

# Efficacy of low-dose rivaroxaban in an 88-year-old female with pulmonary embolism

## A case report

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### Abstract

**Rationale:** Rivaroxaban has numerous advantages over traditional anticoagulation therapy. Fixed doses can be administered without requiring routine monitoring of coagulation, and anticoagulation efficacy is more predictable. Safety, including fewer drug interactions, and reduced bleeding, is also improved with rivaroxaban based on current recommendations. The goal of this report was to explore if low-dose rivaroxaban 10 mg once daily was effective in an elderly patient who developed minor bleeding when treated with rivaroxaban (10 mg twice daily) for a pulmonary embolism.

**Patient concerns:** We present an 88-year-old female with dyspnea and fatigue, which became increasingly worse over a month in the absence of medication. Her weight was 64 kg. Routine coagulation assays and renal function were normal at time of admission.

**Diagnosis:** Deep vein thrombosis and pulmonary embolism were confirmed by venous compression ultrasonography and computed tomography pulmonary angiography.

**Interventions:** Oral rivaroxaban 10 mg twice daily was administered, but the patient developed hemoptysis and gum bleeding 5 days later. The dose of rivaroxaban was reduced to 10 mg once daily, and bleeding gradually disappeared after 3 days.

**Outcome:** At follow-up 90 days after treatment, the patient reported no discomfort. Venous compression ultrasonography and computed tomography pulmonary angiography showed normal results; therefore, treatment was terminated.

**Lessons:** Elderly patients exhibit variable tolerance of anticoagulants, warranting careful consideration of the risk of bleeding. Low-dose rivaroxaban was an effective treatment for pulmonary embolism in the elderly patient presented here.

**Abbreviations:** DVT = deep vein thrombosis, eGFR = estimated glomerular filtration rate, NT-proBNP = N-terminal pro-brain natriuretic peptide, PaO<sub>2</sub> = arterial oxygen partial pressure, PE = pulmonary embolism, VTE = venous thromboembolism.

**Keywords:** bleeding, deep vein thrombosis, low-dose, pulmonary embolism, rivaroxaban, venous thromboembolism

## 1. Introduction

Elderly patients have a significantly higher risk of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), and exhibit worse outcomes compared with younger adults.<sup>[1,2]</sup> Multiple factors contribute to this increased risk are poorly understood. The main treatment for VTE in elderly patients is anticoagulation therapy. Randomized clinical trials demonstrate that novel oral anticoagulants (NOACs) have non-inferior efficacy and potentially superior

safety compared with vitamin K antagonists (VKAs).<sup>[3–6]</sup> The EINSTEIN-PE study established that rivaroxaban exhibits a significantly lower risk of bleeding than observed with VKAs. Thus, rivaroxaban may offer improved safety and efficacy as an anticoagulation therapy in elderly patients.<sup>[7]</sup> Current guidelines provide little information regarding diagnosis and treatment of elderly patients with VTE. Therefore, clinicians need to establish a safe and effective dose of oral rivaroxaban for use in elderly patients with VTE.

Here, we report an 88-year-old female with DVT and PE. Despite hemoptysis and gum bleeding after 5 days of oral rivaroxaban (10 mg twice daily), treatment was continued at a reduced dose of 10 mg once daily. The patient reported no discomfort at her 90-day follow-up exam. In addition, venous compression ultrasonography and computed tomography pulmonary angiography showed normal results. The patient had a good outcome, and treatment was discontinued.

## 2. Case presentation

An 88-year-old female presented with dyspnea and fatigue, which became increasingly worse over a month was admitted to the hospital. Her symptoms were worse after mild activity and resolved after rest without medication. She had a 60-year history of smoking. She was fully conscious at the time of admission and had a blood pressure of 135/64 mm Hg, regular heart rate of 100

