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COMMENTARY

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Clinical significance of subsegmental pulmonary embolism: An ongoing controversy

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The incidence of pulmonary embolism (PE) has substantially increased since the introduction of multidetector computed tomography pulmonary angiography (CTPA) in the late 1990s,[1] which has revolutionized the diagnosis of PE and has largely replaced other diagnostic exams.[2] Multidetector CTPA allows visualization of even the small subsegmental pulmonary arteries due to its higher resolution compared to single-detector CTPA or ventilation-perfusion (V/Q) scanning, thus increasing the sensitivity for the detection of PE.[3] The observed increase in PE incidence associated with the exploding use of CTPA coincided with the increase in the incidence of subsegmental PE (SSPE).[4,5] SSPE nowadays account for approximately 15% of all acute PE diagnoses,[6] and its incidence is likely to further increase with the continuous advancements in CT technology.[1,6]

The overall mortality associated with PEs has remained largely unchanged in the first decade after introduction of CTPA, despite a steep increase in PE incidence during this period.[1] Although nationwide death certificate data of the United States suggests an increase in the rate of deaths caused by PE since 2008,[7] findings from before 2008 implicate that the extra PE diagnosed with multidetector CTPA compared to less sensitive diagnostic modalities represent in average less severe disease. Accordingly, the smallest clots, that is, SSPEs, may be clinically irrelevant and potentially require a different therapeutic approach than segmental or more central PE.[8] However, evidence to inform the optimal clinical management of patients with SSPE and no lower-limb deep vein thrombosis (DVT) is sparse, and thus considerable controversy exists whether or not these patients benefit from anticoagulation.[9,10]

The study by Fernández-Capitán et al in this issue of *Research and Practice in Thrombosis and Haemostasis* is a welcome addition to the limited body of evidence.[11] Using prospectively collected data from the Registro Informatizado de Enfermedad TromboEmbólica (RIETE) Registry, the authors investigated outcomes of patients anticoagulated for a first episode of symptomatic PE according to the most proximal anatomic location of PE. Among 15 963 patients with acute PE from 24 countries, 834 (5.2%) patients had an SSPE, while 3797 (24%) and 11 332 (71%) patients had a segmental and more central PE, respectively. Among those with an SSPE, a total of 198 (24%) patients had a concomitant lower-limb DVT, 242 (29%) had no DVT on ultrasound, and the remaining 394 (47%) had no documented ultrasound examination. The main finding of the study is an almost twofold increased risk of recurrent PE in patients with an SSPE compared to those with a segmental or more central PE (unadjusted hazard ratio [HR], 1.93; 95% confidence interval [CI], 1.16-3.32; and multivariable adjusted HR, 1.75; 95% CI, 1.02-3.03 compared to central PE). The authors investigated explanations for this unexpected finding, but results remained similar after adjustment for potential confounders, accounting for competing events (ie, non–PE-related death), and exclusion of patients with cancer. Moreover, outcomes did not differ according to the presence and absence of lower-limb DVT. Crude rates of recurrent DVT, major bleeding, and all-cause death were similar among the three groups.

The results reported by Fernández-Capitán et al come from the largest study to date comparing outcomes in patients with SSPE and those with more proximal PE. The main result of an increased risk of recurrent PE in patients with SSPE is unexpected and should be interpreted with caution, since there seems to be little biological plausibility for this finding. Nonetheless, the results of the study confirm that SSPE is not per se a benign disease; in this regard, they are consistent with previous studies which have

similarly suggested that SSPEs mimic more proximal PEs in terms of adverse outcomes.[12,13] Potential explanations for the unexpected higher risk of recurrent PE in SSPE compared to more proximal PE include (but are not limited to) selection bias and confounding. The study included only patients in whom anticoagulant therapy was deemed necessary by the treating physician. Consequently, patients with SSPE at a low risk of recurrence may have been underrepresented. As an inherent limitation of observational studies, residual confounding cannot be excluded. Furthermore, the diagnosis of SSPE is challenging, which is reflected by the low interrater agreement for the diagnosis of SSPE.[14] Recurrent PE is also not always a straightforward diagnosis,[15] and progressing or residual PE may be mistaken for early recurrences. Thus, the lack of central adjudication of initial and recurrent PE results in a high likelihood for potential misclassification, particularly in patients with SSPE. However, nondifferential misclassification of the exposure and outcome tends to bias the results toward the null[16] and thus may not adequately explain the unexpectedly higher risk of recurrence in patients with an SSPE compared to those with a more proximal PE. Of note, the risk of recurrent DVT did not differ by PE location.

