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ORIGINAL ARTICLE

A prognostic score to identify low-risk outpatients with acute deep vein thrombosis in the upper extremity

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Summary. *Background:* No studies have identified which patients with upper-extremity deep vein thrombosis (DVT) are at low risk for adverse events within the first week of therapy. *Methods:* We used data from Registro Informatizado de la Enfermedad TromboEmbólica to explore in patients with upper-extremity DVT a prognostic score that correctly identified patients with lower limb DVT at low risk for pulmonary embolism, major bleeding, or death within the first week. *Results:* As of December 2014, 1135 outpatients with upper-extremity DVT were recruited. Of these, 515 (45%) were treated at home. During the first week, three patients (0.26%) experienced pulmonary embolism, two (0.18%) had major bleeding, and four (0.35%) died. We assigned 1 point to patients with chronic heart failure, creatinine clearance levels 30–60 mL min^{-1}, recent bleeding, abnormal platelet count, recent immobility, or cancer without metastases; 2 points to those with metastatic cancer; and 3 points to those with creatinine clearance levels < 30 mL min^{-1}. Overall, 759 (67%) patients scored ≤ 1 point and were considered to be at low risk. The rate of the composite outcome within the first week was 0.26% (95% confidence interval [CI] 0.004–0.87) in patients at low risk and 1.86% (95% CI 0.81–3.68) in the remaining patients. C-statistics was 0.73 (95% CI 0.57–0.88). Net reclassification improvement was 22%, and integrated discrimination improvement was 0.0055. *Conclusions:* Using six easily available variables, we identified outpatients with upper-extremity DVT at low risk for adverse events within the first week. These data may help to safely treat more patients at home.

Keywords: anticoagulant therapy; deep vein thrombosis; hospital; outcome; outpatients; upper extremity.

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Introduction

Current guidelines of antithrombotic therapy recommend that patients with deep vein thrombosis (DVT) and adequate home circumstances be treated with anticoagulant therapy at home rather than in the hospital [1]. However, in a recent study using data from the Registro Informatizado de la Enfermedad TromboEmbólica (RIETE) registry, < 50% of outpatients with lower limb DVT had been treated at home [2], thus suggesting that many physicians are still concerned about the risks of home therapy. This is because, even with adequate anticoagulation, some DVT patients may develop pulmonary embolism (PE), major bleeding, or even die.

RIETE is an ongoing, international (Spain, France, Italy, Israel, Germany, Switzerland, Portugal, Belgium,

Latvia, Czech Republic, Republic of Macedonia, Canada, Argentina, Venezuela, and Brazil), multicenter, prospective registry of consecutive patients presenting with symptomatic acute DVT or PE. Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrences, major bleeding and mortality, and risk factors for such outcomes [3–6]. In the current study, we used the RIETE database to explore in patients with upper-extremity DVT a prognostic score that correctly identified patients with lower limb DVT at low risk for PE, major bleeding, or death within the first week [7].

Methods

Consecutive outpatients with symptomatic acute DVT in the upper extremity confirmed by compression ultrasonography or venography were enrolled in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their relatives) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

In the RIETE registry, participating physicians ensured that eligible patients were consecutively enrolled. Data were recorded onto a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. The study-coordinating center assigned patients with a unique identification number to maintain patient confidentiality and was responsible for all data management. Data quality was regularly monitored electronically, including checks to detect inconsistencies or errors, which were resolved by contacting the local coordinators. Data quality was also monitored by periodic visits to participating hospitals by contract research organizations that compared medical records with the submitted data.

Study design

For this study, only outpatients with acute DVT in the upper extremity with no respiratory symptoms suggesting PE were considered. Home therapy was considered when patients spent in hospital < 24 h from their arrival to the emergency department. Major outcome was the composite of symptomatic, objectively confirmed PE, major bleeding, or death within the first 7 days of therapy. Major bleeding was defined as an overt bleed that required a transfusion of 2 or more units of blood; was retroperitoneal, spinal, or intracranial; or was fatal. Secondary outcomes were the development of fatal PE or fatal bleeding. Fatal PE, in the absence of autopsy, was defined as any death appearing within 10 days of a confirmed PE diagnosis, in the absence of any alternative cause of death. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death.

