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**Title**

# Validation of risk assessment models predicting venous thromboembolism in acutely ill medical inpatients: a cohort study

**Running title**

Predicting venous thromboembolism in medical ward

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**Essentials**

Identifying patients at risk of hospital acquired venous thromboembolism (VTE) is a challenge

Caprini, IMPROVE and Padua scores were assessed to predict VTE in medical inpatients against advanced age alone

Of 14,660 patients, 1.8% experienced VTE. Area under the ROC curve (AUC) for advanced age alone was 0.61

AUC for Caprini, IMPROVE and Padua scores were respectively 0.60, 0.63 and 0.64, no better than advanced age

Advanced age alone might be a practical alternative to complex models to predict VTE in medical inpatients

**Abstract**

*Background*

As hospital-acquired venous thromboembolism (VTE) represents a frequent cause of preventable deaths in medical inpatients, identifying at risk patients requiring thromboprophylaxis is critical. We aimed to externally assess the Caprini, IMPROVE and Padua VTE risk scores and to compare their performance to advanced age as a stand-alone predictor.

*Methods*

We performed a retrospective analysis of patients prospectively enrolled in the PREVENU trial. Patients aged 40-years and older, hospitalised for at least 2-days on a medical ward were consecutively enrolled and followed for three months. Critical ill patients were not recruited. Patients diagnosed with VTE within 48-hours from admission, or receiving full dose anticoagulant treatment or who underwent surgery were excluded. All suspected VTE and deaths occurring during the three-month follow-up were adjudicated by an independent committee. The three scores were retrospectively assessed. Body mass index, needed for the Padua and Caprini scores were missing in 44% of patients.

*Results*

Among 14,910 eligible patients, 14,660 were evaluable, of which 1.8% experienced symptomatic VTE or sudden unexplained death during the three-month follow-up. The area under the receiver operating characteristic curves (AUC) were 0.60 (95%CI 0.57-0.63), 0.63 (95%CI 0.60-0.66) and 0.64 (95%CI 0.61-0.67) for Caprini, IMPROVE and Padua scores, respectively. None of these scores performed significantly better than advanced age as a single predictor (AUC 0.61, 95%CI 0.58-0.64).

*Conclusion*

In our study, Caprini, IMPROVE and Padua VTE risk scores have poor discriminative ability to identify not-critically ill medical inpatients at risk of VTE, and do not perform better than a risk evaluation based on patient's age alone.

**Keywords**

Venous thromboembolism; Pulmonary embolism; Deep vein thrombosis; Inpatients; Risk assessment model

## Introduction

Venous thromboembolism (VTE) is a serious disease, increasing the risk of a life-threatening pulmonary embolism (PE) or long-term complications. Hospital-acquired VTE remains one of the most common etiologies, accounting for more than one third of all diagnosed VTE.[1,2] It is estimated that as many as 71% of PE-related deaths occur as a consequence of hospitalisation.[3] Due to the challenge of diagnosing PE, this proportion may be underestimated. Therefore, a consequent proportion of sudden deaths is attributable to unsuspected PE.[4–7] This highlights the importance of identifying hospitalised patients at high risk of VTE who require thromboprophylaxis.

Although criteria for thromboprophylaxis are well established for surgical patients, there is no international consensus for medical patients. Most recent recommendations are based on risk stratification using clinical prediction rules.[8,9] For this purpose, several risk assessment models (RAMs) are proposed. The Padua, Caprini and IMPROVE scores are the most widely studied, but they have not been assessed in an implementation management study.[10–12]

Age has been showed to be one of the major determinants of the risk of VTE. Moreover, VTE is highly prevalent among elderly medically ill inpatients.[1,13] Age is the only variable constantly identified as an independent predictor in all available RAMs. [10–12] Additionally, age is readily available and does not require complex calculation.

Therefore, we aimed to retrospectively assess whether existing RAMs perform better than advanced age as a stand-alone predictor in predicting the three-month VTE risk in medically ill inpatients.

