Rivaroxaban treatment for young patients with pulmonary embolism (Review)

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Abstract. Pulmonary embolism (PE) is a serious, life-threatening condition that affects young populations (>18 and <50 years old, according to most literature reviews) with improved recognition of its clinical manifestations and the widespread use of sensitive imaging techniques, PE is increasingly diagnosed in younger patients. At present, there is limited understanding of the clinical features and adequate anticoagulant treatment options for this population. Most studies to date have yet to demonstrate significant differences in PE pathophysiology or symptoms between young and elderly patients. Although the overall incidence of PE is lower in young populations compared with elderly patients, important risk factors also apply for young patients. Hereditary thrombophilia is common and is a major cause of PE in younger patients. Immobilization, trauma, obesity, smoking and infection are also becoming increasingly frequent in young patients with PE. Among female patients, oral contraceptive use, pregnancy and postpartum status are predominant risk factors underlying PE. Rivaroxaban is a direct oral anticoagulant with a rapid onset of action that is associated with less drug-drug interactions compared with other therapies. Because the drug is administered at fixed doses with no requirement for routine coagulation monitoring, it is becoming an attractive option for anticoagulation treatment in young patients with PE. Therefore, the present literature review focuses on the clinical characteristics of PE and rivaroxaban therapy in younger patients.

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Contents

1. Introduction

Venous thromboembolism (VTE) is a common and potentially fatal disease that are comprised of deep vein thrombosis (DVT) and pulmonary embolism (PE) (1). The estimated annual incidence rates of VTE among people of European ancestry range from 104 to 183 per 100,000 person-years (2,3), but is more prevalent in elderly subjects. Annually, there are ~72.4 cases per 100,000 adults aged 40-54 years, compared with 280 cases per 100,000 people aged 85-89 years (Table I) (4,5). Although the exact incidence rate of PE in younger populations is unknown, it is typically lower in patients aged <40 years compared with that in the elderly (5), with peak incidence in the sixth decade (6). Nevertheless, PE remains to be a major cause of mortality among young patients (7).

Younger individuals typically present with fewer comorbidities than elderly patients and are generally in better health. Since a substantial number of previous studies mainly focused on PE in elderly instead of that in younger patients (8,9), the risk factors, clinical features and anticoagulation strategies in younger patients with PE remain poorly defined. Guidelines for PE treatment were not designed with age as a parameter, resulting in gaps in the study data for younger patients.

In recent decades, the vitamin K antagonist (VKA) warfarin has been used for PE treatment and prophylaxis (10,11). However, the introduction of the non-vitamin K oral anticoagulant (NOAC) rivaroxaban changed the choice of pharmacological treatment in young patients with PE. Rivaroxaban has several advantages over VKAs, including a rapid onset of action and a more predictable pharmacokinetic

profile, allowing for simplified drug administration in a single, standardized dose, which negates the need for frequent laboratory monitoring and dose adjustment (12,13).

In the EINSTEIN-DVT dose-ranging phase II clinical trials (12) and subsequent phase III clinical trials (EINSTEIN-DVT,EINSTEIN-PEandEINSTEIN-EXT)(14,15),rivaroxaban was found to be non-inferior to VKA in terms of efficacy but conferred a lower risk of serious adverse drug reactions, especially cerebral hemorrhages in all participants with PE (15). Although the aforementioned study did not specify the condition of young patients with PE, the study included young patients (>18 and <50 years) with PE. Following the treatment recommendations of the 2016 American College of Chest Physicians and the 2014 and 2017 European Society of Cardiology guidelines for both DVT and PE (16-18), numerous clinical studies and case reports of rivaroxaban use in real-life have been published, including data from young patients (19-23).

A review of the current literature would allow for the identification of specific risk factors and clinical characteristics in younger patients with PE, in addition to clarifying the current status of rivaroxaban use in this age group. The present article reviews the current literature published prior to January 1, 2019. 'Rivaroxaban' ivaroxabans age group and oxabans age group. The present article reviews the current literature published prior to January 1, 2019. 'acteristics in younger patients with PE, in additvant original research, review articles, guidelines and personal experience were used to summarize the collective understanding regarding the clinical characteristics of PE and rivaroxaban use in young patients to guide clinical decision making in daily practice.

