Trends in Initial Anticoagulation Among US Patients Hospitalized With Acute Pulmonary Embolism 2011-2020

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Study objective: Guidelines recommend low-molecular-weight heparin (LMWH) and direct oral anticoagulants (DOACs) rather than unfractionated heparin (UFH) for treatment of acute pulmonary embolism (PE) given their efficacy and reduced risk of bleeding. Using data from a large consortium of US hospitals, we examined trends in initial anticoagulation among hospitalized patients diagnosed with acute PE.

Methods: We conducted a retrospective study of inpatient and observation cases between January 1, 2011, and December 31, 2020, among individuals aged more than or equal to 18 years treated at acute care hospitals contributing data to the Premier Healthcare Database. Included cases received a diagnosis of acute PE, underwent imaging for PE, and received anticoagulation at the time of admission. The primary outcome was the initial anticoagulant selected for treatment.

Results: Among 299,016 cases at 1,045 hospitals, similar proportions received initial treatment with UFH (47.4%) and LMWH (47.9%). Between 2011 and 2020, the proportion of patients initially treated with UFH increased from 41.9% to 56.3%. Over this period, use of LMWH as the initial anticoagulant was reduced from 58.1% in 2011 to 37.3% in 2020. The proportion of cases admitted to the ICU, treated with mechanical ventilation or vasopressors, and inpatient mortality were stable. Factors most strongly associated with receipt of UFH were admission to the ICU (odds ratio [OR] 6.90; 95% confidence interval [CI] 6.31 to 7.54) or step-down unit (OR 2.30; 95% CI 2.16 to 2.45), receipt of thrombolysis (OR 4.25; 95% CI 3.09 to 5.84) or vasopressors (OR 1.83; 95% CI 1.32 to 2.54), and chronic renal disease (OR 1.67; 95% CI 1.54 to 1.81).

Conclusions: Despite recommendations that LMWH and DOACs be considered first-line for most patients with acute PE, use of UFH is common and increasing. Further research is needed to elucidate factors associated with persistent use of UFH and opportunities for deimplementation of low-value care. [Ann Emerg Med. 2024;■:1-12.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Approximately 0.2% of all emergency department (ED) visits in the United States result in a diagnosis of pulmonary embolism (PE). The majority of these patients end up hospitalized.[1,2] Dating back to the 1940s, anticoagulation, the foundation of acute venous thromboembolism treatment, was initiated with unfractionated heparin (UFH).[3] Although intravenous UFH has the advantage of a short duration of action, making it quick to wear off in the event of bleeding, it has unpredictable pharmacokinetics. Use of UFH requires monitoring of activated partial thromboplastin times (aPTTs) or antifactor Xa levels.[4] Studies of patients with PE treated with UFH have found that only 22% to 25% of levels are in the therapeutic range, which can result in delays to adequate anticoagulation as well as increased risk of bleeding.[5-7] This is of particular concern given that delay in achieving therapeutic aPTTs is associated with increased inhospital and 30-day mortality.[8]

In contrast, low-molecular-weight-heparins (LMWH) have more predictable pharmacokinetics and do not require routing monitoring in most patients.[9] A number of trials have demonstrated that use of LMWH result in reduced risks of major hemorrhage and recurrence of venous thromboembolism compared with UFH in the initial treatment of venous thromboembolism.[10-12] Added to those benefits is reduced risk of heparin-

Editor's Capsule Summary

What is already known on this topic

Multiple guidelines recommend low-molecular-weight heparin (LMWH) over unfractionated heparin as first-line anticoagulation for acute pulmonary embolism (PE).

What question this study addressed

How has the initial emergency department choice of PE anticoagulant changed over time?

What this study adds to our knowledge

In this retrospective multicenter analysis of 299,016 cases of acute PE at 1,045 hospitals from 2011 to 2020, the use of unfractionated heparin has increased and is now more frequent than LMWH.

How this is relevant to clinical practice

This increasing use of unfractionated heparin rather than LMWH is not concordant with multiple PE guidelines.

induced thrombocytopenia. In light of these findings, beginning in 2012 professional society guidelines began recommending LMWH (or fondaparinux) instead of UFH as the initial, preferred anticoagulant for most patients with acute PE.[13-15]

Importance

Little is known about anticoagulation prescribing practices at the time of hospitalization for patients with acute PE in the United States. A multinational registry study including 23,858 individuals with PE found that between 2001 and 2013, use of LMWHs and DOACs increased and UFH decreased.[16] Most of these cases were treated at hospitals in Europe. Treatment patterns for PE vary internationally; thus, it is unclear if these trends exist within the United States. Given the general unfavorable safety and efficacy profiles for UFH and the multiple society guidelines supporting alternative anticoagulants in most clinical situations, we sought to investigate use of anticoagulants for patients hospitalized with acute PE in routine clinical care settings.

Goals of This Investigation

This study seeks to assess trends in initial anticoagulation treatment of patients hospitalized with a new diagnosis of PE.

MATERIALS AND METHODS

Study Design and Setting

We conducted a retrospective trends study using data from 1,045 acute care hospitals in the United States that contributed to the Premier Healthcare Database (Premier, Inc) between January 1, 2011, and December 31, 2020. The Premier Healthcare Database is a comprehensive, voluntary all-payer deidentified database containing approximately 20% of all US hospitalizations each year. Participating hospitals contribute data on all available patient encounters during the period in which they contribute to the Premier Healthcare Database. The database is a product of Premier, Inc, an alliance of more than 1,041 hospitals in the United States. The Premier Healthcare Database contains the elements found in Uniform Billing 04 form as well as an itemized, day-stamped log of all items and services charged to the patient or the insurer, including medications, diagnostic and therapeutic services, and laboratory tests. Although contributors are largely representative of acute care hospitals in the United States, on average they have somewhat more licensed beds, are more likely to be located in urban settings, and to be teaching hospitals. Through a data validation and audit process, Premier returns missing and invalid data to participating hospitals for correction before incorporating into the final database. As a result, missing data are minimal with less than 1% of data missing for most elements and less than 0.01% of data missing for key elements, such as demographics and diagnostic information.[17] Additional details on the Premier Healthcare Database can be found in the Appendix E1 (available at http://www.annemergmed.com). The study was considered nonhuman subjects research by the institutional review board at Baystate Medical Center and therefore exempt from full review. This study reports findings in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (Appendix E1).[18]