## Methods

*Study design*

We performed a secondary analysis of a prospectively recruited and followed cohort of patients hospitalised for acute medical illnesses, participating in a cluster-randomised control trial: The Prevention of Venous Thromboembolism Disease in Emergency Departments (PREVENU) study. The methodology was previously described.[14] Briefly, the PREVENU study took place in 27 French centres (20 academic centres and seven community hospitals) from November 2009 to November 2010. Consecutive patients aged 40 years and older, who presented to the emergency department and were

diagnosed with an acute medical illness requiring hospitalisation were included in the PREVENU trial. Patients were excluded if they: i) received anticoagulant treatment at a therapeutic dosage before hospitalisation or for a reason other than VTE while hospitalised; ii) underwent elective surgery under general anaesthesia; or iii) were diagnosed with VTE or discharged within 48 hours following admission. Critically ill patients admitted to an intensive care unit (ICU) were not included in the PREVENU trial. The randomisation unit was the participating centre. Centers were randomized into the control or intervention arm. In the centres allocated to the intervention group, emergency physicians received educational support reminding them of the guidelines on thromboprophylaxis use for medical inpatients. In the centres allocated to the control group, physicians pursued their usual practices. There was no direct patient intervention.

As part of the PREVENU trial, a standardised case report form was completed during the hospital admission, collecting information on previous and recent medical history, risk factors for VTE, laboratory results, and anticoagulant management. All patients were followed for three months. The main outcome was symptomatic VTE, defined as deep vein thrombosis (proximal and/or distal), nonfatal and fatal pulmonary embolism or unexplained sudden death during the three-month follow- up. All events were adjudicated by an independent committee.

For the present study, the Padua, Caprini and IMPROVE VTE risk scores were calculated using data available in the case report. These scores are depicted in Table 1, along with information on how each predictor was collected and defined in our study. The anticipated length of bed confinement was not collected in the PREVENU study. As a substitute, we used the actual hospital length of stay minus one day. Our study focused on acutely ill medical patients and did not include critically ill patients admitted to ICU or surgical patients. Variables related to ICU admission and surgery included in the IMPROVE score and Caprini score were constantly scored as “no” or “zero”. The only variable with more than 1% of missing values was body mass index, which could not be calculated in 6501 patients (44%), mainly due to missing height values. For this variable, multiple imputation was used, and a sensitivity analysis excluding those patients was conducted.

The primary aim of our analysis was to assess the global discriminatory power of the RAMs in predicting VTE events, as evaluated by their area under the receiver operating characteristics (ROC) curve (AUC), in comparison to advanced age alone, used as a continuous variable.

Secondary aim was to compare the incidence of VTE between low-risk and high-risk patients and assess the robustness of our primary results using time-to-event analysis. Based on derivation and previous validation studies, patients with a Padua score ≥4, Caprini score ≥3, IMPROVE score ≥2 (intermediate and high risk) and IMPROVE score ≥4 (high risk) were considered at increased risk of VTE. Advanced age was defined when reaching 70 years, as defined in the Padua score.

In a first sensitivity analysis, we included only patients not receiving anticoagulant treatment during their hospital stay. In a second sensitivity analysis, we defined the primary outcome as objectively confirmed VTE only and did not consider unexplained sudden death as part of the primary outcome, because reproducibility of adjudication of sudden death as fatal PE is poor.[15] In a third sensitivity analysis, we did not consider distal DVT as part of the primary outcome, because the clinical relevance and optimal management of distal VTE is controversial.[16] In a fourth sensitivity analysis, we excluded patients with missing values for BMI.

*Statistical analyses*

Results were described by their proportion and 95% confidence interval (CI) for categorical variables. Mean and standard deviation or median and interquartile range were used, as appropriate, to describe continuous variables. The AUC were compared using the Delong-Delong tests.[17] When a multiple testing adjustment was required, a closed testing procedure based on intersection-union tests was performed. This methodology allows an optimal correction of the p-values in the context of multiple comparisons of Area Under the ROC curves.[18] This method allows a control of the Family Wise Error Rate at 5%. Calibration plots were depicted and goodness of fit was assessed using Hosmer-Lemeshow test. Brier score was used to compare the accuracy of probabilistic predictions.[19] To determine the accuracy of the scores to predict VTE, we determined sensitivity, specificity, likelihood ratio and Youden index for low- versus

high-risk patients according to the pre-specified thresholds. When sensitivity (Sn) and specificity (Sp) were considered with the same importance, the Youden index captures the best compromise between both. It was calculated as follows: Sn+Sp-1. Time to event (survival) analysis was carried out comparing age to the 3 models to depict event rate over time. In order to gauge the magnitude of the difference in the survival analysis, the advanced age threshold was adjusted so that the event rate at 90 days in low-risk patients based on age would match the event rate in low-risk patients as defined by the RAM. To do so, age threshold was set where the risk of experiencing VTE under this age threshold corresponded to the risk in the low risk group according to the studied risk assessment model. Magnitude of the effect over time would be gauged by the gap between the curves in the high-risk group. The type-I error rate was defined at 5%. Missing values were imputed using the MissForest package in R, which applies random forest theory to impute iteratively missing values.

