Outpatient Treatment of Low-risk Pulmonary Embolism in the Era of Direct Oral Anticoagulants: A Systematic Review

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ABSTRACT

Background: Clinical guidelines have supported outpatient treatment of low-risk pulmonary embolism (PE) since 2014, but adoption of this practice has been slow. Direct oral anticoagulant (DOAC) therapy for venous thromboembolism (VTE) is now as common as vitamin K antagonist treatment, but data are sparse regarding outcomes for patients with low-risk PE treated with DOACs as outpatients. We conducted a systematic review of literature on outcomes of outpatient management for PE, including comparisons to inpatient treatment and differences by anticoagulant class.

Methods: We searched Medline, Embase, PubMed, CENTRAL, clinicaltrials.gov, and ICTRN for studies published from January 1980 through February 2019 using a predefined strategy developed with a medical librarian. We included English-language randomized controlled trials (RCTs) and prospective nonrandomized trials (NRTs) of adult patients diagnosed with acute, symptomatic PE, and discharged from the emergency department or within 48 hours. Our primary outcome included four major adverse outcomes (all-cause mortality, PE-related mortality, recurrent VTE, and major bleeding) within 30 and 90 days. A preplanned subanalysis of high-quality studies assessed outcomes associated with different anticoagulation treatment classes.

Results: Our initial search identified 6,818 records, of which 12 studies (four RCT, eight NRT) with a total of 3,191 patients were included in the review. All RCTs and six NRTs were determined to have low to moderate risk of bias and were classified as high quality. Outpatients in these studies (n = 1,814) had rates of 90-day major adverse outcomes below 1%, including all-cause mortality (0.7%, 95% confidence interval [CI] = 0.4% to 1.2%), PE-related mortality (0.06%, 95% CI = 0.01% to 0.3%), recurrent VTE (0.8%, 95% CI = 0.5% to 1.4%), and major bleeding (0.8%, 95% CI = 0.5% to 1.4%). Exploratory analysis revealed no association between anticoagulant treatment class and rates of major adverse outcomes.

Conclusion: Among patients with low-risk PE treated as outpatients, few patients experienced major adverse outcomes such as mortality, recurrent VTE, or major bleeding within 90 days.

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Pulmonary embolism (PE) is a major cause of cardiovascular morbidity and mortality, with an estimated 300,000 to 600,000 cases and 100,000 deaths annually in the United States.[1] The reported mortality from PE is highly variable, and the exact death rate directly related to PE remains elusive.[2] The majority of patients with acute PE are hemodynamically stable and have 30-day mortality rates of approximately 4.7% to 5.4%.[3,4] Risk assessment models such as the Pulmonary Embolism Severity Index (PESI) score, the simplified PESI (sPESI) score, and the Hestia criteria can identify subsets of hemodynamically stable patients with acute PE whose risk of short-term mortality is even lower (0.5%–2.5%).[5–10] Data from multiple cohorts suggest that approximately 22% to 47% of hemodynamically stable patients with acute PE have a low risk using these validated rules or criteria.[9–12]

Clinical guidelines from professional societies including the American College of Emergency Physicians,[13] the American College of Chest Physicians,[14,15] and the European Society of Cardiology[16,17] suggest that outpatient management may be appropriate for select groups of patients with venous thromboembolism (VTE). However, use of outpatient-only treatment (e.g., without initial hospitalization) differs greatly between patients with PE and those with DVT alone. In a large systematic review of DVT treatment studies from 2006 to 2016, more than 40% of patients in the United States with DVT were treated on an outpatient basis,[18] while data suggest that only 8% to 10% of patients diagnosed with acute PE during a similar period were treated on an outpatient basis.[19,20]

Prior to the FDA clearance to market rivaroxaban and apixaban (and other direct acting anticoagulants [DOACs]) for the treatment of VTE, most patients in the United States with VTE were initially treated with low-molecular-weight heparins (LMWH) followed by months of treatment with either an oral vitamin K antagonist (VKA) such as warfarin or, in patients with malignancy, with continued subcutaneous LMWH. The limitations and problems of VKA treatment are well documented. From the patient perspective, an important advantage of DOACs is the lack of the need for frequent needlesticks.[21–25]

Direct oral anticoagulants have surpassed VKAs to become the leading outpatient therapy for VTE, with 65% to 82% of patients reportedly using DOACs instead of VKAs for VTE therapy during 2012 to 2017.[26,27] Early research suggests outpatient management of DVT in the United States has increased since the release of DOACs,[28] but similar research on management of PE is lacking. Despite the rapid shift in treatment from VKA to DOAC treatment, only one published randomized controlled trial (RCT) has used DOACs for outpatient treatment of PE.[29,30] However, since 2016 several prospective non-randomized trials (NRTs) have assessed outpatient treatment of PE with DOACs. The goal of this study was to systematically examine RCTs and NRTs on outpatient management of PE, including assessment of differences in outcomes based on anticoagulant class and treatment location.

METHODS

Data Sources

We systematically searched Medline, Embase, PubMed, CENTRAL, clinicaltrials.gov, and ICTRN for articles published from January 1, 1980, through February 19, 2019, using a predefined search strategy which was reviewed by a medical librarian (Data Supplement S1, Appendix S1, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.14108/full). We contacted several authors to acquire specific subsets of reported data, to identify relevant unpublished data or studies in press, or to follow-up on the progress of ongoing studies. We also hand-searched references from selected articles to identify sources missed by our review. The initial search was not limited based upon anticoagulant. The study was reviewed and approved by the Oregon Health & Science University Institutional Review Board.

Study Selection and Outcomes

Two independent reviewers (BCM, LF) screened the retrieved references for relevance based on title and abstracts alone. Disagreements were resolved through discussion, and full texts were retrieved for the remaining references. Both reviewers independently reviewed the retrieved full texts for eligibility. Reviewers were not blinded to authorship, journal name, or institution during data extraction. Data were extracted by a single reviewer (LF) and reviewed by a second reviewer (BCM) against the primary literature for accuracy.

