the ED or specialty clinic? Are the outcomes similar to those of patients sent home from the ED or specialty clinic? There is a sizable gap in the literature that needs to be filled if we hope to understand this yet unexplored facet of outpatient PE management. Until then, our third answer to the question, "Can primary care do this?" must be that we do not know for certain yet. We look forward to what we will learn as this field of research expands. ❖

[a] Available at: www.thepermanentejournal.org/files/2020/19.163T.pdf[4,20-34]

Disclosure Statement

The institution of Geert-Jan Geersing, MD, PhD received unrestricted institutional grants from Bayer Healthcare, Boehringer-Ingelheim, Daiichi-Sankyo, and BMS/Pfizer to evaluate the management of nonvalvular atrial fibrillation in elderly patients. David R Vinson, MD; Drahomir Aujesky, MD, MS; and Pierre-Marie Roy, MD, PhD, have nothing to disclose.

Acknowledgments

The pulmonary embolism research of David R Vinson, MD, is supported by The Permanente Medical Group's Delivery Science and Physician Researcher Programs, Oakland, CA. Geert-Jan Geersing, MD, PhD, is supported by personal grants from the Netherlands Organization for Scientific Research, The Hague (Veni, Vidi, grant no. 016.166.030 and 016.196.304). These programs had no role in the design of the study, collection, analysis, and interpretation of data or in manuscript composition.

We are grateful to Laura E Simon, University of California, San Diego School of Medicine, for her help with Table 2 and Table 3[a]. We thank Melissa Spangenberg, MLIS, Health Sciences Library, Kaiser Permanente Northern California, for her assistance with the literature search.

Kathleen Louden, ELS, of Louden Health Communications performed a primary copy edit.

How to Cite this Article

Vinson DR, Aujesky D, Geersing GJ, Roy PM. Comprehensive outpatient management of low-risk pulmonary embolism: Can primary care do this? A narrative review. Perm J 2020;24:19.163. DOI: https://doi.org/10.7812/TPP/19.163

References

1. Roy PM, Moumneh T, Penaloza A, Sanchez O. Outpatient management of pulmonary embolism. Thromb Res 2017 Jul;155:92-100. DOI: https://doi.org/10.1016/j.thromres.2017.05.001 PMID:28525830
2. Klil-Drori AJ, Coulombe J, Suissa S, Hirsch A, Tagalakis V. Temporal trends in outpatient management of incident pulmonary embolism and associated mortality. Thromb Res 2018 Jan;161:111-6. DOI: https://doi.org/10.1016/j.thromres.2017.10.026 PMID:29132688
3. Peacock WF, Singer AJ. Reducing the hospital burden associated with the treatment of pulmonary embolism. J Thromb Haemost 2019 May;17(5):720-36. DOI: https://doi.org/10.1111/jth.14423 PMID:30851227
4. Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: An international, open-label, randomised, non-inferiority trial. Lancet 2011 Jul 2;378(9785):41-8. DOI: https://doi.org/10.1016/S0140-6736(11)60824-6 PMID:21703676
5. Vinson DR, Mark DG, Chettipally UK, et al; eSPEED Investigators of the KP CREST Network. Increasing safe outpatient management of emergency department patients with pulmonary embolism: A controlled pragmatic trial. Ann Intern Med 2018 Dec 18;169(12):855-65. DOI: https://doi.org/10.7326/M18-1206 PMID:30422263
6. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016 Feb;149(2):315-52. DOI: https://doi.org/10.1016/j.chest.2015.11.026 PMID:26867832 Erratum in: Correction to Grade in: Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016 Oct;150(4):988. DOI: https://doi.org/10.1016/j.chest.2016.08.1442
7. Howard LSGE, Barden S, Condliffe R, et al. British Thoracic Society Guideline for the initial outpatient management of pulmonary embolism (PE). Thorax 2018 Jul;73(Suppl 2):ii1-29. DOI: https://doi.org/10.1136/thoraxjnl-2018-211539 PMID:29898978
8. Sanchez O, Benhamou Y, Bertoletti L, et al. [Recommendations of good practice for the management of thromboembolic venous disease in adults. Short version]. Rev Mal Respir 2019 Feb;36(2):249-83. DOI: https://doi.org/10.1016/j.rmr.2019.01.003 PMID:30799126
9. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J. 2019 Sep;54(3). DOI: https://doi.org/10.1093/eurheart/ehz405 PMID:31504429
10. Dalen JE, Dalen JE Jr. Unnecessary hospitalizations for pulmonary embolism: Impact on US health care costs. Am J Med 2016 Sep;129(9):899-900. DOI: https://doi.org/10.1016/j.amjmed.2016.03.041 PMID:27143322
11. Roy PM, Corsi DJ, Carrier M, et al. Net clinical benefit of hospitalization versus outpatient management of patients with acute pulmonary embolism. J Thromb Haemost 2017 Apr;15(4):685-94. DOI: https://doi.org/10.1111/jth.13629 PMID:28106343
12. Reschen ME, Raby J, Bowen J, Singh S, Lasserson D, O'Callaghan CA. A retrospective analysis of outcomes in low- and intermediate-high-risk pulmonary embolism patients managed on an ambulatory medical unit in the UK. ERJ Open Res 2019 Apr 8;5(2):00184-2018. DOI: https://doi.org/10.1183/23120541.00184-2018 PMID:30972349
13. Kabrhel C, Rosovsky R, Baugh C, et al. Multicenter implementation of a novel management protocol increases the outpatient treatment of pulmonary embolism and deep vein thrombosis. Acad Emerg Med 2019 Jun;26(6):657-69. DOI: https://doi.org/10.1111/acem.13640 PMID:30341928
14. Barco S, Schmidtmann I, Ageno W, et al; HoT-PE Investigators. Early discharge and home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban: An international multicentre single-arm clinical trial. Eur Heart J. 2019 May 23. DOI: https://doi.org/10.1093/eurheart/ehz367 PMID:31120118
15. Vinson DR, Ballard DW, Huang J, et al. Outpatient management of Emergency Department patients with acute pulmonary embolism: Variation, patient characteristics, and outcomes. Ann Emerg Med 2018 Jul;72(1):62-72. DOI: https://doi.org/10.1016/j.annemergmed.2017.10.022 PMID:29248335
16. Peacock WF, Coleman CI, Diercks DB, et al. Emergency Department discharge of pulmonary embolus patients. Acad Emerg Med 2018 Sep;25(9):995-1003. DOI: https://doi.org/10.1111/acem.13451 PMID:29757489
17. Ghazvinian R, Gottsäter A, Elf JL. Efficacy and safety of outpatient treatment with direct oral anticoagulation in pulmonary embolism. J Thromb Thrombolysis 2018 Feb;45(2):319-24. DOI: https://doi.org/10.1007/s11239-017-1607-9 PMID:29305675
18. Bledsoe JR, Woller SC, Stevens SM, et al. Management of low-risk pulmonary embolism patients without hospitalization: The Low-Risk Pulmonary Embolism Prospective Management Study. Chest 2018 Aug;154(2):249-56. DOI: https://doi.org/10.1016/j.chest.2018.01.035 PMID:29410163
19. Walen S, Katerberg B, Boomsma MF, van den Berg JWK. Safety, feasibility and patient reported outcome measures of outpatient treatment of pulmonary embolism. Thromb Res 2017 Aug;156:172-6. DOI: https://doi.org/10.1016/j.thromres.2017.06.024 PMID:28666174
20. den Exter PL, Zondag W, Klok FA, et al; Vesta Study Investigators. 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 Oct 15;194(8):998-1006. DOI: https://doi.org/10.1164/rccm.201512-2494OC PMID:27030891
21. Fang MC, Fan D, Sung SH, et al. Outcomes in adults with acute pulmonary embolism who are discharged from emergency departments: The Cardiovascular Research Network Venous Thromboembolism study. JAMA Intern Med 2015 Jun;175(6):1060-2. DOI: https://doi.org/10.1001/jamainternmed.2015.0936 PMID:25894761
22. Elf JE, Jögi J, Bajc M. Home treatment of patients with small to medium sized acute pulmonary embolism. J Thromb Thrombolysis 2015 Feb;39(2):166-72. DOI: https://doi.org/10.1007/s11239-014-1097-y PMID:24942995
23. Beam DM, Kahler ZP, Kline JA. Immediate discharge and home treatment with rivaroxaban of low-risk venous thromboembolism diagnosed in two US Emergency Departments: A one-year preplanned analysis. Acad Emerg Med 2015 Jul;22(7):788-95. DOI: https://doi.org/10.1111/acem.12711 PMID:26113241
24. Zondag W, Mos IC, Creemers-Schild D, et al; Hestia Study Investigators. Outpatient treatment in patients with acute pulmonary embolism: The Hestia Study. J Thromb Haemost 2011 Aug;9(8):1500-7. DOI: https://doi.org/10.1111/j.1538-7836.2011.04388.x PMID:21645235
25. Kovacs MJ, Hawel JD, Rekman JF, Lazo-Langner A. Ambulatory management of pulmonary embolism: A pragmatic evaluation. J Thromb Haemost 2010

