

ORIGINAL ARTICLE

A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score

S. BARBAR,* F. NOVENTA,† V. ROSSETTO,* A. FERRARI,* B. BRANDOLIN,* M. PERLATI,* E. DE BON,* D. TORMENE,* A. PAGNAN* and P. PRANDONI*

*Department of Cardiothoracic and Vascular Sciences, Second Division of Internal Medicine; and †Department of Clinical and Experimental Medicine, Clinical Epidemiology Group, University of Padua, Padova, Italy

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Summary. *Background:* Prophylaxis of venous thromboembolism (VTE) in hospitalized medical patients is largely underused. We sought to assess the value of a simple risk assessment model (RAM) for the identification of patients at risk of VTE. *Methods:* In a prospective cohort study, 1180 consecutive patients admitted to a department of internal medicine in a 2-year period were classified as having a high or low risk of VTE according to a predefined RAM. They were followed-up for up to 90 days to assess the occurrence of symptomatic VTE complications. The primary study outcome was to assess the adjusted hazard ratio (HR) of VTE in high-risk patients who had adequate in-hospital thromboprophylaxis in comparison with those who did not, and that of VTE in the latter group in comparison with low-risk patients. *Results:* Four hundred and sixty-nine patients (39.7%) were labelled as having a high risk of thrombosis. VTE developed in four of the 186 (2.2%) who received thromboprophylaxis, and in 31 of the 283 (11.0%) who did not (HR of VTE, 0.13; 95% CI, 0.04–0.40). VTE developed also in two of the 711 (0.3%) low-risk patients (HR of VTE in high-risk patients without prophylaxis as compared with low-risk patients, 32.0; 95% CI, 4.1–251.0). Bleeding occurred in three of the 186 (1.6%) high-risk patients who had thromboprophylaxis. *Conclusions:* Our RAM can help discriminate between medical patients at high and low risk of VTE. The adoption of adequate thromboprophylaxis in high-risk patients during hospitalization leads to longstanding protection against thromboembolic events with a low risk of bleeding.

Keywords: anticoagulation, deep vein thrombosis, medical patients, prophylaxis, pulmonary embolism, risk assessment, venous thromboembolism.

Introduction

In spite of increasing evidence that a substantial proportion of patients admitted to departments of internal medicine show a high risk of venous thromboembolic (VTE) complications [1–9], the administration of thromboprophylaxis in these patients continues to be largely underused [10–14].

In order to help stratify the risk of VTE in hospitalized medical patients, several risk assessment models (RAMs) and algorithms have been suggested [15–21]. However, most of them have not been validated in prospective studies, and the only two validated models present limitations that preclude widespread implementation [20,21]. The model proposed by Kucher *et al.* refers to selected subgroups of medical patients exhibiting a particularly high risk of VTE. Indeed, 80% of the patients included in this study were affected by cancer, a figure that exceeds by far the rate encountered in most departments of internal medicine [20]. The risk model proposed by Lecumberri *et al.* [21] was assessed in comparison with historical controls, and recruited patients were not followed-up after discharge.

We devised a simple points score system with the potential to detect hospitalized patients at high risk of developing VTE, and assessed its value in a broad spectrum of consecutive patients admitted to our department of internal medicine in a 2-year period. All patients included in this study were prospectively followed-up for up to 3 months after admission in order to assess the incidence of symptomatic VTE.

Methods

Design overview

We planned a prospective cohort study with independent and blinded assessment of study outcomes. The study was designed

Correspondence: Paolo Prandoni, Department of Cardiothoracic and Vascular Sciences, Thromboembolism Unit, University of Padua, Via Giustiniani, 2, 35128 Padova, Italy.

Tel.: +39 049 8212656; fax: +39 049 8218731.

E-mail: paoloprandoni@tin.it

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to assess whether a simple RAM (obtained after substantial modification of the Kucher model [20]) can help discriminate between admitted medical patients at high and low risk of VTE complications, and whether the implementation of adequate thromboprophylaxis in high-risk patients during hospitalization leads to longstanding protection against thromboembolic events.

Patient recruitment started in January 2007 and ended in December 2008. The protocol was approved by the institutional review board of the University of Padua.