## Results

*Study Population*

Among the 20,377 patients enrolled in the PREVENU study, 14,910 were included. The main reasons for exclusion were: enrolled during the pre-intervention period without follow-up (n=1,686), length of stay of less than 48 hours (n=2,442), anticoagulant treatment before admission (n=1,075), or surgery under general anaesthesia (n=523). A total of 164 patients (1.1%) were lost in follow-up and 86 (0.6%) had insufficient data to calculate the RAMSs, leaving 14,660 patients for analysis (Figure 1). Characteristics of the cohort are described in Table 2. Seven thousand eight hundred and ninety-six patients (53.9%) did not receive anticoagulant prophylaxis. Main reasons for admission were sepsis (21%), acute respiratory failure (12%), stroke or neurological condition with motor deficit of a lower limb (10%), acute heart failure (8%) or rheumatologic/inflammatory disease (7%).

*Main outcome*

Overall, 263 patients (1.8%) experienced symptomatic VTE during the three-month follow-up, of which eight (3.0%) were definite fatal PE, 127 (48%) were sudden death with no obvious cause (possible fatal PE) and 33 (13%) were isolated distal DVT. The

median time until VTE occurrence was 22 days (interquartile range, 10-46 days). Among patients who experienced VTE, 57% received anticoagulant prophylaxis, as opposed to 46% of patients who did not develop VTE, p<0.001.

*Primary analysis: Performances of risk assessment models*

ROC curves of the evaluated RAMs are depicted in Figure 2. The AUC for predicting VTE was 0.61 (95% CI 0.58-0.64) for advanced age as a single predictor. None of the three models had a significantly different AUC than that of advanced age alone for identifying patients who developed VTE (p=0.284; Table 3). Calibration plots showed significant miscalibration for Caprini score and advanced age alone (Supplementary Figure 1). However, probabilistic precision of the prediction was close for all models, with a Brier score of 0.0175, 0.0176, 0.0176 and 0.0176 for Padua, Caprini, IMPROVE and advanced age, respectively.

*Secondary analysis: Threshold analysis*

The IMPROVE score and advanced age classified the highest proportion of patients as low-risk (Table 4). Based on the Padua, Caprini, IMPROVE (intermediate-high and high) scores or advanced age in low-risk patients, VTE occurred in 0.6%, 0.5%, 1.0%, 1.6% and 1.2 %, respectively (Table 4). In high-risk patients, VTE occurred in 2.2%, 1.9%, 2.5%, 3.0% and 2.3%, respectively for Padua, Caprini, IMPROVE (intermediate-high and high) scores and advanced age (Table 4). Global performances assessed with the Youden Index were poor for the three RAMs and for advanced age, all below 0.25. Temporal trends for each model according to their reported threshold are depicted in Figure 3.

*Sensitivity analyses*

After exclusion of patients who received anticoagulant prophylaxis during their hospital stay (n=6,764) in a first sensitivity analysis, the AUC of predicting VTE was 0.66 (95% CI, 0.62-0.70) for advanced age and not significantly different for the RAMs (p=0.266, Table 3).

When considering only objectively confirmed VTE as primary outcome (n=137), the AUC was 0.66 (95% CI 0.62-0.70) for the Padua score, 0.61 (95% CI 0.57-0.65) for the Caprini score, 0.65 (95% CI 0.61-0.69) for the IMPROVE score, and 0.59 (95% CI 0.54-0.63) for advanced age (p=0.126 for difference across AUCs).

After exclusion of distal DVT as part of the primary outcome, the AUC was 0.65 (95% CI, 0.62-0.68) for the Padua score, 0.60 (95% CI, 0.57-0.64) for the Caprini score, 0.63 (95% CI, 0.60-0.66] for the IMPROVE score, and 0.62 (95% CI, 0.59-0.65) for advanced age (p=0.195 for difference across AUCs).

Overall, 8,198 patients had available values for BMI. Of those 126 (1.5%) experienced symptomatic VTE. Considering only these patients with BMI values, the AUC was 0.61 (95% CI, 0.57-0.66) for the Padua score, 0.61 [0.56-0.65] for the Caprini score, 0.66 [0.62-0.70] for the IMPROVE score, and 0.59 [0.54-0.63] for advanced age (p=0.100 for difference across AUCs).