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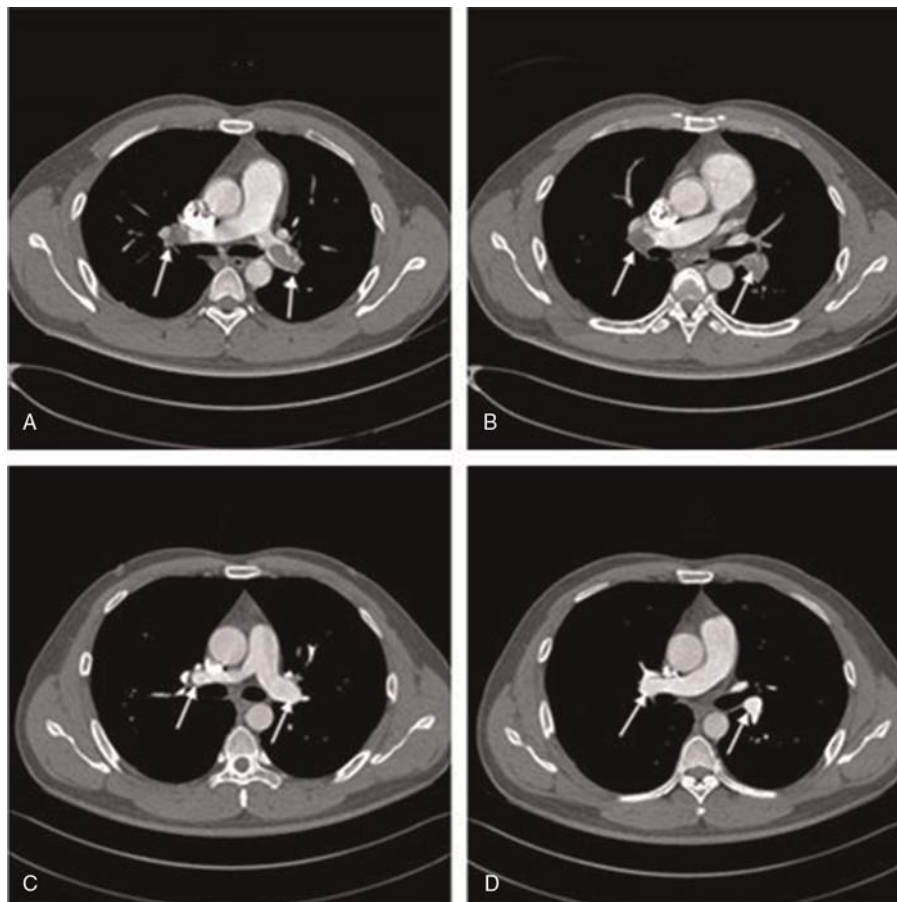
**Table 1****Laboratory results and drug dosage around the time in hospital and at follow-up.**

Results	On admission (10 mg twice daily)	5th d after treatment (10 mg once daily)	20th d after treatment (10 mg once daily)	90th d after treatment (10 mg once daily)	Reference range
P <sub>a</sub> O <sub>2</sub> , mm Hg	62.6	73.4	90.4	93.3	80.0–100.0
eGFR, mL/min	82.1	81.9	79.4	82.7	80
NT-proBNP, pg/mL	2673	107	562	277	<450
D-Dimer, pg/mL	9.37	4.66	1.62	0.39	<0.5
HGB, g/L	129	132	129	125	115–150
INR	0.96	1.11	0.86	1.32	0.84–1.27
PT, s	12.6	11.7	15.6	14.1	11.0–15.0
aPTT, s	33	37.1	29.6	40.8	28.0–42.5

aPTT=activated partial thromboplastin time, eGFR=estimated glomerular rate, HGB=hemoglobin, INR=international normalized ratio, NT-proBNP=N-terminal pro-brain natriuretic peptide, P<sub>2</sub>O<sub>2</sub>=partial pressure of oxygen, PT=prothrombin time.

bpm on auscultation, and oxygen saturation of 93% on room air. She had mild edema in her lower limbs. Her weight was 64 kg. The remainder of her physical examination was normal. Laboratory tests revealed normal platelets, hemoglobin, electrolytes, cardiac troponin-T, liver function, and renal function, including serum creatinine and estimated glomerular filtration rate. Routine coagulation measurements, including prothrombin time, international normalized ratio, and activated partial thromboplastin time, were also normal. However, N-terminal pro-brain natriuretic peptide (NT-proBNP) and D-dimer levels

were elevated, and arterial blood gas (PaO<sub>2</sub>) was lower than normal (Table 1). Electrocardiogram and transthoracic echocardiogram results were normal. Lower limb venous compression ultrasonography showed a DVT involving bilateral intermuscular veins. Computed tomography pulmonary angiography confirmed the presence of an embolus in the main right and left pulmonary artery (Fig. 1A and B). The simplified pulmonary embolism severity index score was 0, and risk stratification of PE was moderate. Considering her age and risk of bleeding, treatment was initiated with 10 mg rivaroxaban twice daily



**Figure 1.** Intraluminal filling defects representing thromboses in the main right and left pulmonary artery (A and B); Disappearance of the intraluminal filling defects after therapy (C and D).