We included English-language studies that prospectively enrolled adult patients who were diagnosed with

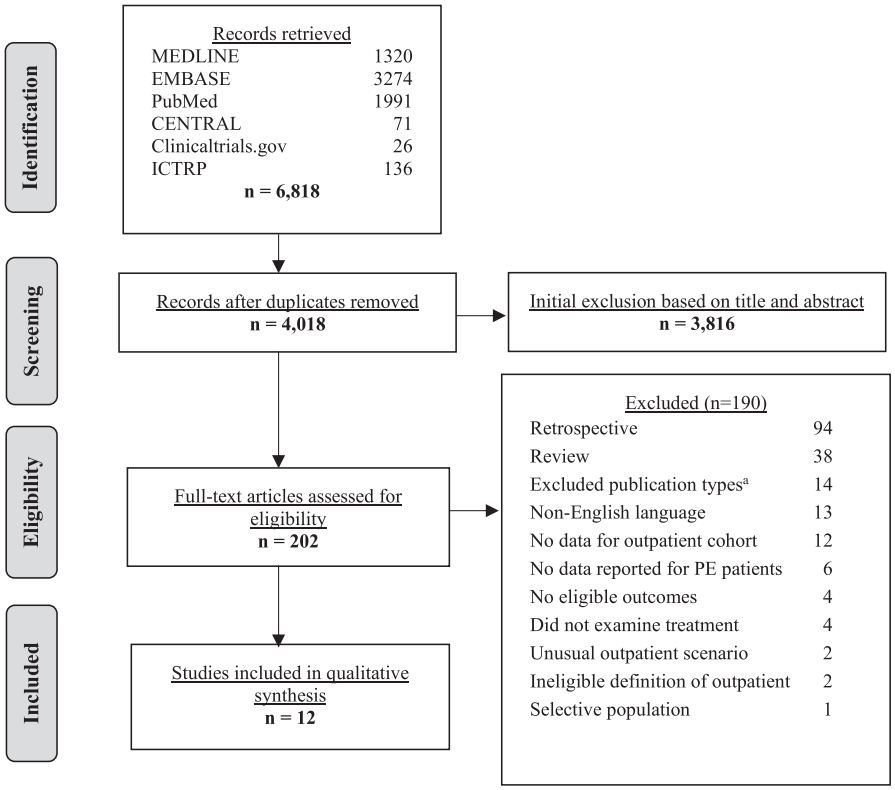

Figure 1. PRISMA flow diagram of the study selection process. [a]Editorials, letters to the editor, corrections, abstracts without required data (e.g., enrollment criteria, PE-specific outcomes, etc.), registered clinical trials without results. PE = pulmonary embolism.

acute, symptomatic PE and discharged either directly from the emergency department (ED) or within 48 hours. We included studies that reported any of seven outcomes, including four major adverse outcomes (all-cause mortality, PE-related mortality, recurrent VTE, and major bleeding) and three minor adverse outcomes (clinically relevant nonmajor bleeding [CRNMB], return visit to ED, and hospital readmission). Outcomes were reported as defined in each study, and we analyzed variation in outcomes based on differences in these definitions. Studies were assumed to have no PE-related mortality if they reported no all-cause mortality, and studies with any instances of all-cause mortality were assumed to have no PE-related mortality if all patient deaths were attributed to another specified cause (e.g., trauma). Eligible studies were required to report outcomes at 30 or 90 days after discharge. If a study reported 90-day outcomes and reported specific times (i.e., number of days after discharge) when each adverse event occurred, we calculated 30-day outcomes if they were not already reported.

Since prior systematic reviews on this topic identified few RCTs, all of which had uniformly small samples,[31] we decided a priori to include both RCTs and prospective NRTs in the review to better characterize the available evidence.[32] Retrospective studies, case reports, editorials, and other publication types were excluded. Eligible studies were required to include patients with radiographic confirmation of PE. We excluded studies about VTE prophylaxis, those that did not have a clearly defined outpatient cohort, and those limited to populations with specified comorbidities (e.g., cancer). We further excluded studies that included none of our specified outcomes as well as those without clearly defined inclusion and exclusion criteria. Finally, we excluded studies with unusual outpatient scenarios, such as hospital-in-the-home or a patient hotel.

Quality Assessment

Included studies were independently assessed for quality by two reviewers (LF and BCM), and differences were resolved through consensus. We used the Cochrane Collaboration ROB2 and ROBINS-I risk-of-bias tools to assess bias in RCTs and NRTs, respectively.[33,34] We defined high-quality studies based on (1) ROB2 classification of "low risk" or "some concerns" or by (2) ROBINS-I classification of "low" or "moderate" risk of bias; studies that did

