Optimal length of oral anticoagulant treatment for maximum benefit within 5 years after discontinuation of oral anticoagulants in patients with acute pulmonary embolism who require secondary thromboprophylaxis

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ABSTRACT

Background Extended oral anticoagulant (OA) use is recommended in patients with acute pulmonary embolism (PE) who require secondary thromboprophylaxis. Nevertheless, the optimal length of OA use for the maximum long-term benefit in this patient population has been undefined to date.

Methods A retrospective study was performed to explore the role of different length of overall OA use (group 1 (≥1 year of OA use and <2 years of OA use), group 2 (≥2 years of OA use and <3 years of OA use), group 3 (≥3 years of OA use)) in outcomes within 5 years after OA discontinuation in patients with acute PE, who required secondary thromboprophylaxis. The primary outcome was mortality rates. The secondary outcomes comprised venous thromboembolism (VTE) recurrence, major bleeding during OA use and net clinical benefit. Net clinical benefit was defined as the composite of recurrent VTE and major bleeding.

Results For a total of 385 patients in group 1 (n=220), group 2 (n=110) and group 3 (n=55), the PE-related mortality in group 1 was higher than that in group 2 (p=0.034) and 3 (p=0.040), respectively, whereas were similar between groups 2 and 3 (p=1.000). The net clinical benefit in group 1 was less than that in group 2 (p=0.024), whereas similar with that in group 3 (p=0.526). The net clinical benefit was comparable between groups 2 and 3 (p=0.716). The length of OA use was positively associated with major bleeding (HR, 2.510 (0.293 to 3.485), p=0.001), whereas negatively associated with PE-related mortality (HR, 0.668 (0.196 to 2.832), p=0.025) and VTE recurrence (HR, 0.694 (0.174 to 2.300), p=0.036), respectively. The sensitivity and specificity of the length of OA use for the tendency of PE-related mortality was 70.2% and 46.2%, respectively. The area under the curve (AUC) was 0.654 (0.514 to 0.793) (p=0.029). The sensitivity and specificity of the length of OA use for the tendency of net clinical benefit was 86.8% and 64.3%, respectively. The AUC was 0.628 (0.565 to 0.690) (p<0.001)

Conclusions For patients with acute PE who require secondary thromboprophylaxis, 2 to 3 years (30 months preferred) of overall OA use after a diagnosis of acute PE could be an optimal length to achieve maximum benefit within 5 years after OA discontinuation.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Despite extended oral anticoagulant (OA) use is recommended in patients with acute pulmonary embolism (PE) who require secondary thromboprophylaxis, the optimal length of OA use for the maximum long-term benefit is still unknown to date.

WHAT THIS STUDY ADDS
⇒ The present study indicates that 30 months of overall OA use after the diagnosis of acute PE could be an optimal length to achieve a maximum benefit within 5 years after OA discontinuation, for patients with acute PE who require secondary thromboprophylaxis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ The present study provides a theoretical basis for the length of OA use in patients with acute PE who require secondary thromboprophylaxis, so that they can acquire the maximum clinical benefit.

INTRODUCTION

Pulmonary embolism (PE) is the main manifestation of venous thromboembolism (VTE) besides deep venous thrombosis. It is associated with relatively high morbidity and mortality worldwide. It is also regarded as a chronic illness since it recurs frequently.1-3 For patients with acute PE or a first episode of PE, treatment with oral anticoagulants (OA) for a period of 3 or 6 months is highly recommended by several authoritative guidelines. Nevertheless, after the completion of
the 3 or 6 months of anticoagulation with OA, whether or how the following extended treatment is going to proceed is nuanced. Extended OA treatment also known as secondary thromboprophylaxis is oftentimes recommended for patients with acute PE at high risk of recurrence and low risk of bleeding.4–7

In an observational cohort study of patients with PE who survived an initial phase of 3–6 months anticoagulation, over a mean follow-up duration of 2.1±0.3 years, the adjusted rate of the all-cause death or recurrent VTE was 2.1% in the extended and 7.7% in the non-extended anticoagulant groups, for patients treated with extended anticoagulant therapy (p<0.001). The rate of bleeding was similar between two groups. Extended OA over 2.5 years after index PE provides a net clinical benefit, compared with no anticoagulation in PE patients being selected to receive extended anticoagulation.8

Nevertheless, the role of length of OA treatment in long-term outcome such as 5 years after OA discontinuation has been understudied to date, despite it has been already recognised that extended OA use is more beneficial than no extended OA use, for patients with acute PE who require secondary thromboprophylaxis. The optimal length of OA use for the maximum benefit within 5 years after OA discontinuation in patients with acute PE requiring secondary thromboprophylaxis has been undefined by far. Consequently, the current study was performed to investigate this subject.