Selection of Participants

We included patients aged equal to or older than 18 years of age hospitalized between January 1, 2011, and December 31, 2020 for an inpatient or observation stay if they received a diagnosis of PE (International Classification of Diseases Clinical Modification [ICD] diagnosis code for PE in any position; Table E1, available at http://www.annemergmed.com).[19-21] To increase the probability that patients included in the study represent those with acute PE, we limited the cohort to cases with one or more charges for a diagnostic test for PE (computed tomography or

ventilation-perfusion scan) on the day of arrival to the hospital or the subsequent day (Table E1) and a charge for at least one therapeutic dose of anticoagulation on day 0/1 (Table E2, available at http://www.annemergmed.com).[22,23] We excluded patients with a diagnosis of deep venous thrombosis or PE in the 90 days prior to the index admission, those with a diagnosis of chronic PE, patients transferred in and/or out of acute care hospital, and those admitted to a hospice bed (Table E3, available at http://www.annemergmed.com). Due to their potential influence on anticoagulation choice, we excluded patients with a diagnosis of pregnancy, bleeding, or acute coronary syndrome on admission.[19,24,25]

Measurements

For each admission, we extracted demographics and insurance coverage. The Premier Health Database categorizes race and ethnicity data as White, Black, or Other and has an additional Hispanic indicator variable. We created a composite race and ethnicity variable with the following categories: non-Hispanic White, non-Hispanic Black, non-Hispanic Other, and Hispanic (any race). Comorbidities and organ failure were assessed using the Elixhauser comorbidity software.[26] Additionally, we used several approaches to characterize the severity of illness. We assessed acute organ failure at the time of hospitalization using present on admission codes.[19,27] We used a combination of ICD-9/10 procedure codes (ICD-9/10-PCS) and daily professional charges to classify respiratory support including invasive mechanical ventilation, noninvasive ventilation, and high-flow nasal cannula use (Table E4, available at http://www.annemergmed.com).[28] Additionally, we used pharmacy charges to assess receipt of vasopressors. We classified "aggressive PE treatment" as the presence of current procedural terminology (CPT) codes and/or pharmacy charges for systemic thrombolysis (alteplase, tenecteplase), embolectomy, or catheter-directed treatments.[19] For each hospital, we abstracted the number of beds (categorized as less than 200, 200 to 400, and more than 400 beds), teaching status (yes/no), geographic region, and whether it served a rural population (yes/no). The Premier Healthcare Database assigns hospital characteristics based on a combination of self-report and the American Hospital Association Annual Survey Database. Geographic regions are determined by census tracts and urban and rural designations are based on census designations. Missing data were excluded.

Outcomes

The primary study outcome was the initial anticoagulant received by the patient. Because ED encounters often extend past midnight (when hospital days are counted), we assessed initial medication administration on the day of hospital arrival or the subsequent hospital day (days 0/1). We used information about dose and frequency to differentiate therapeutic anticoagulation from prophylaxis (Table E2). Initial exposure to UFH was classified by the presence of pharmacy charge codes for a bolus/infusion dose of UFH on day 0/1, regardless of whether the patient received a dose of another anticoagulant. Patients were considered to have initial exposure to LMWH if they had a charge for a therapeutic dose of a LMWH, but did not receive a bolus/infusion dose of UFH. These patients may have also received an oral anticoagulant. Patients were classified as receiving initial treatment with an oral anticoagulant if they had a pharmacy charge code for an oral anticoagulant but did not receive a therapeutic dose of either UFH or LMWH on day 0/1. Secondary outcomes included proportion of hospital days on UFH, bleeding, receipt of blood transfusion or anticoagulation reversal agent, hospital length of stay, and inhospital mortality. Bleeding was defined by the presence of ICD-10 codes (Table E5, available at http://www.annemergmed.com) during the index hospitalization consistent with bleeding.[19,24,25,29,30] Pharmacy charges were used to identify red blood cell transfusion (receipt of any amount was classified as a transfusion) and reversal agents (protamine sulfate, vitamin K, prothrombin complex concentrate, andexanet alfa, and idarucizumab).

Analysis

We calculated descriptive statistics, including frequencies and proportions for categorical factors and means and percentile distributions or medians and interquartile range (IQR) for continuous factors. Using the full cohort, we also report on trends in number of days of treatment for UFH and LMWH each year and describe changes in anticoagulation from admission to discharge by generating a Sankey diagram. For the primary analysis in which we evaluated trends over time, we plotted the proportion of patients initially treated with UFH, LMWH, or DOACs by year. To evaluate the relative change over time in the choice of initial anticoagulation while accounting for changes in cohort composition over time, we then calculated an adjusted probability of receiving UFH as the initial anticoagulant. We modeled the use of UFH as the initial choice of anticoagulation versus any other, including year as a categorical factor, using hierarchical generalized linear models with a logit link, including hospital-level random effects to account for clustering within hospitals. Models adjusted for sex, race and ethnicity, insurance, comorbidities related to treatment

of PE (renal dysfunction, coagulopathy, malignancy, chronic pulmonary disease, and congestive heart failure), acute organ failure present on admission (renal, hematologic, cardiovascular, and respiratory), admission level of care, and respiratory support on initial hospital day, receipt of vasopressors on initial hospital day, and systemic thrombolysis on initial hospital day. We chose these covariates a priori as they are associated with treatment choice and disease severity.[19]

In a secondary analysis, we aimed to identify contemporary factors associated with receipt of UFH (versus another anticoagulant) as the initial anticoagulant agent. We restricted this analysis to data from 2019, which represented the most recent year before the coronavirus disease 2019 pandemic. We used hierarchical generalized linear models with a logit link and hospital-level random effects to account for clustering within hospitals. We adjusted for factors determined a priori to be associated with anticoagulation choice and PE severity.[19] These covariates included age, race and ethnicity, insurance, comorbidities related to treatment of PE (renal dysfunction, coagulopathy, malignancy, chronic pulmonary disease, and congestive heart failure), acute organ failure present on admission (renal, hematologic, cardiovascular, respiratory), admission level of care, respiratory support on initial hospital day, receipt of vasopressors on initial hospital day, and systemic thrombolysis on initial hospital day. We also adjusted for hospital-level covariates including bed size, teaching status, geographic region, and rural status.

