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Rate and duration of hospitalization for acute pulmonary embolism in the real-world clinical practice of different countries: analysis from the RIETE registry

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To the editor:

Latest guidelines suggest considering home treatment or early hospital discharge in low-risk mortality pulmonary embolism (PE) patients, identified through widely validated clinical prediction rules [1,2]. Nevertheless, it is still not clear if these patients are really treated on an outpatient basis in clinical practice.

Thus, we used the RIETE registry (ClinicalTrials.gov identifier: NCT02832245) to assess the proportion of outpatients with acute PE initially treated in-hospital, the mean duration of hospitalization and to identify predictors for home treatment or for early discharge. We included data from 11,473 patients registered in 25 countries participating in the RIETE study from January 2010 to December 2016. Both local and academic hospitals were involved. Rate and duration of hospitalization for acute PE in the four countries with highest enrolment and in other participating countries - grouped together as a unique group - were compared. Namely patients enrolled in Spain (n=8270) were compared with those included in France (n=964), Italy (n=593), Israel (n=429) and in "other countries" (n=1217).

All the variables potentially associated with out-treatment and with early discharge (length of in-hospital stay [LOS] ≤5 days) were evaluated at the univariate analysis using the Mann–Whitney test (for continuous variables) and the chi-square or Fisher's exact test (for dichotomous variables). Statistically or marginally significant variables ($P<0.10$) were introduced in a multivariate model (backward binary logistic regression model). The role of different scores, such as the Pulmonary Embolism Severity Index (PESI) [3], the RIETE score [4] and the scheme suggested by American College of Chest Physicians guidelines (ACCP scheme) for the bleeding risk [2], was assessed performing three different sensitivity analyses, excluding all the variables already included in each score. The SPSS software (version 15, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A two-sided P value of 0.01 was considered to be statistically significant.

A significantly lower proportion of complete outpatient treatment was found among PE subjects treated in Spain (2.5%), France (1.2%) and Israel (0.99%) than among those treated in Italy and in the "other countries" (16% and 21% respectively, $p<0.001$ for both). Conversely, the number of patients discharged within 5 days was significantly lower in Italy (23%), Spain (26%) and France (28%) than in Israel and in the other countries examined

(48% and 32% respectively, p<0.001 for both). The mean LOS was substantially shorter in Israel (6 median days [interquartile-range: 4-9], p<0.001) than in other countries. Only 5% of the overall population and approximately 7% of the low-risk group were fully treated at home. The median duration of hospitalization was 4 days for patients early discharged and 9 days for those with a longer hospitalization.

On multivariate analysis, initial therapy with DOACs and cancer strongly predicted both home treatment and early discharge. Admission to university hospitals was significantly associated with home treatment and showed a tendency toward a shorter hospital permanence. Use of estrogenic therapy was solely a predictor of early discharge.

When scores were entered one by one in the model, results concerning all previous variables were comparable except for the weight of a number of comorbidities and initial presentation parameters (data not shown). Low PESI or low ACCP scores were not associated with home treatment, both resulting uniquely as weak predictors of a shorter LOS. Low RIETE score weakly predicted both home treatment and early discharge (Table I).

In considering real life data collected from several countries, overall, only one in every thirteen patients eligible for home treatment was treated at home and less than half of the low-risk population was hospitalized for ≤5 days.

These results are not surprising since, until now, the level of evidence on out-treatment remains limited for the lack of high-quality research [5]. The variable approaches observed among countries may reflect different healthcare systems and facilities across European and world countries. Various scores, classifying dissimilar low-risk patients, were tested in our cohort, but none of them appeared clearly related to out-treatment. It remains to be verified if, in the near future, further validations of well performing clinical prediction rules, such as the Hestia clinical criteria, may help to increase the rate of out-treated patients in real life settings, reducing barriers concerning this practice [6]. In this regard, the ongoing HOME-PE trial, might clarify if a strategy based on the HESTIA rule, compared to a strategy based on the simplified-PESI score, is at least as safe with regards to the 30-day-rate of adverse events and more effective with regards to the rate of patients eligible for out-treatment [7].