METHODS
Study design
A retrospective study was performed to explore the optimal length of OA treatment for maximum benefit within 5 years after OA discontinuation in patients with acute PE who required secondary thromboprophylaxis. Patients were reviewed if they had an objectively confirmed PE and underwent extended OA treatment for secondary thromboprophylaxis after the completion of at least 6 months of OA treatment following the diagnosis of acute PE and discontinued OA use at least 5 years prior to the current study. The primary outcome was the mortality rates, including all-cause and PE-related mortality within 5 years after OA discontinuation. PE-related mortality was defined as those in which PE or VTE was listed as the underlying cause of death.9 The secondary outcomes comprised VTE recurrence, major bleeding during OA use and net clinical benefit. VTE recurrence was defined as the incidence of recurrent VTE within 5 years after OA discontinuation. Major bleeding during OA use was defined as the incidence of major bleeding during the OA treatment. Net clinical benefit was defined as the composite of recurrent VTE and major bleeding.10 To be specific, it referred to patients with neither recurrent VTE within 5 years after the OA discontinuation nor major bleeding during OA use. VTE recurrence was defined as the presence of new defect on ventilation/perfusion (V/Q) scan or new thrombi on CT pulmonary angiography or newly developed thrombi on compression ultrasonography, in the re-examination during follow-up.11 The determination of VTE recurrence via imaging investigation was conducted in the context of patients having sudden aggravation of VTE symptoms or routine follow-up examination every 3 or 6 months. Major bleeding was defined as fatal bleeding, symptomatic bleeding in critical areas or organs, surgical site bleeding causing second intervention and/ or haemodynamic instability, haemarthrosis, resulting in immobilisation, prolonged hospitalisation, delayed wound healing or deep wound infection, and bleeding causing a fall in haemoglobin level of 20 g/L or more, or a transfusion of two or more units of whole blood or red cells with temporal association within 24–48 hours to the bleeding.12 13

The post hoc analysis was conducted when the required data were completely collected. According to the overall length of OA use that patients had undergone after the diagnosis of acute PE, they were classified into three different groups, which were group 1 (≥1 year of OA use and <2 years of OA use), group 2 (≥2 years of OA use and <3 years of OA use) and group 3 (≥3 years of OA use). We used propensity score-matching methods to abate the bias of potential confounding factors highly related to mortality, VTE recurrence and bleeding in the ESC (European Society of Cardiology) guidelines,3 which mainly included simplified pulmonary embolism severity index, risk strata of PE, D-dimer, age, sex, hormonal therapy (DASH) score and hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, elderly (>65 years), drugs/alcohol concomitantly (HAS-BLED) score. The types of OA and cancer were also incorporated into the propensity score matching. Mortality, VTE recurrence, major bleeding and net clinical benefit were compared among different groups, respectively. The correlation between the length of OA use and mortality, VTE recurrence as well as major bleeding were analysed. Different length of OA use for the tendency of mortality, VTE recurrence, bleeding and net clinical benefit were analysed. The time-dependent incidence of mortality, VTE recurrence and major bleeding were compared among three groups with different length of OA use.

The investigators of Shanghai Xinhua Hospital, Shanghai Pulmonary Hospital and Shanghai Punan Hospital performed the current study. The data needed for study were obtained mainly through the existing electronic medical record system or through telephone communication. No one who is not an author contributes to the writing of manuscript. All authors vouch for the completeness, fidelity and accuracy of the data. All authors have read and approved the submitted version of manuscript for publication. The study protocol was approved by the institutional review board of each participating hospital. Due to the nature of retrospective study, written informed consent for each patient was waived by the institutional review board of each participating institute.
hospital. For patients being contacted through telephone communication, verbal consent was all obtained.

