Prediction of Major Bleeding in Anticoagulated Patients for Venous Thromboembolism: Comparison of the RIETE and the VTE-BLEED Scores

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TH Open 2021;5:e319–e328.

Abstract

The performance of validated bleeding risk scores in patients with venous thromboembolism (VTE) could be different depending on the time after index event or the site of bleeding. In this study we compared the “classic” Registro Informatizado de Enfermedad Tromboembólica (RIETE) score and the more recently developed VTE-BLEED score for the prediction of major bleeding in patients under anticoagulant therapy in different time intervals after VTE diagnosis. Out of 82,239 patients with acute VTE, the proportion of high-risk patients according to the RIETE and VTE-BLEED scores was 7.1 and 62.3%, respectively. The performance of both scores across the different study periods (first 30 days after VTE diagnosis, days 31–90, days 91–180, and days 181–360) was similar, with areas under the receiving operating characteristics (ROC) curve (AUC) ranging between 0.69 and 0.72. However, the positive predictive values were low, ranging between 0.6 and 3.9 (better for early major bleeding than for later periods). A sensitivity analysis limited to patients with unprovoked VTE showed comparable results. Both scores showed a trend toward a better

Keywords
► venous thromboembolism
► anticoagulation
► bleeding
► hemorrhage
► score

*A full list of the RIETE investigators is given in the appendix.
Introduction

Anticoagulant therapy is the mainstream of the management of venous thromboembolism (VTE). Currently, several options are available: (1) initial parenteral therapy with unfractionated heparin, low-molecular weight heparin (LMWH), or fondaparinux followed by long-term oral vitamin K antagonists (VKAs); (2) LMWH for initial and long-term therapy (mostly used in cancer patients); and (3) direct oral anticoagulants (DOACs) alone or after an initial heparin lead-in period, depending on the drug. Usually, the ideal length of treatment ranges between 3 months to indefinite depending on the estimated risk of recurrent VTE in case of discontinuing anticoagulation and the risk of bleeding associated with its maintenance. Indeed, bleeding is the most common and severe adverse event related to anticoagulant drugs. Therefore, identification of patients at increased risk for bleeding is critical for decision-making.

In the latest years, different attempts to develop and validate a prognostic score to identify VTE patients at increased risk for bleeding have been performed, but their predictive values and accuracy are modest. Recently, a new score to predict major bleeding in stable anticoagulated patients has been described (i.e., after the first 30 days) named VTE-BLEED score (Table 1).

The Registro Informatizado de Enfermedad Tromboembólica (RIETE) is a multicenter, ongoing, international registry of consecutive patients with objectively confirmed, symptomatic acute VTE (ClinicalTrials.gov identifier: NCT02832245). Since its inception in 2001, the aim of RIETE is to record data including the clinical characteristics, treatment, and outcomes in patients diagnosed with VTE. In the current study, we aimed to compare the predictive ability of the novel VTE-BLEED score with that of the previously developed RIETE score focusing on different time intervals after the index VTE event, also taking into account other relevant variables such as the site of the hemorrhage.

Methods

Patient Sample

The study population comprised consecutive patients enrolled in the RIETE registry between March 2001 and December 2019.

The rationale and methodology have been already reported elsewhere. Patients participating in a randomized trial with a blind medication were excluded. All suspected VTE events were objectively confirmed by compression ultrasound or contrast venography for deep vein thrombosis; helical computed tomography, or ventilation/perfusion scan or angiography for pulmonary embolism (PE). All patients or their family members provided written or oral consent for participation in the registry, in accordance with Local Ethics Committee’s policies.