Nov;8(11):2406-11. DOI: https://doi.org/10.1111/j.1538-7836.2010.03981.x PMID:20626624

26. Agterof MJ, Schutgens RE, Snijder RJ, et al. Out of hospital treatment of acute pulmonary embolism in patients with a low NT-proBNP level. J Thromb Haemost 2010 Jun;8(6):1235-41. DOI: https://doi.org/10.1111/j.1538-7836.2010.03831.x PMID:20230418
27. Rodríguez-Cerrillo M, Alvarez-Arcaya A, Fernández-Díaz E, Fernández-Cruz A. A prospective study of the management of non-massive pulmonary embolism in the home. Eur J Intern Med 2009 Oct;20(6):598-600. DOI: https://doi.org/10.1016/j.ejim.2009.04.003 PMID:19782920
28. 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 Jul;40(1):26-36. DOI: https://doi.org/10.1007/s11239-014-1141-y PMID:25305091
29. Ozsu S, Bektas H, Abul Y, Ozlu T, Örem A. Value of cardiac troponin and sPESI in treatment of pulmonary thromboembolism at outpatient setting. Lung 2015 Aug;193(4):559-65. DOI: https://doi.org/10.1007/s00408-015-9727-5 PMID:25840529
30. Wells PS, Anderson DR, Rodger MA, et al. A randomized trial comparing 2 low-molecular-weight heparins for the outpatient treatment of deep vein thrombosis and pulmonary embolism. Arch Intern Med 2005 Apr 11;165(7):733-8. DOI: https://doi.org/10.1001/archinte.165.7.733 PMID:15824291
31. Siragusa S, Arcara C, Malato A, et al. Home therapy for deep vein thrombosis and pulmonary embolism in cancer patients. Ann Oncol 2005 May;16(Suppl 4):iv136-9. DOI: https://doi.org/10.1093/annonc/mdi923 PMID:15923414
32. Ong BS, Karr MA, Chan DK, Frankel A, Shen Q. Management of pulmonary embolism in the home. Med J Aust 2005 Sep 5;183(5):239-42. DOI: https://doi.org/10.5694/j.1326-5377.2005.tb07027.x PMID:16138796
33. Beer JH, Burger M, Gretener S, Bernard-Bagattini S, Bounameaux H. Outpatient treatment of pulmonary embolism is feasible and safe in a substantial proportion of patients. J Thromb Haemost 2003 Jan;1(1):186-7. DOI: https://doi.org/10.1046/j.1538-7836.2003.00005.x PMID:12871557
34. Kovacs MJ, Anderson D, Morrow B, Gray L, Touchie D, Wells PS. Outpatient treatment of pulmonary embolism with dalteparin. Thromb Haemost 2000 Feb;83(2):209-11. DOI: https://doi.org/10.1055/s-0037-1613787 PMID:10739374
35. Kline JA, Roy PM, Than MP, et al. Derivation and validation of a multivariate model to predict mortality from pulmonary embolism with cancer: The POMPE-C tool. Thromb Res 2012 May;129(5):e194-9. DOI: https://doi.org/10.1016/j.thromres.2012.03.015 PMID:22475313
36. Raja AS, Greenberg JO, Qaseem A, Denberg TD, Fitterman N, Schuur JD; Clinical Guidelines Committee of the American College of Physicians. Evaluation of patients with suspected acute pulmonary embolism: Best practice advice from the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med 2015 Nov 3;163(9):701-11. DOI: https://doi.org/10.7326/M14-1772 PMID:26414967
37. Stewart M, Bledsoe J, Madsen T, et al. Utilization and safety of a pulmonary embolism treatment protocol in an Emergency Department Observation Unit. Crit Pathw Cardiol 2015 Sep;14(3):87-9. DOI: https://doi.org/10.1097/HPC.0000000000000046 PMID:26214810
38. Jiménez D, Lobo JL, Barrios D, Prandoni P, Yusen RD. Risk stratification of patients with acute symptomatic pulmonary embolism. Intern Emerg Med 2016 Feb;11(1):11-8. DOI: https://doi.org/10.1007/s11739-015-1388-0 PMID:26768476
39. Vinson DR, Ballard DW, Huang J, Rauchwerger AS, Reed ME, Mark DG; Kaiser Permanente CREST Network. Timing of discharge follow-up for acute pulmonary embolism: Retrospective cohort study. West J Emerg Med 2015 Jan;16(1):55-61. DOI: https://doi.org/10.5811/westjem.2014.12.23310 PMID:25671009
40. Kline JA, Kahler ZP, Beam DM. Outpatient treatment of low-risk venous thromboembolism with monotherapy oral anticoagulation: Patient quality of life outcomes and clinician acceptance. Patient Prefer Adherence 2016 Apr 15;10:561-9. DOI: https://doi.org/10.2147/PPA.S104446 PMID:27143861
41. Witt DM, Sadler MA, Shanahan RL, Mazzoli G, Tillman DJ. Effect of a centralized clinical pharmacy anticoagulation service on the outcomes of anticoagulation therapy. Chest 2005 May;127(5):1515-22. DOI: https://doi.org/10.1378/chest.127.5.1515 PMID:15888822
42. Sylvester KW, Ting C, Lewin A, et al. Expanding anticoagulation management services to include direct oral anticoagulants. J Thromb Thrombolysis 2018 Feb;45(2):274-80. DOI: https://doi.org/10.1007/s11239-017-1602-1 PMID:29274044
43. Carter A. The Ambulatory Care Unit at Derriford Hospital. Clin Med (Lond) 2014 Jun;14(3):250-4. DOI: https://doi.org/10.7861/clinmedicine.14-3-250 PMID:24889567
44. Easaw JC, McCall S, Azim A. ClotAssist: A program to treat cancer-associated thrombosis in an outpatient pharmacy setting. J Oncol Pharm Pract 2019 Jun;25(4):818-23. DOI: https://doi.org/10.1177/1078155218760704 PMID:29540105
45. Condliffe R. Pathways for outpatient management of venous thromboembolism in a UK centre. Thromb J 2016 Dec 5;14(1):47. DOI: https://doi.org/10.1186/s12959-016-0120-2 PMID:27980461