Table 1
Study Design and Patient Characteristics of Included Studies

								Outpatient Cohorts						
Author	Year	Study Type	Country	Treat-ment	Sites	Patients, total (*n*)	Sex (% F)	Mean Age (Years)	Patients Assigned to Outpatient Treatment (*n*)	Discharge Criteria to Qualify as Outpatient Treatment	Met Discharge Criteria, *n* (%)	Active Malignancy, *n* (%)	Previous VTE, *n* (%)	Chronic Lung Disease, *n* (%)	Heart Failure, *n* (%)
Wells	2005	RCT	Canada	VKA	4	90	45.9	57.8	90	N/A*	N/A*	113 (22.4%)†	84 (16.6%)†	NR	NR
Agterof	2010	NRT	Netherlands	VKA	5	152	51.3	53.4	152	Within 24 hours of admission	152 (100%)	20 (13.2%)	23 (15.1%)	8 (5.3%)	1 (0.7%)
Zondag	2011	NRT	Netherlands	VKA	12	297	42	55	297	Within 24 hours of PE diagnosis	297 (100%)	28 (9.4%)	74 (24.9%)	11 (3.7%)	1 (0.3%)
Aujesky	2011	RCT	Switzerland, France, Belgium, United States	VKA	19	344	50.9	47	171	Within 24 hours of study enrollment	163 (95.3%)	1 (0.6%)‡	31 (18.1%)	7 (4.1%)	2 (1.2%)
Kline	2016	NRT	United States	DOAC	2	67	45	41.5	67	Discharge from ED (no time specified)	67 (100%)	7 (4.0%)†	NR	18 (7.1%)†	9 (3.6%)†
den Exter	2016	RCT	Netherlands	VKA	17	275	44.7	53	275	Within 24 hours of PE diagnosis	275 (100%)	14 (5.2%)	73 (26.5%)	14 (5.2%)	2 (0.7%)
Walen	2017	NRT	Netherlands	VKA	1	250	52.4	53.2	225	Within 24 hours of admission	221 (88.4%)	4 (1.6%)	NR	8 (3.2%)	1 (0.4%)
Elias	2018	NRT	United States	Multiple	1	55	29.1	62	55	Discharge from ED (no time specified)	55 (100%)	2 (3.6%)	NR	0 (0%)	0 (0%)
Bledsoe	2018	NRT	United States	Multiple	5	200	54	44	200	Within 24 hours of admission	200 (100%)	2 (1.0%)	43 (21.0%)	25 (12.5%)	2 (1.0%)
Vanni	2018	NRT	Italy	Multiple	4	547	53.9	76¶	178§	Within 48 hours of arrival to ED	N/A§	81 (45.5%)	27 (15.3%)	NR	NR
Peacock	2018	RCT	United States	DOAC	35	114	51.8	58.3	51	Within 24 hours of arrival to ED	51 (100%)	3 (5.9%)	10 (19.6%)	NR	1 (1.9%)
Barco	2019	NRT	Germany, Italy, Netherlands, Spain, Portugal, Finland, Greece	DOAC	49	525	45.7	56.7	525	Within 48 hours of arrival to ED	502 (95.6%)	32 (6.2%)	121 (23.4%)	26 (5.0%)	7 (1.3%)

DOAC = direct oral anticoagulant; ED LOS = emergency department length of stay; NR = not reported; NRT = nonrandomized trial; RCT = randomized controlled trial; VKA = vitamin K antagonist.
*Study was conducted an at outpatient clinic.
†Characteristics of full study cohort including patients with DVT but no PE.
‡May include patients with a history of malignancy but no active malignancy.
¶Median age.
§Study was observational; treatment cohort was not assigned. All patients discharged within 48 hours were deemed "outpatients."

Table 2
Outcomes Among Outpatient Cohorts

					Major Adverse Outcomes																				Minor Adverse Outcomes							
					All-cause Mortality				PE-related Mortality				Recurrent VTE				Major bleeding				CRNMB				ED Visits				Hospitalization			
					30 Days		90 Days		30 Days		90 Days		30 Days		90 Days		30 Days		90 Days		30 Days		90 Days		30 Days		90 Days		30 Days		90 Days	
Study	Type	Overall Risk of Bias	Year	*N*	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI	*n* (%)	95% CI
Wells	RCT	Moderate	2005	90	0	—	3 (3.3%)	1.1–9.3	0	—	0	—			2 (2.2%)	0.6–7.7	0	—	0	—									36 (21.1%)	15.6–27.8			18 (10.5%)	6.7–16.0
Aujesky			2011	171	0	—	1 (0.6%)	0.1–3.2	0	—	0	—	0	—	1 (0.6%)	0.1–3.2	2 (1.2%)	0.3–4.1	3 (1.8%)	0.6–5.0													
den Exter			2016	275			3 (1.1%)	0.4–3.2	1 (0.4%)	0.1–2.0	1 (0.4%)	0.1–2.0			3 (1.1%)	0.4–3.2			3 (1.1%)	0.4–3.2													
Peacock			2018	49	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—			1 (2.0%)	0.4–10.7									
Agterof	NRT	Moderate	2010	152	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—													
Zondag			2011	297	2 (0.7%)	0.2–2.4	3 (1.0%)	0.3–2.9	0	—	0	—	4 (1.4%)	0.5–3.4	6 (2.0%)	0.8–4.3	2 (0.7%)	0.2–2.4	2 (0.7%)	0.2–2.4			15 (5.1%)	2.9–8.2									
Kline			2016	67	0	—			0	—			0	—			0	—			1 (1.5%)	0.3–7.8			10 (14.9%)	8.3–25.4			1 (1.5%)	0.3–7.8			
Elias			2018	55	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—													
Bledsoe			2018	200	0	—	0	—	0	—	0	—	0	—	0	—	0	—	1 (0.5%)	0.1–2.8					32 (16.0%)	11–21			5 (3%)	1.0–5.7			
Barco			2019	525	0	—	2 (0.4%)	0.1–1.4	0	—	0	—	2 (0.4%)	0.1–1.4	3 (0.6%)	0.1–1.7	1 (0.2%)	0.03–1.1	2 (0.4%)	0.1–1.4			1 (0.2%)	0.03–1.1									43 (8.2%)	6.1–10.9
Walen		Serious	2017	250	1 (0.4%)	0.1–2.2	1 (0.4%)	0.1–2.2	0	—	0	—	0	—	0	—	2 (0.8%)	0.2–2.9											6 (2.4%)	1.1–5.1			
Vanni			2018	178	3 (1.7%)	0.4–4.9			1 (0.6%)	0.01–3.1			2 (1.1%)	0.1–4.0			0	—															

CRNMB = clinically relevant nonmajor bleeding.

not meet these qualifications were classified as lower quality.

Data Analysis

Our primary analysis reported the rates of adverse events among patients treated for PE on an outpatient basis, with results dichotomized both by study design and by quality. We planned a meta-analysis of RCTs to compare outcomes in patients with low risk who received outpatient or inpatient treatment; however, a Cochrane review on this topic was published shortly after our search began,[29] and as a result we opted to pursue the RCT meta-analysis only if our review identified RCTs not included in that review. Given the high likelihood of different underlying illness severity, we did not compare outcomes associated with inpatient and outpatient treatment among patients in NRTs.

