

BRIEF REPORT

Sex-specific differences in clot resolution 3 weeks after acute pulmonary embolism managed with anticoagulants—A substudy of the EINSTEIN-PE study

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Abstract

Background: It is unknown whether differences in clot structure and resolution contribute to the reported risk differences of recurrent venous thromboembolism (VTE) between men and women.

Patients/Methods: We used data from the EINSTEIN-PE study, a randomized, multicenter, non-inferiority study in which patients 18 years and older with acute symptomatic pulmonary embolism (PE) were randomized to rivaroxaban or enoxaparin followed by a vitamin K antagonist. PE was diagnosed by computed tomography pulmonary angiography scan or high-probability ventilation/perfusion scintigraphy. Three weeks after randomization a follow-up scan was performed. An independent adjudication committee assessed the degree of vascular obstruction.

Results and Conclusions: A total of 371 participants including 174 (46.9%) women and 197 (53.0%) men were included in the present analysis. At 3 weeks, there was no difference between men and women in complete clot resolution: 39.6% and 40.2%, respectively. The absolute reduction in pulmonary vascular obstruction at week 3 was also similar: 12.9% (95% confidence interval [CI]: 11.6–14.2) in men and 12.1% (95% CI: 10.4–13.7) in women, corresponding to a resolution ratio of 0.29 (95% CI: 0.24–0.33) and 0.35 (95% CI: 0.28–0.42), respectively. No differences in clot resolution were observed between men and women diagnosed with acute PE at 3 weeks after start of anticoagulant therapy. These findings suggest that the reported higher rate of VTE recurrence in men cannot be explained by decreased clot resolution.

KEYWORDS

anticoagulants, pulmonary embolism, recurrence, sex characteristics, thrombosis

Manuscript handled by: Zhi-Cheng Jing

Final decision: Zhi-Cheng Jing, 05 April 2021

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1 | BACKGROUND

The clinical presentation of venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), differs distinctly between men and women. First, men have on average a two-fold increased risk of a recurrent VTE compared to women.¹ In part, this can be partly explained by the circumstances surrounding the first thrombotic event. Women, especially under the age of 50 years, typically have VTE in the presence of a transient risk factor such as hormone use or pregnancy. Men, on the other hand, more frequently experience an unprovoked VTE event, that is, VTE in the absence of an apparent provoking risk factor.² As risk factors for VTE in men are probably more often intrinsic and thus permanent, the subsequent risk of a recurrent event is higher. Second, the presenting location of a first VTE seems to differ between men and women.³ In women, PE is more frequently the presenting location, whereas in men DVT without a clinical suspicion of PE is more often observed.³

In a previous analysis of the EINSTEIN-PE study,⁴ complete clot resolution was found in approximately 40% of patients after 3 weeks of anticoagulant therapy. It is not known whether differences in clot structure contribute to the observed risk differences between men and women. For example, more resilient and potentially persistent clots in men could contribute to the higher observed risk of recurrence compared to women, and less resilient clots in women could result in higher embolization rates and thus a more frequent presentation as PE. Therefore, if clot resolution were lower in men than in women, this would provide suggestive evidence toward a potential explanation.

In the present subgroup analysis of the EINSTEIN-PE study, we investigated differences in clot resolution between men and women with symptomatic PE managed with therapeutic anticoagulants.

2 | METHODS

2.1 | Patients

We used data from the EINSTEIN-PE study as described in detail previously.⁴ The EINSTEIN-PE study was a randomized, open-label, non-inferiority study in which patients 18 years and older who presented with acute PE with or without DVT were included.⁵ Diagnosis of PE was established by computed tomography pulmonary angiography (CTPA) scan or high-probability ventilation-perfusion scintigraphy, depending on its availability in the participating hospitals. Participants provided written informed consent. All review boards of the participating hospitals approved the study protocol.