**Discussion**

Our study provides new insights on the prediction of VTE in medically ill admitted patients, by directly comparing Padua, Caprini and IMPROVE scores, with advanced age as a stand-alone predictor in a very large cohort of prospectively enrolled patients. Discriminant ability appears to be low for all RAMs (AUC ranging from 60 to 65%) and none of them are able to perform better than advanced age alone, simple and readily available information. The extent of these observations is restricted to medical patients not admitted to the ICU and limited by the availability of the body mass index, required for some RAMs.

Most recent guideline recommendations for VTE prophylaxis in hospitalized medical patients are based on risk stratification using clinical prediction rules.[8,9] Several RAMs have been proposed, but none of them are strongly validated. Padua and Caprini scores were built by expert consensus, whereas the IMPROVE score was obtained from multivariate logistic regression derivation/validation studies.[10–12] In 2012, the American College of Chest Physicians (ACCP) guidelines based their recommendations on the Padua score, because at the time the guidelines were written, the Padua score represented the “best available basis for judging hospitalized patients’ risk”.[8] However, the ACCP panel acknowledged the small number of events in the derivation study and

suboptimal validation as limitations of this risk model. The Padua score was prospectively validated in a cohort study which included 1,180 patients admitted to an internal medicine ward. The rate of VTE was 3.1% at three-months. In this study, all patients underwent systematic screening for VTE at 3-months. Unexplained sudden deaths were not considered as VTE events. The event rate in the low risk group (Padua score <4) was 0.3% during the three-months follow-up.[10] A prospective multicentre cohort of 1,478 medical inpatients, with a 2.3% incidence of VTE, showed conflicting results. Among the 764 low risk patients according to the Padua score, 1.1% had symptomatic VTE event at three months.[20] Other retrospective studies reported an AUC of 0.62 or less.[21–23] The Caprini score was first evaluated and validated to predict VTE in surgical patients. A retrospective cohort validated the Caprini score in medical patients and reported an AUC of 0.63.[22] Better performances for the Padua and Caprini scores were reported, but the case control design of these studies created higher prevalence resulting in increased sensitivity and thus, biased performance estimates.[24–26] The IMPROVE score was derived using regression analysis in a mixed pro- and retrospective cohort of medical inpatients. As for the Padua and Caprini scores, performances in external validation studies vary widely, with AUC between 0.56 and 0.77.[27–30] It is not uncommon for risk scores in general to be over-optimistic in the dataset they were derived from. In the recent MARINER trial comparing rivaroxaban 10 mg daily to placebo for extended thromboprophylaxis, a modified IMPROVE score incorporating D-dimer levels was used to identify patients at high risk of VTE during the three-month follow-up period.[31] The addition of the D-dimer levels was shown to slightly improve the discriminating ability of the score.[30] In spite of this, the score failed to identify a population at high risk with only 66 out of 6,012 patients (1.2%) in the placebo arm developing VTE during follow-up. 62% of primary outcomes were unexplained sudden deaths, leaving only 22 (0.4%) objectively confirmed symptomatic VTE events in patients treated with placebo. In summary, our results support previous studies indicating poor discriminant ability of the three scores in external validation studies. More recently, a retrospective application of the IMPROVE score combined with a D-dimer test was able to identify a subgroup of patients with a significantly higher risk of VTE.[32]

Age is one of the major determinants of VTE and is taken into account in all risk prediction models for medically ill inpatients.[10–12] As a consequence, recent clinical trials on VTE prophylaxis used advanced age as one of their major selection criteria.[31,33] Our results suggest that age can be used as a single predictor, sufficient to classify patients as having a low or high risk of VTE. Its prediction performance is similar to all risk prediction models that we evaluated. Moreover, a strategy based on age alone is easily implementable in everyday clinical practice. Above the age of 70, the risk of VTE exceeded 2% at 3-months, but the higher the age, the higher the risk of VTE. Advanced age could easily be used in a quantitative way to gauge the risk of VTE.

Some subgroups of patients might benefit from dedicated risk assessment tools, such as cancer patients or those with a prior history of venous thromboembolism. These subgroups respectively represented 12.3% and 6.2% of the overall population. That is the same for patients known to have elevated D-dimer levels.[34] The risk of VTE was shown to gradually increase for each increment of 250µg/L of D-dimer. It is also interesting to note that the rate of anticoagulant prophylaxis was higher in patients who developed VTE. This might be mainly due to the ability of physicians to identify high-risk patients and select them for anticoagulant prophylaxis. However, another hypothesis is that it might be the consequence of a suboptimal efficacy of anticoagulant prophylaxis.