2. Epidemiology data of PE among younger populations

Although the reported incidence of PE in young subjects is inconsistent among studies, it is generally considered to be lower compared with that in the elderly population. The estimated incidence of the first acute VTE is between 0.7 and 1.4 per 1,000 person-years and is mostly observed in patients >55 years old (1). An epidemiological study in Norway suggested that the incidence rates for all first VTE events, DVT and PE to be 1.43, 0.93 and 0.50 per 1,000 person-years, respectively (24). Another study in United States demonstrated that the average annual incidence of DVT alone is 48 per 100,000, whilst the incidence of PE with or without DVT is 23 per 100,000 (25). A Seville prospective study of forensic autopsies reported a similar PE incidence rate of 0.65 per 100,000 (26).

Previously studies on the incidence of PE in young patients have produced controversial data, as the cut-off thresholds for defining the younger and older age groups were set differently. A number of previous studies defined the younger population as those aged ranging from 40 to 65 years. In a Medical University of Bialystok study including 238 retrospectively enrolled patients with confirmed PE, patients <50 years accounted for 19.7% of the cohort (7), whilst another North Carolina study consisting of 387 patients aged >45 years suggested a 5% incidence of PE in a population aged <45 years (27). A USA retrospective study of 631 patients with PE demonstrated a 9.4% PE incidence in a cohort of patients aged between 20 and 50 years (28). In another 232-subject study in Italy, 25% of the patients with PE were found to be aged <65 years (29). A previous France study consisting of 250 patients diagnosed with the first episode of VTE found 25% of the patients were aged <50 years (30). In a Boston cohort study of 547 consecutive patients with PE from 2005 to 2011, 62% of the patients were <65 years old (Table I) (31).

Although PE is less prevalent in younger subjects, it remains to be a life-threatening disorder (32,33). A previous study estimated the number of clear cases of fatal PE among the Danish population and reported an annual mortality rate to be 0.36 cases per 100,000 person-years in the age group of 0-35 years (34). In a University of California retrospective study of 3,456 patients who had idiopathic PE ageing between 18 and 56 years from 1994 to 2001, 10 (0.29%) died due to first-time recurrent thromboembolism between 1 month and 5 years following diagnosis (35).

3. Risk factors for PE in young patients

Unprovoked factors of PE (neither an important transient nor persistent provoking risk factor for thrombosis, with no apparent clinical risk factors and environmental risk factor) are either hereditary or idiopathic, in a manner that is not associated with environmental risk factors. PE do not normally occur spontaneously, but the proportion of unprovoked PE is unclear. These unprovoked causes tend to be more common in young patients with PE (Table II) (36-38). Hereditary thrombophilia typically confers the greatest risk for PE (39). Most cases of inherited thrombophilia are due to Factor V Leiden and prothrombin gene mutations (40,41), whilst the remaining causes are due to deficiencies in protein S, protein C and antithrombin (39). Unprovoked causes also include increased levels of factor VIII or IX, heparin co-factor II deficiency and dysfunctions in plasminogen, factor XII and fibrinogenemia (42-44). A recent study involving 237 patients demonstrated that the levels of protein C antigen, protein S antigen, protein S activity, antithrombin III antigen and factor VIII were significantly increased in patients with unprovoked PE, compared with those with provoked PE (45). A prospective observational study of 331 patients reported that unprovoked PE was more likely to occur at a young age (36). These factors lead to hypercoagulative states, which can result in blood clot formation and frequently affect multiple first-degree family members. Consequently, affected individuals have a higher lifetime probability of developing thrombosis compared with those in the normal population (46-48). Recurrent VTE events often occur when patients discontinue anticoagulation treatments (49,50).

Provoked risk factors (acquired or secondary) for PE include the presence of underlying conditions and/or precipitating factors, including recent surgery or trauma, inflammation, immobilization, malignancy, pregnancy, contraceptive use, hormone replacement therapy, heart failure, atrial fibrillation, obesity, chronic obstructive pulmonary disease and hematological diseases (45,51). Provoked factors can be transient, as it is the case in recent surgery, where patients have a reduced risk of recurrence of PE after the cessation of therapy (52). In addition, provoked risk factors can also be persistent and progressive, such as metastatic cancer, which is

Table I. Outline and key points of young patients with PE.