Study Variables

The following parameters are recorded in the RIETE Registry: patients’ demographics, comorbidities, risk factors for VTE, baseline laboratory data, and treatment received. In this study both, the RIETE bleeding score and the VTE-BLEED score for prediction of extracranial than intracranial major bleeding, the RIETE score resulting more useful for early extracranial bleeding and the VTE-BLEED for late intracranial hemorrhages. Our study reveals that the usefulness of available bleeding scores may vary depending on the characteristics of the patient population and the time frame evaluated. Dynamic scores could be more useful for this purpose.
The positive predictive values (PPVs) were 3.9% for the high-risk group of the RIETE score and 2.0% for the VTE-BLEED score, while the negative predictive values (NPVs) were 98.7 and 99.5%, respectively (Table 3). The AUCs were 0.71 (95% confidence interval [CI] 0.70–0.73) and 0.69 (95% CI, 0.67–0.70), respectively (p < 0.001) (Fig. 1). Interestingly, differences in the AUC were mainly due to the superiority of the RIETE score for extracranial bleeding, while the performance on both scores was similar for intracranial bleeding (Supplementary Fig. S1).

Day 31 to Day 90 after VTE Diagnosis
During this study period, there were 385 major bleeding events. Again, gastrointestinal was the most frequent site (153 events; 39.7%) followed by intracranial bleeding (85; 22.1%). According to the RIETE score, 14,030 patients (19.2%) were classified as low risk for bleeding, 54,610 (74.7%) as intermediate risk, and 4,492 (6.1%) as high risk. Using the VTE-BLEED score, 28,697 patients (39.2%) were classified as low risk and 44,435 (60.8%) as high risk (Table 3).

The PPVs of the high-risk strata were 1.3% for the RIETE score and 0.8% for the VTE-BLEED score, while the NPVs were 99.5 and 99.8%, respectively. The AUCs were almost identical: 0.70 (95% CI, 0.68–0.72) and 0.70 (95% CI, 0.68–0.73), respectively (Fig. 1).

Similar results were obtained in a sensitivity analysis limited to patients with unprovoked VTE (N = 49,659) (Supplementary Table S1 and Supplementary Fig. S2). In this period both scores showed higher AUC for extracranial than for intracranial bleeding, without significant differences between them (Supplementary Fig. S3).

Day 91 to Day 180 after VTE Diagnosis
During this time interval, 243 major bleeding events were recorded. Again, gastrointestinal was the most frequent site (91 events; 37.4%) followed by intracranial (72 events; 29.6%). According to the RIETE score, 12,653 patients (20.1%) were classified as low risk for bleeding, 46,941 (74.4%) as intermediate risk, and 3,489 (5.5%) as high risk. The distribution of bleeding events across the different risk categories of each score and their performance is shown in Table 3.

The PPVs were 2.3% for the RIETE score and 1.3% for the VTE-BLEED score, while the NPVs were 99.7 and 99.9%, respectively. The AUCs were similar: 0.69 (95% CI, 0.67–0.73) and 0.70 (95% CI, 0.67–0.73), respectively (Fig. 1).

In a sensitivity analysis limited to patients with unprovoked VTE (N = 44,375), similar findings were observed (Supplementary Table S2 and Supplementary Fig. S4). Again, in this period both scores showed a trend toward higher AUC for extracranial than for intracranial bleeding, without significant differences between them (Supplementary Fig. S5).

Day 181 to Day 360 after VTE Diagnosis
Of the 164 major bleeding events recorded in this time interval, 69 (42.1%) were gastrointestinal, and 44 (26.8%)
| MB 1–30 d | No MB 1–30 d | MB 31–90 d | No MB 31–90 d | MB 91–180 d | No MB 91–180 d | MB 181–360 d | No MB 181–360 d |
|-----------|-------------|-------------|--------------|-------------|--------------|-------------|--------------|
| Patients, N | 1,187 | 81,052 | 385 | 72,747 | 243 | 62,840 | 164 | 35,521 |