Subgroup Analysis

We preplanned a subgroup analysis of outpatient cohorts from high-quality RCTs and NRTs to assess associations between anticoagulant treatment class and rates of the four major adverse outcomes; we also used a composite outcome defined as patient who experienced one or more of the major adverse outcomes. For this subgroup analysis, we performed an additional quality assessment of RCT outpatient cohorts using the ROBINS-I and selected domains from the Joanna Briggs Institute (JBI) checklist for nonrandomized experimental studies.[35] As an exploratory analysis, we used the Fisher's exact test to compare rates of major adverse outcome by anticoagulant treatment category.

RESULTS

Study Selection

Figure 1 shows the PRISMA flow diagram of our literature search.[36] We initially retrieved 6,818 articles, which were reduced to 4,018 after deduplication in EndNote X9.[37] A total of 3,816 articles were excluded during title/abstract review as irrelevant to our review, leaving 202 articles for full-text review. Of those, 12 articles were eligible for inclusion in the study analysis, and the reasons for excluding the other 190 articles are given in Figure 1. Table 1 lists the 12 eligible studies, which included four RCTs[30,38–40] and eight NRTs[7,25,41–46] that enrolled a total of 3191 patients. Six studies included use of DOACs, and only three used DOACs exclusively.

Table 3
Quality Assessment of Included Studies: RCTs

ROB2 Domains								
Author	Year	Overall Risk of Bias	Randomization	Deviation From Intended Interventions	Missing Data	Measurement of Outcomes	Selection of Reported Results
Wells	2005	Low	Low	Low	Low	Low	Low
Aujesky	2011	Low	Low	Low	Low	Low	Low
Den Exter	2016	Low	Low	Low	Low	Low	Low
Peacock	2018	Some concerns	Low	Some concerns	Low	Low	Low

RCTs = randomized controlled trials.

Table 4
Quality Assessment of Included Studies: NRTs

		ROBINS-I Domains								JBI Domains (Selected)			
Author	Year	Overall Risk of Bias	Confounding	Selection of Participants	Classification of Interventions	Deviations from Intended Interventions	Missing Data	Measurement of Outcomes	Selection of Reported Results	Q2: Were Patients in Comparison Groups Similar?	Q6: Was Follow-up Complete?	Q7: Were Outcomes of Comparison Participants Measured in the Same Way?	Q9: Was Appropriate Statistical Analysis Used?
Agterof	2010	Moderate	Moderate	Moderate	Low	Moderate	Low	Moderate	Low	N/A	Yes	N/A	Yes
Zondag	2011	Moderate	Moderate	Low	Low	Low	Low	Low	Low	N/A	Yes	N/A	Yes
Kline	2016	Moderate	Moderate	Low	Low	Low	Low	Moderate	Low	N/A	Yes	N/A	Yes
Walen	2017	Serious	Moderate	Serious	Serious	Moderate	Low	Moderate	Low	N/A	Yes	N/A	Yes
Elias	2018	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate	Yes	Yes	Yes	Yes
Bledsoe	2018	Moderate	Moderate	Moderate	Low	Moderate	Low	Low	Low	N/A	Yes	N/A	Yes
Vanni	2018	Serious	Serious	Serious	Moderate	Moderate	Low	Low	Serious	No	Yes	Yes	Yes
Barco	2019	Moderate	Moderate	Low	Low	Low	Low	Low	Low	N/A	Yes	N/A	Yes

JBI = Joanna Briggs Institute; NRTs = nonrandomized trials.

Patient Assessment. All studies required that eligible patients had radiographic evidence of PE, although only nine studies explicitly stated the criteria used to make this determination (Data Supplement S1, Appendix S2). Nine studies enrolled patients who were classified as low risk for adverse outcomes from PE, including five studies that used the Hestia rule[7,25,30,39,42] (or a variant) and four that used either PESI or sPESI.[38,43,44,46] The two earliest studies did not use validated PE risk stratification tools to select low-risk patients; no validated PE severity rules were in use at the time those studies was conducted.[40,41] However, both studies excluded patients with high-risk features such as active bleeding, recent stroke, renal failure, thrombocytopenia, hypotension, or hypoxia on room air. The single observational study in our review examined "daily clinical practice" in which decisions regarding patient disposition were made by the treating physician rather than by a study protocol; no consistent approach was used to identify patients who were considered safe for outpatient treatment.[45] This study had the highest reported rates of all-cause mortality, PE-related mortality, and recurrent VTE (Table 2).

Interventions. Eight studies defined outpatient treatment as discharge from the hospital within 24 hours. Two studies required that eligible patients were treated entirely as outpatients (either evaluated initially in an outpatient clinic[40] or discharged directly from the ED without additional observation[44]), and two studies allowed up to 48 hours of care before discharge.[42,45] Despite these concrete time limits, studies varied substantially in how these times were measured; two studies assessed this "discharge time" in relation to the time of the patient's initial presentation to the ED,[30,42] while other studies used the time at which PE was diagnosed,[7,39] the time at which the patient was enrolled in the study,[38] or the time at which the patient was admitted to the hospital or observation unit.[41,43,46] All four RCTs and five NRTs specified the type of anticoagulation treatment that enrolled patients would receive, while three NRTs deferred choice of anticoagulant to the treating physician.[43–45]

Comparisons. Of the four RCTs, only two directly compared inpatient and outpatient treatment for low-risk PE.[30,38] Another RCT compared outpatient treatment for all low-risk PE patients against a strategy in which (1) low-risk PE patients with an elevated normal N-terminal pro-B-natriuretic peptide (NT-

proBNP) level were admitted and (2) those with a normal NT-proBNP level were discharged.[39] The final RCT compared two types of outpatient LMWH treatment.[40] Seven of eight NRTs were prospective management studies with specified criteria that guided aspects of patient care such as treatment type or discharge timing,[7,25,41–44,46] including six studies with single-arm designs and one study that compared results from a prospective outpatient cohort to a retrospectively collected inpatient cohort.[44] The final NRT was solely observational and compared results from outpatient (defined as patients discharged within 48 hours) and inpatient (discharged in more than 48 hours) cohorts.[45]

Reported Outcomes. All eligible studies included data on each of the four major adverse outcomes (Data Supplement S1, Appendix S2). All-cause mortality, recurrent VTE, and major bleeding were reported by all 12 studies for at least one of our specified time intervals. Six studies reported PE-related mortality,[30,39,41,42,44,45] and we derived these outcomes for the six remaining studies based on reported all-cause mortality results. The three minor adverse outcomes were reported less often. One RCT[30] and three NRTs[7,25,42] studies reported CRNMB, one RCT[38] and two NRTs[25,43] reported ED visits, and one RCT[38] and four NRTs[25,42,43,46] reported hospital readmissions.