Outline	Key point	(Refs)
Incidence	In 238 patients tested, (19.7%) of PE cases affect young patients <50 years old (Medical University of Bialystok)	(7)
	In 387 patients examined, PE incidence was 5% in patients <45 years old (North Carolina)	(27)
	In 631 patients tested, PE incidence was 9.4% in patients between 20 and 50 years old (A USA retrospective study)	(28)
	In 232 patients examined, 25% of patients with PE were <65 years old (Italy)	(29)
	In 250 patients examined, 25% of patients with PE were aged ≤50 years old (France)	(30)
	In a study of 540 patients with PE, 62% of were of <65 years old (Boston)	(31)
Unprovoked factors	Factor V Leiden mutations and prothrombin gene mutations	(40,41)
	Deficiencies in protein S, protein C and antithrombin	(39)
	Increased levels of factor VIII or IX, heparin cofactor II deficiencies	(42-44)
	Abnormal functions of plasminogen and Factor XII and fibrinogenemia	(42-44)
	Increased protein C antigen, protein S antigen and protein S activity, antithrombin III antigen and factor VIII	(45)
Provoked (acquired or secondary) factors	Recent surgery or trauma, inflammation, immobilization, malignancy, pregnancy, contraceptive use, hormone replacement therapy	(30,45,51)
	Heart failure, atrial fibrillation, chronic obstructive pulmonary disease, hematologic diseases, obesity and smoking	(58)
Pathogenesis and pathophysiology	There is no single sign or symptom that can accurately diagnose or exclude PE in young patients. The common symptoms are dyspnea and chest pain. Additional signs and symptoms include hemoptysis, cough, tachycardia, syncope, fatigue, hypoxemia, cyanosis and leg pain.	(66-68)

PE, Pulmonary embolism.

Table II. Common risk factors of PE in young and elderly patients.

Patient population	Risk factor	(Refs)
Young	Hereditary thrombophilia; deficiencies in protein S, protein C; deficiencies in antithrombin factor V Leiden mutations	(39-41,45)
	Trauma; obesity; smoking; oral contraceptive use; pregnancy; postpartum hormone replacement therapy	(45,59,60)
Elderly	Recent hospitalization; cancer, infection, immobility	(63,64)
	Chronic cardiopulmonary disease; renal dysfunction; diabetes mellitus; heart failure; venous insufficiency; increasing levels of blood plasma fibrinogen and plasminogen activator inhibitor-1	(65)

associated with a high risk of recurrence of PE after ceasing therapy (53,54). A retrospective study of younger patients aged <50 years with confirmed PE suggested that obesity and smoking were significantly more prevalent in young patients with PE, whilst malignancies, hypertension, diabetes, ischemic heart disease, atrial fibrillation and other comorbidities were less frequently observed compared with older patients (7). By contrast, another previous study reported that tobacco use, immobilization or estrogen use were more common in patients with PE aged <50 years old (30). Smoking was reported as an independent risk factor for VTE in all populations, especially in younger female patients (55,56). A population-based study concluded that the relative risk of VTE in the presence of cancer was highest in patients <50 years of age (57), whilst a study of female patients between the ages of 10 and 29 with PE suggested that oral contraceptive use, pregnancy and post-partum status were predominant factors (58). Other previous studies also demonstrated pregnancy, puerperium, estrogen and oral contraceptive use, family history of VTE and a history of trauma to be more prevalent in younger patients with PE

(ages in three articles were between 21-50 years, 18-40 years and <40 years, respectively) (32,59,60). Inflammatory bowel disease and antiphospholipid syndrome have also been documented to increase the risk of early PE (61,62). The rates of respiratory failure and infection were found to be significantly higher in patients with provoked, compared with those with unprovoked PE (45). Although some risk factors for PE are common among both the young and the elderly, some differences are apparent between the two populations (Table II) (24,63,64).

4. PE pathogenesis and pathophysiology in young patients

PE affects the circulatory and respiratory systems and first develops in the right ventricle (RV), leading to significant right ventricular dysfunction due to increased pressure overload. Severe cases of PE can lead to hemodynamic instability and death at any age (65). Due to RV dysfunction and exacerbated ventricle desynchronization, blood volume in the left ventricle (LV) is reduced, lowering the LV ejection fraction, resulting in systemic hypotension, hemodynamic instability and can lead to death (66). Additionally, low cardiac output results in the mixed venous blood desaturation and a ventilation-perfusion mismatch, contributing to hypoxemia (17). Hypoxemia leads to neurohumoral activation, systemic vasoconstriction, increased pulmonary artery pressure and right ventricular failure (17).