**Study population**

Patients were incorporated according to the inclusion and exclusion criteria. The inclusion criteria consisted of: (1) all patients were 18 years old or older when they were diagnosed with acute PE; (2) all patients had an objectively confirmed PE and underwent extended OA treatment for secondary thromboprophylaxis due to the high risk of recurrence and low risk of bleeding after the completion of at least 6 months of OA anticoagulation following the diagnosis of acute PE; (3) all patients had discontinued OA use for at least 5 years prior to the current study. The exclusion criteria consisted of: (1) patients who already had a definite chronic thromboembolic disease (CTED) history prior to the acute PE onset; (2) patients who underwent a concurrent use of single or dual antiplatelet therapies during OA use; (3) patients whose OA use were interrupted for more than 3 months during the entire anticoagulation course; (4) patients who resumed OA use after discontinuation.

**Statistical analysis**

In the propensity score-matching analysis, nearest-neighbour (greedy) matching without replacement
was adopted.\textsuperscript{14} Since the longer the OA use, the fewer the number of patients, we used a 4:2:1 ratio within a caliper width of 0.2\textsuperscript{15} of the SD of the logit of the propensity score for the number ratio of patients in groups 1, 2 and 3. The matching algorithm first selected a patient in group 3 and then selected two patients in group 2 and 4 patients in group 1 who had a linear propensity score that were closest to that of the first selected patient.

The comparison of measurement data was performed by using t test or ANOVA (Analysis of Variance). The between-group comparison of rates was performed by \( \chi^2 \) test. The correlation between the length of OA use and mortality, VTE recurrence as well as major bleeding were analysed by using Cox regression analysis. Different length of OA use for the tendency of mortality, VTE recurrence, bleeding and net clinical benefit were analysed by using receiver operator characteristic (ROC) curve analysis. The time-dependent incidence of mortality, VTE recurrence (the first episode) and major bleeding (the first episode) were compared among groups with different length of OA use by using Kaplan-Meier curve analysis. The statistical analyses were performed by using SPSS V.26 and R software, V.3.6.1 (R Project for Statistical Computing). A \( p \) value being less than 0.05 denoted statistical significance.

**RESULTS**

**Demographics and characteristics of patients at the PE diagnosis**

A total of 606 patients during the period between 2012 and 2022 were incorporated from the participating hospitals as per the inclusion criteria. Then as per the exclusion criteria, 94 patients were excluded from the current study. As such, 512 patients were acquired via the inclusion and exclusion criteria. After the following propensity-score matching, a total of 385 patients with PE entered into the final analysis at last. The median age of all patients was 69.0 years old. Among them, 177 patients were women, whereas 208 patients were men. The distribution of all 385 patients in the three groups was 220 in group 1 (\( \geq 1 \) year of OA use and <2 years of OA use), 110 in group 2 (\( \geq 2 \) year of OA use and <3 years of OA use) and 55 in group 3 (\( \geq 3 \) years of OA use), respectively. The types of OA included warfarin, dabigatran and rivaroxaban. The dose of extended warfarin was still adjusted to maintain an international normalised ratio to be 2 to 3, whereas that of almost all dabigatran (92.7\%) was 110 mg two times per day, and of almost all rivaroxaban (92.5\%) was 10 mg/day. Almost all patients continued to use the OA type which was used for the initial 6 months in the extended anticoagulation, whereas only 23 (6.0\%) patients ever changed from one type of OA to another.

![Figure 1](http://bmjopenresp.bmj.com/) Comparison of outcomes among groups with different length of OA use. OA, oral anticoagulant; PE, pulmonary embolism; VTE, venous thromboembolism.
Outcomes among groups with different length of OA use