46. Abusibah H, Abdelaziz MM, Standen P, Bhatia P, Hamad MM. Ambulatory management of pulmonary embolism. Br J Hosp Med (Lond) 2018 Jan 2;79(1):18-25. DOI: https://doi.org/10.12968/hmed.2018.79.1.18 PMID:29315054
47. Vinson DR, Berman DA. Outpatient treatment of deep venous thrombosis: A clinical care pathway managed by the emergency department. Ann Emerg Med 2001 Mar;37(3):251-8. DOI: https://doi.org/10.1067/mem.2001.113703 PMID:11223760
48. Vinson DR, Berman DR, Patel PB, Hickey DO. Outpatient management of deep venous thrombosis: 2 models of integrated care. Am J Manag Care 2006 Jul;12(7):405-10. PMID:16834527
49. Othieno R, Okpo E, Forster R. Home versus in-patient treatment for deep vein thrombosis. Cochrane Database Syst Rev 2018 Jan 9;1:CD003076. DOI: https://doi.org/10.1002/14651858.CD003076.pub3 PMID:29315455
50. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism. Cochrane Database Syst Rev 2015 Dec 4;(12):CD010957. DOI: https://doi.org/10.1002/14651858.CD010957.pub2 PMID:26636644
51. Tran HA, Gibbs H, Merriman E, et al. New guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand for the diagnosis and management of venous thromboembolism. Med J Aust 2019 Mar;210(5):227-35. DOI: https://doi.org/10.5694/mja2.50004 PMID:30739331
52. Eldredge JB, Spyropoulos AC. Direct oral anticoagulants in the treatment of pulmonary embolism. Curr Med Res Opin 2018 Jan;34(1):131-40. DOI: https://doi.org/10.1080/03007995.2017.1364227 PMID:28771049
53. Ting C, Fanikos C, Fatani N, Buckley LF, Fanikos J. Use of direct oral anticoagulants among patients with limited income and resources. J Am Coll Cardiol 2019 Feb 5;73(4):526-8. DOI: https://doi.org/10.1016/j.jacc.2018.11.024 PMID:30704585
54. Raskob GE, van Es N, Verhamme P, et al; Hokusai VTE Cancer Investigators. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018 Feb 15;378(7):615-24. DOI: https://doi.org/10.1056/NEJMoa1711948 PMID:29231094
55. Mahé I, Elalamy I, Gerotziafas GT, Girard P. Treatment of cancer-associated thrombosis: Beyond HOKUSAI. TH Open 2019 Sep 16;3(3):e309-15. DOI: https://doi.org/10.1055/s-0039-1696659 PMID:31535076
56. Suryanarayan D, Lee AYY, Wu C. Direct oral anticoagulants in cancer patients. Semin Thromb Hemost 2019 Sep;45(6):638-47. DOI: https://doi.org/10.1055/s-0039-1693479 PMID:31382307
57. NCCN Clinical Practice Guidelines in Oncology. Cancer-associated venous thromboembolic disease, version 1 [Internet]. Plymouth Meeting, PA: National Comprehensive Cancer Center; 2019 [cited 2019 Dec 26]. Available from: www.nccn.org/professionals/physician_gls/pdf/vte.pdf
58. Stein PD, Matta F, Hughes PG, et al. Home treatment of pulmonary embolism in the era of novel oral anticoagulants. Am J Med 2016 Sep;129(9):974-7. DOI: https://doi.org/10.1016/j.amjmed.2016.03.035 PMID:27107921
59. Kline JA, Mitchell AM, Kabrhel C, Richman PB, Courtney DM. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. J Thromb Haemost 2004 Aug;2(8):1247-55. DOI: https://doi.org/10.1111/j.1538-7836.2004.00790.x PMID:15304025
60. Kline JA, Courtney DM, Kabrhel C, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. J Thromb Haemost 2008 May;6(5):772-80. DOI: https://doi.org/10.1111/j.1538-7836.2008.02944.x PMID:18318689
61. Singh B, Mommer SK, Erwin PJ, Mascarenhas SS, Parsaik AK. Pulmonary embolism rule-out criteria (PERC) in pulmonary embolism—revisited: A systematic review and meta-analysis. Emerg Med J 2013 Sep;30(9):701-6. DOI: https://doi.org/10.1136/emermed-2012-201730 PMID:23038695
62. Freund Y, Cachanado M, Aubry A, et al; PROPER Investigator Group. Effect of the pulmonary embolism rule-out criteria on subsequent thromboembolic events among low-risk emergency department patients: The PROPER Randomized Clinical Trial. JAMA 2018 Feb 13;319(6):559-66. DOI: https://doi.org/10.1001/jama.2017.21904 PMID:29450523
63. Kline JA. Utility of a clinical prediction rule to exclude pulmonary embolism among low-risk Emergency Department patients: Reason to PERC up. JAMA 2018 Feb 13;319(6):551-3. DOI: https://doi.org/10.1001/jama.2017.21901 PMID:29450510
64. Hendriksen JM, Geersing GJ, Lucassen WA, et al. Diagnostic prediction models for suspected pulmonary embolism: Systematic review and independent external validation in primary care. BMJ 2015 Sep 8;351:h4438. DOI: https://doi.org/10.1136/bmj.h4438 PMID:26349907
65. Lucassen W, Geersing GJ, Erkens PM, et al. Clinical decision rules for excluding pulmonary embolism: A meta-analysis. Ann Intern Med 2011 Oct 4;155(7):448-60. DOI: https://doi.org/10.7326/0003-4819-155-7-201110040-00007 PMID:21969343
66. Penaloza A, Soulié C, Moumneh T, et al. Pulmonary embolism rule-out criteria (PERC) rule in European patients with low implicit clinical probability (PERCEPIC): A multicentre, prospective,

observational study. Lancet Haematol 2017 Dec;4(12):e615-21. DOI: https://doi.org/10.1016/S2352-3026(17)30210-7 PMID:29150390