Pulmonary artery pressure increases when blocked by thrombi that are >30-50% of the total cross-sectional area of the artery lumen. When LV filling and ejection fraction are reduced, secondary angina develops, which can result in cardiogenic shock, increasing the risk of mortality (67). PE can induce vasoconstriction and subsequent release of inflammatory cytokines and epinephrine, further contributing to the increased pressure in the pulmonary artery, increases in arterial wall tension, myocyte stretching, elevated biomarkers of myocardial injury, neurohumoral activation and the further activation of coagulation factor (68-70). Although most of the observed direct effects of PE are manifested on the circulatory system, respiratory failure is predominantly a consequence of hemodynamic disturbances as a result of PE (71).

5. Clinical presentation of PE in young patients

PE may be completely asymptomatic, where it is diagnosed incidentally during check-up for other unrelated condition or even at autopsy. In younger patients, presenting signs and symptoms are often nonspecific and insufficient for accurate diagnosis because the incidence is generally lower in young patients compared with that in the elderly and the clinical features of PE in younger patients have not been clearly characterized.

Dyspnea and chest pain are among the most common symptoms reported in younger patients with PE. Additional signs and symptoms of PE include hemoptysis, coughing, tachypnea, tachycardia, syncope, fatigue and hypoxemia (60). Previous studies compared the clinical manifestations of PE between younger and older patients (72,73). Most studies defined those aged <40-50 years old as young patients, whilst others used 65 years as a cut-off point. A previous group study showed that patients <65 years old presented with less dyspnea and syncope compared with those aged >65 years (7), whilst in another study, using a cut-off of 65 years, pleuritic chest pain was found to be more prevalent in patients <65 years, with cyanosis and hypoxia being less frequent (73). An observational retrospective study of younger patients (age ≤45 years) reported that the most frequent symptoms were dyspnea, chest pain and cough (74). Among 61 cases of fatal PE (age, 0-35 years), the predominant symptoms were revealed to be dyspnea, syncope, leg pain and chest pain (34). Other previous studies found no difference in the clinical signs and symptoms between young and elderly patients (7,60,72). An insufficient number of studies have comprehensively and prospectively compared PE symptoms in different age groups, where no single indicator or symptom can accurately diagnose or exclude PE in young patients. Therefore, clinicians should use more precise clinical tools and maintain a high index of suspicion when considering PE in younger patients.

6. Anticoagulation therapy in young patients with PE

For decades, antithrombotic regimens for PE consisted of initial treatment with heparin followed by warfarin (75-77). This treatment poses a number of problems associated with the adverse effects of warfarin and the high risk of bleeding events, including frequent laboratory monitoring and dosage changes, a narrow therapeutic range, variable pharmacokinetic profiles, unpredictable anticoagulation outcomes, interactions between food and drug and genetic polymorphism (78). In a previous study, it was found that >70% patients with VTE with high risks of recurrence did not comply with warfarin therapy, where >50% discontinued warfarin therapy within 1 year (79). The primary reasons for changing the treatment regimen included difficulties in managing the international normalized ratio (INR) instability and patient choice. In the EINSTEIN-DVT and EINSTEIN-PE trials, the INRs of patients receiving warfarin were only 62.7 and 57.7% within the therapeutic range, respectively (14,15). These values underscore the difficulties associated with managing the warfarin treatment regimen. Due to unstable vitamin K absorption and metabolism, frequent hospital visits are required for the routine monitoring of coagulation whilst under warfarin treatment (80,81), which is a source of great inconvenience for patients.

NOACs are small molecules that directly inhibit the activated coagulation factor Xa (12). NOACs, including apixaban, edoxaban and rivaroxaban, have similar pharmacological characteristics. The EINSTEIN-DVT and EINSTEIN-PE trials involving patients aged >18 years (14,15) indicated that rivaroxaban was effective in patients with PE of all ages, including young patients (>18 and <50 years). Apixaban and edoxaban also demonstrated promising results for the treatment of VTE in all age groups (82,83). The application of apixaban for the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis as First-line Therapy (AMPLIFY) trial compared single oral apixaban treatments with conventional therapy in 5,395 patients with acute VTE (84). The primary efficacy outcome of the AMPLIFY study was recurrent symptomatic VTE or death related to VTE and the results demonstrated that apixaban was non-inferior compared with conventional therapy for the primary efficacy outcome, where major bleeding occurred less frequently than with conventional therapy. The

Table III. Phase III rivaroxaban safety and efficacy clinical trials in selected subgroups (14,15).