**Clinical characteristics**

- **Male gender**: 494 (42.0%) vs. 39,761 (49.1%), 178 (46.2%) vs. 15,762 (49.0%), 116 (47.7%) vs. 30,953 (49.3%), 75 (45.7%) vs. 17,695 (49.8%)
- **Age >85 y**: 204 (17.0%) vs. 7,298 (9.0%), 58 (15.1%) vs. 6,213 (8.5%), 44 (18.1%) vs. 5,183 (8.2%), 24 (14.6%) vs. 2,630 (7.4%)
- **Body weight <50 kg**: 57 (4.8%) vs. 1,915 (2.4%), 15 (3.9%) vs. 1,572 (2.2%), 8 (3.3%) vs. 1,212 (1.9%), 5 (3.0%) vs. 585 (1.6%)
- **Chronic lung disease**: 192 (16.0%) vs. 9,370 (11.6%), 52 (13.5%) vs. 8,261 (11.4%), 37 (15.2%) vs. 6,994 (11.1%), 25 (15.2%) vs. 3,925 (11.0%)
- **Chronic heart disease**: 140 (12.0%) vs. 5,391 (6.7%), 42 (10.9%) vs. 4,573 (6.3%), 15 (6.2%) vs. 3,815 (6.1%), 23 (14.0%) vs. 2,002 (5.6%)
- **History of stroke**: 67 (5.6%) vs. 3,588 (4.4%), 22 (5.7%) vs. 3,055 (4.2%), 18 (7.4%) vs. 2,501 (4.0%), 7 (4.3%) vs. 1,344 (3.8%)
- **History of high risk for bleeding**: 18 (5.6%) vs. 3,588 (4.4%), 5 (1.5%) vs. 3,055 (4.2%), 3 (0.8%) vs. 2,501 (4.0%), 1 (0.5%) vs. 1,344 (3.8%)

**High risk for bleeding**

- **Recent (<30 d) major bleeding**: 104 (8.8%) vs. 1,720 (2.1%), 22 (5.7%) vs. 1,343 (1.8%), 11 (4.5%) vs. 1,020 (1.6%), 7 (4.3%) vs. 435 (1.2%)
- **Active cancer**: 354 (30.0%) vs. 14,500 (17.9%), 152 (39.5%) vs. 11,668 (16.1%), 77 (31.7%) vs. 8,588 (13.7%), 42 (25.6%) vs. 4,032 (11.4%)
- **Anemia**: 671 (57.0%) vs. 27,235 (33.6%), 215 (55.8%) vs. 23,325 (32.1%), 134 (55.1%) vs. 18,949 (30.2%), 93 (56.7%) vs. 9,539 (29.8%)
- **Platelet count <50,000/µL**: 12 (1.0%) vs. 290 (0.4%), 1 (0.3%) vs. 178 (0.2%), 0 (0.0%) vs. 123 (0.2%), 0 (0.0%) vs. 51 (0.1%)
- **Creatinine levels <30 mL/min**: 304 (26.0%) vs. 8,028 (9.9%), 81 (21.0%) vs. 6,636 (9.1%), 39 (16.0%) vs. 5,484 (8.7%), 34 (20.7%) vs. 2,873 (8.1%)
- **Antiplatelet use at VTE diagnosis**: 257 (22.2%) vs. 11,879 (15%), 72 (19%) vs. 10,386 (14%), 43 (18%) vs. 8,804 (14%), 37 (23%) vs. 7,149 (14%)

**VTE characteristics**

- **PE (with or without DVT)**: 773 (65.0%) vs. 42,613 (52.6%), 209 (54.3%) vs. 37,432 (51.5%), 140 (57.6%) vs. 32,554 (51.8%), 98 (59.8%) vs. 20,043 (56.4%)
- **Proximal DVT**: 580 (49.0%) vs. 44,246 (52.1%), 201 (52.2%) vs. 38,396 (52.8%), 134 (55.1%) vs. 33,396 (53.1%), 83 (50.6%) vs. 18,859 (53.1%)
- **Distal DVT**: 75 (6.3%) vs. 8,707 (10.7%), 26 (6.8%) vs. 7,956 (10.9%), 20 (8.2%) vs. 6,655 (10.6%), 13 (7.9%) vs. 3,127 (8.8%)
- **Unprovoked**: 657 (55.0%) vs. 53,874 (66.5%), 189 (49.1%) vs. 49,470 (68.0%), 126 (51.9%) vs. 44,249 (70.4%), 102 (62.2%) vs. 26,210 (73.8%)
- **Surgery**: 178 (15.0%) vs. 8,966 (11.1%), 36 (9.4%) vs. 8,082 (11.1%), 30 (12.3%) vs. 6,834 (10.9%), 13 (7.9%) vs. 3,397 (9.6%)
- **Immobilization**: 414 (35.0%) vs. 18,377 (22.7%), 118 (30.6%) vs. 15,828 (21.7%), 72 (29.6%) vs. 13,261 (21.1%), 46 (28.0%) vs. 6,628 (18.7%)
- **Estrogen therapy**: 31 (2.6%) vs. 4,416 (5.4%), 13 (3.4%) vs. 4,050 (5.6%), 8 (3.3%) vs. 3,592 (5.7%), 2 (1.2%) vs. 1,464 (5.5%)

