Ambulatory treatment of low-risk pulmonary embolism in fragile patients: a subgroup analysis of the multinational Home Treatment of Pulmonary Embolism (HoT-PE) Trial

To the Editor:

Pulmonary embolism is the third most frequent acute cardiovascular disease with an annual incidence of approximately 100 cases per 100 000 population and an annual mortality of ⩾7 deaths per 100 000 population in the European region [1, 2]. Initial management is adjusted to the risk of in-hospital death or early complications, which depend both on the severity of pulmonary embolism and the presence of comorbidities [3].

In recent years, significant progress was made in the validation of clinical, biochemical and haemodynamic criteria, which can be used to identify patients with low-risk pulmonary embolism [3]. Some of these patients may be candidates for early or immediate discharge from the hospital after pulmonary embolism diagnosis, to be followed by continuation of anticoagulant treatment on an ambulatory basis. In this regard, non-vitamin-K antagonist oral anticoagulants (NOACs) have simplified the regimens of initial anticoagulation and offer the potential of facilitating the transition from hospital to ambulatory care. These considerations justify the assumption that home treatment strategies may be implemented effectively and safely in selected patients with pulmonary embolism, and that they may increase treatment satisfaction and the patients' quality of life while reducing the risk of in-hospital complications. Besides, home treatment may help to reduce some of the substantial costs related to early treatment of pulmonary embolism [4].

Pulmonary embolism incidence and mortality peak among the elderly, who often have (serious) comorbidities and are at increased risk of early death [1, 2]. Existing data based on phase III trials suggest that NOACs are effective and safe in "fragile" patients with acute venous thromboembolism, as defined by older age, renal dysfunction or low body weight [5, 6]. Consequently, we investigated the efficacy and safety of early discharge and home treatment of acute pulmonary embolism in fragile low-risk patients, performing a subgroup analysis of the Home Treatment of Pulmonary Embolism (HoT-PE) trial [7].

HoT-PE was a prospective multicentre multinational management trial. Normotensive patients with acute pulmonary embolism were included based on a combination of clinical and imaging criteria indicating a low-risk status [8]. The first dose of rivaroxaban was given in hospital following diagnosis of acute pulmonary embolism, and patients were discharged within 48 h of presentation. Rivaroxaban was taken for at least 3 months at standard approved doses. The primary efficacy outcome was symptomatic recurrent venous thromboembolism, or pulmonary embolism-related death, within 3 months of enrolment. The safety outcomes included major bleeding, serious adverse outcomes and all-cause death. The trial was stopped following the predefined interim analysis after inclusion of the first 525 patients, as only three of these patients (0.6%) reached the primary efficacy outcome; this rate was sufficiently low to allow the early termination of the study based on the trial protocol [8]. For the present subgroup analysis, patients with

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Early discharge and home treatment of acute pulmonary embolism in fragile patients appears to be feasible and acceptably safe. Caution is warranted due to the higher risk of major bleeding among fragile patients. https://bit.ly/2YtStiU

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TABLE 1 Baseline characteristics and clinical presentation of fragile and non-fragile patients diagnosed with acute pulmonary embolism