The main exclusion criteria of the EINSTEIN-PE study were treatment of the index event with either heparins for more than 48 h, more than a single dose of vitamin K antagonists (VKA), thrombectomy, vena cava filter, or fibrinolytic therapy; a creatinine clearance below 30 ml per minute; clinically significant liver disease; active bleeding or a high risk of bleeding contraindicating anticoagulant treatment;

Essentials

- Sex-specific differences in clot resolution in pulmonary embolism (PE) have not been studied.
- Clot resolution was studied after 3 weeks of anticoagulation in 371 patients with acute PE.
- No differences in clot resolution were observed between men and women.
- Increased recurrence risk in men is not explained by differences in clot resolution.

childbearing potential without proper contraceptive measures; pregnancy; or breast-feeding. Patients were randomized to either rivaroxaban (15 mg twice-daily for 3 weeks, followed by 20 mg once-daily) or comparator treatment with enoxaparin/VKA, with a target international normalized ratio (INR) between 2.0 and 3.0. Patients randomized to comparator treatment received initial enoxaparin therapy for at least 5 days until the INR was >2.0 on two separate measurements. The first 400 randomized patients of the EINSTEIN-PE study participated in the pulmonary vascular obstruction (PVO) substudy, which required a repeated CTPA or perfusion scan 3 weeks from randomization.^{4,6,7} Patients were excluded from the PVO substudy if the repeated scan was not obtained or performed before day 10 or after day 27 after randomization. Patients who had confirmed fatal or non-fatal PE up to day 27 were included and results of the confirmatory scan were used. If no scan was available, the patient was assigned the worst PVO value observed at week 3 in the entire cohort.

2.2 | Imaging protocols to confirm the diagnosis of PE

Standard contrast-enhanced CTPA scans were used with a multidetector row CT scanner, according to state-of-the-art protocols⁸ and ventilation/perfusion scans following the guidelines of the Society of Nuclear Medicine and Molecular Imaging.⁹ For this analysis, only the perfusion scans were used. A detailed description of the standard protocol for CTPA scans and perfusion scans has been provided elsewhere.⁴

2.3 | Assessment of pulmonary vascular obstruction

Baseline and repeated CTPA- and perfusion scans were assessed by the central and independent adjudication committee, which was blinded for treatment allocation, sex, and other clinical details. The percentage of PVO was calculated for each pulmonary lobe and given a score of 0 (normal perfusion), 25, 50, 75, or 100 (no perfusion).^{4,10,11} The calculated PVO was the total sum of the separate lobes with the right lung contributing 55% and the left lung 45% of the total sum.

2.4 | Statistical analyses

Individual absolute (i.e., PVO at 3 weeks minus PVO at baseline) and relative (i.e., ratio of PVO at 3 weeks and PVO at baseline) changes in PVO were calculated and summarized for men and women separately. Linear regression models were applied to assess differences in absolute change of PVO and their 95% confidence intervals (CI) between men and women, adjusted for baseline PVO, age, presentation of index event (i.e., unprovoked or provoked PE), PE with or without DVT, and treatment group (i.e., rivaroxaban or enoxaparin/VKA) overall and per imaging modality.

3 | RESULTS AND DISCUSSION

3.1 | Patients

A total of 400 patients who were enrolled in the EINSTEIN-PE study with documented acute PE were potentially eligible for the present analysis. Of these patients, 29 were excluded because of a missing repeated scan and no recurrent PE ($n = 21$) or performance of the repeated scan after the time window ($n = 8$). Three patients developed recurrent PE before day 27, of whom one had lung scan result imputed because of a missing repeated scan. Therefore, 371 patients were included for this analysis (Table 1) of whom 197 (53.1%) were men (mean age 58.1 years) and 174 (46.9%) were women (mean age 57.9 years). PE was unprovoked in 136 (69.0%) men and 102 (58.6%) women. A total of 108 men (54.8%) and 82 (47.1%) women had been allocated to receive rivaroxaban.

3.2 | Pulmonary vascular obstruction

Table 2 shows PVO results at baseline and at week 3. Complete clot resolution was observed in 78 (39.6%) men and in 70 (40.2%) women. The mean PVO at baseline was 19.7% (95% CI: 17.1–20.9) and 17.9% (95% CI: 15.5–18.5) in men and women, respectively, which was reduced to 6.8% in men and 5.8% in women at week 3, for an absolute reduction in PVO at 3 weeks of 12.9% (95% CI: 11.6–14.2) and 12.1% (95% CI: 10.4–13.7). Therefore, the relative change in PVO was 0.29 and 0.35, respectively.

The results of the adjusted linear regression models are shown in Table 3. The mean change in PVO between baseline and week 3 was -12.6 (95% CI: -13.4 to -11.8) in men and -12.5 (95% CI: -13.7 to -11.2) in women, for a difference between men and women of -0.1 (95% CI: -1.6 to 1.3). Similar results were observed for those who had repeated CTPA or repeated perfusion scans ($p_{\text{interaction}}, 0.16$) and by treatment group ($p_{\text{interaction}}, 0.42$).