Age (years)	Recurrent VTE		Clinically relevant bleeding	
	Rivaroxaban, n/N (%)	Enoxaparin + VKA, n/N (%)	Rivaroxaban, n/N (%)	Enoxaparin + VKA, n/N (%)
A, EINSTEIN-DVT				
2<65	26/1145 (2.3)	30/1111 (2.7)	86/1134 (7.6)	70/1107 (7.1)
65-75	6/371 (1.6)	11/382 (2.9)	34/369 (9.2)	39/381 (10.2)
>75	4/215 (1.9)	10/225 (4.4)	19/215 (8.8)	20/223 (9.0)
B, EINSTEIN-PE				
<65	29/1461 (2.0)	23/1479 (1.6)	132/1458 (9.1)	136/1472 (9.2)
65-75	10/517 (1.9)	8/532 (1.5)	59/514 (11.5)	71/532 (13.3)
>75	11/441 (2.5)	13/401 (3.2)	58/440 (13.2)	67/401 (16.7)
C, EINSTEIN-EXT				
<65	4/360 (1.1)[a]	23/374 (6.2)[a]	22/358 (6.2)[a]	3/373 (0.8)[a]
65-75	3/153 (2.0)	8/121 (6.6)	7/152 (4.6)	1/119 (0.8)
>75	1/89 (1.1)[a]	11/99 (11.1)[a]	7/88 (8.0)	3/98 (3.1)

[a]P<0.05 according to the referenced studies. DVT, deep vein thrombosis; PE, pulmonary embolism; VKA, vitamin antagonist.

composite outcome of major bleeding occurred in 4.3% of the patients in the apixaban group, compared with 9.7% of those in the conventional therapy group (82). In another study, Hokusai-VTE Investigators *et al* (83) compared edoxaban treatment with conventional therapy in 8,240 patients with acute VTE. Edoxaban was also found to be non-inferior compared with warfarin with respect to the primary efficacy outcome of recurrent symptomatic VTE or fatal PE, where the principal safety outcome, major bleeding, occurred less frequently in the edoxaban group. In a study of 938 patients who presented with acute PE and elevated N-terminal-pro hormone brain natriuretic peptide (NT-proBNP) concentrations (≥500 pg/ml), the rate of recurrent VTE was found to be 3.3% in the edoxaban group and 6.2% in the warfarin group (83). In a meta-analysis of NOAC-treated or VKA-treated patients, major bleeding in the critical sites was found to occur less frequently in NOAC-treated patients (85). In particular, there was a significant reduction in intracranial bleeding and in fatal bleeding with patient groups treated with NOACs compared with those treated with VKAs (85).

Rivaroxaban targets specific sites which is a selective direct inhibitor of activated coagulation factor X within the coagulation cascade (86). Advantages of using rivaroxaban include fewer drug interactions and a more predictable pharmacological profile compared with warfarin, thereby minimizing the need for routine laboratory monitoring and frequent dose adjustments. Rivaroxaban has garnered attention for the treatment of PE, especially in young patients (87). It is readily available and was approved in many countries for treating and preventing recurrent VTE whilst offering the same efficacy as warfarin with a lower risk of bleeding. At present, rivaroxaban is approved for the prevention of stroke in nonvalvular atrial fibrillation (88), prevention and treatment of DVT and PE (14,15) and prophylaxis against DVT after knee and hip replacement surgery (89). A recent study indicated that patients with stable atherosclerotic vascular disease achieved superior cardiovascular outcomes following treatment with rivaroxaban and aspirin (90). Results from the EINSTEIN-DVT (65.5% of participants aged <65 years), EINSTEIN-PE (60.9% of participants aged ≤65 years) and EINSTEIN-EXT trials (61.4% of participants aged ≤65 years) demonstrated that rivaroxaban was non-inferior compared with warfarin with respect to efficacy (Table III) and may confer a superior safety profile (14,15). These findings also applied to younger patients.