**Initial therapy**

- **Low-molecular-weight heparin**: 959 (81.0%) vs. 71,088 (87.7%), 353 (91.7%) vs. 64,228 (88.3%), 216 (88.9%) vs. 55,565 (88.4%), 143 (87.2%) vs. 31,517 (89.8%)
- **Unfractionated heparin**: 127 (11.0%) vs. 4,705 (5.8%), 17 (4.4%) vs. 3,958 (5.4%), 17 (7.0%) vs. 3,390 (5.4%), 12 (7.3%) vs. 1,917 (5.4%)
Table 2 (Continued)

|                  | MB 1–30 d | No MB 1–30 d | MBa 31–90 d | No MBa 31–90 d | Mb 91–180 d | No Mb 91–180 d | Mb 181–360 d | No Mb 181–360 d |
|------------------|-----------|--------------|-------------|---------------|-------------|---------------|-------------|----------------|
| Thrombolytics    | 60 (5.1%) | 965 (1.2%)   | 2 (0.5%)    | 830 (1.1%)    | 731 (1.2%)  | 1 (0.6%)      | 482 (1.4%)  |
| DOACs            | 5 (0.4%)  | 1,975 (2.4%) | 3 (0.8%)    | 1,884 (2.6%)  | 1,614 (2.6%)| 3 (1.8%)      | 579 (1.6%)  |
| Fondaparinux     | 17 (1.4%) | 1,573 (1.9%) | 8 (2.1%)    | 1,376 (1.9%)  | 1,126 (1.8%)| 4 (2.4%)      | 411 (1.2%)  |

**Long-term therapy**

|                  | MB 1–30 d | No MB 1–30 d | MBa 31–90 d | No MBa 31–90 d | Mb 91–180 d | No Mb 91–180 d | Mb 181–360 d | No Mb 181–360 d |
|------------------|-----------|--------------|-------------|---------------|-------------|---------------|-------------|----------------|
| Low-molecular-weight heparin | 419 (35.0%) | 22,534 (27.8%) | 195 (50.6%) | 18,855 (25.9%) | 84 (34.6%) | 12,963 (20.6%) | 33 (20.1%) | 4,776 (13.4%) |
| Anti-vitamin K    | 404 (34.0%) | 49,136 (60.6%) | 164 (42.6%) | 47,791 (65.7%) | 150 (61.7%) | 44,690 (71.1%) | 122 (74.4%) | 28,570 (80.4%) |
| DOACs             | 20 (1.7%)  | 6,375 (7.9%)  | 21 (5.5%)   | 5,302 (7.3%)  | 7 (2.9%)    | 4,630 (7.4%)  | 6 (3.7%)    | 2,011 (5.7%)  |