We conducted a sensitivity analysis to assess unadjusted trends in initial anticoagulant exposure in which we considered a patient to have received therapeutic anticoagulation regardless of dose. All analyses were conducted using SAS 9.4 (SAS Institute, Inc).

RESULTS

Characteristics of Study Subjects

Between 2011 and 2020 a total of 299,016 cases were included in our analysis (Figure 1, Table E6, available at http://www.annemergmed.com), of which 95.9% had an ED billing code. Patient and hospital characteristics of the entire cohort as well as samples from 2011, 2015, and 2019 are presented in Table 1. Among the entire cohort, the median age was 63 years (IQR 50 to 74), and approximately half of the patients were women (51.6%). Medicare was the most common primary payer (50.9%), and 29.6% of cases had commercial insurance. Chronic pulmonary disease was present in 25.8% of the sample, 16.2% had congestive heart failure, and 11.1% had chronic renal disease. The proportion of patients with a diagnosis of acute respiratory failure at the time of admission increased throughout the study period from 15.6% in 2011 to 21.1% in 2019. The proportion of patients with a diagnosis of acute renal failure more than doubled from 5% (n=862) in 2011 to 10.6% (n=4,069) in 2019.

Trends in Anticoagulant Use

Over the study period, we observed a gradual but steady increase in the use of UFH at the time of admission, increasing from 41.9% in 2011 to 56.3% in 2020 (Figure 2, Table E7, available at http://www.annemergmed.com). Conversely, the proportion of cases initially treated with LMWH decreased from 58.1% in 2011 to 37.3% in 2020. Initial treatment with a DOAC increased from 0% in 2011 to 6.4% in 2020. When adjusted for changes in patient and hospital characteristics, trends in treatment with heparin and LMWH were similar to the unadjusted values (Table E8, available at http://www.annemergmed.com). When compared with 2011, the adjusted odds of receiving LMWH decreased throughout the study period from an adjusted odds ratio (aOR) of 1.14 (95% CI 1.08 to 1.19) in 2012 to a nadir of aOR 0.41 (95% CI 0.39 to 0.43) in 2020 (Table E9, available at http://www.annemergmed.com). Cases initially treated with UFH spent a median of 60% of their hospital days on UFH. Those initiated on LMWH spent a greater proportion of their hospital days on LMWH although this decreased throughout the study period from 74.0% of hospital days in 2011 to 65.2% in 2020 (Table E7). In a sensitivity analysis that included 327,955 cases in which we did not attempt to differentiate between therapeutic and prophylactic doses of anticoagulants, we observed similar trends in initial anticoagulant management (Table E10, available at http://www.annemergmed.com).

Predictors of UFH Use

In 2019, 38,314 cases from 770 participating hospitals were included in a secondary analysis. The median age was 64 years (IQR 51 to 75), and 51.3% were women. Chronic pulmonary disease was present in 26.4%, congestive heart failure in 18.7%, and 13.1% of cases had a history of chronic renal disease (Table 1). In 2019, 54.9% of cases had initial exposure to UFH, compared with 42.3% who had initial exposure to LMWH (Table E7). The patient factors most strongly associated with receipt of UFH rather than another anticoagulant included admission to ICU (aOR 6.90; 95% CI 6.31 to 7.54), receipt of systemic thrombolysis or vasopressors on day 0/1 (aOR 4.25; 95% CI 3.09 to 5.84 and aOR 1.83; 95% CI 1.32 to 2.54,

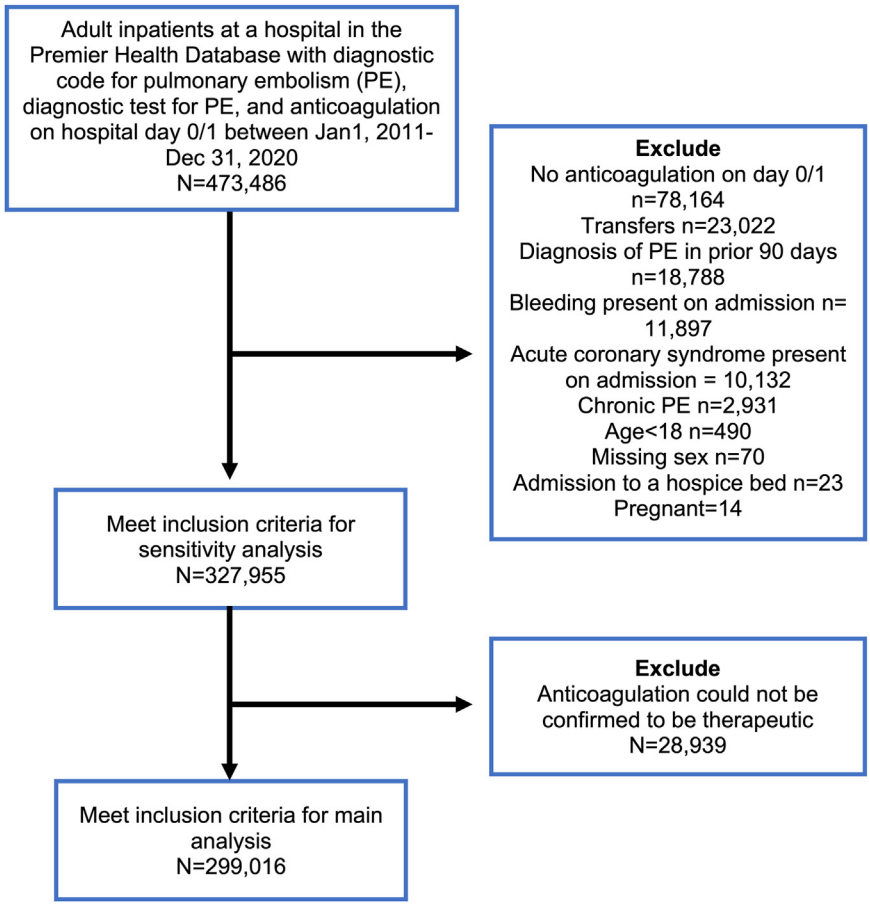

Figure 1. Study cohort.