In this in-depth analysis of the EINSTEIN-PE study, no differences were observed between men and women in complete clot resolution after 3 weeks of anticoagulant treatment. Furthermore, no sex-specific changes in percentage PVO were found after 3 weeks. These results were not different for those who received rivaroxaban

TABLE 1 Clinical characteristics of the study population ($N = 371$)

	Men	Women
Total, n	197	174
Age in years, mean (\pm SD)	58.1 (14.9)	57.9 (19.2)
Body mass index in kg/m^2 , mean (\pm SD)	28.2 (5.1)	28.7 (6.7)
History of VTE, n (%)	40 (20.3)	37 (21.3)
Active malignancy, n (%)	19 (9.6)	11 (6.3)
Use of estrogen-containing drugs	Not applicable	34 (19.5)
Recent surgery or trauma, n (%)	38 (19.3)	28 (16.1)
Prolonged immobilization, n (%)	25 (12.7)	23 (13.2)
Pulmonary diseases, n (%) ^a	22 (11.2%)	27 (15.5%)
COPD	13 (6.6%)	11 (6.3%)
Asthma	6 (3.0%)	16 (9.2%)
Other ^b	4 (2.0%)	6 (3.4%)
Allocated treatment		
Rivaroxaban, n (%)	108 (54.8)	82 (47.1)
Enoxaparin/VKA, n (%)	89 (45.2)	92 (52.9)
Use of platelet aggregation inhibitors	26 (13.2%)	18 (10.3%)
Unprovoked PE	136 (69.0%)	102 (58.6)
Index event		
PE with DVT, n (%)	61 (31.0)	42 (24.1)
PE only, n (%)	136 (69.0)	132 (75.9)

Abbreviations: COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; PE, pulmonary embolism; SD, standard deviation; VKA, vitamin K antagonist; VTE, venous thromboembolism.

^aFrequencies are based on the number of subjects, not the number of events. The subject is counted as once, although a subject may have had 2 or more findings.

^bOther: pneumothorax, bronchiectasis, pulmonary hypertension, pulmonary fibrosis, respiratory failure.

or enoxaparin/VKA and for those whose PE was evaluated by repeated CTPA or repeated perfusion scan.

Our findings suggest that during early treatment of acute PE there are no differences in clot resolution between men and women. Hence, the higher reported risk of recurrent VTE in men compared to women is likely not explained by differences in clot resolution. These findings support the assumption that the higher incidence of recurrence of VTE in men cannot be explained by more persistent thrombus in men, but in more frequent occurrence of new clots. There were no substantial differences in mean baseline PVO between men (19.7%) and women (17.9%), which also does not provide further explanation for the observed difference in presenting location of VTE between men and women.

Previously, PE was demonstrated to be more often the primary location in the presentation of VTE in women,³ which generated the hypothesis that clots could be more resilient in men, and thus would less often embolize and cause a PE, explaining the higher frequency of DVT in men. In our study, there was no difference in clot resolution between men and women, indirectly suggesting no difference in

TABLE 2 Change in percentage of pulmonary vascular obstruction between baseline and week 3 in men and women

	Men (N = 197)		Women (N = 174)		Total (n = 174)
	Rivaroxaban (n = 108)	Enoxaparin/VKA (n = 89)	Rivaroxaban (n = 82)	Enoxaparin/VKA (n = 92)	
Percentage PVO at baseline, mean (SD)	20.5 (14.9)	18.8 (12.5)	17.5 (11.3)	18.2 (10.6)	17.9 (10.9)
Percentage PVO at week 3, mean (SD)	7.5 (10.4)	5.9 (7.6)	6.0 (9.3)	5.6 (6.5)	5.8 (7.9)
Percentage absolute reduction in PVO mean (95% CI)	13.0 (11.2–14.8)	12.9 (10.9–14.8)	11.5 (8.7–14.3)	12.6 (10.6–14.5)	12.1 (10.4–13.7)
Ratio of percentage PVO at week 3/baseline, geometric mean (95% CI)	0.29 (0.23–0.35)	0.29 (0.22–0.35)	0.39 (0.26–0.52)	0.31 (0.24–0.38)	0.35 (0.28–0.42)
Complete resolution of PVO at week 3 (95% CI)					
Complete resolution	43 (30.5–49.7)	35 (29.1–50.3)	33 (29.6–51.7)	37 (30.1–51.0)	70 (32.9–47.9)
No complete resolution	65 (50.3–69.4)	54 (49.7–70.7)	49 (48.3–70.4)	55 (49.0–69.9)	104 (52.1–67.1)