**Bleeding location**

|                  | MB 1–30 d | No MB 1–30 d | MBa 31–90 d | No MBa 31–90 d | Mb 91–180 d | No Mb 91–180 d | Mb 181–360 d | No Mb 181–360 d |
|------------------|-----------|--------------|-------------|---------------|-------------|---------------|-------------|----------------|
| Gastrointestinal tract | 379 (31.9%) | –            | 153 (39.7%) | –             | 91 (37.4%)  | –             | 69 (42.1%)  |
| Genitourinary     | 114 (9.9%) | –            | 41 (10.6%)  | –             | 22 (9.1%)   | –             | 14 (8.5%)   |
| Intracranial      | 134 (11.3%)| –            | 85 (22.1%)  | –             | 72 (29.6%)  | –             | 44 (26.8%)  |
| Retroperitoneal    | 108 (9.1%) | –            | 22 (5.7%)   | –             | 11 (4.5%)   | –             | 8 (4.9%)    |
| Muscle            | 136 (11.5%)| –            | 15 (3.9%)   | –             | 11 (4.5%)   | –             | 8 (4.9%)    |
| Hematoma          | 194 (16.3%)| –            | 31 (8.1%)   | –             | 19 (7.8%)   | –             | 7 (4.3%)    |
| Hemoptysis        | 32 (2.7%)  | –            | 6 (1.6%)    | –             | 7 (2.9%)    | –             | 5 (3%)      |
| Other             | 90 (7.6%)  | –            | 32 (8.3%)   | –             | 10 (4.2%)   | –             | 9 (5.5%)    |

Abbreviations: DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

*Patients on AC therapy by day 30.
*Patients on AC therapy by day 90.
*Patients on AC therapy by day 180.
### Table 3: Distribution of major bleeding events across risk categories and performance of each score during the studied periods

| Days 1–30 | Days 31–90<sup>a</sup> | Days 91–180<sup>b</sup> | Days 181–360<sup>c</sup> |
|-----------|------------------------|------------------------|------------------------|
| **Risk category** | **MB**<sup> (N = 1,187)</sup> | **No MB**<sup> (N = 81,052)</sup> | **MB**<sup> (N = 385)</sup> | **No MB**<sup> (N = 72,747)</sup> | **MB**<sup> (N = 243)</sup> | **No MB**<sup> (N = 62,840)</sup> | **MB**<sup> (N = 164)</sup> | **No MB**<sup> (N = 35,521)</sup> |
| RIETE low | 23 (0.2%) | 14,690 (99.8%) | RIETE low | 13 (0.1%) | 14,017 (99.9%) | RIETE low | 11 (0.1%) | 12,642 (99.9%) | RIETE low | 6 (0.1%) | 7,035 (99.9%) |
| RIETE interm. | 934 (1.5%) | 60,717 (98.5%) | RIETE interm. | 312 (0.6%) | 54,298 (99.4%) | RIETE interm. | 192 (0.4%) | 46,749 (99.6%) | RIETE interm. | 127 (0.5%) | 26,712 (99.5%) |
| RIETE high | 230 (3.9%) | 5,645 (96.1%) | RIETE high | 60 (1.3%) | 4,432 (98.7%) | RIETE high | 40 (1.1%) | 3,449 (98.9%) | RIETE high | 31 (1.7%) | 1,774 (98.3%) |
| VTE-Bleed low | 150 (0.5%) | 30,824 (99.5%) | VTE-Bleed low | 46 (0.2%) | 28,651 (99.8%) | VTE-Bleed low | 31 (0.1%) | 25,712 (99.9%) | VTE-Bleed low | 32 (0.2%) | 15,192 (99.8%) |
| VTE-Bleed high | 1,037 (2.0%) | 50,228 (98.0%) | VTE-Bleed high | 339 (0.8%) | 44,096 (99.2%) | VTE-Bleed high | 212 (0.6%) | 37,128 (99.4%) | VTE-Bleed high | 132 (0.6%) | 20,329 (99.4%) |
| VTE-Bleed | RIETE (High) | VTE-Bleed | RIETE (High) | VTE-Bleed | RIETE (High) | VTE-Bleed | RIETE (High) | VTE-Bleed | RIETE (High) |
| Sensitivity | 87.4 | 19.4 | Sensitivity | 88.1 | 15.6 | Sensitivity | 87.2 | 16.5 | Sensitivity | 80.5 | 18.9 |
| Specificity | 38.0 | 93.0 | Specificity | 39.4 | 93.9 | Specificity | 40.9 | 94.5 | Specificity | 42.8 | 95.0 |
| PPV | 2.0 | 3.9 | PPV | 0.8 | 1.3 | PPV | 0.6 | 1.1 | PPV | 0.5 | 0.6 |
| NPV | 99.5 | 98.7 | NPV | 99.8 | 99.5 | NPV | 99.9 | 99.7 | NPV | 99.8 | 99.6 |
| Accuracy | 89.7 | 92.0 | Accuracy | 39.6 | 93.5 | Accuracy | 41.1 | 94.2 | Accuracy | 42.9 | 94.7 |
| LR+ | 1.4 | 2.1 | LR+ | 1.45 | 2.56 | LR+ | 1.48 | 3.0 | LR+ | 1.41 | 3.78 |
| LR− | 0.33 | 0.87 | LR− | 0.30 | 0.90 | LR− | 0.31 | 0.88 | LR− | 0.46 | 0.85 |