A real-world study (a non-randomized, practical clinical study based on the patient's actual condition and willingness) involving 103 patients with PE (including 27 patients aged <50 years old) suggested that rivaroxaban provided advantages over warfarin (exhibiting, fast-start action pharmacokinetic and pharmacodynamic characteristics, and has an enhanced predictable anticoagulant effect with fewer drug-drug interactions) (22), whilst another study found that patients with VTE who continued rivaroxaban therapy after the initial 3- or 6 month treatment period had a significantly lower risk of VTE recurrence without a statistically significant increased risk for major bleeding (91). Among 13,609 rivaroxaban and 32,244 warfarin users with VTE, rivaroxaban was found to be

Table IV. Laboratory test results on admission and at 90-day follow-up.

Result	On admission	Follow-up at 90 days	Reference range
Total protein (g/l)	46.40	64.2	65.0-85.0
Albumin (g/l)	16.80	38.4	40.0-55.0
Urine protein/24 h (mg)	2,668.00	208.12	0-00.00
Proteinuria	3+	Negative	Negative
TC (mmol/l)	8.97	6.75	2.60-6.00
LDL-C (mmol/l)	6.10	3.3	2.07-3.10
D-dimer (pg/ml)	>20	1.04	<0.50
PaO_2 (mmHg)	59.00	93.2	80.0-100.0
$PaCO_2$ (mmHg)	35.00	43.5	35.0-45.0
SaO_2 (%)	93.00	97.5	95.0-98.0

LDL-C, low-density lipoprotein-cholesterol; Pa, partial pressure; SaO_2, blood oxygen saturation, TC, total cholesterol.