Prognostic score in patients with lower-limb DVT

We recently developed a prognostic score that correctly identified patients with acute DVT in the lower limbs who were at low risk for the composite of symptomatic PE, major bleeding, or death within the first 7 days of therapy [3]. The score was built by assigning 1 point to patients with chronic heart failure, creatinine clearance (CrCl) levels 30–60 mL min^{-1}, recent major bleeding, abnormal platelet count, recent immobility, and cancer without metastases; 2 points to those with metastatic cancer; and 3 points to those with CrCl levels < 30 mL min^{-1}. Patients scoring ≤ 1 point were considered to be at low risk.

Baseline variables

The following parameters were recorded when the qualifying episode of DVT was diagnosed: patient's sex, age, and body weight; presence of coexisting conditions such as chronic heart or lung disease; recent (< 30 days before DVT) major bleeding; presence of risk factors for DVT including active cancer (defined as newly diagnosed cancer or cancer that is being treated [i.e. with surgery, chemotherapy, radiotherapy, hormonal or supportive therapy]), recent immobilization (defined as non-surgical patients who were confined to bed with bathroom privileges for ≥ 4 days in the 2-months before DVT diagnosis), surgery (defined as those who had undergone surgery in the 2 months before DVT) and laboratory data, including whole blood counts and serum CrCl levels at baseline. CrCl levels were measured according to the Cockcroft–Gault formula [8].

Treatment and follow-up

Patients were managed according to the current clinical practice of each participating hospital (i.e. there was no standardization of treatment). The type, dose, and duration of anticoagulant therapy were recorded. The decision to treat patients in hospital or at home was left to the attending physicians. Each episode of symptomatic PE was investigated by lung scanning, helical computed tomography scanning, or pulmonary angiography as appropriate. Most outcomes were classified as reported by the clinical centers. However, if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (< 10% of events).

Statistical analysis

We assessed the prognostic value of the original score using a logistic regression model. Then, the area under ROC curve was calculated. Finally, we calculated the net reclassification improvement and integrated discrimination improvement to assess the incremental prognostic

value of the score compared with the clinical decision to treat patients at home [9–11]. In the net reclassification improvement, only changes in estimated prediction probabilities that imply a change from one category to another are considered, in patients both with or without events. Thus, the net reclassification improvement expresses the global net improvement in reclassification with a new model. In contrast, the integrated discrimination improvement does not require a prior definition of strata risk, thus considering the change in the estimation prediction probabilities as continuous variable. SPSS software (version 20, SPSS Inc, Chicago, IL, USA) and Epidat 3.1 (Xunta de Galicia, OPS. Epidat 3.1 Coruña, Washington, DC, USA; 2006) were used for the statistical management of the data, and a two-sided $P < 0.05$ was considered to be statistically significant.

Results

As of December 2014, 54 185 VTE patients had been enrolled in RIETE. Of these, 1135 (2.09%) were outpatients with acute DVT in the upper limb and had no respiratory symptoms suggesting PE. They were the subject for the current analysis. In all, 515 patients (45%) were treated at home and 620 in hospital. For patients treated in hospital, mean duration of hospital stay was 8.1 days (95% CI 6.5–9.7 days). No patients were lost for follow-up. Patients treated at home were less likely to have chronic heart failure, renal insufficiency, or cancer than those treated in hospital (Table 1). The majority of patients in both groups (91% vs. 90%) received initial therapy with low molecular weight heparin, then half (43% vs. 51%) switched to vitamin K antagonists.

During the first week of therapy, three patients (0.26%) experienced symptomatic PE, two (0.18%) had major bleeding (one died of bleeding), four (0.35%) died, and nine (0.79%) sustained the composite outcome (Table 2). Among 402 patients with catheter-related DVT, four (1.00%) suffered the composite outcome. Among 733 patients without catheter-related DVT, five (0.68%) had the composite outcome. Overall, 759 (67%) patients scored ≤ 1 point, and were considered to be at low risk. The rate of the composite outcome within the first week was 0.26% (95% CI 0.004–0.87%) in patients at low risk and 1.86% (95% CI 0.81–3.68%) in the remaining patients.

When the global score was applied, the area under ROC curve was 0.78 (95% CI 0.57–0.88). However, when we compared the discrimination power for patients with a low-risk score vs. those with a non–low-risk score, the area under ROC curve was 0.73 (95% CI 0.57–0.88). Using the prognostic score, 22% of patients were well reclassified ($P = 0.17$), with a significant improvement in reclassification in patients not suffering the composite outcome. Net reclassification improvement was 22% ($P < 0.001$). Integrated discrimination improvement was 0.0055 ($P = 0.048$).