*Strengths and limitations*

To our knowledge, the PREVENU study is the largest cohort of consecutively and prospectively followed medical inpatients.[14] Some larger registries of VTE patients are available, but these retrospective registries faced challenges for the calculation of risk scores.[27,29,35] Moreover, the case-control design artificially increases the prevalence of the disease, modifying the tests properties.[27,29] The prospective and consecutive inclusion of patients in the PREVENU study ensures high data quality. Our main outcome was symptomatic VTE, and all events were adjudicated by an independent committee. In contrast, most randomised control trials of thromboprophylaxis for medical inpatients used systematic screening of asymptomatic VTE.[33] The clinical implications and the need for treatment of asymptomatic VTE remain controversial, especially for distal VTE.[16] Excluding symptomatic below the knee DVT did not modify our conclusion.

Nevertheless, our study has limitations. Firstly, as a substitute of bed confinement duration, we used the actual hospital length of stay minus one day, collected during

follow-up. However, we do not expect that this limitation explains the observed low performances of the scores. Quite the contrary, the anticipated duration of bed confinement appears arduous to predict at admission. The effective hospital length of stay provides a much more precise estimate of the exposure to the risk of VTE. Moreover, there is a wide variability in the definition of bed confinement between scores, making it difficult to implement in clinical practice and complicating its interpretation in retrospective studies. It is to be recalled that patients admitted in the ICU were not included in the study, not allowing to conclude on this specific subgroup. Patients were eligible to the study if still present beyond 48hours from admission. So, patients admitted in medical ward presenting early deterioration and transferred to the ICU were not recruited. Secondly, body mass index was not always available, leading to perform random forest multiple imputation. BMI was part of Padua and Caprini risk scores which may represent a cause of miscalibration. Nevertheless, the sensitivity analysis excluding patients with unknown body mass index did not alter our results. The absence of ICU stay and BMI might have especially decreased the IMPROVE score discrimination abilities, as both a required to assess this score. Thirdly, nearly half of the main outcome events were sudden death without objectively confirmed cause. As necropsy was not regularly performed, some events might not have been the direct consequence of a pulmonary embolism. Including those patients in the primary outcome constituted a more sensitive approach. Furthermore, a sensitivity analysis having only consider objectively confirmed VTE did not alter the results. Lastly, around half of patients received thromboprophylaxis with a wide panel of different regimens depending on physicians' clinical practice. This may have influenced the occurrence of venous thromboembolism. However, our results were unchanged when restricting the analysis to patients who did not receive anticoagulant prophylaxis during their stay.

**Conclusion**

In this cohort of patients hospitalised for an acute medical illness, the Padua, Caprini and IMPROVE VTE RAMs have poor discrimination ability to identify patients at risk of VTE and do not offer a better prediction than advanced age alone. These results do not apply to critically ill patients, but if confirmed, suggest that using an age above 70 years might

be easiest and a practical way to identify medical inpatients requiring thromboprophylaxis.

**Funding**

None.

**Conflicts of interest**

Thomas Moumneh reports grants from University Hospital on Angers, during the conduct of the study; grants from CanVECTOR, grants from Société Française de Médecine d'Urgence, outside the submitted work. Tobias Tritschler reports grants from Swiss National Science Foundation SNSF P2ZHP3_177999, non-financial support from Pfizer, outside the submitted work. Grégoire Le Gal reports other from Portola Pharmaceuticals, other from Boehringer-Ingelheim, other from Pfizer, other from Bristol-Myers Squibb, other from LEO Pharma, other from Daiichi Sankyo, other from Bayer, personal fees from Bayer, personal fees from Pfizer, personal fees from LEO Pharma, personal fees from Sanofi, personal fees from bioMérieux, outside the submitted work. Jérémie Riou, Delphine Douillet, Samir Henni, Dominique Mottier and Pierre-Marie Roy has nothing to disclose.

**Author Contributions:**

Thomas Moumneh and Pierre-Marie Roy conceptualised and designed the study. Dominique. Mottier, Grégoire Le Gal, Pierre-Marie Roy and the INNOVTE – F-CRIN research network for the PREVENU study group provided the data. Thomas Moumneh and Jérémie Riou analysed the data. Thomas Moumneh and Pierre-Marie Roy interpreted the data, with assistance from Jérémie Riou. The manuscript was written primarily by Thomas Moumneh and Pierre-Marie Roy; Delphine Douillet, Tobias Tritschler and Grégoire Le Gal provided assistance and contributed to revisions. All authors substantially contributed to this project, read and approved the manuscript, and assume responsibility for the contents of the manuscript.

