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Original Article: Stroke, Systemic or Venous Thromboembolism

Temporal Trend and Geographic Variation in Anticoagulation of Patients Hospitalized with Acute Pulmonary Embolism: the RIETE Registry from 2013 to 2024

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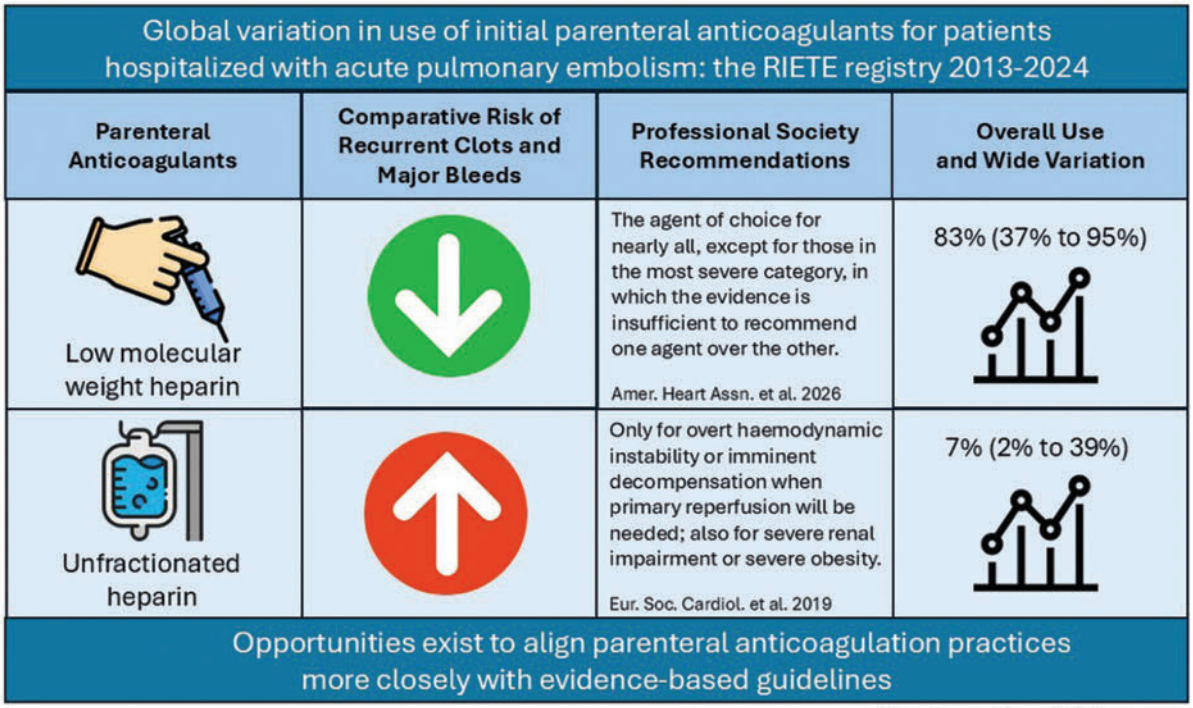
GRAPHICAL ABSTRACT



Images courtesy of Flaticon.com

ABSTRACT

Background A recent U.S. study of initial anticoagulation in adults with acute pulmonary embolism (PE) requiring hospitalization found intravenous unfractionated heparin (UFH) use exceeded 50%. Guidelines, however, recommend low molecular weight heparin (LMWH) over UFH for most patients requiring parenteral anticoagulation. Use patterns in other geographic regions are unclear.

Methods We analyzed data from Registro Informatizado de la Enfermedad TromboEmbólica, a prospective multinational registry of consecutive patients with venous thromboembolism. We included adults hospitalized for acute PE from 2013 through 2024 in 273 hospitals across 31 countries. We assessed temporal trend and regional variation in initial anticoagulation. Using multivariable regression, we identified variables independently associated with UFH.

Results Among 36,210 adults, 83.2% received subcutaneous LMWH, 7.1% UFH, and 6.8% direct oral anticoagulants. LMWH use decreased slightly from 2013 to 2024 (85.8–79.2%; unadjusted), while UFH increased (8.9–10.4%). Wide geographic variation was observed in overall use of LMWH (37–95%) and UFH (2–39%). When adjusted for demographic and clinical covariates, increased weight, recent surgery, recent major bleeding, severe anemia, thrombocytopenia, severe renal dysfunction, abnormal vital signs, and early reperfusion therapy were positively associated, whereas age > 80 years, active cancer, chronic lung disease, prior ischemic stroke, and year were negatively associated with UFH. Compared with Spanish hospitals, hospitals in other European countries, the United States, and Asia were independently associated with UFH use.

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Conclusion Results highlight opportunities for some geographic regions to align anticoagulation practices more closely with evidence-based guidelines recommending LMWH as the preferred parenteral agent in most patients with PE requiring hospitalization.

Keywords pulmonary embolism, guidelines, anticoagulants, hospitalization

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Introduction

Prompt anticoagulation remains the mainstay of treatment for acute pulmonary embolism (PE), with delays linked to increased in-hospital and 30-day mortality.[1–8] Initial treatment options include oral and parenteral agents. Among oral anticoagulants, direct oral anticoagulants (DOACs) are generally preferred over vitamin K antagonists (VKAs) due to their rapid onset, fixed dosing, and favorable safety profile.[1,4,9,10] Among parenteral agents, fixed-dose low-molecular-weight heparin (LMWH) is favored over intravenous unfractionated heparin (UFH) in most hemodynamically stable patients, as recommended across numerous clinical guidelines.[1,4,7,11–15]

Compared with LMWH, UFH is associated with higher rates of recurrent venous thromboembolism (VTE) and major bleeding.[1,2,4,16–18] Its pharmacokinetics are also less predictable, requiring intensive monitoring and dose adjustments. LMWH, by contrast, offers fixed dosing, more predictable absorption, and fewer bleeding complications.[19,20] Accordingly, current guidelines recommend reserving UFH for patients in whom LMWH may be suboptimal, such as those with severe renal impairment or hemodynamic instability requiring vasopressors (**Table 1**).[2,4,7,11–14,21–25]

Despite these recommendations, UFH use has been increasing in some settings. In a large U.S. study involving nearly 300,000 hospitalized patients with PE, initial use of UFH rose from 42% in 2011 to 56% in 2020, while LMWH use declined from 58 to 37%.[26] Another large U.S. study that included more recent data noted significant increases in UFH use from 2016 to 2024 in both high-risk (54–66%) and non-high-risk (33–63%) patients hospitalized with acute PE.[27] This U.S. trend contrasts with earlier European data from Registro Informatizado de la Enfermedad TromboEmbólica (RIETE), which showed that UFH use had decreased from 22% in 2001 to 8% in 2013, while LMWH use increased modestly.[28]

Whether the recent U.S. pattern of greater UFH use is also occurring in other regions is unclear, as the last international RIETE analysis ended in 2013.[28] No contemporary studies have compared international patterns of anticoagulation selection in patients hospitalized for PE. To address this knowledge gap, we analyzed data from RIETE from 2013 to 2024 to assess temporal trends and geographic variation in initial anticoagulant selection. We also sought to identify clinical and regional factors associated with UFH use. Our findings aim to evaluate alignment of anticoagulation practices with guideline recommendations for patients being hospitalized for acute PE.[4,7,11,13,14]

Methods

Study Design, Setting, and Population

We analyzed data from RIETE, an ongoing prospective multinational registry of consecutive patients with objectively confirmed VTE.[29] This study included patients with acute symptomatic PE from January 1, 2013, to December 31, 2024. We included 273 hospitals across 31 countries, which were categorized as follows: Spain; Europe (excluding Spain; Andorra, Austria, Belgium, Czech Republic, France, Germany, Greece, Hungary, Italy, Ireland, Latvia, Macedonia Republic, Portugal, Switzerland, and the United Kingdom); Canada; the United States; South America (Argentina, Bolivia, Brazil, Colombia, Ecuador, Honduras, and Venezuela); Morocco; Israel; and Asia (excluding Israel; Iran, Vietnam, Japan, and China). All patients provided written or oral consent for participation in the registry in accordance with local ethics committee requirements. Patients were not included in the registry if they were participating in a therapeutic clinical trial that involved receiving a blinded medication.