67. Geersing GJ, Janssen KJ, Oudega R, et al. Excluding venous thromboembolism using point of care D-dimer tests in outpatients: A diagnostic meta-analysis. BMJ 2009 Aug 14;339(aug14 1):b2990. DOI: https://doi.org/10.1136/bmj.b2990 PMID:19684102
68. Geersing GJ, Erkens PM, Lucassen WA, et al. Safe exclusion of pulmonary embolism using the Wells rule and qualitative D-dimer testing in primary care: Prospective cohort study. BMJ 2012 Oct 4;345(oct04 2):e6564. DOI: https://doi.org/10.1136/bmj.e6564 PMID:23036917
69. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: The ADJUST-PE study. JAMA 2014 Mar 19;311(11):1117-24. DOI: https://doi.org/10.1001/jama.2014.2135 PMID:24643601
70. van der Hulle T, Cheung WY, Kooij S, et al.; YEARS study group. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): A prospective, multicentre, cohort study. Lancet 2017 Jul 15;390(10091):289-97. DOI: https://doi.org/10.1016/S0140-6736(17)30885-1 PMID:28549662
71. Kearon C, de Wit K, Parpia S, et al; PEGeD Study Investigators. Diagnosis of pulmonary embolism with d-Dimer adjusted to clinical probability. N Engl J Med 2019 Nov 28;381(22):2125-34. DOI: https://doi.org/10.1056/NEJMoa1909159 PMID:31774957
72. van Maanen R, Rutten FH, Klok FA, et al. Validation and impact of a simplified clinical decision rule for diagnosing pulmonary embolism in primary care: Design of the PECAN prospective diagnostic cohort management study. BMJ Open 2019 Oct 10;9(10):e031639. DOI: https://doi.org/10.1136/bmjopen-2019-031639 PMID:31601598
73. Hendriksen JM, Lucassen WA, Erkens PM, et al. Ruling out pulmonary embolism in primary care: Comparison of the diagnostic performance of "Gestalt" and the Wells rule. Ann Fam Med 2016 May;14(3):227-34. DOI: https://doi.org/10.1370/afm.1930 PMID:27184993
74. Vinson DR, Zehtabchi S, Yealy DM. Can selected patients with newly diagnosed pulmonary embolism be safely treated without hospitalization? A systematic review. Ann Emerg Med 2012 Nov;60(5):651-62 e4. DOI: https://doi.org/10.1016/j.annemergmed.2012.05.041. PMID:22944455
75. Elias A, Mallett S, Daoud-Elias M, Poggi JN, Clarke M. Prognostic models in acute pulmonary embolism: A systematic review and meta-analysis. BMJ Open 2016 Apr 29;6(4):e010324. DOI: https://doi.org/10.1136/bmjopen-2015-010324 PMID:27130162
76. Jiménez D, Aujesky D, Moores L, et al.; RIETE Investigators. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010 Aug 9;170(15):1383-9. DOI: https://doi.org/10.1001/archinternmed.2010.199 PMID:20696966
77. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005 Oct 15;172(8):1041-6. DOI: https://doi.org/10.1164/rccm.200506-862OC PMID:16020800
78. Fermann GJ, Erkens PM, Prins MH, Wells PS, Pap AF, Lensing AW. Treatment of pulmonary embolism with rivaroxaban: Outcomes by simplified Pulmonary Embolism Severity Index score from a post hoc analysis of the EINSTEIN PE study. Acad Emerg Med 2015 Mar;22(3):299-307. DOI: https://doi.org/10.1111/acem.12615 PMID:25716463
79. Zhou XY, Ben SQ, Chen HL, Ni SS. The prognostic value of pulmonary embolism severity index in acute pulmonary embolism: A meta-analysis. Respir Res 2012 Dec 4;13(1):111. DOI: https://doi.org/10.1186/1465-9921-13-111 PMID:23210843
80. Vinson DR, Ballard DW, Mark DG, et al; MAPLE investigators of the KP CREST Network. Risk stratifying emergency department patients with acute pulmonary embolism: Does the simplified Pulmonary Embolism Severity Index perform as well as the original? Thromb Res 2016 Dec;148:1-8. DOI: https://doi.org/10.1016/j.thromres.2016.09.023 PMID:27764729
81. Vinson DR, Drenten CE, Huang J, et al; Kaiser Permanente Clinical Research on Emergency Services and Treatment (CREST) Network. Impact of relative contraindications to home management in emergency department patients with low-risk pulmonary embolism. Ann Am Thorac Soc 2015 May;12(5):666-73. DOI: https://doi.org/10.1513/AnnalsATS.201411-548OC PMID:25695933
82. Vinson DR, Mark DG, Ballard DW. Outpatient Management of Patients with pulmonary embolism. Ann Intern Med 2019 Aug 6;171(3):228. DOI: https://doi.org/10.7326/L19-0208 PMID:31382285
83. Francis NA, Cals JW, Butler CC, et al; GRACE Project Group. Severity assessment for lower respiratory tract infections: Potential use and validity of the CRB-65 in primary care. Prim Care Respir J 2012 Mar;21(1):65-70. DOI: https://doi.org/10.4104/pcrj.2011.00083 PMID:21938349