instead of the standard recommendation of 15 mg twice daily. After 5 days of therapy, dyspnea and fatigue improved, D-dimer levels decreased, and arterial blood gases increased (Table 1). At that time, the patient developed hemoptysis and coughed up 100 ml fresh blood and produced 30 ml blood from the gums. Laboratory assays revealed normal platelets, hemoglobin, and coagulation. Rivaroxaban was reduced to 10 mg once daily. Bleeding ceased 3 days later with approximately 280 ml of total blood loss. The patient was hospitalized for 20 days. Symptoms resolved before discharge, with NT-proBNP, D-dimer levels, and PaO<sub>2</sub> returning to normal. However, a DVT involving bilateral intermuscular veins remained present on lower limb venous compression ultrasonography. At her 90-day follow-up evaluation, the patient reported no discomfort, and venous compression ultrasonography and computed tomography pulmonary angiography results were normal (Fig. 1C and D, Table 1). Thus, treatment was terminated. Our case report was waived from the First Hospital of Jilin University Ethical Board, based upon their policy to review all intervention and observational study except for a case report. The patient provided written informed consent for the publication of her clinical data. The presented data are anonymized and risk of identification is minimal.

### 3. Discussion

The annual incidence of an initial VTE is approximately 0.1%; this increases to 0.5% for adults older than 80 years.<sup>[2,8–11]</sup> Individuals may accumulate multiple risk factors for VTE as they age. Elderly patients usually have more than 1 risk factor at diagnosis. Risk factors for VTE in elderly patients include recent hospitalization, cancer, infection, immobility, chronic cardiopulmonary disease, recent surgery, and prior VTE.<sup>[8]</sup> Frailty was also recently identified as a risk factor for VTE in elderly patients.<sup>[12]</sup> Aging is associated with altered levels of coagulation factors and fibrinolytic proteins, activating the coagulation cascade.<sup>[13]</sup> Plasma fibrinogen levels, von Willebrand factor, FVIII levels, and components of the fibrinolytic pathway, such as plasminogen activator inhibitor-1, also increase with aging, contributing to thrombotic risk.<sup>[14]</sup> These unique aspects of anticoagulation should be considered when deciding on initial treatment, dosage, and risk of bleeding in elderly patients.<sup>[15]</sup> Although our patient was elderly, she did not have multiple risk factors for VTE. However, she had characteristics consistent with hypercoagulation. In a case with moderate risk stratification for PE, such as with the current patient, anticoagulation therapy should be initiated immediately.

Rivaroxaban is a novel, target-specific anticoagulant approved for prevention of stroke in patients with nonvalvular atrial fibrillation, prevention of DVT in patients who received knee or hip replacement, and treatment or prevention of recurrence of DVT and PE.<sup>[16]</sup> Rivaroxaban binds plasma proteins strongly (>90%), peaks in plasma 2 to 4 hours after oral administration, and has a half-life of 5 to 9 hours in healthy, young adults or 11 to 12 hours in elderly patients. Rivaroxaban has a dual mode of elimination, with two-thirds of the administered drug metabolized by the liver and one-third excreted in an unaltered form by the kidneys. Rivaroxaban requires fewer considerations for food and drug interactions and exhibits improved efficacy and safety profiles than those of VKAs.<sup>[17]</sup> Rivaroxaban displays linear pharmacokinetics; thus, therapeutic laboratory monitoring is not required, and changes in routine coagulation are rare.<sup>[18]</sup> Three large studies (EINSTEIN-PE, -DVT, and -EXT) evaluated bleeding

events with rivaroxaban as a treatment for recurrent VTE.<sup>[19–21]</sup> Results from EINSTEIN-DVT showed that rivaroxaban is equivalent to standard treatment in the overall population, including elderly and frail patients and those with renal insufficiency. Further, EINSTEIN-EXT demonstrated that rivaroxaban extended VTE protection beyond that achieved by placebo. Patients enrolled in EINSTEIN-PE, -DVT, and -EXT included 34.5%, 39.1%, and 38.6%, respectively, who were older than 65 years. The primary safety outcome of major or clinically relevant non-major bleeding was equivalent in control groups.

Guidelines on the diagnosis and management of acute PE recommend oral rivaroxaban 15 mg twice daily for 21 days followed by 20 mg daily for treatment of DVT and PE.<sup>[22]</sup> To reduce bleeding events, the elderly patient in this case report was administered oral rivaroxaban 10 mg twice daily for the first 21 days of treatment instead of the standard dose of 15 mg twice daily. Her clinical symptoms and laboratory results improved within 5 days. However, minor bleeding in the form of hemoptysis and gum bleeding developed. Thus, our proof-of-concept and dose-finding case study suggests that oral rivaroxaban (10 mg once daily) may be an effective and safe treatment for DVT. After weighing thrombosis and bleeding, rivaroxaban was reduced to 10 mg once daily. Finally, the patient recovered after 3 months of oral rivaroxaban (Fig. 1, Table 1), and therapy was discontinued.