Quality Assessment

Tables 3 and 4 illustrate the quality assessment of the included studies. As shown in Table 2, three RCTs had low overall risk of bias[38–40] while one had moderate risk (classified as "some concerns" in ROB2 terminology).[30] Of the eight NRTs, six[7,25,41–44] had moderate overall risk of bias and two[45,46] had serious risk (using ROBINS-I terminology; Table 4). The most substantial risks for all NRTs came from potential confounding in single-arm study designs or from use of retrospective comparison cohorts. In addition, one study did not report characteristics of excluded patients,[46] and another study used no criteria to classify low-risk patients.[45]

Subgroup Analysis

Among the 10 high-quality studies, we examined the four major adverse outcomes after stratifying by type of outpatient anticoagulation treatment. This group was composed of 1,881 patients (1,018 LMWH/VKA, 863 DOAC), although denominators differed for individual outcomes based on outcomes and time intervals reported by each study. Among the 814 patients on DOAC treatment for whom a specific drug choice was reported, 790 (97%) received rivaroxaban and the remainder received apixaban. Outpatient cohorts from the four RCTs were evaluated using ROBINS-I and JBI tools as planned, and all four were judged to have only a moderate overall risk of bias (i.e., high quality) based on risk of confounding.

Patient Demographics and Comorbidities

Demographics of the outpatient cohorts are shown in Table 1. The average age of study participants varied from 41.5 years to 62 years, with the exception of one lower-quality study that enrolled patients with a median age of 76 years.[45] Patient comorbidity profiles across studies suggested low variation regarding a history of heart failure (range = 0%–3.6%, 10 studies) and moderate variation in rates of prior VTE (range = 15.1%–26.5%, nine studies) or chronic lung disease (range = 0%–12.5%, nine studies). In contrast, there was a very substantial difference across eligible studies regarding the prevalence of active malignancy: 10 studies reported a range of enrolled patients with malignancy between 0 and 13.2%, while two others (one RCT and one NRT) reported higher rates of 22.4 and 45.5%.

Clinical Outcomes

All-cause Mortality. As reported by individual studies, all-cause mortality was uncommon at both 30 days (range = 0%–1.7%, median = 0%, 11 studies) and 90 days (range = 0%–3.3%, median = 0.4%, 10 studies), as shown in Table 2. In the pooled analysis of high-quality studies (Table 5), we observed 30-day all-cause mortality rates of 0.3% (95% CI = 0.1% to 1.0%) and 0% among patients on VKA therapy and DOAC therapy, respectively. Pooled 90-day all-cause mortality was at or below 1% for patients treated with either VKA (1.0%, 95% CI = 0.5% to 1.8%) or DOAC (0.3%, 95% CI = 0.1% to 0.9) therapy. These differences were not statistically significant at either time point.

PE-related Mortality. Outpatient PE-related mortality was rare at both 30 days (range = 0%–0.6%, median = 0%, 12 studies) and 90 days (range = 0%–0.4%, median = 0%, 10 studies). In pooled analysis, we identified no statistically significant different in PE-

Table 5
Major Adverse Outcomes in Outpatient Cohorts from High-quality Studies, Stratified by Anticoagulant Class

Drug Class	All-cause Mortality			PE-related Mortality			Recurrent VTE			Major Bleeding			Any	
	Patients	Events (%)	95% CI	Patients	Events (%)	95% CI	Patients	Events (%)	95% CI	Patients	Events (%)	95% CI	Patients	Events (%)	95% CI
30-day outcomes															
VKA	743	2 (0.3%)	0.1–1.0	1,018	1 (0.1%)	0.02–0.6	653	4 (0.6%)	0.2–1.6	743	4 (0.5%)	0.2–1.4			
DOAC	863	0	—	863	0	—	796	2 (0.3%)	0.1–0.9	796	1 (0.1%)	0.02–0.7			
Total	1,606	2 (0.1%)	0.03–0.5	1,881	1 (0.05%)	0.01–0.3	1,449	6 (0.4%)	0.2–0.9	1,539	5 (0.3%)	0.1–0.8			
90-day outcomes															
VKA	1,018	10 (1.0%)	0.5–1.8	1,018	1 (0.1%)	0.02–0.6	1,018	12 (1.2%)	0.7–2.1	1,018	8 (0.8%)	0.4–1.6	1,018	28 (2.8%)	1.9–4.0
DOAC	796	2 (0.3%)	0.1–0.9	796	0	—	796	3 (0.4%)	0.1–1.2	796	7 (0.9%)	0.4–1.8	796	12 (1.5%)	0.9–2.6
Total	1,814	12 (0.7%)	0.4–1.2	1,814	1 (0.06%)	0.01–0.3	1,814	15 (0.8%)	0.5–1.4	1,814	15 (0.8%)	0.5–1.4	1,814	40 (2.2%)	1.3–3.0

DOAC = direct oral anticoagulant; PE = pulmonary embolism; VKA = vitamin K antagonist; VTE = venous thromboembolism.

related mortality at either 30 days (VKA 0.1% [95% CI = 0.02% to 0.6%] vs. DOAC 0%) or 90 days (VKA (0.1% [95% CI = 0.02% to 0.6%] vs. DOAC 0%).

Recurrent VTE. Ten studies rates of recurrent VTE at 30 days (range = 0%–1.4%, median = 0%) and 90 days (range = 0%–2.2%, median = 0.3%). When stratified by treatment type, pooled data from high-quality studies indicated recurrent VTE within 30 days among 0.6% (95% CI = 0.2% to 1.6%) of patients on VKA therapy and 0.3% (95% CI = 0.1% to 0.9%) of patients on DOAC therapy. At 90 days, rates of recurrent VTE were 1.2% (95% CI = 0.7% to 2.1%) for VKA and 0.4% (95% CI = 0.1% to 1.2%) for DOAC therapy. These comparisons were not statistically significantly different at either time point.