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**Table 1.** Covariates in the Padua, Caprini and IMPROVE scores, method of collection and availability. CCU: critical care unit, ICU: intensive care unit, VTE: venous thromboembolism.

| Covariate | Padua | Caprini | IMPROVE | Method of collection | Missing |
|---|---|---|---|---|---|
| Age | ≥70: +1 | 41-60: +1<br>61-74: +2<br>≥75: +3 | >60: +1 | Prospectively collected | none |
| Body Mass Index | ≥30: +1 | >25: +1 | NA | Prospectively collected | 44% |
| Medical history | | | | | |
| Cancer | +3 | +2 | +2 | Prospectively collected | none |
| Previous VTE | +3 | +3 | +3 | Prospectively collected | none |
| Known thrombophilia | +3 | +3 for each | +2 | Prospectively collected | none |
| Family history VTE | NA | +3 | NA | Not collected | Not collected |
| Unexplained abortion | NA | +1 | NA | Not collected | Not collected |
| Varicose veins | NA | +1 | NA | Prospectively collected | <1‰ |
| Inflammatory bowel disease | NA | +1 | NA | Prospectively collected | <1‰ |
| Heparin induced thrombocytopenia | NA | +3 | NA | Collected from serious adverse events | none |
| Recent condition (<1 month) | | | | | |
| Stroke | NA | +5 | NA | Named “neurological condition with lower limb paralysis” | none |
| Spinal cord injury | NA | +5 | NA | | |
| Surgery | +2 | +1 | NA | Prospectively collected | <1‰ |
| Trauma | | NA | NA | Prospectively collected | none |
| Peripartum | NA | +1 | NA | Prospectively collected | none |
| Heart failure | NA | +1 | NA | Prospectively collected | none |
| Sepsis | NA | +1 | NA | Prospectively collected | none |
| Pneumonia | NA | +1 | NA | Named “recent acute respiratory failure” | none |
| Condition during hospitalisation | | | | | |
| Reduced mobility | ≥3days: +3 | On bed: +1<br>>72h: +2 | ≥7days: +1 | Not collected<br>Imputed with length of hospital stay minus one day | none |
| Heart failure | +1 | +1 | NA | Prospectively collected | none |
| Respiratory failure | | +1 | NA | Prospectively collected | none |
| Myocardial infarction | | +1 | NA | Prospectively collected | none |
| Stroke | +1 | +5 | NA | Prospectively collected | none |
| Lower limb paralysis | | | +2 | Prospectively collected | none |
| Acute infection | +1 | +1 | NA | Prospectively collected | none |
| Rheumatologic disease | | NA | NA | Prospectively collected | none |
| Hormonal treatment | +1 | +1 | NA | Prospectively collected | <1% |
| Swollen legs | NA | +1 | NA | Not collected | Not collected |
| Central venous access | NA | +2 | NA | Prospectively collected | none |

| | | | | | |
|---|---|---|---|---|---|
| Type of surgery | NA | +1/+2 /+5 | NA | Excluded* | none |
| Major bone fracture | NA | +5 | NA | Prospectively collected | none |
| Plaster cast | NA | +2 | NA | Prospectively collected | none |
| ICU/CCU stay | NA | NA | +1 | Not recruited | Not collected |

* Except surgery under local analgesia, considered +1 point

NA: Not applicable, items are not part of the risk assessment model.