respectively), admission to a step-down unit (OR 2.30; 95% CI 2.16 to 2.45), chronic renal disease (OR 1.67; 95% CI 1.54 to 1.81), and acute renal failure on admission (OR 1.60; 95% CI 1.46 to 1.75). Individuals with a coagulopathy comorbidity were more likely to receive initial treatment with UFH, whereas those with malignancy or chronic pulmonary disease were less likely to receive UFH on admission. Individuals treated at hospitals in the Northeast were more likely to be treated with UFH (OR 1.62; 95% CI 1.11 to 2.37), whereas those treated at smaller (less than 200 beds), nonteaching, and rural hospitals were less likely to receive initial treatment with UFH (Table 2).

Secondary Outcomes

Secondary outcomes are reported in Table 3. The median hospital length of stay was 3 days (IQR 2 to 5). This value declined from 4 days (IQR 3 to 6) in 2011 to 3 days (IQR 2 to 5) in 2019. Inhospital mortality occurred in 2.4% (n=7,323) of the overall cohort and did not change throughout the study period (2.4% in 2011; 2.3% in 2015; and 2.4% in 2019). Changes in choice of anticoagulant occurred throughout the hospitalization. Most patients were eventually transitioned to oral anticoagulation with a minority receiving a LMWH on their final hospital day (Figure 3). Although the proportion of individuals with a diagnosis of bleeding increased from 1.5% in 2011 to 3.1% in 2019, the proportion of cases receiving blood transfusions remained stable, whereas use of anticoagulation reversal agents declined from 2.5% in 2011 to 0.7% in 2019.

LIMITATIONS

Our results should be interpreted in light of several limitations. First, we relied on enhanced administrative data to assess diagnoses, comorbidities, organ failure, treatments, and other outcomes. During the time-period studied, coding classifications changed from ICD-9 to ICD-10. Throughout this same period many hospitals undertook initiatives to improve documentation and coding of comorbidities and severity of illness. These two factors may explain why we observed increases in some

Table 1. Characteristics of patients hospitalized with acute PE between 2011 and 2020.

Case Characteristic	2011 Number (%)	2015 Number (%)	2019 Number (%)	All years (2011-2020) Number (%)
Number of cases	17,090	30,099	38,314	299,016
Age (median; IQR)	62 (49-74)	63 (50-74)	64 (51-75)	63 (50-74)
Female	8,956 (52.4)	15,431 (51.3)	19,669 (51.3)	154,173 (51.6)
Race and ethnicity				
Black	2,616 (15.3)	4,389 (14.6)	6,878 (18)	48,573 (16.2)
Hispanic	727 (4.3)	1,012 (3.4)	2,049 (5.4)	13,239 (4.4)
Other	1,671 (9.8)	1,826 (6.1)	2,206 (5.8)	19,392 (6.5)
White	12,076 (70.7)	22,872 (76)	27,181 (70.9)	217,812 (72.8)
Primary payer				
Medicare	8,225 (48.1)	15,181 (50.4)	20,028 (52.3)	152,148 (50.9)
Commercial	5,409 (31.7)	9,077 (30.2)	10,785 (28.2)	88,412 (29.6)
Medicaid	1,449 (8.5)	3,629 (12.1)	4,603 (12)	33,819 (11.3)
Uninsured	1,236 (7.2)	1,169 (3.9)	1,698 (4.4)	14,694 (4.9)
Other/Unknown	771 (4.5)	1,043 (3.5)	1,200 (3.1)	9,943 (3.3)
Comorbidities				
Pulmonary disease	4,058 (23.7)	7,923 (26.3)	10,132 (26.4)	77,158 (25.8)
Congestive heart failure	2,159 (12.6)	4,584 (15.2)	7,153 (18.7)	48,463 (16.2)
Malignancy	2,455 (14.4)	4,341 (14.4)	6,056 (15.8)	44,337 (14.8)
Renal	1,211 (7.1)	3,184 (10.6)	5,020 (13.1)	33,258 (11.1)
Coagulopathy	1,069 (6.3)	2,206 (7.3)	3,891 (10.2)	26,432 (8.8)
Acute organ failures present on admission				
Respiratory failure	2,669 (15.6)	6,295 (20.9)	8,097 (21.1)	59,574 (19.9)
Renal failure	862 (5)	2,456 (8.2)	4,059 (10.6)	26,428 (8.8)
Cardiovascular failure	670 (3.9)	1,433 (4.8)	1,810 (4.7)	13,067 (4.4)
Hematologic failure	789 (4.6)	1,195 (4)	702 (1.8)	8,787 (2.9)
Admission level of care				
Ward	6,972 (40.8)	12,783 (42.5)	18,311 (47.8)	133,124 (44.5)
Step down	7,007 (41)	12,245 (40.7)	13,551 (35.4)	115,732 (38.7)
ICU	3,111 (18.2)	5,071 (16.9)	6,452 (16.8)	50,160 (16.8)
Received advanced treatment for PE				
Systemic thrombolytics on day 0/1	146 (0.9)	233 (0.7)	241 (0.6)	2,094 (0.7)
Any systemic thrombolytic during hospital stay	276 (1.6)	384 (1.3)	354 (0.9)	3,430 (1.1)
Catheter-directed treatment during hospital stay	71 (0.4)	173 (0.6)	406 (1.1)	2,442 (0.8)
Markers of severity of illness				
Vasopressor on day 0/1	191 (1.1)	304 (1)	4.7 (1.1)	3,217 (1.1)
Vasopressors	534 (3.1)	830 (2.8)	1,316 (3.4)	9,461 (3.2)
Invasive mechanical ventilation	347 (2.0)	530 (1.8)	893 (2.3)	6,194 (2.1)
Invasive mechanical ventilation	660 (3.9)	1,040 (3.5)	1,487 (3.9)	11,292 (3.8)
Noninvasive ventilation on day 0/1	487 (2.8)	1,109 (3.7)	1,825 (4.8)	11,792 (3.9)
Noninvasive ventilation	1,022 (6)	2,117 (7)	3,249 (8.5)	22,341 (7.5)
High-flow nasal cannula on day 0/1	6 (0)	46 (0.2)	106 (0.3)	631 (0.2)
High-flow nasal cannula	38 (0.2)	144 (0.5)	248 (0.6)	1,752 (0.6)