Major Bleeding. Reported rates of major bleeding within 30 days ranged from 0% to 1.2% (median = 0%) across 11 studies, while 90-day rates ranged from 0% to 1.8% (median = 0%) across nine studies (Table 2). Eleven studies used the definition of major bleeding from the International Society on Thrombosis and Haemostasis (ISTH),[47] while the remaining lower quality study defined major bleeding as "any bleeding described by the patient as severe."[46] The rate of 30-day major bleeding reported by this particular study (3.3%) was substantially higher than the next-highest study (1.2%).[38] Fortunately, the study in question also reported the subset of bleeding episodes that required hospitalization, and our Table 2 lists the reported rate of 30-day major bleeding among this subset of patients (0.8%) to improve consistency in outcomes reporting between this study and others in the review. In pooled analysis among high-quality studies, outpatients on VKA or DOAC therapy experienced statistically similar rates of major bleeding at both 30 days (VKA 0.5% [95% CI = 0.2% to 1.4%] vs. DOAC 0.1% [95% CI = 0.02% to 0.7%]) and at 90 days (VKA 0.8% [95% CI = 0.4% to 1.6%] vs. DOAC 0.9% [95% CI = 0.4% to 1.8%]; Table 5).

Composite Outcome of Major Adverse Events. For the composite outcome of major adverse outcomes at 90 days, we observed 28 major adverse outcomes among 1,018 patients on VKAs (2.8% [95% CI = 1.9% to 4.0%]) compared to 12 major adverse outcomes among 796 patients on

DOACs (1.5% [95% CI = 0.9% to 2.6%]). This difference was not statistically significant.

Minor Adverse Outcomes. The rate of CRNMB at 30 days was reported as 1.5% (one study), and three studies reported a wide range of CRNMB at 90 days (range = 0.2%–5.1%, median = 2.0%; Table 2) One of three studies used the ISTH definition for nonmajor bleeding.[48] In contrast, rates of ED visits and rehospitalization were more consistent across studies. Rates of ED visits within 30 days were similar across two studies (range = 14.9%–16.0%, median = 15.5%), and rates at 90 days were only slightly higher (21.1%) as reported by one study. Hospital readmission rates at 30 days ranged from 1.5% to 3.0% (median = 2.4%, three studies), and at 90 days the rates ranged from 8.2% to 10.5% (median = 9.4%, two studies).

DISCUSSION

This systematic review examined adverse outcomes among patients treated for PE on an outpatient basis. We have three major findings.

Few Controlled Studies

First, we identified few recent studies that used a control group to compare management strategies for low-risk PE, either across location (e.g., inpatient vs. outpatient) or anticoagulant class. In particular, RCTs on outpatient management of low-risk PE remain sparse. Of the eight studies in this review that were published since DOAC treatment became available in the United States, only two used a randomized study design. Of the NRTs included in our review, none used a prospectively identified control group.

More than 100,000 patients with PE could potentially be eligible for outpatient management each year in the United States. There is a substantial unmet need for high-quality randomized trial data on identifying these low-risk patients and optimizing their outpatient treatment. Fortunately, additional RCTs data may soon be available. The HOME-PE study (NCT02811237) is a RCT of patients with acute PE at 28 hospitals in Europe that compares Hestia criteria and simplified PESI score in regard to a composite 30-day outcome of mortality, recurrent VTE, and major bleeding.[49] Secondary outcomes will examine the proportion of patients managed as outpatients (defined as discharge home within 24 hours of study enrollment) as well as outcomes on patient safety, hospital length of stay, and patient satisfaction. The study was completed in October 2019, but no results were published as of June 2020. Additional randomized studies are warranted to examine the differences in treatment outcome based on the type and duration of anticoagulation.

Low Rates of Major Adverse Outcomes

Our second major finding is that major adverse outcomes were rare among the cohorts included in this review, especially in those without serious risk of bias. Pooled 90-day all-cause mortality was 0.7% among outpatients in high-quality studies, suggesting that physicians were generally successful at identify patients at low risk for short-term mortality who could be considered for outpatient treatment. There was a single instance of PE-related mortality within 90 days among the 1,814 outpatients (0.06%) in high-quality studies. While there is no consensus on an optimal approach to selecting patients with PE who are appropriate for outpatient treatment, the PESI, sPESI, and Hestia criteria all appear to select patients at low risk of short-term mortality.[5–7,50] Of the three studies that did not use a validated PE severity assessment tool, two studies reported the highest mortality rates (1.7% at 30 days and 3.3% at 90 days) of all studies in the review.[40,45] (The third study reported no mortality.) One of these two studies, the observational NRT which delegated disposition decisions to the treating physician, included an individual who died after requesting to be discharged early despite having high-risk features (i.e., right ventricular dilation) on imaging. Furthermore, all three patients in this study cohort that died during outpatient treatment would have been deemed high risk by PESI and sPESI (although not by Hestia criteria). Until the HOME-PE study and other investigations provide direct comparisons of PE-risk prediction tools, it seems reasonable to use either approach.

Major adverse outcomes other than mortality were also uncommon among studies in our review. A majority of included studies showed no episodes of recurrent VTE (7/10 studies) or major bleeding (7/11 studies) at 30 days, and cohorts that did have these adverse outcomes reported rates of 1.4% or less. These risks are similar to or lower than the rate of complications in other ED patients who are often treated on an outpatient basis, such as patients with undifferentiated chest pain and a HEART score of 1 to 3 (0.9%–1.7% risk of major adverse cardiac events

within 30 days),[51] patients with suspected transient ischemic attack who have an ABCD2 score of 1 to 3 (3.1% risk of stroke within 90 days),[52] or patients with community-acquired pneumonia who have a CURB-65 score of 0 or 1 (0.6%–2.7% mortality within 30 days).[53] These comparisons suggest that outpatient management of PE in appropriately selected patients remains a reasonable treatment option, even in the absence of RCT data.