Interestingly, in our study, cancer patients were treated more often at home or promptly discharged despite evident higher haemorrhagic and thrombotic risk [8]. Notably, incidentally detected asymptomatic cancer related PE were not included in the population analysed. Commonly, cancer patients may be monitored by oncologists with close follow-up visits and such well-defined assistance programs may facilitate either an outpatient strategy or a post-

discharge management. At the same time, this category of patients may achieve more benefits from home treatment than the others, since a new hospitalization usually deteriorates their quality of life [9].

As expected, initial treatment with DOACs appeared correlated with out-treatment and a shorter LOS. At the time of data collection, only 196 patients in the initial phase of therapy and 996 in the long-term period were treated with DOACs. These drugs, especially those permitting the "single drug approach", may broadly facilitate a quick discharge from emergency wards after a comprehensive risk assessment of PE patients [10-13]. The ongoing Mercury-PE trial, designed to test the hypothesis that management with rivaroxaban, if compared with standard care, reduces the number of initial and subsequent hospitalization days of low-risk PE, probably will confirm these findings [14]. However, in this observational analysis we are not able to exclude that in daily clinical practice DOACs were preferred in the acute phase of treatment mainly for less complex subgroups of patients.

Finally, additional considerations should be taken into account. Up to the end of 2013, previous guidelines only suggested early discharge for low-risk PE [15] and use of DOACs was not allowed for most countries. From 2014, for the first time ESC guidelines suggested both use of DOACs and home treatment for low-risk PE patients [1]. In analysing data from 2010 to 2016, we are probably observing a period of great change with regard to managing PE. Our results relating to academic institutions may suggest that, in these centers, guideline recommendations could potentially be implemented more easily and quickly than in other institutions since a paradigm shift requires more time to be adopted in all clinical settings.

Our study has some limitations. Principally, RIETE is an ongoing observational registry. Therefore, our findings should be treated with caution considering the limitation of observational studies. Moreover, the data collected from multiple centers in different countries participating in the RIETE registry may not be representative of the general treatment in those countries, only patients evaluated in a specific setting may be included, and thus our results may not be fully generalizable.

In the near future, recent diagnostic and therapeutic advances may be able to optimise low-risk PE patient selection and at the same time improve the management of this disease, providing an approach as safe as and more cost-effective than the current one.

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Bibliography

1. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie` N, et al. Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35:3033–69.

2. Kearon C, Akl EA, Ornelas J et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016 Feb;149(2):315-52.

3. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, Roy PM, Fine MJ. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005; 172(8):1041–1046.

4. Maestre A, Trujillo-Santos J, Riera-Mestre A, Jimenez D, Di Micco P, Bascunana J, Vela JR, Peris L, Malfante PC, Monreal M; RIETE Investigators. Identification of Low-Risk Patients with Acute Symptomatic Pulmonary Embolism for Outpatient Therapy. Ann Am Thorac Soc. 2015 Aug;12(8):1122-9.

5. Zondag W, Kooiman J, Klok FA, Dekkers OM, Huisman MV. Outpatient versus inpatient treatment in patients with pulmonary embolism: a meta-analysis. Eur Respir J. 2013;42(1):134-144.

6. Zondag W, Mos IC, Creemers-Schild D, Hoogerbrugge AD, Dekkers OM, Dolsma J, Eijsvogel M, Faber LM, Hofstee HM, Hovens MM, Jonkers GJ, van Kralingen KW, Kruip MJ, Vlasveld T, DE Vreede MJ, Huisman MV. Outpatient treatment in patients

with acute pulmonary embolism: the Hestia Study. J Thromb Haemost 2011;9(8):1500–1507.

7. Hospitalization or Out-treatment ManagEment of Patients With Pulmonary Embolism: a Randomized Controlled Trial (HOME-PE). ClinicalTrials.gov Identifier: NCT02811237.

8. Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, Marchiori A, Sabbion P, Prins MH, Noventa F, Girolami A. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 2002 Nov 15;100(10):3484-8.

9. Siragusa S, Arcara C, Malato A, Anastasio R, Valerio MR, Fulfaro F, Lo Coco L, Grimaudo S, Bajardi G, Abbadessa V, Gebbia N. Home therapy for deep vein thrombosis and pulmonary embolism in cancer patients. Ann Oncol. 2005 May;16 Suppl 4:iv136-139.

10. Konstantinides S, Torbicki A. Management of venous thrombo-embolism: an update. Eur Heart J. 2014 Nov 1;35(41):2855-63.