Abbreviations: CI, confidence interval; PVO, pulmonary vascular obstruction; SD, standard deviation; VKA, vitamin K antagonist.

effect of anticoagulant therapy on thrombus load, which could suggest no differences in clot structure for men and women. It should be emphasized that whether true differences in clot structure exist between men and women requires further and different studies. Furthermore, our findings also provide no further explanation for the reported differences in presenting location of VTE between men and women.

Our study has several strengths. We were able to analyze the differences in clot resolution between men and women in a large group of 371 consecutive patients with acute PE and all scans were evaluated independently. Some limitations merit consideration. First, the time window of observation is limited to the initial weeks after presentation of the acute PE. Differences between clot resolution could still occur after this time, as a retrospective study found complete clot resolution in 77.4% of the patients between 29 and 90 days and almost 94.1% clot resolution after 90 days.¹² Second, there might have been inclusion bias, as patients with substantial comorbidity were likely to be excluded from the randomized trial. However, we do not expect this to affect the differences between included men and women. Third, several limitations regarding pulmonary imaging techniques have been proposed;⁴ however, these limitations are not relevant for the current analysis, because men and women both were exposed to these imaging techniques. Although this study provides important mechanistic insight, the direct clinical consequences are limited.

4 | CONCLUSION

In conclusion, no differences in clot resolution were observed between men and women with acute PE after 3 weeks of therapeutic-dose anticoagulant therapy and, therefore, cannot explain the sex-specific clinical differences in VTE that were observed previously.

CONFLICTS OF INTEREST

A.W.A. Lensing and A.F. Pap are employees of Bayer AG, which sponsored the EINSTEIN-PE study and currently markets rivaroxaban. L.J.J.S. received funding for the printing of his doctoral thesis (2019) from the Dutch Heart Foundation, Dutch Federation of Coagulation Clinics, Stichting tot Steun Promovendi Vasculaire Geneeskunde, Bayer, Daiichi Sankyo, LEO Pharma, and Pfizer. S.M. reports grants and personal fees from Bayer, BMS Pfizer, Boehringer Ingelheim, Daiichi Sankyo, and Portola, during the conduct of the study; grants and personal fees from GSK, Aspen; and personal fees from Sanofi, outside the submitted work.

AUTHOR CONTRIBUTIONS

H.M.G. Wiegers and L.J.J. Scheres wrote the manuscript and designed the study. J. van Es and A.W.A. Lensing participated in collecting the data and critically reviewed the final manuscript. A.F. Pap was responsible for the statistical analysis. All authors critically revised and approved the final version of the manuscript.

TABLE 3 Differences in change of pulmonary vascular obstruction between baseline and week 3 based on adjusted linear regression models

	Men mean (95% CI) ^a N = 197	Women mean (95% CI) ^a N = 174	Difference between men and women (95% CI)
Type of lung scan			
All	-12.6 (-13.4 to -11.8)	-12.5 (-13.7 to -11.2)	-0.1 (-1.6 to 1.3)
CTPA scan	-12.8 (-13.7 to -11.8)	-13.2 (-14.4 to -12.1)	0.5 (-1.1 to 2.0)
Perfusion scan	-12.8 (-14.2 to -11.3)	-10.1 (-12.7 to -7.6)	-2.6 (-5.6 to 0.4)

Note: Based on linear regression models, women as reference. Adjusted for baseline PVO, age, type presentation of index event (i.e., unprovoked or provoked PE), PE with or without DVT, and treatment group (i.e., rivaroxaban or enoxaparin/VKA).

Abbreviations: CI, confidence interval; CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; PE, pulmonary embolism; PVO, pulmonary vascular obstruction.

^aLeast-square means.

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How to cite this article: Wiegers HM, van Es J, Pap ÁF, Lensing AW, Middeldorp S, Scheres LJ. Sex-specific differences in clot resolution 3 weeks after acute pulmonary embolism managed with anticoagulants—A substudy of the EINSTEIN-PE study. *J Thromb Haemost*. 2021;19:1759-1763.
<https://doi.org/10.1111/jth.15326>