Outcomes Associated With Anticoagulant Class

Our third and final major finding is that we identified no statistically significant association between anticoagulant treatment class and rates of major adverse events. These results are consistent with prior RCTs that compared rates of recurrent VTE between LMWH/VKA and DOAC anticoagulation regimens, although most of those trials assessed outcomes at time periods beyond 90 days.[21,22,54–56] The observed rates of major bleeding were also similar across classes of anticoagulation. This is consistent with other research which suggests similar bleeding outcomes for VKA and rivaroxaban, the far most common DOAC used in the included studies.[57,58] Prior research has found that treatment of acute VTE with apixaban is associated with lower rates of major bleeding in comparison to patients treated with either rivaroxaban or warfarin, but only 3% of patients in our study treated with a specified DOAC were given apixaban.[57,59]

Finally, several confounders could bias our results. For instance, there was substantial variation across studies in prevalence of cancer among outpatient cohorts, and the diagnosis of PE in the setting of malignancy is associated with much higher mortality than PE without associated malignancy.[60] DOACs are not recommended for use in patients with malignancy-associated VTE who have a high risk of bleeding,[61] and as a result our subgroup analysis (Table 5) could be confounded by this association between a high-risk condition and the type of drug treatment. In addition, the subgroup analysis in Table 5 could also suffer from confounding as it includes patient data from both RCTs and NRTs. Outcomes could be confounded by study-level differences in the type of testing and duration of observation that patients were eligible to receive prior to discharge; we suggest that future studies use a consistent standard of measuring these times in relation to a uniform and unmodifiable reference such as time of ED arrival. Rather than simply reporting a time interval before discharge, future research should assess the prognostic value of the additional diagnostic tests (e.g., echocardiography, lower-extremity compression ultrasound) that patients with low-risk PE may undergo in the ED or during these periods of observation. Emergency care researchers should prioritize future studies that assess the value of these diagnostic tests among patients with low-risk PE and measure efforts to implement expedited discharge pathways for these patients.[62]

LIMITATIONS

There are several important limitations to this study. First, despite the significant number of published studies on outpatient PE management in recent years, there remain little data from RCTs or high-quality two-arm NRTs to assess optimal patient selection or treatment approaches.

The second major study limitation is a lack of diversity in DOAC treatment regimens. Although apixaban is one of the most common treatments for VTE,[27] only two studies included in this review reported its use,[43,44] and in both cases it was used in a minority of patients. Third, our analysis was limited by a low number of adverse events. For instance, when comparing outcomes rates by drug treatment class, our composite 90-day outcome had the largest number observed events and nonetheless had low statistical power (power = 0.38) for this comparison.

CONCLUSION

Controlled trials of outpatient management for low-risk pulmonary embolism remain uncommon. Rates of all-cause and pulmonary embolism–related mortality at 30 days were consistently well below 1% in all high-quality studies in our review, suggesting that outpatient management is a safe option for appropriately selected patients with pulmonary embolism. Furthermore, rates of nonfatal adverse events among patients treated for low-risk pulmonary embolism on an outpatient basis appear similar to other conditions that are frequently diagnosed in EDs and treated without hospitalization. Finally, we identified no association between anticoagulant treatment class and rates of adverse outcomes, although this conclusion must be addressed in more rigorous (i.e., randomized) studies addressing a broader set of direct acting anticoagulants than used in prior research.