The overall number of cumulative all-cause mortality, PE-related mortality, VTE recurrence, major bleeding and net clinical benefit were 135 (35.1%), 20 (5.2%), 111 (28.8%), 15 (3.9%) and 259 (67.3%), in all 385 patients. The number of cumulative all-cause mortality 5 years after the OA discontinuation was 80 (36.4%), 37 (33.6%) and 18 (32.7%), in the group 1, 2 and 3, respectively (p=0.821). No statistical difference existed in pairwise comparison (all p>0.05). Among all deceased patients, the number of PE-related mortality was 14 (6.4%), 4 (3.6%) and 2 (3.6%), in the group 1, 2 and 3, respectively (p=0.491). Nevertheless, a pairwise comparison demonstrated that the PE-related mortality in group 1 was higher than that in group 2 (p=0.034) and 3 (p=0.040), respectively, whereas were similar between groups 2 and 3 (p=1.000). The number of patients who had at least one time of VTE recurrence were 73 (33.2%), 26 (23.6%) and 12 (21.8%), in the group 1, 2 and 3, respectively (p=0.038). A pairwise comparison showed that the VTE recurrence in group 1 was higher than that in group 2 (p=0.021) and 3 (p=0.035), respectively, whereas no statistical difference existed between group 2 and 3 (p=0.794). The number of patients who had at least one time of major bleeding during OA use were 5 (2.3%), 5 (4.5%) and 5 (9.1%), in the groups 1, 2 and 3, respectively (p=0.025). None of them was fatal bleeding. A pairwise comparison showed that the major bleeding in group 3 was higher than that in groups 1 (p=0.020) and 2 (p=0.029), respectively, whereas no statistical difference existed between group 1 and 2 (p=0.091). The number of patients who had net clinical benefit were 142 (64.5%), 79 (71.8%) and 38 (69.1%), in the groups 1, 2 and 3, respectively (p=0.095). A pairwise comparison showed that the net clinical benefit in group 1 was less than that in group 2 (p=0.024), whereas similar with that in group 3 (p=0.520). The net clinical benefit was comparable between group 2 and 3 (p=0.716). The comparison of outcomes among groups with different length of OA use is demonstrated in figure 1.

Correlation between the length of OA use and mortality, VTE recurrence, bleeding as well as net clinical benefit

By incorporating outcome-related factors for PE such as sPESI, risk strata of PE, DASH score and HAS-BLED score, a multivariate Cox regression analysis demonstrated that the length of OA use was positively associated with major bleeding (HR, 2.510 (0.293 to 3.485), p=0.001), whereas negatively associated with PE-related mortality (HR, 0.668 (0.196 to 2.832), p=0.025) and VTE recurrence (HR, 0.694 (0.174–2.300), p=0.036), respectively. The length of OA use was not associated with all-cause mortality (HR, 1.033 (0.588 to 1.815), p=0.854). The correlation between the length of OA use and mortality, VTE recurrence as well as major bleeding is demonstrated in table 2.

Different length of OA use for tendency of mortality, VTE recurrence, bleeding, net clinical benefit

In an ROC curve analysis, the length of OA use had no trend towards the all-cause mortality within 5 years after OA discontinuation. The area under the curve (AUC) was 0.508 (0.444 to 0.572) (p=0.802). Nevertheless, the sensitivity and specificity of the length of OA use for the
tendency of PE-related mortality within 5 years after OA discontinuation was 70.2% and 46.2%, respectively. The AUC was 0.654 (0.514 to 0.793) (p=0.029). The cut-off point was 27 months (figure 2A). It means that OA use being longer than 27 months may yield lower PE-related mortality than OA use being shorter than 27 months. The ROC curve analysis also demonstrated that the sensitivity and specificity of the length of OA use for the tendency of VTE recurrence within 5 years after OA discontinuation was 70.1% and 55.4%, respectively. The AUC was 0.587 (0.526 to 0.647) (p=0.006). The cut-off point was 33 months (figure 2B). It means that OA use being longer than 33 months may yield lower incidence of VTE recurrence than OA use being shorter than 33 months. The sensitivity and specificity of the length of OA use for the tendency of major bleeding during the OA medication was 91.7% and 61.9%, respectively. The AUC was 0.771 (0.648 to 0.894) (p=0.001). The cut-off point was 25 months (figure 2C). It means that OA use being longer than 25 months may yield higher incidence of major bleeding than OA use being shorter than 25 months. The sensitivity and specificity of the length of OA use for the tendency of net clinical benefit within 5 years after OA discontinuation was 86.8% and 64.3%, respectively. The AUC was 0.628 (0.565 to 0.690) (p<0.001). The cut-off point was 30 months (figure 2D). It means that OA use being longer than 30 months may yield more net clinical benefit than OA use being shorter than 30 months. Different length of OA use for the tendency of mortality, VTE recurrence, bleeding and net clinical benefit are illustrated in figure 2.