84. National Clinical Guideline Centre. National Institute for Health and Care Excellence: Clinical Guidelines. In: Pneumonia: Diagnosis and management of community- and hospital-acquired pneumonia in adults. London, UK: National Institute for Health and Care Excellence; 2014.
85. Erkens PM, Gandara E, Wells P, et al. Safety of outpatient treatment in acute pulmonary embolism. J Thromb Haemost 2010 Nov;8(11):2412-7. DOI: https://doi.org/10.1111/j.1538-7836.2010.04041.x PMID:20735722
86. Wells PS, Kovacs MJ, Bormanis J, et al. Expanding eligibility for outpatient treatment of deep venous thrombosis and pulmonary embolism with low-molecular-weight heparin: A comparison of patient self-injection with homecare injection. Arch Intern Med 1998 Sep 14;158(16):1809-12. DOI: https://doi.org/10.1001/archinte.158.16.1809 PMID:9738611
87. Roy PM, Meyer G, Sanchez O, Huisman M. Outpatient management of patients with pulmonary embolism. Ann Intern Med 2019 Aug 6;171(3):227. DOI: https://doi.org/10.7326/L19-0206 PMID:31382283
88. Barco S, Mahmoudpour SH, Planquette B, Sanchez O, Konstantinides SV, Meyer G. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: A systematic review and meta-analysis. Eur Heart J 2019 Mar 14;40(11):902-10. DOI: https://doi.org/10.1093/eurheartj/ehy873 PMID:30590531
89. Vinson DR, Arasu VA, Trujillo-Santos J. Detecting right ventricular dysfunction in patients diagnosed with low-risk pulmonary embolism: Is routine computed tomographic pulmonary angiography sufficient? Eur Heart J 2019 Oct 21;40(40):3356. DOI: https://doi.org/10.1093/eurheartj/ehz616 PMID:31544929
90. Barco S, Konstantinides SV, Lankeit M. Response to 'Detecting right ventricular dysfunction in patients diagnosed with low-risk pulmonary embolism: Is routine computed tomographic pulmonary angiography sufficient?' Eur Heart J 2019 Oct 21;40(40):3357-8. DOI: https://doi.org/10.1093/eurheartj/ehz656 PMID:31539033
91. Dabbouseh NM, Patel JJ, Bergl PA. Role of echocardiography in managing acute pulmonary embolism. Heart 2019 Dec;105(23):1785-92. DOI: https://doi.org/10.1136/heartjnl-2019-314776 PMID:31439657
92. Kabrhel C, Rosovsky R, Baugh C, et al. The creation and implementation of an outpatient pulmonary embolism treatment protocol. Hosp Pract (1995). 2017 Aug:45(3):123-9. DOI: https://doi.org/10.1080/21548331.2017.1318651 PMID:28402686
93. Elwyn G, Frosch D, Thomson R, et al. Shared decision making: A model for clinical practice. J Gen Intern Med 2012 Oct;27(10):1361-7. DOI: https://doi.org/10.1007/s11606-012-2077-6 PMID:22618581
94. Barry MJ, Edgman-Levitan S. Shared decision making—Pinnacle of patient-centered care. N Engl J Med 2012 Mar 1;366(9):780-1. DOI: https://doi.org/10.1056/NEJMp1109283 PMID:22375967
95. Barnes GD, Izzo B, Conte ML, Chopra V, Holbrook A, Fagerlin A. Use of decision aids for shared decision making in venous thromboembolism: A systematic review. Thromb Res 2016 Jul;143:71-5. DOI: https://doi.org/10.1016/j.thromres.2016.05.009 PMID:27203185
96. Albani S, Biondi F, Stolfo D, Lo Giudice F, Sinagra G. Chronic thromboembolic pulmonary hypertension (CTEPH): What do we know about it? A comprehensive review of the literature. J Cardiovasc Med (Hagerstown) 2019 Apr;20(4):159-68. DOI: https://doi.org/10.2459/JCM.0000000000000774 PMID:30720636
97. Transitions of care: Technical series on safer primary care [Internet]. Geneva, Switzerland: World Health Organization; 2016 [cited 2019 Nov 15]. Available from: https://apps.who.int/iris/bitstream/handle/10665/252272/9789241511599-eng.pdf
98. Greene SJ, Mentz RJ, Felker GM. Outpatient Worsening Heart Failure as a Target for Therapy: A Review. JAMA Cardiol 2018 Mar 1;3(3):252-9. DOI: https://doi.org/10.1001/jamacardio.2017.5250 PMID:29387880
99. Fonarow GC, Liang L, Thomas L, et al. Assessment of home-time after acute ischemic stroke in medicare beneficiaries. Stroke 2016 Mar;47(3):836-42. DOI: https://doi.org/10.1161/STROKEAHA.115.011599 PMID:26892279
100. Fanikos J, Rao A, Seger AC, Carter D, Piazza G, Goldhaber SZ. Hospital costs of acute pulmonary embolism. Am J Med 2013 Feb;126(2):127-32. DOI: https://doi.org/10.1016/j.amjmed.2012.07.025 PMID:23331440
101. Isaacs DJ, Johnson EJ, Vinson DR. Comprehensive management of acute pulmonary embolism in the primary clinic setting without transfer of care: A case report [Abstract]. Am J Respir Crit Care Med 2020; [in press]