Table 1 Clinical characteristics and treatment of 1135 patients with upper-extremity DVT, according to site of initial therapy

	At home	In hospital
Patients, *N*	515	620
Clinical characteristics		
Gender (males)	247 (48%)	326 (53%)
Mean age (years ± SD)	52 ± 18	54 ± 19
Body weight (kg ± SD)	72 ± 16	72 ± 14
Chronic heart failure	14 (2.7%)	44 (7.1%)
Chronic lung disease	29 (5.6%)	46 (7.4%)
	91 ± 45	85 ± 37
CrCl levels (mL min^{-1})		
Recent major bleeding	3 (0.6%)	7 (1.1%)
Anemia*	183 (36%)	228 (37%)
Platelet count < 100 000 or > 450 000	32 (6.2%)	44 (7.1%)
Risk factors for VTE		
Postoperative	47 (9.1%)	61 (9.8%)
Immobility ≥ 4 days	24 (4.7%)	43 (6.9%)
Cancer	223 (43%)	222 (36%)
None of the above	258 (50%)	333 (54%)
Prior VTE	43 (8.3%)	58 (9.4%)
Characteristics of the DVT		
Bilateral DVT	5 (1.0%)	27 (4.4%)
Catheter-related DVT	198 (38%)	204 (33%)
Initial therapy		
Low molecular weight heparin	470 (91%)	558 (90%)
Unfractionated heparin	3 (0.6%)	33 (5.3%)
Fondaparinux	29 (5.6%)	12 (1.9%)
Thrombolytics	1 (0.2%)	14 (2.3%)
Direct oral anticoagulants	6 (1.2%)	1 (0.2%)
No treatment	6 (1.2%)	2 (0.3%)
Long-term therapy		
Vitamin K antagonists	220 (43%)	310 (51%)
Low molecular weight heparin	237 (46%)	235 (39%)
Fondaparinux	28 (5.4%)	33 (5.3%)
Direct oral anticoagulants	10 (1.9%)	11 (1.8%)
7-Day outcome		
Symptomatic PE	2 (0.4%)	1 (0.2%)
Recurrent DVT	1 (0.2%)	0
Major bleeding	0	2 (0.3%)
Overall death	0	4 (0.6%)
Fatal PE	0	0
Fatal bleeding	0	1 (0.2%)
Composite outcome	2 (0.4%)	7 (1.1%)

SD, standard deviation; CrCl, creatinine clearance; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism. *Hemoglobin levels < 12 g dL−1 in women, < 13 g dL−1 in men.

Discussion

Our data, obtained from a large series of consecutive outpatients with upper-extremity DVT, confirm that the rate of symptomatic PE and major bleeding within the first week in this patient population is rather low (0.26% and 0.18%, respectively). However, one of these patients died within the first week. Thus, in the emergency unit, it is important to identify patient characteristics associated

Table 2 Application of the clinical prediction score at 7 days

Points	*n*	PE	Fatal PE	Major bleeding	Fatal bleeding	Death	Composite outcome (%)
Any	1135	3 (0.26%)	0	2 (0.18%)	1 (0.09%)	4 (0.35%)	9 (0.79)
0	490	1 (0.20%)	0	0	0	0	1 (0.20)
1	269	1 (0.37%)	0	0	0	0	1 (0.37)
2	211	0	0	0	0	2 (0.95%)	2 (0.95)
3	124	1 (0.81%)	0	1 (0.81%)	0	1 (0.81%)	3 (2.42)
≥ 4	41	0	0	1 (2.44%)	1 (2.44%)	1 (2.44%)	2 (4.88)
≤ 1	759	2 (0.26%)	0	0	0	0	2 (0.26)
Treated at home	515	2 (0.39%)	0	0	0	0	2 (0.39)

PE, pulmonary embolism; DVT, deep vein thrombosis. Composite outcome: PE recurrence, major bleeding, or death.

with the risk for PE or major bleeding before deciding if they may be safely treated at home. The attending physicians decided to treat in hospital the four patients who subsequently died, the two patients who bled, and one of three who sustained PE. Our score would also identify all patients who subsequently died or bled, and one of those who subsequently had PE, but the proportion of patients who might have been treated at home was higher (67% vs. 45%). Thus, we compared our score with the decision to treat at home made by attending physicians using net reclassification improvement and integrated discrimination improvement and found that it significantly improved the selection of patients at low risk.