Abbreviations: AC, anticoagulant; Interm., intermediate; LR, likelihood ratio; MB, major bleeding; NPV, negative predictive value; PPV, positive predictive value; VTE, venous thromboembolism.

<sup>a</sup>Patients treated with AC >30 d.

<sup>b</sup>Patients treated with AC >90 d.

<sup>c</sup>Patients treated with AC >180 d.

<sup>p < 0.001</sup>.
According to the RIETE score, 7,041 patients (19.7%) were at low risk for bleeding, 26,839 (75.2%) at intermediate risk, and 1,805 (5.1%) at high risk. Using the VTE-BLEED score, 15,224 patients (42.7%) were classified as low risk and 20,461 (57.3%) as high risk (►Table 3).

The PPVs were 1.7% for the RIETE score and 0.6% for the VTE-BLEED score, while the NPVs were 99.6 and 99.8%, respectively. The AUCs were 0.72; (95% CI, 0.68–0.76) and 0.71 (95% CI, 0.67–0.75), respectively (►Fig. 1). Again, similar results were obtained in a sensitivity analysis limited to patients with unprovoked VTE (N = 26,312) (►Supplementary Table S3 and ►Supplementary Fig. S6).

In this time interval the RIETE score showed a better AUC for extracranial bleeding than for intracranial bleeding, while the opposite trend was observed for the VTE-BLEED score. A trend toward a better performance of the RIETE score for extracranial bleeding and of the VTE-BLEED score for intracranial bleeding was noted (►Supplementary Fig. S7).

**Discussion**

Although the RIETE and the VTE-BLEED scores share several common variables, we appreciate some differences in their performance. The RIETE score performed slightly better than the VTE-BLEED score for the evaluation of the risk within the first month of therapy. This was not unexpected since the VTE-BLEED score was derived to assess the risk for bleeding in patients under stable anticoagulation, at least 1 month after the index VTE event.7,8,17 The possibility of presentation as PE (variable included in the RIETE score but not in the VTE-BLEED score) being a marker of early major bleeding cannot be discarded. However, a difference of 0.02 in the AUC may not be clinically relevant. Regarding later time intervals, despite the RIETE score was initially validated for the prediction of bleeding in the first 3 months, both scores performed rather similar, even in patients with unprovoked VTE. Indeed, this subgroup of patients is particularly relevant in clinical practice since most guidelines recommend the use of indefinite anticoagulation if the risk of bleeding is not high.1,3

Accurate tools for the evaluation of the bleeding risk during the course of anticoagulant therapy for VTE are needed. In the short-term, high-risk patients could benefit from a narrower surveillance and selection of drugs with a better safety profile.18 In the long-term, the risk assessment should be considered to decide the duration of anticoagulant therapy.19 Our study suggests that the usefulness of available bleeding scores may vary depending on the characteristics of the patient population and the time frame evaluated. In this real-world population we confirm that the proportion of patients with VTE classified at high-risk using the VTE-BLEED score is much higher than that initially found in the randomized clinical trials that led to derivation and validation of the score (62% in our series vs. 25–35%).10 According to the RIETE score, 75% of the patients were allocated to the intermediate risk category and 7% to the high-risk stratum.