In summary, age-related changes, including decreasing body size, occur continuously but are most pronounced after 75 to 80 years of age. Higher serum concentrations of a given dose of drug are generally found in elderly patients than in younger patients. Age-based dose adjustments have previously been reported in elderly, low-weight, and female patients, especially those with a narrow therapeutic index.<sup>[23]</sup> Elderly patients have increased risk and incidence of PE and DVT and exhibit poor outcomes. Although NOACs have fewer drug interactions than older anticoagulants, pharmacokinetic interactions with co-administered drugs and comorbidities must still be considered. There is rationale for reducing the dose of NOACs in patients at high risk of bleeding. Individualized therapy for elderly patients is critical. Currently, the NOAC rivaroxaban is recognized as a safe and effective treatment option in a subset of elderly patients, with a reduced dose recommended for minor bleeding to obtain adequate anticoagulation efficacy.

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### Author contributions

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### References

- [1] Mitchell AP, Conway SE. Rivaroxaban for treatment of venous thromboembolism in older adults. *Consult Pharm* 2014;29:627–30.
- [2] Stein PD, Hull RD, Kayali F, et al. Venous thromboembolism according to age: the impact of an aging population. *Arch Intern Med* 2004;164:2260–5.

- [3] Investigators E, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499–510.
- [4] Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369:799–808.
- [5] Hokusai VTEI, Buller HR, Decousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369:1406–15.
- [6] Geldhof V, Vandenbrielle C, Verhamme P, et al. Venous thromboembolism in the elderly: efficacy and safety of non-VKA oral anticoagulants. *Thromb J* 2014;12:21–31.
- [7] Investigators E-P, Buller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366:1287–97.
- [8] Engbers MJ, van Hylckama Vlieg A, Rosendaal FR. Venous thrombosis in the elderly: incidence, risk factors and risk groups. *J Thromb Haemost* 2010;8:2105–12.
- [9] Spencer FA, Gore JM, Lessard D, et al. Venous thromboembolism in the elderly. A community-based perspective. *Thromb Haemost* 2008;100:780–8.
- [10] Spencer FA, Gurwitz JH, Schulman S, et al. Venous thromboembolism in older adults: a community-based study. *Am J Med* 2014;127:530–7.
- [11] Ageno W, Agnelli G, Imberti D, et al. Risk factors for venous thromboembolism in the elderly: results of the master registry. *Blood Coagul Fibrinolysis* 2008;19:663–7.
- [12] Folsom AR, Boland LL, Cushman M, et al. Frailty and risk of venous thromboembolism in older adults. *J Gerontol A Biol Sci Med Sci* 2007;62:79–82.
- [13] Mohebali D, Kaplan D, Carlisle M, et al. Alterations in platelet function during aging: clinical correlations with thromboinflammatory disease in older adults. *J Am Geriatr Soc* 2014;62:529–35.
- [14] Johnson SA, Eleazer GP, Rondina MT. Pathogenesis, diagnosis, and treatment of venous thromboembolism in older adults. *J Am Geriatr Soc* 2016;64:1869–78.
- [15] Ho P, Brooy BL, Hayes L, et al. Direct oral anticoagulants in frail older adults: a geriatric perspective. *Semin Thromb Hemost* 2015;41:389–94.
- [16] Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;39:1330–93.
- [17] DeWald TA, Becker RC. The pharmacology of novel oral anticoagulants. *J Thromb Thrombolysis* 2014;37:217–33.
- [18] Song Z, Wu H, Cao H, et al. Routine coagulation test abnormalities caused by rivaroxaban: a case report. *Medicine (Baltimore)* 2018;97:e13104.
- [19] Wells PS, Prins MH, Levitan B, et al. Long-term anticoagulation with rivaroxaban for preventing recurrent VTE: a benefit-risk analysis of EINSTEIN-extension. *Chest* 2016;150:1059–68.
- [20] Konstantinides SV. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;35:3145–6.
- [21] Agnelli G, Gallus A, Goldhaber SZ, et al. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (oral direct factor Xa inhibitor BAY 59-7939 in patients with acute symptomatic deep-vein thrombosis) study. *Circulation* 2007;116:180–7.
- [22] Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;35:3033–69.
- [23] Kubitzka D, Becka M, Roth A, et al. Dose-escalation study of the pharmacokinetics and pharmacodynamics of rivaroxaban in healthy elderly subjects. *Curr Med Res Opin* 2008;24:2757–65.