Table 1. Continued.

Case Characteristic	2011 Number (%)	2015 Number (%)	2019 Number (%)	All years (2011-2020) Number (%)
Hospital characteristics (N)	481	725	770	1,045
Bed size				
(>400)	6,764 (39.6)	11,892 (39.5)	15,231 (39.8)	121,731 (40.7)
(200-400)	6,459 (37.8)	11,651 (38.7)	13,696 (35.8)	108,818 (36.4)
(<200)	3,867 (22.6)	6,556 (21.8)	9,387 (24.5)	68,467 (22.9)
Region				
South	8,880 (52)	13,395 (44.5)	17,687 (46.2)	139,015 (46.5)
Midwest	3,665 (21.5)	7,186 (23.9)	9,836 (25.7)	71,400 (23.9)
West	2,855 (16.7)	6,919 (23)	5,320 (13.9)	52,334 (17.5)
Northeast	1,690 (9.9)	2,599 (8.6)	5,471 (14.3)	36,267 (12.1)
Population served				
Urban	14,996 (87.8)	26,559 (88.2)	33,495 (87.4)	261,477 (87.5)
Rural	2,094 (12.3)	3,540 (11.8)	4,819 (12.6)	37,539 (12.6)
Teaching status				
Teaching hospital	6,021 (35.2)	11,331 (37.7)	16,273 (42.5)	119,421 (39.9)
Nonteaching hospital	11,069 (64.8)	18,768 (62.3)	22,041 (57.5)	179,595 (60.1)

comorbidities and markers of illness severity that paradoxically were not associated with expected changes in other outcomes, such as mortality, ICU level of care, or vasopressor use. The Premier Healthcare Database does not include radiographic impressions. Although it is possible that we included patients who had a negative computed tomographic pulmonary angiography impression, patients were required to have received therapeutic anticoagulation along with the diagnosis of PE. Additionally, our results may not be generalizable to patients from hospitals that do not share the characteristics of those that contribute to the Premier Healthcare Database. Another limitation of the study was our inability to link encounters that occurred at different hospitals. As a result, we may have misclassified some patients as having acute PE if they were previously treated at another institution. However, patients with a previously diagnosed PE with an unrelated diagnosis would likely receive continuation of outpatient anticoagulant or LMWH. Additionally, we did not have access to laboratory or vital sign data and were thus unable to stratify patients

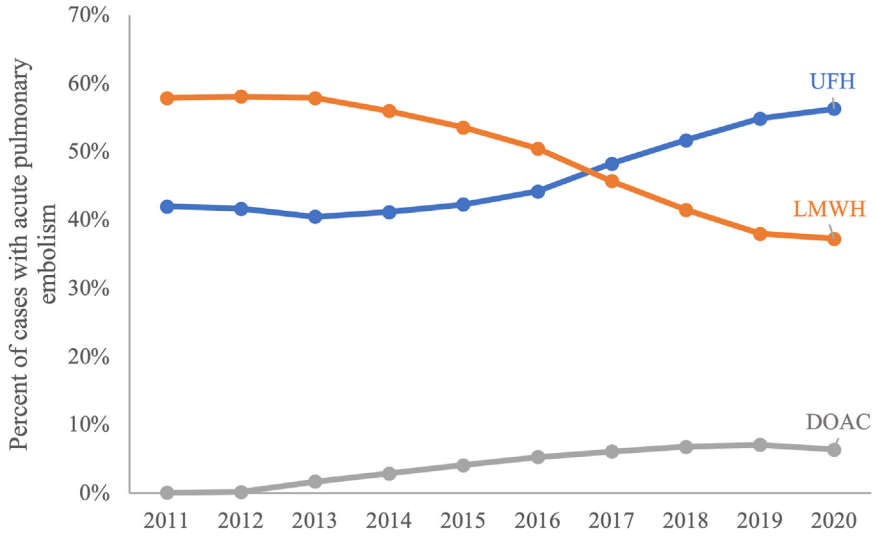

Figure 2. Trends in initial therapeutic anticoagulation for PE between 2011 and 2020. *DOAC* indicates direct oral anticoagulant; *LMWH*, low-molecular-weight heparin; *UFH*, unfractionated heparin.

Table 2. Factors associated with receipt of intravenous unfractionated heparin on first day of hospitalization in 2019.