Table 2. Characteristics of recent studies of ambulatory nongravid adult patients with acute objectively confirmed pulmonary embolism stratified by site of discharge[a]

Author, y	Design	Country	Academic or community center (no.)	Outpatient cases: No. (%), qualification	Site of discharge	Major criteria for outpatient eligibility[b]	Outpatient anticoagulation	Follow-up after initial discharge[c]	Clinical outcomes (%)
Traditional hospital-based Emergency Department (may include short-term observation or inpatient care)									
Barco,[14] 2019	Prospective single-arm phase 4 management trial	Germany, Italy, the Netherlands, Spain, Portugal, Finland, Greece	Not specified (49)	502 (hospitalized for ≤ 2 nights) among 525 patients included in study with aim of outpatient treatment and 2854 patients with diagnosed PE (17.6)	ED (n = 61) or hospital (n = 441; 219 hospitalized 1 night, 222 hospitalized 2 nights). Total of 11 patients had prolonged hospitalization.	Explicit protocol requiring absence of the following: Hestia criteria; contraindication to rivaroxaban; RV enlargement or dysfunction; and free-floating thrombi in right atrium or ventricle, by echo or CTPA.	DOAC	Not specified; patients were provided a 24-h emergency telephone number and were instructed on how to respond to symptoms suggestive of VTE recurrence or bleeding.	• 90-d VTE recurrence: 3/525 (0.6) • 90-d major bleeding: 6/519 (1.2) • 90-d mortality: 2/519 (0.4) Includes larger cohort of those intended for outpatient care
Kabrhel,[13] 2019	Retrospective and prospective	US	Academic (2)	199 among 1324 patients with diagnosed PE (15.0): 12.0% (pre) and 18.1% (post)	ED (n = 80) and ED observation (n = 119)	Explicit protocol required clinical evaluation, troponin measurement, and selective evaluation of RV function and CUS. Exclusion criteria were abnormal vital signs, cardiac disease, high bleeding risk, elevated troponin, large PE, high-risk DVT, RV dysfunction, and psychological or social barriers to outpatient care.	LMWH, VKA, DOAC, none	Patients received follow-up within 7 d in a clinic staffed by hematologists and vascular medicine physicians.	• 30-d VTE recurrence: 0/197 (0) • 30-d major bleeding: 3/197 (1.5) • 30-d mortality: 2/197 (1.0) Outcomes reported for 197 of 199 patients (7-d outcomes not reported here)
Vinson,[5] 2018	Controlled pragmatic trial comparing centers with decision support (intervention) vs none (control)	US	Community (21)	324 among 1703 patients with diagnosed PE (19.0); 17.8% (pre) and 28.3% (post) in intervention group; 14.9% (pre) and 14.1% (post) in control group	ED (n = 152) and short-term outpatient observation < 24 h (n = 172)	At intervention sites: Physician judgment informed by PESI class with corresponding loose site-of-care recommendation and list of relative contraindications; laboratory testing, CUS, and echo were not required.	LMWH, VKA	Timing of follow-up was left to physician discretion; most patients (> 90%) were called within 3 d by the anticoagulation management service and were seen within 7 d by their primary care physician.[39]	• 30-d VTE recurrence: 3/324 (0.9) • 30-d major bleeding: 4/324 (1.2) • 30-d mortality: 2/324 (0.6)
Bledsoe,[18] 2018	Prospective	US	Academic and community (5)	200 among 1003 patients with diagnosed PE (19.9)	ED (n = 122) or inpatient observation (n = 78) (each 12-24 h in duration)	Explicit protocol required low-risk PESI classification, routine CUS and echo; exclusion criteria included hypoxia (SpO2 < 90%), hypotension, hepatic or renal failure, contraindication to therapeutic anticoagulation, concomitant proximal DVT or RV dysfunction, another condition requiring hospitalization or social barriers to outpatient care.	LMWH, VKA, DOAC	Follow-up with an internal medicine physician specializing in thrombosis care or the patient's primary care physician was scheduled before discharge, although the timing was not reported.	• 90-d VTE recurrence: 0/200 (0) • 90-d major bleeding: 1/200 (0.5) • 90-d mortality: 0/200 (0)
Peacock,[16] 2018	Randomized clinical trial comparing DOAC and expedited discharge vs usual care	US	Academic and community (35)	51 among 1894 patients with diagnosed PE (2.7) vs 63 patients with usual care	ED < 24 h	Explicit protocol required absence of modified Hestia criteria, adapted by removing 24-h requirements and allowing treating physicians to define instability; additional exclusion criteria: Elevated troponin level, contraindications to anticoagulation, or barriers to treatment or follow-up.	DOAC (30% of patients also received LMWH or unfractionated heparin in ED before DOAC)	Study follow-up at 7, 14, 30 and 90 d after inclusion.	• 90-d VTE recurrence: 0/51 (0) • 90-d major bleeding: 0/51 (0) • 90-d mortality: 0/51 (0)
Ghazvinian,[17] 2018	Retrospective	Sweden	Academic (1) and community (7)	245 among 881 patients treated with DOACs for PE (27.8)	ED (≤ 24 h in duration)	Explicit protocol required a low-risk modified sPESI score, with the following exclusion criteria: Affected general condition, abnormal vital signs, presence of cardiopulmonary disease, presence of central PE, obstruction of > 40% on V/Q scan, RV dysfunction, high bleeding risk, poor social support, or compliance problem.	DOAC	Not reported.	• 6-mo VTE recurrence: 0/245 (0) • 6-mo major bleeding: 1/245 (0.4) • 6-mo mortality: 1/245 (0.4)

(continued on next page)

(continued from previous page)

Vinson,[15] 2018	Retrospective	US	Community (21)	179 among 2387 ED patients with diagnosed PE included in final cohort (7.5)	ED	Clinician judgment: No protocol was then in place.	LMWH, VKA	Timing of follow-up was left to physician discretion; most patients (> 90%) were called within 3 d by anticoagulation management service and were seen within 7 d by their primary care provider.[39]	• 30-d VTE recurrence: 3/179 (1.7) • 30-d major bleeding: 3/179 (1.7) • 30-d mortality: 2/179 (1.1)
Walen,[19] 2017	Prospective	The Netherlands	Community (1)	250 among 770 patients with diagnosed PE (32.5)	Hospital < 24 h (n = 221; the other 29 patients were hospitalized > 24 h)	Explicit protocol required PESI classes I-II (although 2% were class III); exclusion criteria: Hospital admission > 24 h before PE, prediagnostic use of anticoagulants, residence > 30 km from the hospital, inability to fill in the queries (eg, because of dementia or analphabetism), or pregnancy.	LMWH, VKA	Daily visit of a home health nurse during first 5 d; scheduled visit to the attending physician at 4 wk and 6 mo.	• 30-d VTE recurrence: 0/250 (0) • 30-d "relevant" bleeding: 8/250 (3.2) • 30-d mortality: 1/250 (0.4) (6-mo outcomes not reported here)
Roy,[11] 2017	Retrospective	Canada	Academic (1)	544 among 1127 patients with diagnosed PE (48.3)	ED or outpatient thrombosis unit (n = 485) or hospital < 48 h (n = 59)	Explicit protocol required SBP > 100 mmHg, no sustained tachycardia (≤ 120/min), room-air O_2 saturation > 92%; exclusion criteria: Contraindication to LMWH or DOAC (eg, renal failure), or comorbidity requiring hospitalization.	LMWH, VKA, DOAC (few)	Follow-up visits were scheduled within 24 h, 7-14 d and 90 d at a thrombosis clinic.	Results reported for the 505 in matched cohort. • 90-d VTE recurrence: 24/505 (4.8) • 90-d major bleeding: 4/505 (0.8) • 90-d mortality: 16/505 (3.2)
Hospital-based ambulatory emergency care unit									
Reschen,[12] 2019	Retrospective	United Kingdom	Academic (1)	136 among 199 patients with diagnosed PE (68.3)	Ambulatory care unit	Clinician judgment: no protocol was in place.	DOAC, and some also received a concurrent dose of LMWH at treatment initiation.	Phone follow-up within 7 d.	• 30-d VTE recurrence: not reported • 30-d major bleeding: not reported • 30-d mortality: 1/136 (0.7)

[a] This table includes studies published since January 1, 2017. Earlier studies can be found in Table 3. Studies are presented in reverse chronology of year of publication by study design (prospective, then retrospective) and size of PE cohort. We tried to contact corresponding authors of eligible studies, if needed, to identify table variables not found in the studies.

[b] PESI variables and Hestia criteria are defined in Tables 4 and 5, respectively.

[c] Patients receiving VKA treatment underwent standardized serial laboratory monitoring, details of which are not reported in this table.