Comparison of time-dependent incidence of outcomes among groups with different length of OA use
In a Kaplan-Meier curve analysis, no overall difference of time-dependent cumulative all-cause mortality rates was observed among groups 1, 2 and 3 (p=0.853) (figure 3A).
Likewise, no overall difference of time-dependent cumulative PE-related mortality rates existed among all three groups (p=0.469). Nevertheless, PE-related death in group one evidently occurred earlier than that in both of groups 2 and 3 (figure 3B). The Kaplan-Meier curve analysis demonstrated that the time-dependent cumulative VTE recurrence-free rates were different among groups 1, 2 and 3 (p=0.010). The patients in group 1 yielded VTE recurrence earlier than those in group 2, who yielded VTE recurrence earlier than those in group 3 (figure 3C). It also revealed that the time-dependent cumulative major bleeding rates during OA use were similar among group 1, 2 and 3 (p=0.443) (figure 3D).

**DISCUSSION**

Since inadequate length of OA use may lead to VTE recurrence, whereas excessive length of OA use may result in bleeding, it is warranted to determine the optimal length of OA use for patients with acute PE who require secondary thromboprophylaxis, in order to achieve the maximum benefit. In the current study that investigated the optimal length of OA use to achieve maximum benefit within 5 years after OA discontinuation in patients with acute PE who required secondary thromboprophylaxis, a 2 to 3 years of OA use demonstrated superiority or non-inferiority with respect to all items of outcomes, compared with either longer or shorter length of OA use.

In the current study, the median course of PE of all patients was 7.3 (6.2 to 8.4) years. In some previous studies, for the long-term outcomes in patients with acute PE, the cumulative all-cause mortality rates 5–10 years after the occurrence of acute PE was 30% to 45%, the 5-year PE-related mortality rate was 2.9%, the cumulative VTE recurrence incidence 5–10 years after index diagnosis was 25%–36%, and the 5-year major bleeding incidence was 1.3%. The current cumulative all-cause mortality, PE-related mortality, VTE recurrence, major bleeding were basically consistent with those in the previous studies.

To our best knowledge, the studies which are comparable to the current one are scarce, despite there were several relevant studies. The results from the current study were basically consistent with that from the study of Chopard et al., in which extended OA treatment over 2.5 years after acute PE diagnosis may provide a net clinical benefit, compared with those without extended anticoagulation, although its mean duration of study follow-up was only 2.1±0.3 years. In the PADIS-PE randomised clinical trial, for 371 patients who had experienced a first episode of symptomatic unprovoked PE and had been treated initially for six uninterrupted months with a vitamin K antagonist (VKA), an additional 18 months of anticoagulation treatment with warfarin reduced the composite outcome of recurrent venous thrombosis and major bleeding compared with placebo. However, such benefit was not maintained at the end of 42 months of follow-up after the discontinuation of anticoagulation therapy (20.8% of events in the warfarin group vs 24.0% in the placebo, HR 0.75; 95% CI 0.47 to 1.18). The PADIS-PE study suggested that an overall 2-year VKA anticoagulant therapy can benefit patients with unprovoked acute PE.
Nevertheless, such duration is not an optimal one since its legacy effect could not sustain after the discontinuation of anticoagulation treatment. In a meta-analysis of six randomised trials including 5920 patients with VTE at intermediate risk of recurrence, compared with the shorter anticoagulation arm (7.5 months), the longer anticoagulation arm (18.6 months) was associated with a statistically significant reduction in all-cause mortality (RR 0.47, 95% CI 0.29 to 0.75; 0.8% vs 1.8%). PE-related death was also lower in the longer anticoagulation arm (RR 0.32, 95% CI 0.12 to 0.83; 0.2% vs 0.6%), compared with the shorter one. It is partly consistent with the result of the current study with respect to the PE-related mortality, whereas it is inconsistent with the result of the current study with regards to the all-cause mortality. The reason for the disparity in all-cause mortality may lie in that the all-cause mortality could be impacted by a variety of causes of death during an average follow-up period being longer than 7 years after PE diagnosis in the present study, which was much longer than the average 18.6 months after PE diagnosis in the previous study. In the SURVET Study, for 615 patients with first-ever unprovoked VTE who had completed 3–12 months of OA treatment and were randomly assigned to sulodexide, which is a natural glycosaminoglycan with antithrombotic and profibrinolytic activities or placebo for 2 years in addition to elastic stockings, VTE recurred in 15 patients who received sulodexide (N=307) and in 30 patients who received placebo (N=308) (HR: 0.49 (0.27 to 0.92); p=0.025). It indicated that a 2–3 years of antithrombotic therapy is beneficial for patients with unprovoked VTE, being basically consistent with the results of the current study.