Study Variables and Outcomes

Patients enrolled in RIETE had data collected from near the time of VTE diagnosis that included but were not limited to the following variables[29]: age; sex; body weight; comorbidities such as chronic heart and lung disease; recent (< 30 days prior to VTE diagnosis) major bleeding; presence of risk factors for PE, including active cancer (defined as newly diagnosed cancer or cancer undergoing treatment in the prior 12 months [i.e., surgery, chemotherapy, radiotherapy, hormonal, or support therapy]); recent immobility (defined as nonsurgical patients assigned to bed rest with bathroom privileges for > 4 days in the 2 months prior to VTE); recent surgery (defined as major surgery in the prior 2 months); concomitant medications (statins, psychotropic agents, corticosteroids, and antiplatelet agents)[30,31]; clinical signs and symptoms on admission, including systolic blood pressure, heart rate, and peripheral capillary oxygen saturation (SpO_2); laboratory results at hospital admission, including hemoglobin, platelet count, serum creatinine, and partial pressure of arterial oxygen (PaO_2); duration of index hospitalization; early (administered on calendar day of PE diagnosis or the following day) reperfusion therapies (systemic thrombolysis, percutaneous embolectomy, catheter-directed thrombolysis, and surgical embolectomy); other early advanced therapies (inferior vena cava filter and extracorporeal membrane oxygenation); and 30-day major outcomes (as previously defined)[29]: recurrent PE and deep

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Table 1 Examples of professional society recommendations from English-language guidelines from 2012 through 2026 on choosing between parenteral anticoagulants in the treatment of acute PE

Society, year (in reverse chronology)	Recommendations (verbatim without references; summaries of select content are introduced as authors' comments)
AHA et al, 2026[1]	For patients requiring initial parenteral therapy, LMWH is recommended over UFH due to its reduced risk of recurrent VTE and lower incidence of complications like HIT. Patients with specific comorbidities, including obesity, CKD, and liver disease, require tailored dosing strategies. For instance, dose reductions for LMWH may be reasonable in severely obese patients to mitigate bleeding risks. Anticoagulation therapy and endovascular procedures • In patients with acute PE likely to undergo endovascular procedures for PE management, LMWH is reasonable over UFH to provide more effective anticoagulation. • In patients with acute PE undergoing CDL, concurrent therapeutic anticoagulation (LMWH or UFH) or subtherapeutic anticoagulation (UFH) is recommended over no anticoagulation to prevent recurrent PE. • In patients with acute PE who have undergone an endovascular procedure or received thrombolytic therapy, initial parenteral anticoagulation with LMWH is preferred over UFH to provide reliable therapeutic anticoagulation and reduce the risk of recurrent VTE. Management by acute PE clinical categories [Comments by the authors of this RIETE study: LMWH is recommended as the parenteral anticoagulant of choice for treatment of acute PE, except in patients in the most severe category (E2), i.e., those with cardiopulmonary failure and refractory cardiogenic shock or cardiopulmonary arrest. In this population, the AHA guideline recommends that clinicians should "initiate LMWH or UFH"].
Thrombosis Canada, 2025[11]	LMWH offers advantages over UFH, including significantly more rapid attainment of therapeutic levels, better bioavailability when administered subcutaneously, longer duration of anticoagulant effect enabling once- or twice-daily treatment, lower risk of HIT, predictable anticoagulant effect allowing fixed dosing based on body weight and renal function, less effect on bone metabolism, and no requirement for routine laboratory monitoring. UFH use in the treatment of PE is limited by a narrow therapeutic range, inter-individual variation in anticoagulant effect, need for continuous intravenous infusion with laboratory monitoring, and increased risk of HIT. Moreover, UFH should be avoided for the initial treatment of PE as therapeutic levels may not be obtained for several hours, and in some cases, days. The use of UFH should be limited to: (1) patients with severe renal insufficiency (CrCl < 30 mL/min); (2) patients at very high risk for bleeding, in whom rapid reversal of the anticoagulant effect may be needed; and (3) patients who receive thrombolytic therapy.
International Consensus Statement, 2024[14]	Parenteral therapy is the treatment of choice for patients needing hospitalization because of high risk of bleeding or threatening clinical manifestations of PE (level of evidence moderate, recommendation strong). In patients with end-stage renal failure, UFH as well as other drugs with no or minimal dependence on renal clearance should be used (level of evidence low, recommendation strong).
German Society for Angiology—Society for Vascular Medicine, 2023[13]	If therapy is initiated with a parenteral anticoagulant, LMWH and fondaparinux are preferable to UFH, as they have been shown to be more effective and safer than UFH in individual studies and meta-analyses. Advantages include better practicability due to once- or twice-daily injections, no need for laboratory controls and dosage adjustment, and a lower risk of developing HIT. There is a significant restriction in the use of LMWH or fondaparinux in patients with advanced renal insufficiency. Today, use of UFH is almost exclusively limited to patients with severe renal insufficiency (GFR < 30 mL/minute) or dialysis dependence, when LMWH, fondaparinux, and oral anticoagulants are contraindicated. UFH is also used when an anticoagulant with a short half-life (t_h) is preferred in interventional procedures or peripartum due to the increased risk of bleeding. Here, UFH is usually administered continuously intravenously. Therapy is initiated in a weight-adapted fashion with subsequent dosage adjustment of the continuous infusion to the activated partial thromboplastin time (aPTT).
European Society for Vascular Surgery, 2021[15]	UFH is currently only used in special clinical situations, such as severe renal insufficiency, haemodialysis, pending interventions, or for critically ill patients
NICE, 2020[24]	For people with confirmed PE and hemodynamic instability, offer continuous UFH infusion and consider thrombolytic therapy. Offer people with confirmed proximal DVT or PE and established renal failure (estimated creatinine clearance less than 15 mL/minute) one of: LMWH, UFH, or LMWH or UFH concurrently with a VKA for at least 5 days or until the INR is at least 2.0 in two consecutive readings, followed by a VKA on its own.
ESC, 2019[4]	LMWH and fondaparinux are preferred over UFH for initial anticoagulation in PE, as they carry a lower risk of inducing major bleeding and HIT. Neither LMWH nor fondaparinux needs routine monitoring of anti-Xa levels. Use of UFH is nowadays largely restricted to patients with overt hemodynamic instability or imminent hemodynamic decompensation in whom primary reperfusion treatment will be necessary. UFH is also recommended for patients with serious renal impairment (CrCl < 30 mL/minute) or severe obesity. LMWH is the treatment of choice for PE during pregnancy. In contrast to VKAs and NOACs, LMWH does not cross the placenta, and consequently does not confer a risk of foetal hemorrhage or teratogenicity. Moreover, while UFH is also safe in pregnancy, LMWH has more predictable pharmacokinetics and a more favorable risk profile.

(*Continued*)

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Table 1 (*Continued*)

Society, year (in reverse chronology)	Recommendations (verbatim without references; summaries of select content are introduced as authors' comments)
	In high-risk situations, for example, in patients with recent PE, it is recommended that LMWH be converted to UFH > 36 h prior to delivery. The UFH infusion should be stopped 4–6 h prior to anticipated delivery, and the aPTT should be normal (i.e., not prolonged) prior to regional anesthesia.
The PERT Consortium, 2019[6]	Selection of the initial anticoagulation agent is dependent on many factors, including risk stratification, patient clinical factors (e.g., hepatic and renal function and bleeding risk), and clinician judgment. In the case of intermediate- and high-risk PE in which advanced therapies such as thrombolysis, catheter-based interventions, surgical pulmonary embolectomy, or mechanical circulatory support are being considered, UFH may be the preferred agent as it allows for interventional and surgical teams optimal management flexibility.
ASH for pregnancy, 2018[7]	For pregnant women with acute VTE, the ASH guideline panel recommends LMWH over UFH (strong recommendation, moderate certainty in evidence about effects). UFH with aPTT monitoring would be preferred in pregnant women with significant renal dysfunction who require therapeutic anticoagulation for treatment of VTE. The guideline panel determined that there is clear evidence for a net health benefit with antithrombotic therapy for acute VTE in pregnancy and that LMWH has a better safety profile than UFH in this setting.
ACOG, 2018[47]; see also SOAP, 2018[48]	Women receiving anticoagulation therapy may be converted from low-molecular-weight heparin to the shorter half-life UFH in anticipation of delivery, depending upon the institution's protocol. An alternative option may be to stop anticoagulation and induce labor within 24 h, if clinically appropriate. If conversion to UFH is planned, timing for this should be based upon the clinical scenario, including incorporation of the likelihood of spontaneous labor and the goal of minimizing the time that appropriate anticoagulation is not being administered. Given the potential need for urgent or emergent procedures in obstetrics, the Society for Obstetric Anesthesia and Perinatology's guidelines incorporate decision support to provide guidance regarding the use of neuraxial anesthesia if the recommended time since the last dose has not elapsed.
ESC, 2014[23]	LMWH or fondaparinux are preferred over UFH for initial anticoagulation in PE, as they carry a lower risk of inducing major bleeding and HIT. On the other hand, UFH is recommended for patients in whom primary reperfusion is considered, as well as for those with serious renal impairment (creatinine clearance < 30 mL/minute) or severe obesity. These recommendations are based on the short half-life of UFH, the ease of monitoring its anticoagulant effects, and its rapid reversal by protamine.
ACCP, 2012, 9th edition[22]	In patients with acute PE, we suggest LMWH or fondaparinux over IV UFH (Grade 2C for LMWH; Grade 2B for fondaparinux) and over SC UFH (Grade 2B for LMWH; Grade 2C for fondaparinux). LMWH and fondaparinux are retained in patients with renal impairment, whereas this is not a concern with UFH. In patients with PE where there is concern about the adequacy of SC absorption or in patients in whom thrombolytic therapy is being considered or planned, initial treatment with IV UFH is preferred to use of SC therapies. [Comments by the authors of this RIETE study: Neither the first update (2016) nor the second update (2021) of the 9th edition (2012) provided updates on this topic].