CTPA = computed tomographic pulmonary angiography; CUS = compression ultrasonography; DOAC = direct oral anticoagulant (also referred to as novel oral anticoagulants and non-vitamin K oral anticoagulants); DVT = deep venous thrombosis; echo = echocardiography; ED = Emergency Department; LMWH = low-molecular-weight heparin; O2 = oxygen; PE = pulmonary embolism; PESI = Pulmonary Embolism Severity Index; RV = right ventricle; sPESI = simplified Pulmonary Embolism Severity Index; SBP = systolic blood pressure; SpO2 = oxygen saturation measured by pulse oximetry; VKA = vitamin K antagonists (eg, warfarin); V/Q = ventilation-perfusion; VTE = venous thromboembolism.

Table 3. Characteristics of studies (through 2016) of ambulatory nongravid adult patients with acute objectively confirmed pulmonary embolism stratified by site of discharge[a]

First author, y	Design	Country	Academic or community (centers, n)	Outpatient cases: n (%), qualification[b]	Site of discharge	Major criteria for outpatient eligibility[c]	Outpatient anticoagulation	Follow-up after initial discharge[d]	Clinical outcomes
Traditional hospital-based Emergency Department (may include short-term observation or inpatient care)									
den Exter,[20] 2016	Randomized clinical trial, comparing Hestia criteria with and without addition of NT-proBNP >500 pg/mL as indication for hospitalization	The Netherlands	Academic (2) and community (15)	513[e] among 1102 patients diagnosed with PE and assessed for eligibility (46.6) and among 558 enrolled patients meeting Hestia criteria (91.9)	ED	Explicit protocol required absence of Hestia criteria; additional exclusion criteria: No symptoms, symptoms > 14 d, life expectancy < 3 mo, inability to achieve the required 3-mo follow-up; also NT-proBNP > 500 pg/mL in those randomized to this arm.	LMWH, VKA	Initial clinical follow-up was scheduled at the Outpatient Department 5-9 d after discharge and study visits were arranged at 4-6 wk and 3 mo.	90-d VTE recurrence: 4/513 (0.8) 90-d major bleeding: 3/513 (0.6) 90-d mortality: 5/513 (1.0)
Fang,[21] 2015	Retrospective	US	Community (from 4 integrated health care delivery systems)	494 among 5927 patients with PE as primary diagnosis (8.3)	ED	Not reported.	LMWH, VKA, fondaparinux	Not reported.	90-d VTE recurrence: Not reported 90-d major bleeding: Not reported 90-d mortality: 2/464 (0.4)
Elf,[22] 2015	Retrospective	Sweden	Academic (1)	260 among 416 outpatients diagnosed with PE in the ED (62.5)	ED	Explicit protocol required hemodynamic stability (SBP ≥ 100 mmHg, pulse < 100 bpm, no syncope) and small-to-medium-sized PE (< 40% perfusion defect on V/Q scan); exclusion criteria: O_2 requirement, parenteral analgesia, or contraindications to anticoagulant treatment.	LMWH, VKA	Not reported.	90-d VTE recurrence: 1/260 (0.4) 90-d major bleeding: 6/260 (2.3) 90-d mortality: 6/260 (2.3)
Beam,[23] 2015	Prospective	US	Academic (2)	35 among 131 patients diagnosed with PE (26.7)	ED	Explicit protocol required absence of modified Hestia criteria (eg, platelet count threshold reduced to 50 x 10^9/L, hypotension designation required absence of a history of low blood pressure at baseline, the three 24-hour qualifications were removed); additional exclusion criteria: contraindications to LMWH, history of warfarin skin necrosis, INR > 1.7. Patients with active malignancy were further risk stratified using the POMPE-C tool.[35]	DOAC	Patients received a phone call in 1 d - 2 d and clinic follow-up at 3 wk and 3 mo-6 mo.	90-d VTE recurrence: 0/35 (0) 90-d major bleeding: 0/35 (0) 90-d mortality: 1/35 (2.9)
Zondag,[24] 2011	Prospective	The Netherlands	Academic (3) and community (9)	297 among 581 patients diagnosed with PE and assessed for eligibility (51.1)	ED (n = 229) or inpatient unit < 24h (n = 68)	Explicit protocol required absence of Hestia criteria; additional exclusion criteria: impossibility of achieving the required 90-d follow-up (eg, no fixed address, or foreign citizen) or life-expectancy < 3 mo.	LMWH, VKA	Patients had a scheduled visit at the outpatient clinic at 1 wk and 3 mo.	90-d VTE recurrence: 6/297 (2.0) 90-d major bleeding: 2/297 (0.7) 90-d mortality: 3/297 (1.0)
Aujesky,[4] 2011	Randomized controlled trial, comparing outpatient vs inpatient treatment setting	Switzerland, France, Belgium, the US	Academic (19)	172 (vs 172 in the inpatient group), among 1557 patients diagnosed with PE and assessed for eligibility (11.0% of those diagnosed with PE)	ED or inpatient unit (patients discharged < 24 h from randomization, usually < 36 h from ED arrival)	Explicit protocol required PESI Class I-II; exclusion criteria: SBP < 100 mmHg, hypoxemia, chest pain necessitating parenteral opioids, therapeutic oral anticoagulation, active bleeding or high risk of bleeding, severe renal failure, pregnancy, extreme obesity, history of HIT or heparin allergy, barriers to adherence or follow-up, or imprisonment.	LMWH, VKA	Patients were contacted every day during the initial week, then at 14 d, 30 d, 60 d, and 90 d.	90-d VTE recurrence: 1/171 (0.6) 90-d major bleeding: 3/171 (1.7) 90-d mortality: 1/171 (0.6) 1/172 lost to follow-up

(continued on next page)

(continued from previous page)