Setting and participants

All consecutive patients admitted to the Second Division of Internal Medicine of the University of Padua (Italy) were eligible for this investigation provided they were not on full-dose anticoagulant therapy, did not require it for whatever indication, had no contraindications to pharmacological prophylaxis (recent or ongoing major bleeding, platelet count lower than $100 \times 10^9 \text{ L}^{-1}$, creatinine clearance lower than 30 mL min^{-1}), and were not pregnant or under 18 years. Study patients had to give written informed consent to participate in the study.

Risk assessment model

The RAM adopted in this study (the Padua Prediction Score) was empirically generated by integrating the Kucher's model [20] with additional items and by slightly modifying the assigned scores in order to permit identification of all those conditions for which the latest international guidelines strongly recommend thromboprophylaxis [4,5]. Table 1 shows the RAM. To be consistent with the Kucher score, an increased risk of VTE was defined as a cumulative score of at least four. Prior to the study start, we assessed the clinical charts of 300 consecutive patients who had been discharged from our institution, and verified that in all 120 patients in whom thromboprophylaxis was indicated (based on international guidelines [4,5]) a cumulative score of at least four had been achieved.

Interventions

All recruited patients were classified by a study operator as being at high or low risk of VTE complications according to the predefined RAM. Attending physicians were not notified of the VTE risk of their patients. The screener reviewed orders to identify the implementation of thromboprophylaxis during hospitalization. Thromboprophylaxis was deemed to be adequate if it was implemented within 48 h of hospital admission, included the daily administration of at least 15 000 U of unfractionated heparin, 4000 U of enoxaparin, 5000 U of dalteparin, 3800 U of nadroparin or 2.5 mg of fondaparinux, and covered at least 80% of the hospital stay. Patients receiving inadequate prophylaxis were regarded as not having received prophylaxis at all.

Table 1 Risk assessment model (high risk of VTE: ≥ 4)

Baseline features	Score
Active cancer*	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility†	3
Already known thrombophilic condition‡	3
Recent (≤ 1 month) trauma and/or surgery	2
Elderly age (≥ 70 years)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (BMI ≥ 30)	1
Ongoing hormonal treatment	1

*Patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been performed in the previous 6 months.

†Bedrest with bathroom privileges (either due to patient's limitations or on physicians order) for at least 3 days. ‡Carriage of defects of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome.

Recruited patients were closely supervised during hospitalization and followed-up for up to 90 days after admission. They were instructed to refer to the study center in the case of clinical symptoms and/or signs suggestive of DVT of the lower extremities or PE. In addition, they were instructed to report to the study center on an emergency basis if any bleeding had occurred. Dedicated operators involved in the study recorded all information potentially useful for adjudication by the central independent committee. All patients were interviewed by telephone at the end of the 90-day study period in order to ascertain the clinical conditions, the use of antithrombotic drugs, the development of events of interest for the study, and the occurrence of death. If patients were not retrievable or had died, their family physician was interviewed and asked for details of the cause of death.

Outcomes and measurements

The primary study outcome was to assess during the 3-month follow-up period the risk of VTE complications in high-risk patients who received proper prophylaxis in comparison with those who did not, and the risk of VTE complications in the latter group in comparison with low-risk patients. The rate of clinically relevant bleeding in the three study groups was also recorded.

Patients with a low pretest clinical probability of either DVT or PE (according to widely accepted score systems [22,23]) were assessed by D-dimer, and those with negative test had the clinical suspicion ruled out [22,23]. In all other combinations objective tests were performed in order to confirm or exclude the clinical suspicion (compression ultrasonography of the whole deep vein system in the case of suspected DVT; spiral CT or V/Q scanning of the lungs in the case of suspected PE) with the use of widely accepted diagnostic criteria. In the event of death, the diagnosis of PE was accepted if it was confirmed at autopsy or anteceded in the immediate period before death by confirmed non-fatal PE or DVT [24].

For the purpose of this investigation only major or clinically relevant bleeding complications were recorded and analyzed. A bleeding event was defined as major if: it was overt and associated with the requirement of at least two units of blood; it was retroperitoneal, spinal or intracranial; or it occurred in a critical organ or contributed to death. Relevant bleedings were considered those episodes that were clinically important but did not qualify as major (for example, epistaxis that required intervention, or spontaneous macroscopic hematuria).

All outcome events were reviewed by an independent adjudication committee whose members were unaware of the patients' risk and use of thromboprophylaxis.