Abbreviations: ACC, American College of Cardiology; ACCP, American College of Chest Physicians; ACOG, American College of Obstetricians and Gynecologists; AHA, American Heart Association; ASH, American Society of Hematology; CDL, catheter-directed thrombolysis; CKD, chronic kidney disease; CrCl; creatinine clearance; ESC, European Society of Cardiology; GFR, glomerular filtration rate; HIT, heparin-induced thrombocytopenia; IV, intravenous; LMWH, low-molecular-weight heparin; NICE, National Institute for Health and Care Excellence; NOAC, nonvitamin K antagonist oral anticoagulant; PE, pulmonary embolism; SC, subcutaneous; SOAP, Society for Obstetric Anesthesia and Perinatology; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.
Note: Adapted with permission from Vinson et al.[25]

vein thrombosis (DVT), major bleeding (gastrointestinal, hematoma, intracranial, retroperitoneal, and others), and death (i.e., fatal PE, fatal bleeding, and sudden, unexpected death). Fatal PE, in the absence of autopsy, was defined as any death appearing within 10 days of an objectively confirmed recurrent PE in the absence of any alternative cause of death.

Initial anticoagulants included intravenous UFH, subcutaneous fixed-dose LMWH and fondaparinux, and oral warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban. Anticoagulants were categorized as initial if they were administered on the calendar day of PE diagnosis. When LMWH or UFH was given as a lead-in agent for a DOAC (i.e., for dabigatran and edoxaban), the delayed administration of the DOAC was not identified as an initial anticoagulant. When LMWH or UFH was used as a bridging agent for a VKA, both medications could be captured as initial anticoagulants if both were administered on the day of PE diagnosis.

We stratified PE severity using the four-tiered classification of risk of early (in-hospital or 30-day) death from the European Society of Cardiology (ESC): low risk, intermediate-low risk, intermediate-high risk, high risk.[4] We used the simplified PE Severity Index (sPESI) in determining ESC risk class, with cancer defined as active cancer, as defined above.[28] Right ventricular (RV) dysfunction for ESC risk stratification was defined by the presence of any one of the following: tricuspid annular plane systolic excursion < 18 mm, RV free wall hypokinesis, or RV/left ventricular ratio ≥ 1.0 on either computed tomography or echocardiography. We also evaluated the duration of UFH use (in 2-day intervals), stratified by ESC PE risk class.

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Statistical Analysis

We assessed temporal trends in initial anticoagulation and clinical characteristics over four separate 3-year intervals (2013–2015, 2016–2018, 2019–2021, and 2022–2024). To evaluate changes in baseline characteristics by year, we used logistic regression for categorical variables and linear regression for continuous variables. We used logistic regression to determine the statistical significance of changes over time in initial anticoagulation use. We performed a multivariable regression model to identify independent predictors of UFH as the initial anticoagulant. We included in the model geographic region, year, and the following candidate covariates plausibly associated with anticoagulant selection, PE severity, and bleeding risk: age, sex, weight >100 kg, active cancer, chronic lung disease, prior ischemic stroke, recent surgery, recent major bleeding, antiplatelet agents, vital signs at presentation (systolic blood pressure <100 mm Hg and pulse ≥ 110 beats/minute), laboratory results (hemoglobin <8.0 g/dL [severe anemia], platelet count $<100{,}000$/mL, and creatinine clearance <30 mL/minute), early reperfusion therapies (intravenous thrombolytic therapy and other reperfusion therapies), geographic region, and year of PE diagnosis as a continuous variable. Reperfusion therapies were included because they reflect patients in whom clinicians may preferentially select UFH owing to anticipated invasive procedures. To account for potential nonindependence of observations within participating centers and countries, the analysis adjusted for clustering at both the hospital and country levels. Crude and adjusted odds ratios with 95% confidence intervals were estimated.

Data were complete for all covariates except the following, with the proportion of missing reported in parentheses: weight (2.9%), heart rate (2.9%), oxygen saturation (42.6%; as this was not a required registry variable in the earlier study period), chronic heart disease (2.8%), prior myocardial infarction (4.2%), prior ischemic stroke (4.2%), antiplatelet agents (9.1%), corticosteroids (9.0%), psychotropic drugs (8.1%), statins (4.5%) at the time of PE diagnosis, length of hospitalization (6.1%), as well as serum troponin (39%), RV dysfunction (42%), and sPESI (21%). If a patient had missing information on only one item of the sPESI, but the remaining items indicated low risk, we assumed the missing value was normal and classified the patient as low risk.

Missing data were handled according to the proportion of missing values. Variables with less than 5% missing data were imputed by assuming missing values were within the normal range. For variables with 5 to 10% missing data, multiple imputation was performed under the assumption that data were missing at random. Variables with more than 10% missing data were excluded from the multivariable analysis.

We conducted statistical analyses using IBM SPSS Statistics for Windows version 25.0 (IBM Corp., Armonk, New York, United States). All hypothesis tests were two-sided, with a significance level of 0.05.

Results

The study included 36,210 patients hospitalized for acute symptomatic PE over a 12-year period. The number of study patients during each 3-year period increased (**Table 2**). The apparent decrease in 2021 to 2024 is an artifact of a time lag in data collection, as enrolled patients were not uploaded to the registry until after follow-up data were complete. Overall, the median age was 69 years (IQR: 55–79), and 17,930 (49.5%) were male. Over time, hospitalized patients with PE decreased in age and increased in weight (**Table 2**). Temporal variations were common in PE risk factors, comorbid diseases, and concomitant medications. Vital sign measurements at presentation were similar across study periods. The exception was oxygen saturation, the results of which were unreliable given the inconsistent capture of values and a high proportion of missingness. ESC risk classes varied over time, with increasing percentages of intermediate-high risk patients. The median length of hospitalization decreased from 8 to 6 days over the 12-year period (**Table 2**).

Initial Anticoagulation

Nearly all patients (99.7%) received initial anticoagulation on the day of PE diagnosis (**Table 3**). Oral agents alone were uncommonly used (7.6%). The majority of the cohort received subcutaneous agents, LMWH (83.2%) or fondaparinux (1.5%), whereas 7.1% received intravenous UFH. Over time, the proportion of patients who received initial LMWH decreased slightly (85.8–79.2%), while the proportion of patients receiving initial UFH began increasing in 2018 and, after a reduction during the COVID-19 pandemic, resumed an annual climb from 2020 to 2024 (**Fig. 1**). Initial anticoagulation selection varied by risk strata: higher-risk patients less commonly received oral and subcutaneous agents and more commonly received UFH compared with their lower-risk counterparts (**Table 3**). Across regions, LMWH was the most frequently used initial anticoagulant. Wide geographic variation was observed in use of LMWH (37–95%) and UFH (2–39%; **Fig. 2**). Canada (95%) and Spain (93%) had the highest proportions of patients receiving LMWH, while the United States (44%) and non-Israeli Asian countries (Iran, Vietnam, Japan, and China; 37%) had the lowest proportions.

Early Reperfusion Therapies

Early reperfusion therapies were administered to 3.7% of patients (**Table 3**). The proportion of patients receiving early reperfusion therapies increased over time and was greater for patients with increased ESC risk class, with 27% of high-risk patients receiving reperfusion therapy. Increases in reperfusion therapies from 2020 to 2024 were coupled with a corresponding increase in the use of initial UFH (**Fig. 2**). Duration of UFH treatment was as follows: <2 days (30.0%), ≥ 2 days and <4 days (33.4%), and >4 days (36.6%; **Supplementary Table S1**, available in the online version only).

Thirty-day outcomes included recurrent VTE (0.5%), major bleeding (1.9%), and all-cause mortality (4.5%). We report 30-day outcomes stratified by ESC PE severity and risk class in **Supplementary Table S2** (available in the online version only) and by initial PE treatment in **Supplementary Table S3** (available in the online version only). We report major bleeding for patients in intermediate-high risk and high-risk classes stratified by type of parenteral anticoagulant (LMWH or UFH) and reperfusion therapy in **Supplementary Table S4** (available in the online version only).