Patient Factors	Adjusted Odds Ratio (95% CI)
Age (per 1 y increment)	1.00 (1.0-1.0)
Sex	
Female	Reference
Male	1.13 (1.08-1.19)
Race and ethnicity	
White	Reference
Black	1.00 (0.93-1.07)
Hispanic	1.01 (0.89-1.15)
Other	1.04 (0.92-1.17)
Insurance	
Medicare	Reference
Commercial insurance	1.16 (1.08-1.25)
Uninsured	1.00 (0.88-1.15)
Other/unknown	0.99 (0.85-1.15)
Medicaid	0.97 (0.88-1.07)
Comorbidities	
Congestive heart failure	0.94 (0.88-1.00)
Renal dysfunction	1.67 (1.54-1.81)
Malignancy	0.90 (0.84-0.96)
Pulmonary disease	0.77 (0.73-0.82)
Coagulopathy	1.29 (1.18-1.41)
Organ failure, present on admission	
Respiratory failure	1.20 (1.12-1.29)
Renal failure	1.60 (1.46-1.75)
Cardiovascular shock	1.20 (1.05-1.37)
Hematologic dysfunction	1.18 (0.97-1.43)
Admission unit	
General medical unit	Reference
Initial admission to ICU	6.90 (6.31-7.54)
Initial admission to step-down unit	2.30 (2.16-2.45)
Additional support received on day 0/1	
Systemic thrombolysis	4.25 (3.09-5.84)
Vasopressors	1.83 (1.32-2.54)
Invasive mechanical ventilation	0.89 (0.71-1.10)
Noninvasive ventilation or high-flow nasal cannula	0.98 (0.87-1.11)
Hospital factors	
Region	
West	Reference
Midwest	1.32 (0.94-1.85)
Northeast	1.62 (1.11-2.37)
South	0.79 (0.58-1.07)
Size	
>400 beds	Reference
200-400 beds	1.04 (0.78-1.40)
<200 beds	0.64 (0.47-0.87)
Teaching status	
Teaching hospital	Reference
Nonteaching hospital	0.73 (0.56-0.94)
Urban vs rural designation	
Urban hospital	Reference
Rural hospital	0.60 (0.46-0.78)

with PE according to risk category. Prior work assessing outpatient treatment of acute PE using this database found only 4.1% of cases of acute PE diagnosed in an ED between 2016 and 2018 were initially treated as outpatients, suggesting that outpatient management of PE is unlikely to explain the trends we observed.[2] Lastly, in this study we did not attempt to assess harms associated with anticoagulation strategies, which was beyond the scope of this analysis.

DISCUSSION

In this analysis of nearly 300,000 patients hospitalized with acute PE between 2011 and 2020, we found that nearly half were initially treated with UFH. Despite guidelines that have promoted use of other agents and contrary to our expectations, we observed an increase in treatment with UFH and a decrease in treatment with LMWH over time. Although the vast majority of patients were treated with LMWH or UFH, the use of DOACs increased dramatically during the study period. Oral agents that do not require parenteral anticoagulation bridging were first approved for use in PE by the US Food and Drug Administration in 2012 and recommended in guidelines in 2016, likely explaining this finding.[31,32] These trends were unchanged after adjustment for patient-level characteristics.

Although the increasing use of UFH in this study is consistent with several small retrospective United States-based studies, they are at odds with trends observed in other countries.[33-35] For example, the Registro Informatizado de Enfermedad TromboEmbólica registry, largely comprised patients from Spain, reported decreasing rates of anticoagulation with UFH from 2003 to 2013, with fewer than 10% of patients receiving UFH by 2013.[16] There are several possible explanations for the observed increase in UFH use for acute PE in the United States. First, the treatment of high-risk and intermediate-high risk PE has evolved over the past decade. Guidelines recommend that

Table 3. Outcomes among patients hospitalized with acute PE.

Secondary Outcome	All Years (2011-2020)	Milestone Years		
		2011 Number (%)	2015 Number (%)	2019 Number (%)
Days on unfractionated heparin; median [IQR]	3 (2-4)	3 (2-5)	3 (2-5)	2 (1-4)
Days on low-molecular-weight heparin (median [IQR])	3 (2-4)	4 (2-5)	3 (2-4)	2 (1-3)
Length of stay; median (median [IQR])	3 (2-5)	4 (3-6)	3 (2-6)	3 (2-5)
Inhospital mortality	7,323 (2.4)	418 (2.4)	694 (2.3)	923 (2.4)
Inhospital diagnosis of bleeding or hemorrhage	7,250 (2.4)	254 (1.5)	574 (1.9)	1,179 (3.1)
Received a blood transfusion	453 (0.2)	95 (0.6)	54 (0.2)	6 (0)
Received anticoagulation reversal agent	4,010 (1.3)	421 (2.5)	421 (1.4)	282 (0.7)

patients with high-risk PE, namely, those with hemodynamic instability not explained by alternative causes, receive systemic thrombolysis unless contraindications exist.[13,32] Several clinical trials evaluating the efficacy and safety of systemic thrombolysis in patients with intermediate-risk PE, including those with signs of impaired right ventricle dysfunction but without hemodynamic instability, occurred during the study period.[36-40] Despite this interest, there is considerable debate over the role of thrombolysis in intermediate-risk PE. Although we did not observe a significant increase in the proportion of patients who received thrombolysis over time, it is possible that in anticipation of possible thrombolysis, clinicians initiated UFH. Additionally, although it is possible that patients who presented later in the study period had more severe PEs and clinicians anticipated decompensation, the proportion of patients experiencing indirect markers of PE severity such as ICU level of care, vasopressor use, and mechanical ventilation did not increase during the study period. Most patients hospitalized with a PE do not decompensate to the point of requiring reperfusion therapy. A registry of over 5,000 patients with acute PE hospitalized in Italy between 2018 and 2021 found that only 5.5% of patients underwent reperfusion treatment.[41] In addition, patients who receive thrombolysis or catheter-directed treatments do not necessarily require UFH. Systemic thrombolytics and catheter-directed therapies can be used with LMWH.[38,40,42]

Notably, LMWH is renally excreted and, as a result, UFH has been the initial anticoagulant of choice in acute PE for patients with renal insufficiency.[13] The proportion of individuals with a diagnosis of renal dysfunction increased over our study period; however, when we adjusted for comorbidities and severity of illness, including renal dysfunction, the trends in anticoagulation exposure