11. Stein PD, Matta F, Hughes PG, Hourmouzis ZN, Hourmouzis NP, White RM, Ghiardi MM, Schwartz MA, Moore HL, Bach JA, Schweiss RE, Kazan VM, Kakish EJ, Keyes DC, Hughes MJ. Home Treatment of Pulmonary Embolism in the Era of Novel Oral Anticoagulants. Am J Med. 2016 Sep;129(9):974-7.

12. Lankeit M, Konstantinides S. Is it time for home treatment of pulmonary embolism? Eur Respir J. 2012 Sep;40(3):742-9.

13. Barco S, Lankeit M, Binder H, Schellong S, Christ M, Beyer-Westendorf , Duerschmied D, Bauersachs R, Empen K, Held M, Schwaiblmair M, Fonseca C, Jimenez D, Becattini C, Quitzau K, Konstantinides S. 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.

14. Singer AJ, Xiang J, Kabrhel C, Merli GJ, Pollack C, Tapson VF, Wildgoose P, Peacock WF. Multicenter Trial of Rivaroxaban for Early Discharge of Pulmonary Embolism From the Emergency Department (MERCURY PE): Rationale and Design. Acad Emerg Med. 2016 Nov;23(11):1280-1286.

15. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR; American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e419S-94S.

Table I. Multivariate analysis using complete home treatment and early discharge as dependent variable. Patients dying ≤24 hours after the index event were excluded from this analysis.

Variables (number of patients)	Home vs. in hospital therapy OR (CI)	Early discharge (≤5 days) or home treatment vs. admission >5 days OR (CI)
Clinical characteristics		
Age > 65 years	0.59 (0.46-0.76)‡	0.77 (0.69-0.86)‡
Male gender (5413)		1.19 (1.08-1.32)‡
Body weight < 75 Kg		1.12 (1.02-1.24)*
Initial presentation		
Pulse > 110 bpm (2214)	0.33 (0.23-0.48)‡	0.62 (0.55-0.71)‡
Systolic BP levels <100mmHg (888)	0.50 (0.26-0.93)*	
Temperature < 36 °C (756)		0.82 (0.68-0.99)*
Risk factors		
Cancer (2550)	2.55 (2.00-3.27)‡	1.30 (1.16-1.45)‡
Immobility ≥ 4 days (1663)		0.82 (0.71-0.95)†
Estrogen therapy (630)		1.68 (1.37-2.07)‡
Underlying conditions		
Chronic heart failure (931)		0.74 (0.61-0.89)†
Chronic lung disease (1598)		0.80 (0.70-0.92)†
CrCl levels <60 mL/min (3963)		0.81 (0.72-0.91)‡
Countries		
Spain (8270)	Ref.‡	Ref.‡
Italy (593)	5.17 (3.11-8.58)‡	
France (964)	0.48 (0.25-0.90)*	
Israel (429)	0.36 (0.13-0.97)*	2.12 (1.68-2.67)‡
Other countries (1217)	11.50 (9.02-14.66)‡	2.25 (1.93-2.62)‡
Initial therapy		
LMWH (9935)	Ref.‡	Ref.‡
Unfractionated heparin (647)	0.16 (0.07-0.35)‡	0.36 (0.28-0.46)‡
Thrombolytics (328)		0.35 (0.24-0.50)‡
DOACs (196)	5.26 (3.36-8.24)‡	2.92 (2.08-4.09)‡
Fondaparinux (297)	0.41 (0.25-0.67)‡	
Type of Hospital		
University Hospital (7025)	2.29 (1.74-3.01)‡	1.11 (1.01-1.23)*
Scores		
PESI <85 points (4792)	1.20 (0.98-1.47)	1.33 (1.21-1.46)‡
RIETE < 1 point (3347)	1.29 (1.04-1.60)*	1.57 (1.42-1.74)‡
ACCP scheme¶ ≤ 1 point (1759)	1.29 (0.98-1.69)	1.46 (1.28-1.66)‡

[*]p <0.05; [†]p <0.01; [‡]p <0.001 ¶ modified version (information on control of anticoagulation unavailable in RIETE registry). Scores included one by one excluding all the variables already counted in each score.

Abbreviations: BP, blood pressure; CrCl, creatinine clearance; LMWH, Low-molecular-weight heparin; DOACs, direct oral anticoagulants; OR odds ratio; CI, confidence intervals.