What do we learn from this important study for our daily practice? First and foremost, patients with an acute first SSPE, in whom anticoagulation is deemed necessary, have a high risk of recurrent PE (2.6 events per 100 patient-years), major bleeding (4.8 events per 100 patient-years) and mortality (12 events per 100 patient-years) during anticoagulant therapy. However, the case fatality rate of an initial SSPE (ie, the number of fatal PEs divided by the total number of patients with SSPEs) appears to be low (2/834 patients; 0.2%). This is an important consideration for clinical scenarios in which anticoagulation needs to be interrupted during the early course of treatment. The study results also highlight the important risk of major bleeding associated with anticoagulation, regardless of PE location. This fuels the controversy about withholding anticoagulation in patients with SSPEs and no lower-limb DVT who are considered at low risk of recurrent venous thromboembolism, as treatment in those patients may cause more harm than benefit.

The rationale for conservative management of such patients, as suggested by the 2016 American College of Chest Physician guideline,[17] is based on indirect evidence indicating that not all SSPEs may be clinically relevant and certain patients may not need anticoagulant therapy. Epidemiologic data not only suggest overdiagnosis of PE in the first decade after the introduction of multidetector CTPA, but also show potential harms from overtreatment: In parallel with the rising incidence of PEs, an increase in the incidence of presumed anticoagulation-related complications has been observed.[1] The failure to diagnose certain cases of SSPE and thus forgoing treatment may not be associated with negative consequences, as shown in diagnostic studies in patients with a suspected PE. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, 17% of patients with a low-probability V/Q scan had SSPEs on pulmonary angiography.[18] In the absence of a concomitant DVT, anticoagulation can be safely withheld in such patients.[19,20] Furthermore, in a randomized trial comparing outcomes of patients with suspected PEs who were managed with CTPA or V/Q scans,[3] there was no difference in the 3-month risk of recurrent venous thromboembolism or mortality, even though the proportion of PE diagnoses and subsequently the proportion of patients receiving anticoagulant therapy was higher in the CTPA group (19% vs 14%). Thus, the additional cases of PE diagnosed with the more sensitive CTPA (many of these presumably representing SSPE) were not clinically relevant and may not need treatment. While small observational studies suggest that patients with SSPE who do not receive anticoagulation have a similar risk of recurrent venous thromboembolism and mortality compared to patients who received anticoagulation,[21] an ongoing prospective cohort study, in which low-risk patients with an SSPE and no concomitant DVT are left untreated, will provide important insights on the safety of conservative management of such patients (ClinicalTrials.gov number, NCT01455818). In addition, the randomized multicenter Surveillance Versus Anticoagulation for Low-Risk Patients With Isolated Subsegmental Pulmonary Embolism (SAFE-SSPE) trial (ClinicalTrials.gov number, NCT04263038) aims to provide high-quality evidence regarding the risk-benefit ratio of anticoagulant therapy in low-risk patients with SSPE by directly comparing the efficacy and safety of clinical surveillance without anticoagulation and anticoagulation treatment with rivaroxaban.

While awaiting results from ongoing studies regarding the optimal management of patients with SSPE at low risk of recurrence, the study by Fernández-Capitán and colleagues provides an important contribution to help estimate the risk of adverse outcomes in patients with SSPE who are treated with anticoagulants.

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AUTHOR CONTRIBUTIONS

Both authors contributed to writing of the manuscript and approved the final version.

RELATIONSHIP DISCLOSURE

The authors declare no conflict of interest.

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