**Figure 1.** Flow Chart.

VTE: Venous thromboembolism, PE: Pulmonary embolism, DVT: Deep vein thrombosis

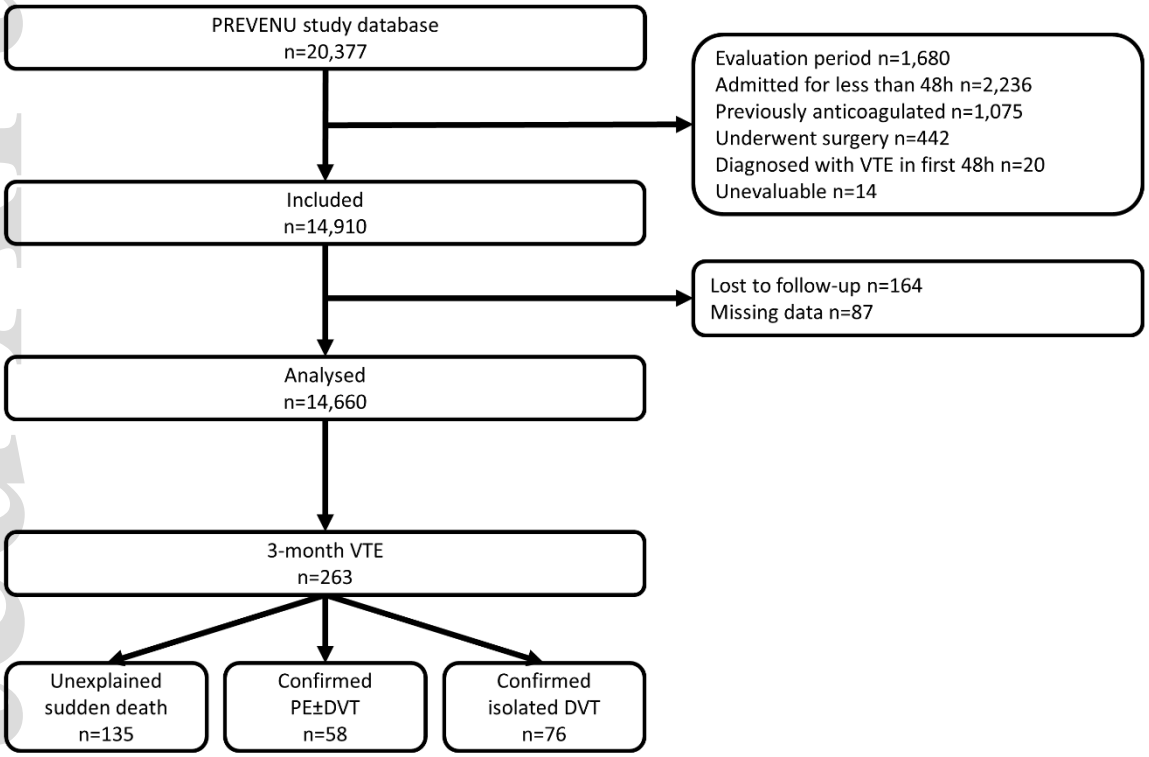

**Table 2.** Characteristics of studied patients

Data are in median [interquartile range] or % [95% confidence interval]

| Characteristics | Values |
|---|---|
| Age, years | 0.73 [59-83] |
| Sex Male | 49.9% [49.1-50.7] |
| Body mass index, kg/m$^2$ | 25.5 (±4.75) |
| Hospital length of stay, days | .007 [4-13] |
| Medical history | |
| Venous thromboembolism | 06.2% [5.8-6.6] |
| Cancer | 12.3% [11.8-12.8] |
| Myeloma | 01.0% [0.8-1.1%] |
| Nephrotic syndrome | 00.8% [0.7-1.0] |
| Thrombophilia | 00.2% [0.1-0.2] |
| Recent condition (<1 month) | |
| Stroke | 09.9% [9.4-10.4] |
| Heart failure | 08.0% [7.6-8.5] |
| Respiratory failure | 11.9% [11.4-12.4] |
| Acute myocardial infarction | 02.9% [2.6-3.2] |
| Aspirin treatment | 25.4% [24.7-26.2] |
| Estrogenic treatment | 00.3% [0.3-0.5] |
| Clinical venous insufficiency | 08.0% [7.6-8.5] |
| Bone fracture or cast of lower leg | 00.6% [0.5-0.7] |
| Current lower limb paralysis | 0.6% [0.4-0.7] |
| Not receiving any anticoagulant prophylaxis during hospital stay | 53.9% [53.1-54.7] |

**Table 3.** Area Under the ROC curve according the different models. Data is in % [95% confidence interval]. p-values are the probability of at least one of the three AUC of the risk assessment models greater than the AUC of advanced age alone.

| Models | All patients | p | No anticoagulant | p |
|---|---|---|---|---|
| Age | 0.61 [0.58-0.64] | -ref- | 0.66 [0.62-0.70] | -ref- |
| Padua | 0.64 [0.61-0.67] | | 0.66 [0.62-0.71] | |
| IMPROVE | 0.63 [0.60-0.66] | 0.284 | 0.66 [0.62-0.70] | 0.266 |
| Caprini | 0.60 [0.57-0.63] | | 0.63 [0.59-0.68] | |