REFERENCES

1. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. Am J Prev Med 2010;38:S495–501.
2. Laporte S, Mismetti P, Decousus H, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. Circulation 2008;117:1711–1716.
3. Jiménez D, Bikdeli B, Barrios D, et al. Epidemiology, patterns of care and mortality for patients with hemodynamically unstable acute symptomatic pulmonary embolism. Int J Cardiol 2018;269:327–333.
4. Lin BW, Schreiber DH, Liu G, et al. Therapy and outcomes in massive pulmonary embolism from the Emergency Medicine Pulmonary Embolism in the Real World Registry. Am J Emerg Med 2012;30:1774–1781.
5. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005;172:1041–1046.
6. Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010;170:1383–1389.
7. Zondag W, Mos IC, Creemers-Schild D, et al. Outpatient treatment in patients with acute pulmonary embolism: the Hestia study. J Thromb Haemost 2011;9:1500–1507.
8. 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;13:111.
9. Yamashita Y, Morimoto T, Amano H, et al. Validation of simplified PESI score for identification of low-risk patients with pulmonary embolism: From the COMMAND VTE Registry. Eur Heart J Acute Cardiovasc Care 2018;204887261879999.
10. Wells P, Peacock WF, Fermann GJ, et al. The value of sPESI for risk stratification in patients with pulmonary embolism. J Thromb Thrombolysis 2019;48:149–157.
11. Aujesky D, Perrier A, Roy PM, et al. Validation of a clinical prognostic model to identify low-risk patients with pulmonary embolism. J Intern Med 2007;261:597–604.
12. Lankeit M, Jiménez D, Kostrubiec M, et al. Predictive value of the high-sensitivity troponin T assay and the simplified pulmonary embolism severity index in hemodynamically stable patients with acute pulmonary embolism. Circulation 2011;124:2716–24.
13. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Thromboembolic Disease; Wolf SJ, Hahn SA, et al. Clinical policy: critical issues in the evaluation and management of adult patients presenting to the emergency department with suspected acute venous thromboembolic disease. Ann Emerg Med 2018;71:e59–109.
14. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141:e419S–e496.
15. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149:315–52.
16. Mazzolai L, Aboyans V, Ageno W, et al. Diagnosis and management of acute deep vein thrombosis: a joint consensus document from the European Society of Cardiology working groups of aorta and peripheral vascular diseases and pulmonary circulation and right ventricular function. Eur Heart J 2018;39:4208–18.
17. 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 Heart J 2019;54:1901647.
18. Weeda ER, Butt S. Systematic review of real-world studies evaluating characteristics associated with or programs designed to facilitate outpatient management of deep vein thrombosis. Clin Appl Thromb Hemost 2018;107602961 8811082.
19. Singer AJ, Thode HC, Peacock WF. Admission rates for emergency department patients with venous thromboembolism and estimation of the proportion of low risk pulmonary embolism patients: a US perspective. Clin Exp Emerg Med 2016;3:126–31.
20. 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;175:1060–2.
21. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369:799–808.
22. EINSTEIN-PE Investigators, Büller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287–97.
23. Hokusai-VTE Investigators; Büller HR, Décousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013;369:1406–15.
24. Goldhaber SZ, Schellong S, Kakkar A, et al. Treatment of acute pulmonary embolism with dabigatran versus warfarin. Thromb Haemost 2016;116:714–21.
25. 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;10:561–9.
26. Nathan AS, Geng Z, Dayoub EJ, et al. Racial, ethnic, and socioeconomic inequities in the prescription of direct oral anticoagulants in patients with venous thromboembolism in the United States. Circ Cardiovasc Qual Outcomes 2019;12:e005600.
27. Lutsey PL, Walker RF, MacLehose RF, Alonso A, Adam TJ, Zakai NA. Direct oral anticoagulants and warfarin for venous thromboembolism treatment: trends from 2012 to 2017. Res Pract Thromb Haemost 2019;3:668–73.
28. Merli GJ, Hollander JE, Lefebvre P, et al. Rates of hospitalization among patients with deep vein thrombosis before and after the introduction of rivaroxaban. Hosp Pract (1995) 2015;43:85–93.
29. Yoo HH, Nunes-Nogueira VS, Fortes Villas Boas PJ, Broderick C. Outpatient versus inpatient treatment for acute pulmonary embolism. Cochrane Database Syst Rev 2019;(3):CD010019.
30. Frank Peacock W, Coleman CI, Diercks DB, et al. Emergency department discharge of pulmonary embolus patients. Acad Emerg Med 2018;25:995–1003.
31. Yoo HH, Queluz TH, El Dib R. Outpatient versus inpatient treatment for acute pulmonary embolism. Cochrane Database Syst Rev 2014;(11):CD010019.
32. Valentine JC, Thompson SG. Issues relating to confounding and meta-analysis when including non-randomized studies in systematic reviews on the effects of interventions. Res Synth Methods 2013;4:26–35.
33. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
34. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019:l4898.
35. The Joanna Briggs Institute. Checklist for Quasi-Experimental Studies (non-randomized experimental studies). 2017. Available at: https://joannabriggs.org/sites/default/files/2019-05/JBI_Quasi-Experimental_Appraisal_Tool2017_0.pdf. Accessed Mar 10, 2020
36. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine 2009;6:e1000097.
37. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. J Med Libr Assoc 2016;104:240–3.
38. 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;378:41–8.
39. Den Exter PL, Zondag W, Klok FA, et al. Efficacy and safety of outpatient treatment based on the hestia clinical decision rule with or without N-terminal pro-brain natriuretic peptide testing in patients with acute pulmonary embolism: a randomized clinical trial. Am J Respir Crit Care Med 2016;194:998–1006.
40. 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;165:733–8.
41. 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;8:1235–41.
42. Barco S, Schmidtmann I, Ageno W, et al. 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 2020;41:509–18.
43. 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;154:249–256.
44. Elias DJ, Beneze A, Waalen J, Averell PM, Dworsky D. Outpatient Management and Early Discharge Compared to Standard Care in Patients with Acute Pulmonary Embolism in a Southern California Teaching Hospital. American Thoracic Society 2018 International Conference; San Diego, CA, 2018.
45. Vanni S, Becattini C, Nazerian P, et al. Early discharge of patients with pulmonary embolism in daily clinical practice: a prospective observational study comparing clinical gestalt and clinical rules. Thromb Res 2018;167:37–43.
46. Walen S, Katerberg B, Boomsma MF, van den Berg JW. Safety, feasibility and patient reported outcome measures of outpatient treatment of pulmonary embolism. Thromb Res 2017;156:172–6.
47. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692–4.
48. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S; Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015;13:2119–26.
49. Roy PM, Gable B.Hospitalization or Out-treatment ManagEment of Patients With Pulmonary Embolism: a Randomized Controlled Trial (HOME-PE). Updated Aug 15, 2018. Available at: https://clinicaltrials.gov/ct2/show/NCT02811237. Accessed Oct 24, 2019

50. Weeda ER, Kohn CG, Peacock WF, et al. External validation of the Hestia criteria for identifying acute pulmonary embolism patients at low risk of early mortality. Clin Appl Thromb Hemost 2017;23:769–74.
51. Mahler SA, Riley RF, Hiestand BC, et al. The HEART Pathway randomized trial: identifying emergency department patients with acute chest pain for early discharge. Circ Cardiovasc Qual Outcomes 2015;8:195–203.
52. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007;369:283–92.
53. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003;58:377–82.
54. Goldhaber SZ, Schellong S, Kakkar A, et al. Treatment of acute pulmonary embolism with dabigatran versus warfarin. A pooled analysis of data from RE-COVER and RE-COVER II. Thromb Haemost 2016;116:714–21.
55. Hokusai VT, Buller HR, Decousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013;369:1406–15.
56. 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;(6):CD010957.
57. Lutsey PL, Zakai NA, MacLehose RF, et al. Risk of hospitalised bleeding in comparisons of oral anticoagulant options for the primary treatment of venous thromboembolism. Br J Haematol 2019;185:903–11.
58. van Es N, Coppens M, Schulman S, Middeldorp S, Buller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood 2014;124:1968–1975.
59. Aryal MR, Gosain R, Donato A, et al. Systematic review and meta-analysis of the efficacy and safety of apixaban compared to rivaroxaban in acute VTE in the real world. Blood Adv 2019 3:2381–7.
60. Gussoni G, Frasson S, La Regina M, Di Micco P, Monreal M. Three-month mortality rate and clinical predictors in patients with venous thromboembolism and cancer. Findings from the RIETE registry. Thromb Res 2013;131:24–30.
61. Khorana AA, Noble S, Lee AY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. J Thromb Haemost 2018;16:1891–4.
62. 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;26:657–69.

Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.14108/full

Data Supplement S1. Supplemental material.