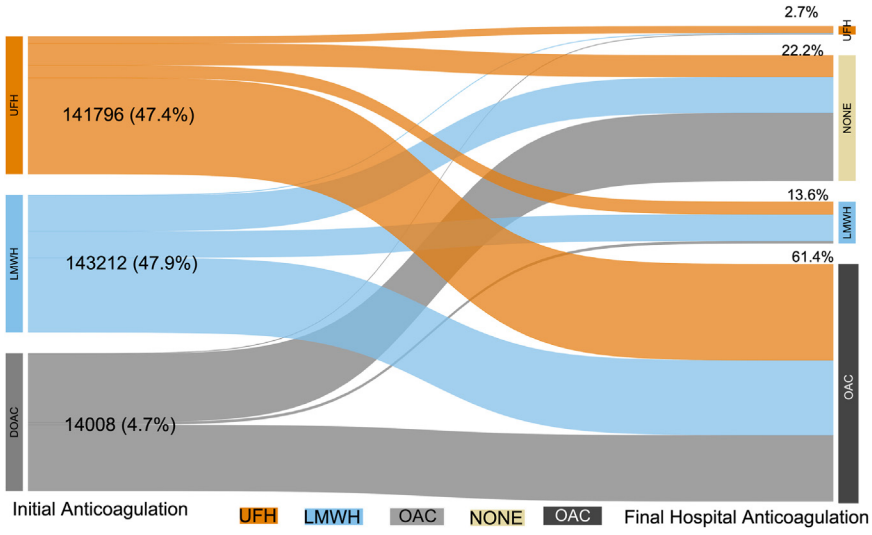

Figure 3. Changes in anticoagulation over the course of hospitalization. Note: "None" includes cases who had a length of stay of 1, so these cases did not crossover to a different class of medications. *OAC indicates* oral anticoagulant (including agents that required bridging such as edoxaban, dabigatran, and warfarin).

remain unchanged. Importantly, patients with acute PE are transitioned to another non-UFH anticoagulant on hospital discharge, including those with renal dysfunction. Further, a substantial proportion of patients with renal dysfunction and venous thromboembolism are treated with DOACs.[43,44] Despite recommendations, the value of initial anticoagulation with UFH over alternative agents in patients with renal impairment is unknown. As efforts focus on decreasing low-value hospitalizations for acute PE, clinicians would benefit from guidance on initial anticoagulation for patients for whom UFH might be the only reason for admission.[45]

Lastly, in our secondary analysis, hospital-level factors were associated with the receipt of UFH as the initial anticoagulant, suggesting local practice patterns may differ. Patients treated at nonteaching hospitals, hospitals with less than 200 beds, and rural hospitals were less likely to receive UFH. It is possible that these hospitals may be less likely to have an ICU or interdisciplinary treatment teams, obviating the anticipation of catheter-directed treatment. Further, the sickest patients from these facilities may have been transferred and thus excluded from this analysis. Further research is needed to determine hospital-level variation.

Although the use of UFH is indicated in some patients with acute PE, our study suggests a gap between routine clinical practice and guidelines for inhospital anticoagulation of patients with acute PE. Because treatment initiated in the ED is often carried forward during hospitalization, even when a better alternative exists, it is important to understand determinants of initial anticoagulation choice and barriers and facilitators to following clinical practice guidelines.[46,47]

Despite the presence of safer and more effective alternatives, a large and increasing percentage of patients with acute PE in the United States are treated with UFH. This practice appears to be a prime target for deimplementation strategies intended to reduce the use of low-value care. Future research is needed to understand the reasons behind this trend as well as potential deimplementation strategies.

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REFERENCES

1. Hsu SH, Ko CH, Chou EH, et al. Pulmonary embolism in United States emergency departments, 2010–2018. *Sci Rep*. 2023;13:9070.
2. Westafer LM, Shieh MS, Pekow PS, et al. Outpatient management of patients following diagnosis of acute pulmonary embolism. *Acad Emerg Med*. 2021;28:336-345.
3. Galanaud JP, Laroche JP, Righini M. The history and historical treatments of deep vein thrombosis. *J Thromb Haemost*. 2013;11:402-411.