The results of the current study may yield some clinical implications for clinicians. First, for patients with acute PE who require secondary thromboprophylaxis, it is recommended to use OA for more than 2 years in order to reduce long-term PE-related mortality, although it is futile for the improvement of all-cause mortality. Second, overall OA use for 2 to 3 years after PE diagnosis may be the optimal length to acquire long-term low incidence of VTE recurrence, an acceptable bleeding rates and the best net clinical benefit, for patients with acute PE who require secondary thromboprophylaxis. Third, unfortunately, the cumulative risk of bleeding increases gradually along with the gradual elongation of length of OA use. It is not recommended to use OA for more than 3 years due to the possibly high bleeding risk and inferior net clinical benefit. Of note, notwithstanding the results of the current study suggested that 2 to 3 years of OA use is the optimal length for an outcome 5 years after OA discontinuation in patients with acute PE who require extended anticoagulation, whether the results still hold true longer than 5 years after OA discontinuation is unclear. In addition, due to the inconsiderable number of patients who underwent OA use for more than 3 years, this patient population was not subdivided according to the specific length of OA use. As such, the relationship is unknown between the specific length of OA use in patients who underwent OA use for more than 3 years and the 5-year outcomes after OA discontinuation. Nevertheless, the benefit of an overall OA use for 2–3 years is at least non-inferior to an OA use for more than 3 years with respect to outcomes by and large. Taking into account of the increasing bleeding risk along with the gradual extension of OA use, the OA use for 2 to 3 years should be preferred than that for more than 3 years. Finally, despite a general length of 3 or 6 months of anticoagulation is defined for acute PE patients, it does not mean that they have to neither more nor less undergo 3 or 6 months of anticoagulation without any variation, due to unpredictable change of risk factors for thrombosis or bleeding. OA may be prematurely terminated due to major bleeding or proceed owing to unsolved risk factors for thrombosis. Likewise, the same applies to PE patients requiring secondary thromboprophylaxis. Being similar to the initial 3 or 6 months of anticoagulation for acute PE, the 2–3 years of anticoagulation for secondary thromboprophylaxis is also a general recommendation.

Several limitations have to be acknowledged. First, a prospective study is warranted since the current one was a retrospective study. Nevertheless, the propensity score matching may minimise bias caused by confounding factors although not comparable to randomised controlled trial. Second, the sample is relatively inconsiderable since the number of patients who adhere to long-term OA use are relatively small, not to mention that the subjects are required to be followed up for 5 years after OA discontinuation. Third, the incidence of chronic thromboembolic pulmonary hypertension (CTEPH) was not included in the outcomes of the subjects due to most of the patients have not been investigated for the presence or absence of CTEPH by using right heart catheterisation. Fourth, we only adopted major bleeding incidence instead of the incidence of all kinds of bleeding for the evaluation of adverse events in the current study since non-major bleeding events especially minor ones were intractable to be precisely collected in a post hoc review. The results might have been different if all the other kinds of bleeding had been included. Nevertheless, in the study of Wells et al, which assessed the benefit–risk of extended anticoagulation versus placebo in VTE patients who had undergone 6–12 months of anticoagulation, the net clinical benefit was defined as the composite of recurrent VTE and major bleeding. Fifth, heterogeneity may exist because the present study that covered different types of OA; however, subgroup analysis revealed consistency among different types of OA. Sixth, detailed medication adherence diaries were not obtained despite compliance was excellent based on the self-reports of all patients. Finally, the present results are not applicable to edoxaban and apixaban since these two agents were not incorporated into the current study.

In conclusion, the results of the current study suggest that, for patients with acute PE who require secondary thromboprophylaxis, 2–3 years (30 months preferred) of
overall OA use after PE diagnosis could be an optimal length of treatment course to achieve maximum benefit within 5 years after OA discontinuation. The prospective validation of the current results is warranted in the future. The results of this study may be favourable for clinicians to make decisions about the length of OA use in this patient population.

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Competing interests
None declared.

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication
Not applicable.

Ethics approval
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Data are available upon reasonable request.

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