**Table 4.** Distribution on patients according the different scores.

| **Models** | **Proportion in low risk** | **VTE in low risk (1-NPV)** | **VTE in high risk (PPV)** | **Sensitivity (Sn)** | **Specificity (Sp)** | **Youden index (Sn+Sp-1)** |
|---|---|---|---|---|---|---|
| | n (%) | % [95% CI] | % [95% CI] | % [95% CI] | % [95% CI] | % [95% CI] |
| Padua ≥ 4 | 3,706 (25.3) | 0.59 [0.39-0.90] | 2.20 [1.93-2.49] | 91.6 [87.6-94.7] | 25.6 [24.9-26.3] | 0.17 [0.12-0.21] |
| Caprini ≥ 3 | 1,086 (7.4) | 0.46 [0.20-1.07] | 1.90 [1.68-2.14] | 98.1 [95.6-99.4] | 7.5 [7.1-8.0] | 0.06 [0.03-0.07] |
| IMPROVE ≥ 2 | 6,848 (46.7) | 1.01 [0.80-1.27] | 2.48 [2.16-2.85] | 73.8 [68.0-79.0] | 47.1 [46.3-47.9] | 0.21 [0.14-0.27] |
| IMPROVE ≥ 4 | 12,509 (85.3) | 1.58 [1.38-1.82] | 3.02 [2.38-3.83] | 24.7 [19.6-30.4] | 85.5 [84.9-86.1] | 0.10 [0.05-0.16] |
| Age ≥ 70 | 6,255 (42.7) | 1.18 [0.94-1.48] | 2.25 [1.95-2.59] | 71.9 [66.0-77.2] | 42.9 [42.1-43.8] | 0.15 [0.08-0.21] |

NPV: Negative predictive value; PPV: Positive predictive value; CI: Confidence interval

**Figure 2.** ROC curves of performances of models and age (continuous) in overall cohort (**A**) and in the subgroup of patients who did not receive prophylactic anticoagulation (**B**)

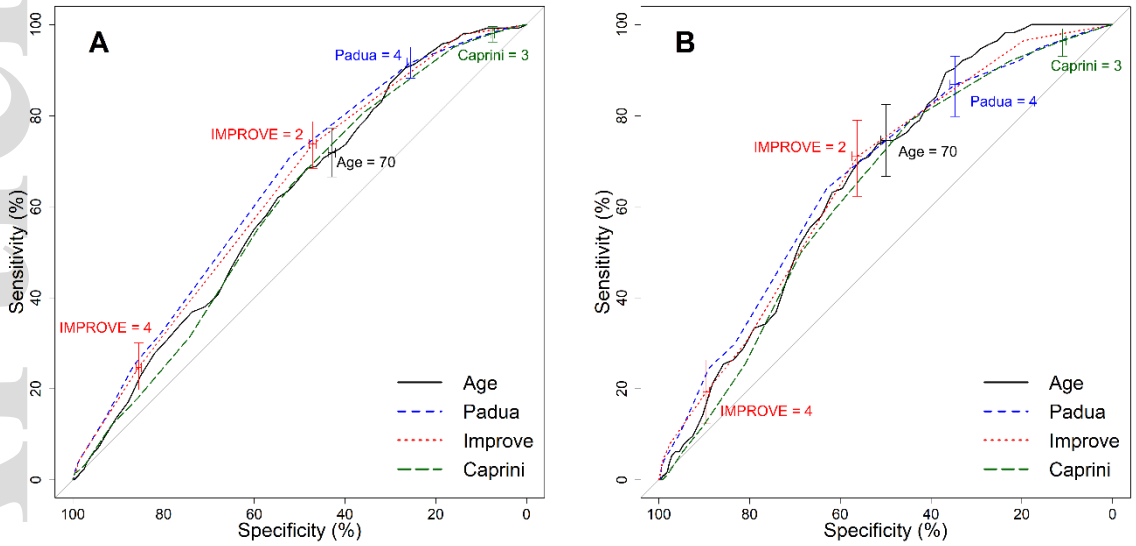

**Figure 3.** Kaplan-Meier plot for the occurrence of symptomatic venous thromboembolism (VTE) over 90-days in low vs high-risk patients according to the Padua score (**A**), the IMPROVE score (**B**) and the Caprini score (**C**) compared to advanced age. Advanced age thresholds were adjusted so than the probability of VTE was equal in the low risk group at day 90 of follow-up.