4. Garcia DA, Baglin TP, Weitz JI, et al. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e24S-e43S.
5. Prucnal CK, Jansson PS, Deadmon E, et al. Analysis of partial thromboplastin times in patients with pulmonary embolism during the first 48 hours of anticoagulation with unfractionated heparin. *Acad Emerg Med*. 2020;27:117-127.
6. Khor YH, Smith R, McDonald CF. Suboptimal management of unfractionated heparin compared with low-molecular-weight heparin in the management of pulmonary embolism. *Intern Med J*. 2014;44:339-344.
7. Hylek EM, Regan S, Henault LE, et al. Challenges to the effective use of unfractionated heparin in the hospitalized management of acute thrombosis. *Arch Intern Med*. 2003;163:621-627.
8. Smith SB, Geske JB, Maguire JM, et al. Early anticoagulation is associated with reduced mortality for acute pulmonary embolism. *Chest*. 2010;137:1382-1390.
9. Gouin-Thibault I, Pautas E, et al. Safety profile of different low-molecular weight heparins used at therapeutic dose. *Drug Saf*. 2005;28:333-349.
10. van Den Belt AG, Prins MH, Lensing AW, et al. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev*. 2000:CD001100.
11. Stein PD, Hull RD, Matta F, et al. Incidence of thrombocytopenia in hospitalized patients with venous thromboembolism. *Am J Med*. 2009;122:919-930.
12. Robertson L, Jones LE. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for the initial treatment of venous thromboembolism. *Cochrane Database Syst Rev*. 2017:1465-1858.
13. 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). *Eur Respir J*. 2019;54:1901647.
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-e496S.
15. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;35:3033-3080.
16. Jiménez D, De Miguel-Díez J, Guijarro R, et al. Trends in the management and outcomes of acute pulmonary embolism analysis from the RIETE registry. *J Am Coll Cardiol*. 2016;67:162-170.
17. PINC AI™ Healthcare Database: Data That Informs and Performs (White Paper). March 2024. Accessed April 24, 2024. https://offers.pinc-ai.com/PINC-AI-Healthcare-Database-White-Paper-LP.html
18. von Elm E, Altman DG, Egger M, et al. The Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies [published correction appears in *Ann Intern Med*. 2008;148:168]. *Ann Intern Med*. 2007;147:573-577.
19. Cohen DM, Winter M, Lindenauer PK, et al. Echocardiogram in the evaluation of hemodynamically stable acute pulmonary embolism: National practices and clinical outcomes. *Ann Am Thorac Soc*. 2018;15:581-588.
20. Fang MC, Fan D, Sung SH, et al. Validity of using inpatient and outpatient administrative codes to identify acute venous thromboembolism: The CVRN VTE study. *Med Care*. 2017;55:e137-e143.
21. Casez P, Labarère J, Sevestre MA, et al. ICD-10 hospital discharge diagnosis codes were sensitive for identifying pulmonary embolism but not deep vein thrombosis. *J Clin Epidemiol*. 2010;63:790-797.
22. Alotaibi GS, Wu C, Senthilselvan A, et al. The validity of ICD codes coupled with imaging procedure codes for identifying acute venous thromboembolism using administrative data. *Vasc Med*. 2015;20:364-368.
23. Klil-Drori AJ, Prajapati D, Liang Z, et al. External validation of ASPECT (Algorithm for Suspected Pulmonary Embolism Confirmation and Treatment). *Med Care*. 2019;57:e47-e52.
24. Varas-Lorenzo C, Castellsague J, Stang MR, et al. Positive predictive value of ICD-9 codes 410 and 411 in the identification of cases of acute coronary syndromes in the Saskatchewan Hospital automated database. *Pharmacoepidemiol Drug Saf*. 2008;17:842-852.
25. Lamberts M, Staerk L, Olesen JB, et al. Major bleeding complications and persistence with oral anticoagulation in non-valvular atrial fibrillation: Contemporary findings in real-life Danish patients. *J Am Heart Assoc*. 2017;6:e004517.
26. Elixhauser comorbidity software refined for ICD-10-CM. Healthcare Cost and Utilization Project-Agency for Healthcare Reearch and Quality. Accessed April 12, 2024. https://hcup-us.ahrq.gov/toolssoftware/comorbidityicd10/comorbidity_icd10.jsp
27. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29:1303-1310.
28. Lindenauer PK, Stefan MS, Shieh MS, et al. Outcomes associated with invasive and noninvasive ventilation among patients hospitalized with exacerbations of chronic obstructive pulmonary disease. *JAMA Intern Med*. 2014;174:1982-1993.
29. Arnason T, Wells PS, van Walraven C, et al. Accuracy of coding for possible warfarin complications in hospital discharge abstracts. *Thromb Res*. 2006;118:253-262.
30. Al-Ani F, Shariff S, Siqueira L, et al. Identifying venous thromboembolism and major bleeding in emergency room discharges using administrative data. *Thromb Res*. 2015;136:1195-1198.
31. Singh R, Emmady PD. Rivaroxaban. StatPearls. Published April 17, 2023. Accessed November 17, 2023. https://www.ncbi.nlm.nih.gov/books/NBK557502/
32. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149:315-352.
33. Prabhu S, Kumar SA, Dasari M, et al. 427: Uunfractionated heparin: a knee-jerk response for intital management of pulmonsry embolism? *Crit Care Med*. 2024;52:S187.
34. Schrag D, Uno H, Rosovsky R, et al. Direct oral anticoagulants vs low-molecular-weight heparin and recurrent VTE in patients with cancer: A randomized clinical trial. *JAMA*. 2023;329:1924-1933.
35. Zhai Z, Wang D, Lei J, et al. Trends in risk stratification, in-hospital management and mortality of patients with acute pulmonary embolism: an analysis from the China pUlmonary thromboembolism REgistry Study (CURES). *Eur Respir J*. 2021;58.
36. Sharifi M, Bay C, Skrocki L, et al. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). *Am J Cardiol*. 2013;111:273-277.
37. Keller K, Hobohm L, Ebner M, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. *Eur Heart J*. 2020;41:522-529.
38. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*. 2014;370:1402-1411.
39. Tapson VF, Sterling K, Jones N, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: The OPTALYSE PE trial. *JACC Cardiovasc Interv*. 2018;11:1401-1410.
40. Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. *J Thromb Haemost*. 2014;12:459-468.

41. Becattini C, Agnelli G, Maggioni AP, et al. Contemporary management and clinical course of acute pulmonary embolism: The COPE Study. *Thromb Haemost*. 2023;123:613-626.
42. Tu T, Toma C, Tapson VF, et al. A prospective, single-arm, multicenter trial of catheter-directed mechanical thrombectomy for intermediate-risk acute pulmonary embolism. *JACC Cardiovasc Interv*. 2019;12:859-869.
43. Eliquis. Food and Drug Administration. Accessed April 6, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202155s006lbl.pdf
44. Goto S, Haas S, Ageno W, et al. Assessment of outcomes among patients with venous thromboembolism with and without chronic kidney disease. *JAMA Netw Open*. 2020;3:e2022886.
45. Vinson DR, Mark DG, Chettipally UK, et al. Increasing safe outpatient management of emergency department patients with pulmonary embolism: a controlled pragmatic trial. *Ann Intern Med*. 2018;169:855-865.
46. Kiyatkin D, Bessman E, McKenzie R. Impact of antibiotic choices made in the emergency department on appropriateness of antibiotic treatment of urinary tract infections in hospitalized patients. *J Hosp Med*. 2016;11:181-184.
47. Jones TM, Dodds AE, Johnson MD, et al. 1006. Do antibiotic choices made in the ED influence inpatient therapy? *Open Forum Infect Dis*. 2019;6; S354-S354.