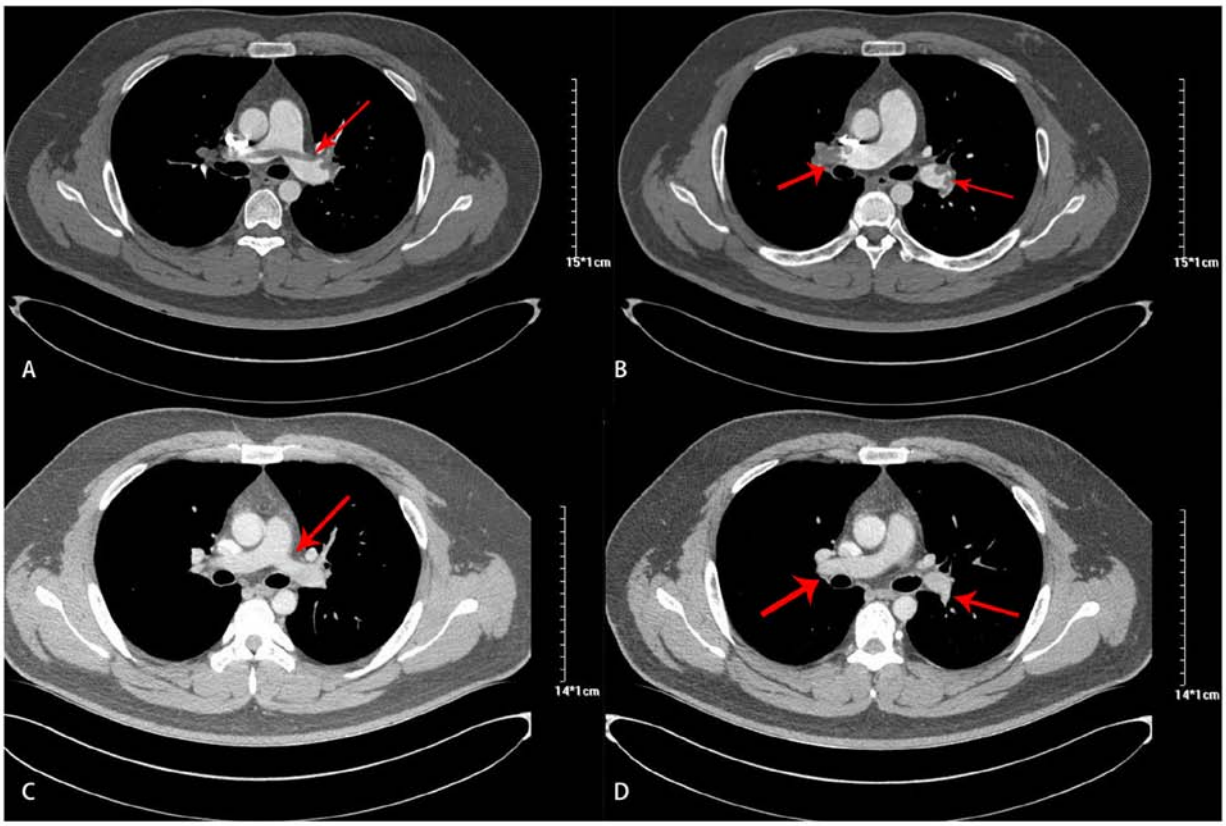

Figure 1. Results of computed tomography pulmonary angiography before rivaroxaban treatment and after 90 days of rivaroxaban treatment. (A and B) CTPA was performed to confirm diagnosis and showed intraluminal filling defects representing thromboses in the bilateral pulmonary artery trunk and branches; (C and D) Follow-up CTPA was normal after 90 days on rivaroxaban. CTPA, Computed tomography pulmonary angiography (indicated by red arrows).

associated with less recurrent VTE and reduced risk of major bleeding compared with warfarin (92). In a clinical setting, rivaroxaban use in patients with unprovoked VTE was demonstrated to be associated with reduced risk of recurrent VTE compared with standard treatment (93). In a study comparing 2,619 patients on rivaroxaban and 2,149 on standard anticoagulant therapy, rivaroxaban-treated patients had a lower risk profile at baseline compared with those treated with standard anticoagulation, where the rates of major bleeding and recurrent VTE were low in rivaroxaban-treated patients (94). Despite the lack of younger PE patient analysis, the previous studies aforementioned included younger patients with PE and found that they achieved good outcomes with rivaroxaban.

In a retrospective observational study comparing the length of stay in hospitals (LOS) and hospitalization costs for patients with VTE treated with rivaroxaban compared with those treated with warfarin, the mean LOS was found to be significantly shortened by 1.57 days in the rivaroxaban treatment group, where

the hospitalization costs were also significantly lower (95,96). In the EINSTEIN trials, rivaroxaban was demonstrated to be associated with a shorter LOS, which was consistent across all included hospitals and countries as patients did not need to remain hospitalized during the transition from heparin/warfarin to warfarin (14,15). Subsequent economic assessments of the EINSTEIN trials demonstrated that rivaroxaban was associated with increased cost effectiveness and increased quality-adjusted years of life (82,97).

7. Alternative treatment methods in young patients with PE

Although anticoagulation is crucial to PE treatment, including that in younger patients, other treatment methods can provide better outcomes in certain cases. Thrombolytic therapy using recombinant tissue-type plasminogen activator, streptokinase or urokinase have been shown to result in faster improvements in pulmonary obstruction (98) with the associated significant reductions in the risk of hemodynamic decompensation or collapse, despite an increased risk of severe extracranial and intracranial bleeding (99). Percutaneous catheter-directed treatment and endovascular thrombolysis by means of catheter are also important alternatives for PE treatment (100). Vena cava filters can mechanically prevent venous clots from reaching the pulmonary circulation. Most filters in current use are inserted percutaneously and can be retrieved after several weeks or months, or left in place long-term in patients with contraindications to anticoagulant treatment or recurrent PE despite adequate anticoagulation (101).

8. Adverse effects or toxicity associated with rivaroxaban

Despite fewer interactions which may cause unpredictable anticoagulation outcomes with rivaroxaban and other NOACs, every patient should be considered on a personalized basis, especially when a combination of interfering underlying factors is present. NOACs differ in their rates of absorption, distribution, metabolism and excretion. An important interaction for all NOACs involves significant gastrointestinal re-secretion through the P-glycoprotein (P-gp) transporter following absorption (88). Many drugs used in patients with PE are either inhibitors of P-gp and cytochrome P450 family 3 subfamily A member 4 (CYP3A4) or activators affecting plasma NOAC concentrations (102). Rivaroxaban is generally not recommended in combination with drugs that are strong inhibitors of CYP3A4 and/or P-gp. Conversely, strong activators of P-gp and/or CYP3A4 markedly reduce NOAC plasma levels (88). In phase III VTE trials, the dosages of rivaroxaban and apixaban were not reduced in patients with creatinine clearance (CrCl) at 30-60 ml/min (mild-moderate renal dysfunction), whilst patients with CrCl <30 ml/min were required to avoid rivaroxaban and edoxaban and were not enrolled in the study (12,82,83). Advanced age, frailty and low weight are associated with higher risks of bleeding, where a reduction in the dose of rivaroxaban is required (103).