Another interesting finding of the present study is that the predictive ability of the two scores may also vary according to the site of bleeding. Both, the RIETE and VTE-BLEED scores showed higher AUC for extracranial than for intracranial hemorrhages (ICHs) during the first 6 months. On the contrary, for later bleeding events, the AUC of the VTE-BLEED score was better for ICH than for extracranial bleeding. In fact, the better performance of the RIETE score for early bleeding was associated mainly with extracranial bleedings, while late (beyond the first 6 months) ICH was better predicted by the VTE-BLEED score. A possible explanation is that the variable uncontrolled hypertension is not included in the RIETE score. On the other hand, extracranial hemorrhages occur more often in the first days after VTE diagnosis compared with ICH.20 In a recent sub-analysis of the Hokusai-VTE and Recover trials, the pooled
odds ratio of the VTE-BLEED score for predicting ICH or fatal bleeding was 4.7 (95% CI 2.2–10), although the incidence of the outcome was low.\textsuperscript{21} Similarly, in our series, the OR of the VTE-BLEED score for ICH between day 31 and day 180 was 4.2 (data not shown).

It could be argued that the performance of the RIETE score might have been overestimated, due to the inclusion of the population from which it was developed. However, the current study includes more than 82,000 patients while the original report included 19,000 patients and was limited to the first 3 months after index VTE. Similar results were observed if the analysis was limited to patients registered in RIETE after 2010 (data not shown). The higher number of patients and events in the current study is a strength to take into account regarding other previous studies that have compared bleeding scores in VTE patients, in which the c-statistic of the RIETE score was more modest.\textsuperscript{6,22}

In another recent prospective study, the AUC of the RIETE and VTE-BLEED scores for the detection of in-hospital bleeding in patients with acute PE were also high: 0.77 and 0.75, respectively. The addition of D-dimer values could help to improve their performance.\textsuperscript{23}

Despite the results highlighted by this study, both scores have a suboptimal predictive ability, particularly their PPV is poor. Their usefulness should be tested in appropriately designed clinical trials, for example as decision tools for prolongation or withdrawal of anticoagulant therapy in patients with unprovoked VTE after completion of 3 to 6 months of treatment. Our results open the debate about the need of different scores depending on the time frame evaluated, what would imply a more complex scenario.

Several limitations of the study are acknowledged. First, the use of a single baseline evaluation for the assessment of delayed bleeding risk is controversial. Probably, for decisions on extension of anticoagulant therapy periodic evaluations are required. Dynamic scores, not available yet, could be more useful for this purpose. Second, most patients in our registry received long-term therapy with VKAs. We lack reliable data about the quality of INR monitoring. This data could be particularly valuable for the evaluation of early bleeding, sometimes related with the transition from LMWH to VKAs. In addition, the HAS-BLED and Seiler’s scores could not be included in the evaluation, since we lacked information for the item “labile INR”.\textsuperscript{24,25} Finally, the number of patients receiving treatment with DOACs is very low. A different behavior of a score in a population of patients uniformly treated with these drugs cannot be ruled out.

In conclusion, the RIETE and the VTE-BLEED score performed similarly for the prediction of early and late bleeds, with small differences depending on the time since VTE diagnosis and the site of hemorrhage.

Authors’ Contribution
R.L., J.A.N., and M.M. were involved in study design, data collection and interpretation, writing and critical review, and final approval of the manuscript. L.J. was involved in data collection, data analysis and interpretation, writing and critical review, and final approval of the manuscript. All other authors were involved in data collection and interpretation, writing and critical review, and final approval of the manuscript.

Conflict of Interest
None declared.

Acknowledgment
The authors express their gratitude to Sanofi Spain and Leo Pharma for supporting this Registry with an unrestricted educational grant. We also thank the RIETE Registry Coordinating Center, S&H Medical Science Service, for their quality control data, logistic and administrative support.

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Appendix

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