	Fragile	Non-fragile	Absolute risk difference (95% CI)
Subjects n	112	412	
Women	64 (57.1%)	175 (42.5%)	+14.6% (+4.2% to +24.6%)
Age years	77 (74–80)	53 (43–65)	
In-hospital stay h	42 (25–47)	32 (23–46)	
Clinical signs and symptoms			
Dyspnoea	68 (60.7%)	251 (60.9%)	−0.2% (−10.5% to +9.6%)
Pleuritic pain	32 (28.6%)	169 (41.0%)	−12.5% (−21.4% to −2.4%)
Cough	19 (17.0%)	92 (22.3%)	−5.4% (−12.6% to +3.5%)
Retrosternal pain	30 (26.8%)	80 (19.4%)	+7.4% (−1.0 to +16.9%)
Fever	4 (3.6%)	36 (8.7%)	−5.2% (−8.9% to +0.6%)
Haemoptysis	7 (6.3%)	20 (4.9%)	+1.4% (−2.7% to +7.7%)
Syncope	5 (4.5%)	9 (2.2%)	+2.3% (−0.9% to +7.9%)
Signs of deep vein thrombosis	22 (19.6%)	129 (31.3%)	−11.7% (−19.5% to −2.3%)
Comorbidities			
COPD	8 (7.1%)	18 (4.4%)	+2.8% (−1.5% to +9.3%)
Chronic heart failure	2 (1.8%)	5 (1.2%)	+0.6% (−14.8% to +5.1%)
Arterial hypertension	70 (62.5%)	141 (34.2%)	+28.3% (+17.9% to +37.8%)
Diabetes mellitus	15 (13.4%)	20 (4.9%)	+8.5% (+2.8% to +16.3%)
Creatinine clearance <50 mL·min^{-1} (MDRD formula)	29 (25.9%)	0 (0.0%)	+25.9% (+18.6% to +34.7%)
Risk factors for venous thromboembolism			
Oestrogen containing hormonal treatment	8 (7.1%)	72 (17.5%)	−10.3% (−15.6% to −3.2%)
Immobilisation (⩾3 days)	8 (7.1%)	46 (11.2%)	−4.0% (−8.9% to +2.9%)
Previous venous thromboembolism	26 (23.1%)	89 (21.6%)	+1.6% (−6.4% to +11.0%)
Recent major surgery (<30 days)	10 (8.9%)	27 (6.6%)	+2.4% (−2.5% to +9.4%)
Recent major trauma (<30 days)	4 (3.6%)	19 (4.6%)	−1.0% (−4.3% to +4.5%)
Long trip (>4 h, past 30 days)	9 (8.0%)	57 (13.8%)	−5.8% (−11.1% to +1.4%)
Active cancer	14 (12.5%)	18 (4.4%)	+8.1% (+2.7% to +15.7%)
Outcomes (over 3-month follow-up)			
Primary outcome (recurrent symptomatic venous thromboembolism or pulmonary embolism-related death)	1 (0.9%)	2 (0.5%)	+0.4% (−1.1% to +4.4%)
Major bleeding	3 (2.7%)	3 (0.7%)	+2.0% (+0.3% to +6.9%)
Serious adverse events	11 (9.8%)	43 (10.4%)	+0.6% (−6.0% to +6.8%)
Death from any cause	1 (0.9%)	1 (0.2%)	+0.7% (−0.7% to +4.7%)

Data are presented as n (%) or median (interquartile range), unless otherwise stated. MDRD: Modification of Diet in Renal Disease.

acute low-risk pulmonary embolism were further stratified based on the presence of at least one criterion of "fragility" corresponding to those used in prior studies: age >75 years, renal dysfunction (creatinine clearance <50 mL·min^{-1} based on the Modification of Diet in Renal Disease, MDRD, equation), and body mass index <18.5 kg·m^{-2} (used in place of a body weight <50 kg). We compared the 3-month rate of the primary efficacy and safety outcome, and of other serious adverse events, as recorded by the HoT-PE investigators, between fragile and non-fragile patients calculating absolute risk differences and the corresponding 95% confidence intervals. A sensitivity analysis was performed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula to estimate the glomerular filtration rate.

A total of 524 patients with complete information (one patient was excluded due to missing values) were included in this analysis; of these, 112 (21.4%) were categorised as being fragile. Median (interquartile range) age of fragile and non-fragile patients was 77 (74–80) and 53 (43–65) years, respectively. Table 1 provides an overview of the demographic and baseline characteristics of the two groups. Overall, 104 of 112 (92.9%) fragile and 397 of 412 (96.4%) non-fragile patients spent a maximum of two nights in hospital in compliance with the study protocol; the median hospital stay was 42 (25–47) and 32 (23–46) h, respectively. The primary efficacy outcome of symptomatic recurrent venous thromboembolism or pulmonary embolism-related death within 3 months occurred in one (0.9%) fragile and two (0.5%) non-fragile patients (absolute risk difference +0.4%; 95% CI −1.1% to +4.4%; table 1). Major bleeding occurred in three (2.7%) fragile and three (0.7%) non-fragile patients for an absolute risk difference of +2.0% (table 1). One patient in each group suffered intracranial haemorrhage. In the fragile patient population, all of the bleeding events and recurrent episodes of venous thromboembolism occurred after

the first 30 days following the diagnosis of acute pulmonary embolism. Among fragile patients who experienced major bleeding, the main risk factors appeared to be older age (n=3), male sex (n=2), moderate renal dysfunction (n=3) and arterial hypertension (n=1); none of the patients had (active) cancer, a history of alcohol abuse or recent trauma/surgery. The 3-month rate of serious adverse events did not differ between the two groups. All-cause 3-month mortality was low in both groups (0.9% *versus* 0.2%; table 1), and all deaths were cancer-related.

A total of 207 (39.4%) patients were classified as fragile using the CKD-EPI formula for the glomerular filtration rate. The primary efficacy outcome occurred in two (1.0%) fragile and one (0.3%) non-fragile patient. Major bleeding occurred in three (1.5%) fragile and three (1.0%) non-fragile patients. All-cause 3-month mortality was 0.5% and 0.3%, respectively.