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Table 2 Trends in baseline characteristics of patients hospitalized with acute PE

	Year group				*p*-Trend
	Total; *n* = 36,210	**2013–2015; *n* = 8,660**	**2016–2018; *n* = 9,879**	**2019–2021; *n* = 10,803**	**2022–2024; *n* = 6,868**	
Clinical characteristics						
Age, median (IQR), years	69 (55–79)	70 (56–80)	70 (56–80)	68 (55–78)	68 (55–78)	< 0.001
Age > 80 y	7,920 (22)	2,051 (24)	2,265 (23)	2,228 (21)	1,376 (20)	< 0.001
Male	17,930 (50)	4,125 (48)	4,762 (48)	5,602 (52)	3,441 (50)	< 0.001
Weight, median (IQR), kg	77 (67–88)	76 (66–86)	77 (67–87)	78 (67–88)	78 (66–89)	< 0.001
Weight ≥ 100 kg	4,122 (11)	888 (10)	1,055 (11)	1,316 (12)	863 (13)	< 0.001
Risk factors for VTE						
Immobilization ≥ 4 d (within 2 mo)	7,840 (22)	1,650 (19)	1,925 (19)	2,929 (27)	1,336 (19)	< 0.001
Active cancer or recent treatment (within 12 mo)	5,583 (15)	1,409 (16)	1,646 (17)	1,502 (14)	1,026 (15)	< 0.001
History of VTE	4,833 (13)	1,259 (15)	1,436 (15)	1,251 (12)	887 (13)	< 0.001
Recent surgery (within 2 mo)	3,634 (10)	1,001 (12)	1,047 (11)	880 (8.1)	706 (10)	< 0.001
Comorbid disease						
Chronic lung disease	4,664 (13)	1,294 (15)	1,317 (13)	1,219 (11)	834 (12)	< 0.001
Chronic heart disease	2,709 (7.7)	748 (8.6)	771 (7.9)	714 (7.0)	476 (7.3)	< 0.001
Prior ischemic stroke	2,372 (6.8)	651 (7.8)	692 (7.2)	611 (6.0)	418 (6.4)	< 0.001
Prior myocardial infarction	2,348 (6.8)	610 (7.3)	706 (7.4)	644 (6.3)	388 (6.0)	< 0.001
Recent major bleeding (within 30 d)	982 (2.7)	239 (2.8)	283 (2.9)	274 (2.5)	186 (2.7)	0.470
Pregnancy	125 (0.35)	24 (0.28)	25 (0.25)	52 (0.48)	24 (0.35)	0.278
Concomitant medications						
Statins	8,883 (26)	2,069 (25)	2,412 (25)	2,595 (25)	1,807 (28)	< 0.001
Psychotropic drugs	8,556 (26)	1,997 (25)	2,512 (28)	2,424 (25)	1,623 (26)	0.792
Corticosteroids	3,521 (11)	947 (12)	931 (10)	1,065 (11)	578 (9.4)	< 0.001
Antiplatelet agents	2,042 (6.2)	706 (8.9)	593 (6.6)	540 (5.5)	203 (3.3)	< 0.001
Clinical symptoms and signs at presentation						
Systolic blood pressure, mm Hg, median (IQR)	130 (115–144)	130 (114–144)	130 (115–143)	129 (116–144)	130 (115–145)	0.045
Systolic blood pressure < 100 mm Hg	2,743 (8)	717 (8.3)	710 (7.2)	742 (6.9)	574 (8.4)	0.498
Pulse, beats/min, median (IQR)	90 (78–105)	90 (78–105)	90 (77–105)	90 (78–104)	90 (78–105)	0.133
Pulse ≥ 110 beats/min	5,659 (16)	1,416 (17)	1,555 (16)	1,582 (15)	1,106 (17)	0.042
Peripheral capillary oxygen saturation (SpO_2) < 90%	4,464 (21)	1,285 (28)	1,337 (27)	1,045 (19)	797 (14)	< 0.001
Laboratory findings						
PaO_2 < 60 mm Hg	4,672 (35)	1,593 (39)	1,439 (38)	1,033 (29)	607 (29)	< 0.001
Hemoglobin < 13 g/dL for men and < 12 g/dL for women (anemia)	11,724 (32)	2,852 (33)	3,164 (32)	3,519 (33)	2,189 (32)	0.277
Hemoglobin < 8 g/dL (severe anemia)	479 (1.3)	99 (1.1)	142 (1.4)	139 (1.3)	99 (1.4)	0.303
Platelet count < 100,000/mL	830 (2.3)	217 (2.5)	231 (2.3)	233 (2.2)	149 (2.2)	0.060
Creatinine clearance, mL/min[a]	81 (55–108)	76 (52–105)	78 (54–106)	85 (58–113)	83 (58–107)	< 0.001
≥ 60	25,502 (70)	5,788 (67)	6,820 (69)	7,907 (73)	4,987 (73)	< 0.001
45–59	5,175 (14)	1,347 (16)	1,482 (15)	1,423 (13)	923 (13)	< 0.001
30–44	3,825 (11)	1,043 (12)	1,129 (11)	1,007 (9.3)	646 (9.4)	< 0.001
< 30	1,708 (4.7)	482 (5.6)	448 (4.5)	466 (4.3)	312 (4.5)	0.001
Simplified PESI risk class (points)						
Low (0)	14,224 (39)	3,204 (37)	3,693 (37)	4,593 (43)	2,734 (40)	< 0.001
Higher (≥ 1)	21,986 (61)	5,456 (63)	6,186 (63)	6,210 (57)	4,134 (60)	< 0.001

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Table 2 (*Continued*)

	Year group				*p*-Trend
	Total; *n* = 36,210	**2013–2015; *n* = 8,660**	**2016–2018; *n* = 9,879**	**2019–2021; *n* = 10,803**	**2022–2024; *n* = 6,868**	
ESC PE severity and risk class						
Low	10,364 (29)	2,473 (29)	2,766 (28)	3,417 (32)	1,708 (25)	0.088
Intermediate-low	21,198 (59)	5,263 (61)	5,979 (61)	6,061 (56)	3,895 (57)	< 0.001
Intermediate-high	3,524 (10)	607 (7.0)	840 (8.5)	1,029 (9.5)	1,048 (15)	< 0.001
High	1,124 (3.1)	317 (3.7)	294 (3.0)	296 (2.7)	217 (3.2)	0.009
Length of hospitalization, days, median (IQR; if available)	7 (5–11)	8 (5–11)	7 (5–10)	7 (5–11)	6 (4–10)	0.009

Abbreviations: ESC, European Society of Cardiology; IQR, interquartile range; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; SD, standard deviation.
Note: Values are no. (%) throughout, except where noted.
[a]Based on the Cockcroft–Gault equation.

Table 3 Initial anticoagulation and advanced therapies in patients hospitalized for acute PE, stratified by ESC PE severity and risk class

	ESC PE severity and risk class				
Initial treatments	**Total; *n* = 36,210**	**Low risk; *n* = 10,364**	**Intermediate-low risk; *n* = 21,198**	**Intermediate-high risk; *n* = 3,524**	**High risk; *n* = 1,124**
Initial anticoagulation[a]	36,113 (99.7)	10,345 (100)	21,137 (100)	3,515 (100)	1,116 (99)[b]
Subcutaneous	30,676 (84.7)	8,903 (86)	18,312 (86)	2,729 (77)[c]	732 (65)[c]
LMWH	30,132 (83.2)	8,680 (84)	18,035 (85)[b]	2,694 (76)[c]	723 (64)[c]
Fondaparinux	554 (1.5)	225 (2.2)	283 (1.3)[c]	37 (1.0)[c]	9 (0.8)[b]
Intravenous UFH	2,567 (7.1)	390 (3.8)	1,338 (6.3)[c]	584 (17)[c]	255 (23)[c]
Oral agents	2,747 (7.6)	1,120 (10.8)	1,502 (7.1)[c]	94 (2.7)[c]	31 (2.8)[c]
Direct-acting oral anticoagulants	2,445 (6.8)	1,030 (9.9)	1,312 (6.2)[c]	82 (2.3)[c]	21 (1.9)[c]
Rivaroxaban	1,481 (4.1)	621 (6.0)	816 (3.8)[c]	26 (0.7)[c]	18 (1.6)[c]
Apixaban	941 (2.6)	404 (3.9)	481 (2.3)[c]	53 (1.5)[c]	3 (0.3)[c]
Edoxaban[d]	14 (0.04)	4 (0.04)	9 (0.04)	1 (0.03)	0
Dabigatran[d]	9 (0.02)	1 (0.01)	6 (0.03)	2 (0.06)	0
Vitamin K antagonists	302 (0.8)	90 (0.9)	190 (0.9)	12 (0.3)[b]	10 (0.9)
No anticoagulation	97 (0.3)	19 (0.2)	61 (0.3)	9 (0.3)	8 (0.7)[b]
Early reperfusion therapies[e]	1,356 (3.7)	56 (0.5)	496 (2.3)[c]	501 (14)[c]	303 (27)[c]
Early systemic thrombolysis	944 (2.6)	33 (0.3)	332 (1.6)[c]	327 (9.3)[c]	252 (22)[c]
Early percutaneous embolectomy	268 (0.7)	11 (0.1)	84 (0.4)[c]	124 (3.5)[c]	49 (4.4)[c]
Early catheter-directed thrombolysis	234 (0.7)	12 (0.1)	81 (0.4)[c]	118 (3.3)[c]	23 (2.0)[c]
Early surgical embolectomy	144 (0.4)	15 (0.1)	90 (0.4)[c]	25 (0.7)[c]	14 (1.2)[c]
Other PE therapies[e]					
Early Inferior vena cava filter placement	297 (0.8)	66 (0.6)	170 (0.8)	37 (1.0)	24 (2.1)[c]
Early extracorporeal membrane oxygenation	51 (0.1)	7 (0.1)	16 (0.1)	7 (0.2)	21 (1.9)[c]

Abbreviations: ESC, European Society of Cardiology; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin.
Note: Data are presented as no. (%) throughout.
[a]Initial anticoagulants were those administered on the calendar day of PE diagnosis. Some patients were administered more than one initial anticoagulant.
[b]$p < 0.01$.
[c]$p < 0.001$.
[d]Edoxaban and dabigatran were rarely documented as the initial anticoagulant instead of the required lead-in LMWH. This reflects either documentation error or cases in which lead-in LMWH had been completed prior to presentation.
[e]Early advanced therapies were those administered within the first 2 days, starting with the calendar day of PE diagnosis. Some patients were administered more than one early advanced therapy.