9. A case report

A 28 year-old male with a 10 year smoking history was admitted to the hospital following a cough and gradually worsening dyspnea over 10 days. Upon arrival, the heart rate was 95 beats/min, blood pressure at 140/84 mmHg, respiratory rate at 23 breaths/min and oxygen saturation of 93% on room air. His physical examination results were normal. Complete blood cell count, liver function and renal function tests did not reveal abnormalities. Cardiac troponin-T and NT-proBNP levels were also normal. However, urinalysis showed 3+ proteinuria, where blood tests indicated low plasma total protein and albumin, high low-density lipoprotein (LDL) and elevated D-dimer levels. Arterial blood gas analysis was indicative of hypoxemia (Table IV). Echocardiography and lower extremity venous compression ultrasound results were also normal. Since PE was highly suspected based on the patient's clinical presentation, hypoalbuminemia, hypoxemia and high D-dimer levels, computed tomography pulmonary angiography (CTPA) was performed to confirm the diagnosis, which showed intraluminal filling defects representing thromboses in the bilateral pulmonary artery trunk and branches (Fig. 1A and B). Nephrotic syndrome (NS) due to minimal change disease and PE were diagnosed by renal biopsy and CTPA, respectively. The patient therefore received oral prednisone treatment. PE risk stratification was performed to determine the simplified PE severity index (sPESI) and guide treatment strategy. His initial stratification was determined as 'not high-risk' with a sPESI of 0. Therefore, anticoagulation therapy with 15 mg rivaroxaban twice daily was initiated. The patient was discharged from the hospital after 10 days. After 3 weeks, the rivaroxaban dose was reduced to 20 mg once daily and prednisone was continued. At follow-up 90 days after discharge, the symptoms had disappeared and the laboratory results, including those of plasma total protein and albumin, 24 h urine protein quantification, total cholesterol and LDL, D-dimer and arterial blood gas levels had nearly normalized (Table IV). Repeat CTPA yielded normal results after 90 days on rivaroxaban (Fig. 1C and D), following which the drug was discontinued.

In summary, NS was identified as a risk factor in the young patient with PE. The pathological process of NS involves increased glomerular permeability resulting in leakage of albumin through the glomerulus into the urine. As hypoalbuminemia occurs, the plasma colloid osmotic pressure decreases, inducing water movement from the blood to the tissues. This, in turn, decreases the circulating blood volume and leads to increased levels of blood coagulation factors. Concurrently, the liver increases production of many substances, including albumin, coagulation factors, cholesterol and LDL, whereas the kidney reduces the excretion of these substances (except albumin), leading to an imbalance between procoagulant and anticoagulant factors, thereby triggering thrombosis (104). The patient, in this case, presented with normotension without RV injury and elevated biomarkers and was classified as 'low-risk' based on the 2014 European Society of Cardiology guidelines for PE (17). Therefore, rivaroxiban was used for 3 months as recommended by the guidelines (17), producing satisfactory results.

10. Conclusions

The incidence of PE in young populations remain unclear due to differing definitions of youth across previous studies,

ranging from 40 to 65 years. Since there is also limited understanding on the clinical features of PE, anticoagulant treatment selection difficult for younger patients. Although existing guidelines, randomized controlled trials and large clinical studies lacked subgroups of young patients, they did include younger patients. Real-world studies also provided valuable insights into PE in this particular population. The present literature review suggests that the incidence of PE in the younger population should not be ignored, especially for individuals presenting with the various risk factors mentioned in the present article. Unprovoked risk factors pose a potential threat to young subjects and can lead to long-term hypercoagulation. Screening for hereditary causes should also be performed, followed by monitoring. Smoking and obesity are among the concerning provoked causes of PE in younger patients. Based on existing guideline, the results of large phase III clinical studies and real-life studies, rivaroxaban is demonstrated to be safe and effective, providing a new anticoagulant treatment option for young patients with PE.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

HW and HC made substantial contributions to the conception and design of the study and wrote the original draft of the manuscript. ZS and XX conducted data analysis and interpretation. MT, SY and YL were responsible for data acquisition. LQ designed the current article and revised it critically for important intellectual content. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Ethics approval was waived by The First Hospital of Jilin University Ethical Board (Changchun, China), based on their policy of reviewing all intervention and observational studies, except for case reports.

Patient consent for publication

All patients provided informed consent for the publication of his clinical data. The presented data are anonymized and the risk of identification is minimal.

Competing interests

The authors declare that they have no competing interests.

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