The present analysis of the population of HoT-PE, a multinational prospective management trial, support the feasibility and safety of early discharge and home treatment of carefully selected patients with acute low-risk pulmonary embolism, based on the modified Hestia criteria and the absence of signs of right ventricular dysfunction, but with characteristics of fragility (or frailty). Of note, the 3-month rate of recurrent venous thromboembolism observed in the HoT-PE trial was almost identical to that observed among patients with acute pulmonary embolism included in a large European registry (0.9% *versus* 0.8%, respectively) [9]. Our results also indicate that fragile patients have higher rates of major bleeding compared with non-fragile patients. This has been previously described in phase III trials and cohort studies [9, 10] and is most likely related to older age itself along with a higher prevalence of concomitant diseases, such as renal impairment (one of the items defining frailty), arterial hypertension, active malignancy and diabetes, which are known to affect the risk of bleeding [11]. Rivaroxaban use may be associated with up to 70% lower risk of major bleeding compared with vitamin K antagonist therapy among fragile patients [6]; nevertheless, careful follow-up of the patients and family/social support remains necessary to monitor renal function, the prescription of new co-medications and drug compliance. This is irrespective of whether the patient may be a candidate for early discharge and home treatment.

In the population of HoT-PE, we found that the patients' outcome, particularly mortality, was similar to that reported in earlier studies of patients with acute low-risk pulmonary embolism [12–15]. Thus, the results available to date support the recommendation of the 2019 European guidelines [3] to employ careful risk stratification and patient selection based on validated criteria as a prerequisite for early discharge. We also showed that the use of different formulas to estimate renal function may lead to discrepancies in the classification of a patient as fragile. This, however, might not have a major impact on efficacy and safety in the context of a low-risk patient population [16].

In conclusion, early discharge and home treatment of fragile patients with acute low-risk pulmonary embolism appears to be feasible and safe. Our results support the notion that these patients should not be *a priori* excluded from early discharge strategies. At the same time, caution is warranted due to a possibly higher risk of major bleeding on anticoagulant treatment in the presence of frailty.

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References

1 Barco S, Mahmoudpour SH, Valerio L, *et al.* Trends in mortality related to pulmonary embolism in the European Region, 2000-15: analysis of vital registration data from the WHO Mortality Database. *Lancet Respir Med* 2020; 8: 277–287.
2 Keller K, Hobohm L, Ebner M, *et al.* Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. *Eur Heart J* 2020; 41: 522–529.
3 Konstantinides SV, Meyer G, Becattini C, *et al.* 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Respir J* 2019; 54: 1901647.
4 Barco S, Woersching AL, Spyropoulos AC, *et al.* European Union-28: an annualised cost-of-illness model for venous thromboembolism. *Thromb Haemost* 2016; 115: 800–808.
5 van Es N, Coppens M, Schulman S, *et al.* Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood* 2014; 124: 1968–1975.
6 Prins MH, Lensing AW, Bauersachs R, *et al.* Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J* 2013; 11: 21.
7 Barco S, Schmidtmann I, Ageno W, *et al.* Early discharge and home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban: an international multicentre single-arm clinical trial. *Eur Heart J* 2020; 41: 509–518.
8 Barco S, Lankeit M, Binder H, *et al.* Home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban. Rationale and design of the HoT-PE Trial. *Thromb Haemost* 2016; 116: 191–197.
9 Moustafa F, Giorgi Pierfranceschi M, Di Micco P, *et al.* Clinical outcomes during anticoagulant therapy in fragile patients with venous thromboembolism. *Res Pract Thromb Haemost* 2017; 1: 172–179.
10 Ruiz-Gimenez N, Suarez C, Gonzalez R, *et al.* Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost* 2008; 100: 26–31.
11 Klok FA, Barco S, Konstantinides SV. External validation of the VTE-BLEED score for predicting major bleeding in stable anticoagulated patients with venous thromboembolism. *Thromb Haemost* 2017; 117: 1164–1170.
12 Vinson DR, Mark DG, Chettipally UK, *et al.* Increasing safe outpatient management of emergency department patients with pulmonary embolism: a controlled pragmatic trial. *Ann Intern Med* 2018; 169: 855–865.
13 den Exter PL, Zondag W, Klok FA, *et al.* Efficacy and safety of outpatient treatment based on the Hestia Clinical Decision Rule with or without N-terminal pro-brain natriuretic peptide testing in patients with acute pulmonary embolism. A randomized clinical trial. *Am J Respir Crit Care Med* 2016; 194: 998–1006.
14 Zondag W, Mos ICM, Creemers-Schild D, *et al.* Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study. *J Thromb Haemost* 2011; 9: 1500–1507.
15 Aujesky D, Roy PM, Verschuren F, *et al.* Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. *Lancet* 2011; 378: 41–48.
16 Catella J, Bertoletti L, Mismetti P, *et al.* Severe renal impairment and risk of bleeding during anticoagulation for venous thromboembolism. *J Thromb Haemost* 2020; 18: 1728–1737.