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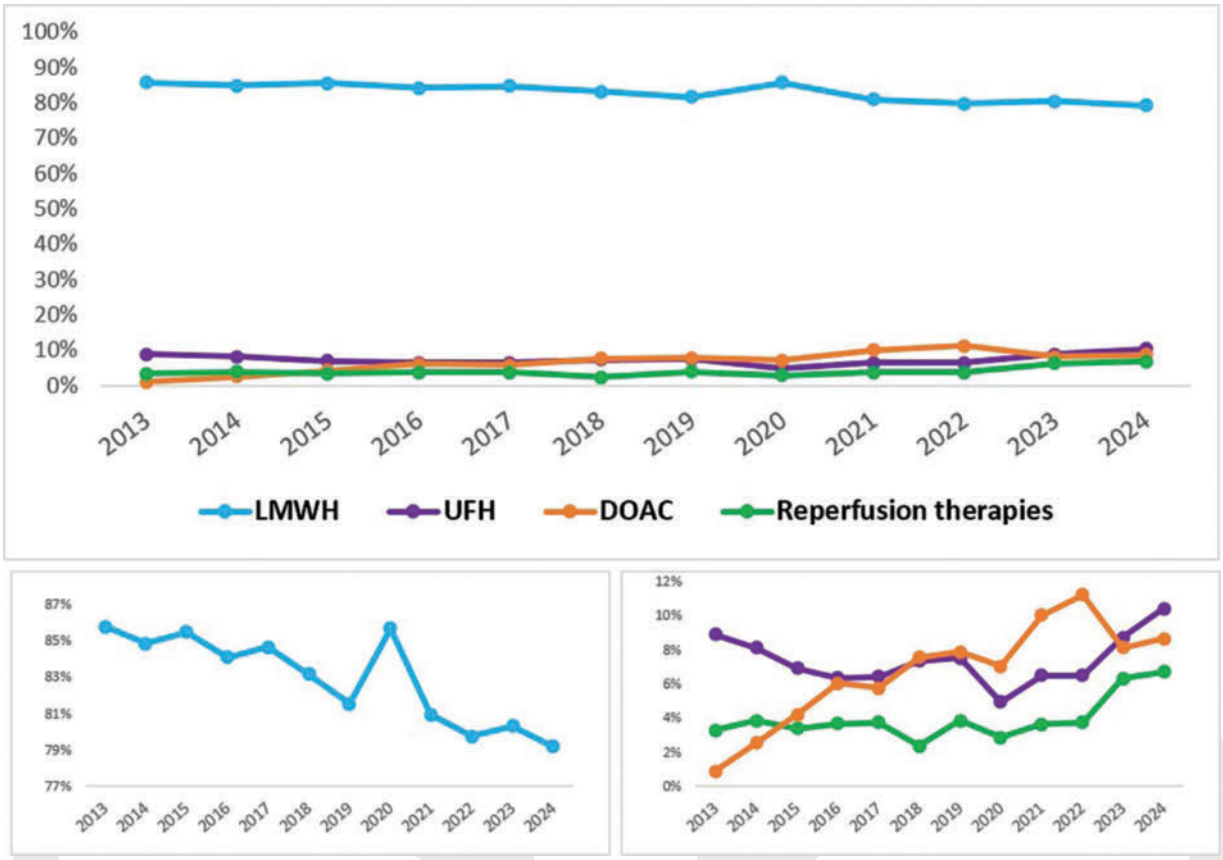

Fig. 1 Temporal trends in initial anticoagulation and reperfusion therapies in patients hospitalized with acute pulmonary embolism. DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; reperfusion therapies: systemic thrombolysis, percutaneous embolectomy, catheter-directed thrombolysis, and surgical embolectomy; UFH, unfractionated heparin.

Modeling

The following variables were independently associated with UFH as initial anticoagulation: elevated weight ($\geq$100 kg), recent surgery, recent major bleeding, tachycardia (pulse $\geq$110 beats/minute), hypotension (systolic blood pressure <100 mm Hg), severe anemia (hemoglobin <8 g/dL), thrombocytopenia (platelet count <100,000/mL), creatinine clearance <30 mL/minute, reperfusion therapies, and the following geographic regions: the United States, Asia (apart from Israel), and Europe (apart from Spain; **Table 4**). Geographic region, reperfusion therapy, and severe renal failure were the strongest independent predictors of UFH use. Age >80 years, active cancer, chronic lung disease, prior ischemic stroke, South America (reference Spain), and year of PE diagnosis were independently associated with decreased UFH use. Although the observed proportion of patients receiving intravenous UFH increased slightly during the final study years (**Fig. 1**), the adjusted regression analysis reflected the overall temporal trend across the entire study period, which remained significantly downward. Results of the multivariable model were similar when we included only cases with a complete set of covariates.

Discussion

In this multinational study of over 36,000 adults hospitalized with acute symptomatic PE, we observed evolving trends in initial anticoagulant selection and significant geographic variation. Large registries have previously documented international variation in VTE management, but few have focused specifically on PE or examined temporal patterns in hospitalized patients.[32,33] We found that LMWH remained the most frequently used initial anticoagulant (83%) in hospitalized patients. Its use, however, varied widely across regions from 37 to 93% and declined slightly over time from 86 to 79%. UFH, used in only 7% of cases overall, was significantly more common in certain geographic regions, particularly parts of Asia and the United States (39%). This U.S. finding is concordant with a large national study by Westafer et al, which reported UFH use in 47% of patients with PE (averaged: 2011–2020) and peaking at 56% in 2020.[26] Our results suggest this pattern of elevated UFH use, while more muted, is also occurring outside of the United States.

Over the 12-year study period, UFH use began to rise after 2018, dipped during the early COVID-19 pandemic, and then climbed again from 2021 onward. This upward trend paralleled increased use of reperfusion therapies. Although we found UFH to be more common among patients who received reperfusion therapies, its use may not always be necessary in these scenarios. Clinical trials of thrombolysis (both systemic and catheter-directed) have shown that LMWH is safe, and its administration is often protocolized prior to thrombolysis.[34–39] LMWH administration should not be perceived as a barrier to reperfusion therapies.[40,41] The 2026 PE guideline from the American Heart Association (AHA)

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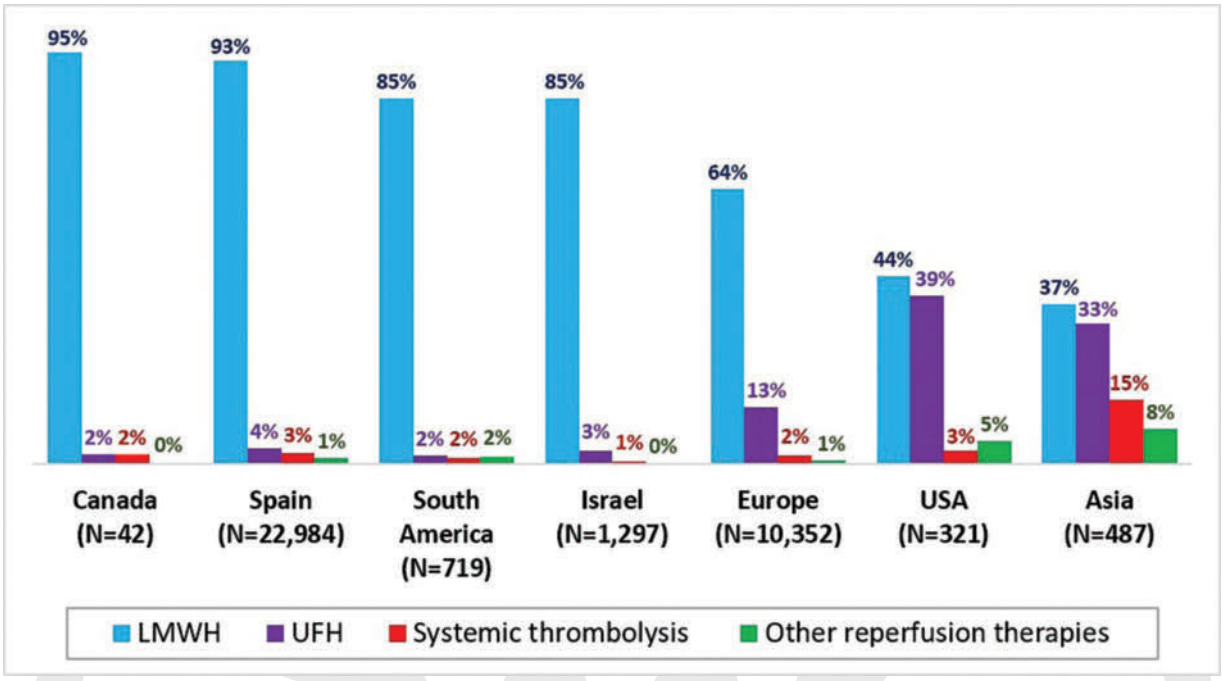