Our findings may have several limitations. Selection bias could have skewed the study sample, since RIETE is a registry and patients were not randomly allocated but received the prescription of their physician's choice. Each physician had a different mode of approach regarding home vs. in-hospital therapy, and some patients may not have been properly trained to follow the appropriate guidelines for treating DVT. However, the broad range of patients from multiple medical centers, countries, and treatment settings enrolled in the RIETE registry decreased the likelihood of the inclusion of a skewed population in this study. Moreover, registration of short-term complications in hospitalized patients might have been better than in patients treated at home, and this might introduce severe bias. But all patients developing PE or bleeding at home were readmitted in the same hospital, thus reducing the risk of bias. Another strength of this study is the prospective collection of data from real world practice, from a large number of consecutive patients with objectively confirmed upper-extremity DVT, in whom the diagnosis of symptomatic PE or bleeding had been obtained by strictly applying objective criteria.

In summary, we built a prognostic score that correctly identifies patients with upper extremity DVT at low risk for the composite outcome of PE occurrence, major bleeding or death within the first week. These data may help safely treat more patients at home. This score, however, should be externally validated.

Addendum

V. Rosa-Salazar contributed to the design, interpretation of data, collected patients, and wrote the article. J. Trujillo-Santos contributed to the design, analysis, and interpretation of data, collected patients, and approved the final version of the article. J. A. Díaz contributed to the interpretation of data, collected patients, and approved the final version of the article. A. Apollonio contributed to the interpretation of data, collected patients and approved the final version of the article. O. Sanz contributed to the interpretation of data, collected patients, and approved the final version of the article. R. Maly contributed to the interpretation of data, collected patients, and approved the final version of the article. F. J. Muñoz-Rodríguez contributed to the interpretation of data, collected patients, and approved the final version of the article. J. C. Serrano contributed to the interpretation of data, collected patients, and approved the final version of the article. S. Soler contributed to the interpretation of data, collected patients, and approved the final version of the article. M. Monreal contributed to the design, analysis and interpretation of data, collected patients, wrote the article, and obtained funding.

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Disclosure of Conflict of Interests

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References

1 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; **141** (Suppl. 2): e419S–94S.
2 Lozano F, Trujillo-Santos J, Barrón M, Gallego P, Babalis D, Santos M, Falgá C, Monreal M. Home versus in-hospital treatment of outpatients with acute deep venous thrombosis of the lower limbs. *J Vasc Surg* 2014; **59**: 1362–7.
3 Muñoz FJ, Mismetti P, Poggio R, Valle R, Barron M, Guil M, Monreal M. Clinical outcome of patients with upper-extremity deep vein thrombosis: results from the RIETE Registry. *Chest* 2008; **133**: 143–8.
4 Trujillo-Santos J, Herrera S, Page MA, Soto MJ, Raventós A, Sánchez R, Monreal M. Predicting adverse outcome in outpatients with acute deep vein thrombosis. Findings from the RIETE Registry. *J Vasc Surg* 2006; **44**: 789–93.
5 Sánchez Muñoz-Torrero JF, Bounameaux H, Pedrajas JM, Lorenzo A, Rubio S, Kearon C, Hernández L, Monreal M. Effects of age on the risk of dying from pulmonary embolism or bleeding during treatment of deep vein thrombosis. *J Vasc Surg* 2011; **54**: 26S–32S.
6 Nieto JA, Solano R, Ruiz-Ribó MD, Ruiz-Giménez N, Prandoni P, Kearon C, Monreal M. Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: findings from the RIETE Registry. *J Thromb Haemost* 2010; **8**: 1216–22.
7 Trujillo-Santos J, Lozano F, Lorente MA, Adarraga D, Hirmerova J, Del Toro J, Mazzolai L, Barillari G, Barrón M, Monreal M. A prognostic score to identify low-risk outpatients with acute deep vein thrombosis in the lower limbs. *Am J Med* 2015; **128**: 90.e9–15.
8 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41.
9 Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008; **27**: 157–72.
10 Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, Pencina MJ, Kattan MW. Assessing the performance of prediction models. A framework for traditional and novel measures. *Epidemiology* 2010; **21**: 128–38.
11 Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation* 2007; **115**: 928–35.