Agterof,[26] 2010	Prospective	The Netherlands	Academic (1) and community (4)	152 among 351 patients diagnosed with PE and assessed for eligibility (43.3)	ED or inpatient unit < 24h	Explicit protocol required hemodynamic and respiratory stability and NT-proBNP level < 500 pg/mL; exclusion criteria: syncope, SBP < 90 mmHg, heart rate > 100 bpm, O_2 requirement to keep saturation > 90%, pain requiring IV analgesia, need for thrombolysis at presentation, active bleeding or known hemorrhagic diathesis, pregnancy; renal insufficiency, concomitant illness requiring hospitalization > 24 h, likelihood of poor compliance, or no support system at home.	LMWH, VKA	Patients were called at 2 d and 4 d, then seen in the Outpatient Department at 10 d.	90-d VTE recurrence: 0/152 (0) 90-d major bleeding: 0/152 (0) 90-d mortality: 0/152 (0)
Rodriguez-Cerrillo,[27] 2009	Prospective	Spain	Academic (1)	30 among 286 patients diagnosed with PE and assessed for eligibility (10.5)	ED	Explicit protocol required residence in health area and a home-carer available around-the-clock; exclusion criteria: Large PE (involving two or more lobar branches), hemodynamic instability, O_2 saturation < 92% on room air, heart failure, moderate to severe renal failure, hemoptysis, arrhythmia, or contraindication to LMWH.	LMWH, VKA	Patients were admitted in a home-hospitalization unit and were visited daily for 7 d-14 d.	90-d VTE recurrence: 0/30 (0) 90-d major bleeding: 0/30 (0) 90-d mortality: 0/30 (0)
Beer,[33] 2003	Prospective	Switzerland	Academic (2)	43 among 255 patients diagnosed with PE (16.9)	ED	Explicit protocol with the following exclusion criteria: contraindication to anticoagulation or LMWH, drug addiction, psychiatric condition, high probability of noncompliance, body weight > 110 kg, renal impairment, thrombocytopenia, concomitant fibrinolytic therapy, or oral anticoagulant 24 h before the study.	LMWH, VKA	Not reported.	90-d VTE recurrence: 1/43 (2.3) 90-d major bleeding: 0/43 (0) 90-d mortality: 0/43 (0)
Specialty-run clinic									
Ozsu,[29] 2015	Prospective	Turkey	Academic (1)	31 among 213 patients diagnosed with PE (14.6) and among 206 patients enrolled in the study (15.0)	Outpatient pulmonary clinic	Explicit protocol required low-risk sPESI classification and negative troponin; exclusion criteria: hypoxemia, SBP < 100 mmHg, active or high risk of bleeding, renal insufficiency, history of HIT, risk of non-compliance, or concomitant illness requiring hospitalization.	LMWH, VKA	Patients were followed with clinic visits for 3 mo, though the timing was not reported.	90-d VTE recurrence: 0/31 (0) 90-d major bleeding: 0/31 (0) 90-d mortality: 1/31 (3.2)
Werth,[28] 2015	Retrospective	Germany	Academic (1)	49 among 429 patients diagnosed with recent (< 15 d) symptomatic PE (11.2)	Outpatient vascular ward; discharged from hospital < 24 h	Physician discretion; no protocol in place.	Not reported (presumed LMWH, VKA)	Not reported.	6-mo VTE recurrence: 3/49 (6.1) 6-mo major bleeding: Not reported 6-mo mortality: 0/49 (0)
Kovacs.[25] 2010	Retrospective	Canada	Academic (1)	314 among 639 patients diagnosed with PE (49.1)	Outpatient Thrombosis Unit	Explicit protocol required hemodynamic stability; exclusion criteria: requiring O_2 therapy, requiring parenteral opioids, or high risk for a major hemorrhage.	LMWH, VKA	Not reported.	90-d VTE recurrence: 3/314 (1.0) 90-d major bleeding: 3/314 (1.0) 90-d mortality: 9/314 (2.9)

(continued on next page)

(continued from previous page)

Wells,[30] 2005	Clinical randomized trial, comparing 2 LMWHs	Canada	Academic (4)	90 among 505 patients with VTE (DVT or PE) enrolled in the study (unknown percentage of patients diagnosed with PE)	Outpatient Thrombosis Unit	Explicit protocol with exclusion criteria: Hypotension, hypoxia on room air, pain needing IV opioids, active bleeding or high risk for major bleeding (eg, stroke < 10 d, gastrointestinal bleeding < 14 d, platelets < $75x10^3/\mu L$), HIT history, creatinine > 2.3 mg/dL, concomitant illness requiring hospitalization, or no fixed address	LMWH, VKA	Patients were contacted by phone every 24-48 h during the first week.	90-d VTE recurrence: 2/90 (2.2) 90-d major bleeding: 0/90 (0) 90-d mortality: 3/90 (3.3)
Siragusa,[31] 2005	Prospective study of patients with active cancer	Italy	Academic (1)	36 among 68 patients referred for evaluation and diagnosed with symptomatic PE (52.9)	Thrombosis and Hemostasis Unit	Explicit protocol with exclusion criteria: Poor clinical condition or compliance, active bleeding or high risk of bleeding, renal insufficiency, acute anemia, pain requiring parenteral opioids, or concomitant illness requiring hospitalization	LMWH, VKA	Not reported	6-mo VTE recurrence: 2/36 (5.6) 6-mo major bleeding: 1/36 (2.8) 6-mo mortality: 11/36 (30.6)
Ong,[32] 2005	Retrospective	Australia	Academic (1)	60 among 194 patients diagnosed with PE (30.9)	Ambulatory Care Program	Explicit protocol with exclusion criteria: Hemodynamic instability, O_2 saturation < 90%, pain requiring IV opioids, active bleeding, concomitant illness that requires admission, likelihood of noncompliance, or lack of telephone, transport or home support	LMWH, VKA	Patients received daily visits by a nurse and once or twice a week by a physician at home or in the outpatient unit until stabilization	90-d VTE recurrence: 3/60 (5.0) 90-d major bleeding: 1/60 (1.7) 90-d mortality: 1/60 (1.7) 1/60 lost to follow-up
Kovacs,[34] 2000	Prospective	Canada	Academic (3)	81 among 158 patients referred for evaluation and diagnosed with symptomatic PE (51.3)	Outpatient Thrombosis Unit	Explicit protocol with exclusion criteria: Hemodynamic instability, pain needing IV opioids, O_2 requirement to maintain saturation > 90%, active bleeding or high risk for major bleeding, risk of noncompliance, or concomitant illness requiring hospitalization	LMWH, VKA	Patients received daily phone calls during the first week, then clinic visits at 1 wk, 1 mo and 3 mo	90-d VTE recurrence: 5/81 (6.2) 90-d major bleeding: 1/81 (1.2) 90-d mortality: 4/81 (4.9)

[a] Studies are presented in reverse annual chronology by study design (prospective, then retrospective) and size of PE cohort. We tried to contact corresponding authors of eligible studies if needed to identify Table variables not found in the studies.

[b] Patients seen in specialty clinics are most often a selected, referred population; eg, unstable ED patients with acute PE would generally not be discharged to a specialty clinic for definitive care.

[c] PESI variables and Hestia criteria are defined in Tables 4 and 5, respectively.

[d] Patients receiving VKA treatment underwent standardized serial laboratory monitoring, details of which are not reported in this Table.

[e] 513 = 550 minus 34 (hospitalized for NT-proBNP value) minus 3 (hospitalized outside protocol); results among the 513 patients were provided by the authors of the study.

bpm = beats per minute; DOAC = direct oral anticoagulant (also referred to as novel oral anticoagulant and non-vitamin-K oral anticoagulant); DVT = deep venous thrombosis; ED = Emergency Department; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; IV = intravenous; LMWH = low-molecular-weight heparin; NT-proBNP = N-terminal B-type natriuretic peptide; O_2 = oxygen; PE = pulmonary embolism; PESI = PE Severity Index; SBP = systolic blood pressure; sPESI: simplified PE Severity Index; VKA: vitamin K antagonists (eg, warfarin); VTE = venous thromboembolism; V/Q = ventilation-perfusion.