Fig. 2 Initial nonoral anticoagulation and reperfusion therapies in patients hospitalized with acute pulmonary embolism across geographic regions. Europe (excluding Spain) is comprised of the following countries (no. of patients): France ($n = 5,379$), Italy ($n = 2,127$), Latvia ($n = 751$), Macedonia Republic ($n = 612$), Switzerland ($n = 471$), Portugal ($n = 358$), Belgium ($n = 248$), Germany ($n = 137$), Czech Republic ($n = 123$), the United Kingdom ($n = 48$), Austria ($n = 46$), Greece ($n = 26$), Andorra ($n = 12$), Ireland ($n = 12$), Hungary ($n = 2$). South America includes Colombia ($n = 312$), Brazil ($n = 191$), Argentina ($n = 128$), Ecuador ($n = 79$), Bolivia ($n = 4$), Honduras ($n = 3$), and Venezuela ($n = 2$). Asia (excluding Israel) includes Iran ($n = 431$), Vietnam ($n = 31$), Japan ($n = 23$), and China ($n = 2$). Africa was not depicted due to a small sample size ($n = 8$ patients). LMWH, low-molecular-weight heparin; other reperfusion therapies: catheter-directed thrombolysis, percutaneous embolectomy, and surgical embolectomy; UFH, unfractionated heparin.

states that "LMWH is reasonable over UFH to provide more effective anticoagulation" in patients with acute PE likely to undergo endovascular procedures for PE management.[1] In patients with acute PE undergoing catheter-directed thrombolysis, the guideline recommends concurrent therapeutic anticoagulation with either LMWH or UFH (**Table 1**).

Some variables we identified as independently associated with UFH use (e.g., hemodynamic instability and severe renal dysfunction) align with many professional society guidelines (**Table 1**).[2,4,7,11–15,21–24] In some cases, tachycardia may have been an indicator of instability in patients with borderline blood pressure. However, some variables may reflect factors other than direct contraindications to LMWH.[42] Geographic location, for example, was one of the strongest predictors of UFH use. Compared with Spanish hospitals, those in other European countries, the United States, and several countries in Asia were significantly more likely to use UFH. Cultural, educational, and institutional factors likely contribute to these variations. In a qualitative study by Stubblefield et al, U.S. physicians cited inertia, misconceptions about UFH being "stronger" or faster than LMWH, and fear of precluding procedures as common reasons for favoring UFH over LMWH.[40,42]

These perceptions are not fully supported by existing evidence and trial protocols that support LMWH as the preferred parenteral anticoagulant in most patients being hospitalized for acute PE. UFH use has a less favorable safety and efficacy profile compared with LMWH. It also requires complex dosing protocols and frequent monitoring, contributing to delays in achieving therapeutic anticoagulation.[41,43,44] Such delays are associated with worse outcomes.[8] The 2019 ESC PE guidelines, for example, recommend restricting UFH to patients with hemodynamic instability or severe renal impairment, as well as to high-risk gravid patients with PE who are approaching delivery.[4] The 2026 PE guideline from AHA does not specifically recommend UFH over LMWH in any scenario.[1] Only in patients undergoing thrombolytic drug infusion or in cardiopulmonary failure with refractory cardiogenic shock or cardiac arrest is UFH recommended as an alternative to LMWH. Our findings suggest broader use of UFH in clinical practice than guidelines recommend (**Table 1**).

Patterns of UFH use in patients with established risk factors for anticoagulant-related bleeding were complex. Several guidelines recommend UFH for patients with PE staged to undergo select interventions associated with higher bleeding risk, like systemic thrombolysis, labor epidural analgesia, or neuraxial anesthesia.[4,11,45–48] With these high-risk interventions, UFH has advantages over LMWH, particularly a shorter half-life and a greater responsiveness to protamine reversal if needed.[20] An extension of this reasoning to patients with lesser risk factors for bleeding might account for the association we found between recent bleeding, severe anemia, and thrombocytopenia and UFH use,

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Table 4 Analyses of candidate variables associated with use of intravenous unfractionated heparin as initial anticoagulant in the treatment of patients hospitalized for acute PE

	Univariable analysis		Multivariable analysis	
	Odds ratio	95% confidence interval	Adjusted odds ratio	95% confidence interval
Clinical characteristics				
Age > 80 y	0.64[c]	0.57–0.71	0.73[c]	0.65–0.83
Male	1.08	1.00–1.17	1.08	0.99–1.18
Weight ≥ 100 kg	1.82[c]	1.64–2.03	1.61[c]	1.43–1.81
Active cancer	0.83[b]	0.73–0.93	0.80[c]	0.71–0.91
Recent surgery	1.33[c]	1.18–1.51	1.28[c]	1.12–1.46
Chronic lung disease	0.77[c]	0.67–0.87	0.81[b]	0.71–0.94
Recent major bleeding	2.33[c]	1.94–2.79	2.27[c]	1.85–2.79
Prior ischemic stroke	0.81[a]	0.68–0.97	0.81[a]	0.67–0.98
Antiplatelet agents	0.82[a]	0.68–0.98	1.02	0.83–1.25
Vital signs at presentation				
Pulse ≥ 110 beats/min	2.10[c]	1.92–2.31	1.75[c]	1.57–1.94
Systolic blood pressure < 100 mm Hg	2.60[c]	2.32–2.91	1.88[c]	1.64–2.14
Laboratory results				
Haemoglobin < 8 g/dL	1.86[c]	1.41–2.45	1.60[b]	1.18–2.18
Platelet count < 100,000/mL	1.66[c]	1.33–2.07	1.45[b]	1.14–1.86
Creatinine clearance < 30 mL/min	2.06[c]	1.77–2.38	3.07[c]	2.58–3.65
Early reperfusion therapies				
Systemic thrombolysis	7.61[c]	6.61–8.77	5.05[c]	4.26–5.98
Other reperfusion therapies	8.92[c]	7.42–10.7	7.26[c]	5.81–9.07
Geographic region[d]				
Spain	Ref.	Ref.	Ref.	Ref.
United States	16.5[c]	13.1–20.9	18.8[c]	14.6–24.2
Asia (without Israel)	12.5[c]	10.3–15.3	11.4[c]	8.99–14.3
Europe (without Spain)	3.95[c]	3.62–4.32	4.85[c]	4.41–5.33
Israel	0.85	0.61–1.16	0.89	0.64–1.24
Canada	0.63	0.09–4.60	0.41	0.05–3.18
South America	0.55[a]	0.33–0.92	0.55[a]	0.32–0.94
Year of PE diagnosis[e]	1.00	0.98–1.01	0.96[c]	0.94–0.97

Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.
[d] Africa was not included due to a small sample size ($n = 8$ patients).
[e] Year was a continuous variable.

even though LMWH is not contraindicated in patients with these conditions. Preparing for a high-risk intervention like delivery where cessation of anticoagulation will be necessary, however, is different than treating a stable patient with a platelet count of 75,000/mL in which bleeding is only a theoretical possibility. The aforementioned qualitative study by Stubblefield et al may shed light on the use of UFH in these nonintervention, lower-risk cases.[40,42] U.S. physicians had a misperception that UFH was necessarily the better anticoagulant for patients with acute PE at risk of bleeding, which runs counter to the evidence that UFH has a higher incidence of bleeding than LMWH.[16] U.S. physicians also believed that no treatment was available to reverse LMWH-related bleeding if it were to occur. Protamine, however, does have a role in life-threatening bleeding associated with LMWH as it achieves partial reversal of LMWH and improves hemostasis.[49–52]

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We found that some established bleeding risk factors were inversely associated with UFH use (e.g., age > 80 years and active cancer).[53,54] Preference for LMWH in such patients accords with its lower incidence of bleeding.[16] In these cases, clinicians thought it better to reduce the overall risk of bleeding in the first place than to increase the risk of bleeding with UFH but be better prepared to respond to a bleeding complication that was unlikely to occur.

Strengths and Limitations

The multinational scope and large sample size of RIETE are key strengths of this study, allowing comparisons across diverse healthcare settings. However, as with all observational studies, residual confounding due to unmeasured or incompletely measured variables remains possible despite multivariable adjustment. Underrepresentation of U.S. and Asian sites is a shortcoming of our dataset. Lack of patient height data, which precluded analysis of body mass index, prevented an interpretation of our finding that increased weight (≥ 100 kg) was associated with UFH, which would be concordant with the 2019 ESC guidelines[4] in cases where obesity was severe (i.e., body mass index > 40 kg/m^2), although other contemporary guidelines recommend adjusted-dose LMWH rather than routine use of UFH in this setting. Clustering some countries together for analysis of larger geographic regions may have obscured between-country distinctions. Also, initial use of DOACs for patients hospitalized with PE may be underreported in this analysis, as most recipients of dabigatran and edoxaban were categorized as receiving only initial LMWH or UFH because the administration of these two DOACs was often delayed for a minimum 5 days of heparin lead-in therapy. Nonetheless, the observed trends and variation in initial anticoagulation are robust and informative.

Conclusion

In this international cohort of over 36,000 patients hospitalized for acute PE between 2013 and 2024, we observed significant variation in initial anticoagulant selection across geographic regions. While LMWH remained the predominant anticoagulant for PE treatment, its use declined modestly over time, with a corresponding rise in UFH starting in 2018 and continuing post-pandemic. In the adjusted model, we identified guideline-concordant use of initial anticoagulation in both UFH selection (e.g., in patients with hemodynamic instability, severe renal dysfunction, and those receiving systemic thrombolysis) and UFH avoidance (e.g., in patients > 80 years of age and those with active cancer). Our results also found that UFH use varied substantially by geographic region, exposing use patterns that do not correlate with patient-level characteristics recommended in clinical guidelines as indications for UFH.

These findings suggest that regional practice patterns and institutional norms play a role in parenteral anticoagulant selection for acute PE, sometimes exceeding clinical indication. The increase in UFH use, particularly in conjunction with risk factors for bleeding and advanced therapies, may reflect at times appropriate clinical reasoning and at other times persistent misconceptions about UFH and LMWH. Our results highlight opportunities for some geographic regions to align their practices more closely with evidence-based guidelines recommending LMWH as the preferred parenteral anticoagulant in most patients being hospitalized for acute PE.

What is known about this topic?

- Society guidelines recommend low molecular weight heparin (LMWH) over intravenous unfractionated heparin (UFH) for most hemodynamically stable patients requiring parenteral anticoagulation for acute pulmonary embolism (PE).
- The evidence shows that LMWH is safer and more effective, associated with lower rates of major bleeding and recurrent venous thromboembolism compared with UFH.
- However, use of intravenous UFH in the treatment of PE is prevalent in the United States and is increasing, but whether this pattern of care is present in other regions of the world is unclear.

What does this paper add?

- This registry-based study of over 36,000 patients with acute PE treated over 12 years in 31 countries found that UFH use has recently increased with wide variation in use (up to 20-fold) between geographic regions.
- Opportunities exist to align parenteral anticoagulation practices more closely with evidence-based guidelines recommending LMWH as the preferred agent in most hospitalized patients with acute PE.

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Statements and Additional Information

Conflict of Interest D.R.V. time was partially covered by an internal career development award from The Permanente Medical Group's Delivery Science and Applied Research Program. M.M. received unrestricted grants to sponsor the RIETE registry from Rovi and the Universidad Católica de Murcia (Spain).

Contributors' Statement D.R.V. and M.M. take responsibility for the content of the manuscript. M.M. had access to the data, oversaw the statistical analyses, and takes responsibility for the integrity of the data and the accuracy of the analyses. All authors contributed to the study design, participated in the interpretation of the data, provided critical feedback for important intellectual content, and take final responsibility for submitting for publication.

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Temporal trend and geographic variation in anticoagulation of patients hospitalized with acute pulmonary embolism: the RIETE registry 2013-2024

e-Appendix

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Supplement

Supplementary TABLE S1 Duration of intravenous UFH as initial anticoagulant in the treatment of patients hospitalized for acute PE stratified by ESC PE Severity and Risk Class

	Total	**Duration of initial UFH administration, days**		
ESC PE severity and risk class	2,567	<2 n=771 (30.0)	≥2 and <4 n=857 (33.4)	≥4 n=939 (36.6)
Low	390	127 (32.6)	114 (29.2)	149 (38.2)
Intermediate-low	1,338	372 (27.8)	436 (32.6)	530 (39.6)
Intermediate-high	584	202 (34.6)	227 (38.9)	155 (26.5)
High	255	70 (27.5)	80 (31.4)	105 (41.2)

Data are presented as no. or no. (row %) throughout. ESC, European Society of Cardiology; PE, pulmonary embolism; UFH, unfractionated heparin.

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Supplementary TABLE S2 Thirty-day outcomes of patients with acute PE requiring hospitalization stratified by ESC PE Severity and Risk Class

		ESC PE Severity and Risk Class			
	Total n=36,210	**Low risk** n=10,364	**Intermediate-low risk** n=21,198	**Intermediate-high risk** n=3,524	**High risk** n=1,124
Recurrent VTE	197 (0.5)	42 (0.4)	129 (0.6)[a]	14 (0.4)	12 (1.1)[b]
Recurrent PE	106 (0.3)	22 (0.2)	74 (0.3)[a]	5 (0.1)	5 (0.4)
Recurrent DVT	91 (0.3)	20 (0.2)	55 (0.3)	9 (0.3)	7 (0.6)[a]
Major bleeding	679 (1.9)	101 (1.0)	415 (2.0)[c]	87 (2.5)[c]	76 (6.8)[c]
Gastrointestinal	159 (0.4)	18 (0.2)	105 (0.5)[c]	22 (0.6)[c]	14 (1.2)[c]
Hematoma	196 (0.5)	28 (0.3)	117 (0.6)[b]	23 (0.7)[b]	28 (2.5)[c]
Intracranial	86 (0.2)	14 (0.1)	45 (0.2)	20 (0.6)[c]	7 (0.6)[b]
Retroperitoneal	67 (0.2)	10 (0.1)	49 (0.2)[a]	1 (0.03)	7 (0.6)[b]
Other	171 (0.5)	31 (0.3)	99 (0.5)[a]	21 (0.6)[a]	20 (1.8)[c]
Death	1,645 (4.5)	93 (0.9)	1,267 (6.0)[c]	123 (3.5)[c]	162 (14.4)[c]
Fatal PE	267 (0.7)	11 (0.1)	160 (0.8)[c]	34 (1.0)[c]	62 (5.5)[c]
Fatal bleeding	79 (0.2)	6 (0.1)	56 (0.3)[c]	8 (0.2)[a]	9 (0.8)[c]
Sudden, unexpected death	44 (0.1)	5 (0.1)	32 (0.2)[a]	6 (0.2)[a]	1 (0.1)

Data are presented as no. (%) throughout. DVT, deep vein thrombosis; ESC, European Society of Cardiology; PE, pulmonary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism.

a. P <0.05

b. P <0.01

c. P <0.001

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Supplementary TABLE S3 Thirty-day outcomes of patients with acute PE requiring hospitalization stratified by initial PE treatment with parenteral heparin

	Initial PE treatment with parenteral heparin				
	Total n=32,627	**LMWH without early reperfusion therapy** n=29,638	**LMWH with early reperfusion therapy** n=494	**UFH without early reperfusion therapy** n=2,080	**UFH with early reperfusion therapy** n=487
Recurrent VTE	173 (0.5)	144 (0.5)	6 (1.2)	22 (1.1)	1 (0.2)
Recurrent PE	94 (0.3)	85 (0.3)	1 (0.2)	7 (0.3)	1 (0.2)
Recurrent DVT	79 (0.2)	59 (0.2)	5 (1.0)	15 (0.7)	0
Major bleeding	616 (1.9)	481 (1.6)	24 (4.9)	72 (3.5)	39 (8.0)
Gastrointestinal	147 (0.4)	118 (0.4)	4 (0.8)	22 (1.1)	3 (0.6)
Hematoma	180 (0.6)	137 (0.5)	8 (1.7)	16 (0.8)	19 (3.9)
Intracranial	71 (0.2)	48 (0.2)	6 (1.2)	11 (0.5)	6 (1.2)
Retroperitoneal	62 (0.2)	57 (0.2)	0	4 (0.2)	1 (0.2)
Other	154 (0.5)	121 (0.4)	4 (0.8)	19 (0.9)	10 (2.1)
Death	1,490 (4.6)	1,301 (4.4)	26 (5.4)	134 (6.4)	29 (6.0)
Fatal PE	221 (0.7)	171 (0.6)	9 (1.9)	27 (1.3)	14 (2.9)
Fatal bleeding	65 (0.2)	55 (0.2)	3 (0.6)	4 (0.2)	3 (0.6)
Sudden, unexpected death	38 (0.1)	30 (0.1)	2 (0.4)	6 (0.3)	0

Data are presented as no. or no. (%) throughout. DVT, deep vein thrombosis; LMWH, low molecular weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism.

Patients who received both LMWH and UFH (n=72) were classified in the UFH group.

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Supplementary Table S4. Major bleeding among ESC intermediate- and high-risk patients with acute PE who received initial parenteral anticoagulation, stratified by early reperfusion therapy and type of parenteral anticoagulation[a]

	Initial Parenteral Anticoagulation		
	LMWH or UFH	**LMWH**	**UFH**
Both ESC Intermediate-high and High-risk Patients	n=4,239	n=3,417	n=839
No reperfusion therapy	85/3,669 (2.3)	62/3,141 (2.0)	23/538 (4.3)
Reperfusion therapy	45/570 (7.9)	19/276 (6.9)	28/301 (9.3)
Systemic thrombolysis	36/350 (10.3)	15/160 (9.4)	23/197 (11.7)
Other[b]	13/251 (5.2)	7/133 (5.3)	8/122 (6.6)
Only ESC Intermediate-high Risk Patients	n=3,267	n=2,694	n=584
No reperfusion therapy	53/2,901 (1.8)	45/2,493 (1.8)	8/414 (1.9)
Reperfusion therapy	22/366 (6.0)	14/201 (7.0)	9/170 (5.3)
Systemic thrombolysis	15/196 (7.7)	10/109 (9.2)	6/92 (6.5)
Other[b]	9/192 (4.7)	6/107 (5.6)	4/88 (4.5)
Only ESC High-risk Patients	n=972	n=723	n=255
No reperfusion therapy	32/768 (4.2)	17/648 (2.6)	15/124 (12.1)
Reperfusion therapy	23/204 (11.3)	5/75 (6.7)	19/131 (14.5)
Systemic thrombolysis	21/154 (13.6)	5/51 (9.8)	17/105 (16.2)
Other[b]	4/59 (6.8)	1/26 (3.8)	4/34 (11.8)

Data are presented throughout as n/N (%), in which the numerator = cases of major bleeding and the denominator = total cases with the combination of column variable (type of parenteral anticoagulation) and row variable (reperfusion therapy category). ESC, European Society of Cardiology; PE, pulmonary embolism.

a. A small fraction of patients were administered both LMWH and UFH on the day of PE diagnosis. The small number of bleeding cases precluded analysis adjusting for covariates that may have contributed to bleeding.

b. Other reperfusion therapies include percutaneous embolectomy, catheter-directed thrombolysis, and surgical embolectomy.

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Supplement

Supplementary TABLE S1 Duration of intravenous UFH as initial anticoagulant in the treatment of patients hospitalized for acute PE stratified by ESC PE Severity and Risk Class

	Total	**Duration of initial UFH administration, days**		
ESC PE severity and risk class	2,567	<2 n=771 (30.0)	≥2 and <4 n=857 (33.4)	≥4 n=939 (36.6)
Low	390	127 (32.6)	114 (29.2)	149 (38.2)
Intermediate-low	1,338	372 (27.8)	436 (32.6)	530 (39.6)
Intermediate-high	584	202 (34.6)	227 (38.9)	155 (26.5)
High	255	70 (27.5)	80 (31.4)	105 (41.2)

Data are presented as no. or no. (row %) throughout. ESC, European Society of Cardiology; PE, pulmonary embolism; UFH, unfractionated heparin.

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Supplementary TABLE S2 Thirty-day outcomes of patients with acute PE requiring hospitalization stratified by ESC PE Severity and Risk Class

		ESC PE Severity and Risk Class			
	Total n=36,210	**Low risk** n=10,364	**Intermediate-low risk** n=21,198	**Intermediate-high risk** n=3,524	**High risk** n=1,124
Recurrent VTE	197 (0.5)	42 (0.4)	129 (0.6)[a]	14 (0.4)	12 (1.1)[b]
Recurrent PE	106 (0.3)	22 (0.2)	74 (0.3)[a]	5 (0.1)	5 (0.4)
Recurrent DVT	91 (0.3)	20 (0.2)	55 (0.3)	9 (0.3)	7 (0.6)[a]
Major bleeding	679 (1.9)	101 (1.0)	415 (2.0)[c]	87 (2.5)[c]	76 (6.8)[c]
Gastrointestinal	159 (0.4)	18 (0.2)	105 (0.5)[c]	22 (0.6)[c]	14 (1.2)[c]
Hematoma	196 (0.5)	28 (0.3)	117 (0.6)[b]	23 (0.7)[b]	28 (2.5)[c]
Intracranial	86 (0.2)	14 (0.1)	45 (0.2)	20 (0.6)[c]	7 (0.6)[b]
Retroperitoneal	67 (0.2)	10 (0.1)	49 (0.2)[a]	1 (0.03)	7 (0.6)[b]
Other	171 (0.5)	31 (0.3)	99 (0.5)[a]	21 (0.6)[a]	20 (1.8)[c]
Death	1,645 (4.5)	93 (0.9)	1,267 (6.0)[c]	123 (3.5)[c]	162 (14.4)[c]
Fatal PE	267 (0.7)	11 (0.1)	160 (0.8)[c]	34 (1.0)[c]	62 (5.5)[c]
Fatal bleeding	79 (0.2)	6 (0.1)	56 (0.3)[c]	8 (0.2)[a]	9 (0.8)[c]
Sudden, unexpected death	44 (0.1)	5 (0.1)	32 (0.2)[a]	6 (0.2)[a]	1 (0.1)

Data are presented as no. (%) throughout. DVT, deep vein thrombosis; ESC, European Society of Cardiology; PE, pulmonary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism.

a. P <0.05

b. P <0.01

c. P <0.001

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Supplementary TABLE S3 Thirty-day outcomes of patients with acute PE requiring hospitalization stratified by initial PE treatment with parenteral heparin

	Initial PE treatment with parenteral heparin				
	Total n=32,627	**LMWH without early reperfusion therapy** n=29,638	**LMWH with early reperfusion therapy** n=494	**UFH without early reperfusion therapy** n=2,080	**UFH with early reperfusion therapy** n=487
Recurrent VTE	173 (0.5)	144 (0.5)	6 (1.2)	22 (1.1)	1 (0.2)
Recurrent PE	94 (0.3)	85 (0.3)	1 (0.2)	7 (0.3)	1 (0.2)
Recurrent DVT	79 (0.2)	59 (0.2)	5 (1.0)	15 (0.7)	0
Major bleeding	616 (1.9)	481 (1.6)	24 (4.9)	72 (3.5)	39 (8.0)
Gastrointestinal	147 (0.4)	118 (0.4)	4 (0.8)	22 (1.1)	3 (0.6)
Hematoma	180 (0.6)	137 (0.5)	8 (1.7)	16 (0.8)	19 (3.9)
Intracranial	71 (0.2)	48 (0.2)	6 (1.2)	11 (0.5)	6 (1.2)
Retroperitoneal	62 (0.2)	57 (0.2)	0	4 (0.2)	1 (0.2)
Other	154 (0.5)	121 (0.4)	4 (0.8)	19 (0.9)	10 (2.1)
Death	1,490 (4.6)	1,301 (4.4)	26 (5.4)	134 (6.4)	29 (6.0)
Fatal PE	221 (0.7)	171 (0.6)	9 (1.9)	27 (1.3)	14 (2.9)
Fatal bleeding	65 (0.2)	55 (0.2)	3 (0.6)	4 (0.2)	3 (0.6)
Sudden, unexpected death	38 (0.1)	30 (0.1)	2 (0.4)	6 (0.3)	0

Data are presented as no. or no. (%) throughout. DVT, deep vein thrombosis; LMWH, low molecular weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism.

Patients who received both LMWH and UFH (n=72) were classified in the UFH group.

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Supplementary Table S4. Major bleeding among ESC intermediate- and high-risk patients with acute PE who received initial parenteral anticoagulation, stratified by early reperfusion therapy and type of parenteral anticoagulation[a]

	Initial Parenteral Anticoagulation		
	LMWH or UFH	**LMWH**	**UFH**
Both ESC Intermediate-high and High-risk Patients	n=4,239	n=3,417	n=839
No reperfusion therapy	85/3,669 (2.3)	62/3,141 (2.0)	23/538 (4.3)
Reperfusion therapy	45/570 (7.9)	19/276 (6.9)	28/301 (9.3)
Systemic thrombolysis	36/350 (10.3)	15/160 (9.4)	23/197 (11.7)
Other[b]	13/251 (5.2)	7/133 (5.3)	8/122 (6.6)
Only ESC Intermediate-high Risk Patients	n=3,267	n=2,694	n=584
No reperfusion therapy	53/2,901 (1.8)	45/2,493 (1.8)	8/414 (1.9)
Reperfusion therapy	22/366 (6.0)	14/201 (7.0)	9/170 (5.3)
Systemic thrombolysis	15/196 (7.7)	10/109 (9.2)	6/92 (6.5)
Other[b]	9/192 (4.7)	6/107 (5.6)	4/88 (4.5)
Only ESC High-risk Patients	n=972	n=723	n=255
No reperfusion therapy	32/768 (4.2)	17/648 (2.6)	15/124 (12.1)
Reperfusion therapy	23/204 (11.3)	5/75 (6.7)	19/131 (14.5)
Systemic thrombolysis	21/154 (13.6)	5/51 (9.8)	17/105 (16.2)
Other[b]	4/59 (6.8)	1/26 (3.8)	4/34 (11.8)

Data are presented throughout as n/N (%), in which the numerator = cases of major bleeding and the denominator = total cases with the combination of column variable (type of parenteral anticoagulation) and row variable (reperfusion therapy category). ESC, European Society of Cardiology; PE, pulmonary embolism.

a. A small fraction of patients were administered both LMWH and UFH on the day of PE diagnosis. The small number of bleeding cases precluded analysis adjusting for covariates that may have contributed to bleeding.

b. Other reperfusion therapies include percutaneous embolectomy, catheter-directed thrombolysis, and surgical embolectomy.

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