Statistical analysis

We assumed a one in three admission rate of high-risk patients, and 50% failure to administer prophylaxis in these patients [10,11]. We estimated a 12% rate for the primary endpoint in the 3-month follow-up of high-risk patients managed without prophylaxis [18]. Accordingly, we estimated a sample size of approximately 200 patients for each high-risk group (with and without prophylaxis) to have 80% power to detect a 70% reduction in the incidence of subsequent VTE in patients managed with proper prophylaxis during hospitalization, and therefore an overall sample size of approximately 1200 patients.

We determined the proportion, and its 95% confidence intervals (CIs), of patients who developed VTE and clinically relevant bleeding in each of the following three groups: low-risk patients, high-risk patients who received prophylaxis, and high-risk patients who did not. For the purpose of sensitivity analysis, the analysis of the risk of VTE complications was repeated after also including 'sudden otherwise unexplained deaths' in thrombotic complications.

We calculated the crude relative risk (RR) for the development of thromboembolic complications (and its 95% CIs) in high-risk patients who were managed with prophylaxis

compared with those who were not, and in high-risk patients who were not managed with prophylaxis compared with low-risk patients. To adjust for the unbalanced distribution of the considered risk factors (listed in Table 2), the Cox's product-limit multivariate analysis with forward stepwise variables selection (LR method) was used to estimate the adjusted hazard risk (HR) and its 95% CIs for the study events in high-risk patients with and without prophylaxis, and in high-risk patients managed without thromboprophylaxis versus low-risk patients.

For the comparison of baseline features between high-risk patients who received prophylaxis and those who did not we used the chi-square test (with Yates' correction) for qualitative variables and the Student's *t*-test for quantitative variables.

The 95% CIs and *P*-values were calculated according to the normal approximation of the binomial distribution.

All calculations were performed with spss version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients and thromboprophylaxis

Out of 2208 eligible patients, 964 were excluded because of ongoing anticoagulant treatment or medical conditions requiring it, 54 because of contraindications to pharmacological prophylaxis, and 10 for failure to give informed consent. Thus, 1180 patients were recruited for the current investigations, of whom 469 (39.7%) were labelled as having a high risk of VTE (score ≥ 4) and 711 a low risk (score < 4) based on the predefined RAM (Fig. 1). Table 2 shows the main demographic and clinical characteristics of the study patients.

Of the 469 patients at high risk, 186 (39.7%) received adequate thromboprophylaxis, alone or associated with compression elastic stockings during the whole hospitalization period, while the remaining 283 (60.7%) either did not receive

Table 2 Main demographic characteristics and distribution of RAM items in the three population groups

Baseline features	RAM < 4 (<i>n</i> = 711)	RAM ≥ 4 and prophylaxis (<i>n</i> = 186)	RAM ≥ 4 and no prophylaxis (<i>n</i> = 283)	<i>P</i> -value*
Age (mean $\pm$ SD)	67.3 $\pm$ 16.0	82.0 $\pm$ 9.0	77.7 $\pm$ 11.3	< 0.01
Male sex	365 (51.3)	68 (36.6)	122 (43.1)	0.19
Duration of hospitalization, days (mean $\pm$ SD)	7.9 $\pm$ 5.0	9.0 $\pm$ 6.0%	9.5 $\pm$ 6.6	0.49
Active cancer	41 (5.8)	68 (36.6)	125 (44.2)	0.12
Previous VTE	5 (0.7)	9 (4.8)	32 (11.3)	0.02
Reduced mobility	6 (0.8)	141 (75.8)	125 (44.2)	< 0.01
Thrombophilia	0 (0.0)	1 (0.5)	2 (0.7)	1.00
Recent trauma/surgery	18 (2.5)	6 (3.2)	7 (2.5)	0.84
Elderly age	356 (50.1)	168 (90.3)	255 (90.1)	1.00
Heart and/or respiratory failure	127 (17.9)	76 (40.9)	51 (18.0)	< 0.01
Acute myocardial infarction or ischemic stroke	0 (0.0)	6 (3.2)	6 (2.1)	0.66
Acute infection or rheumatologic disorder	84 (11.8)	79 (42.5)	57 (20.1)	< 0.01
Obesity	45 (6.3)	19 (10.2)	12 (4.2)	0.02
Hormonal treatment	8 (1.1)	4 (2.2)	1 (0.4)	0.16

Numbers in parentheses are percentages unless otherwise specified. *Comparison between the features of high-risk patients who received prophylaxis and those who did not.

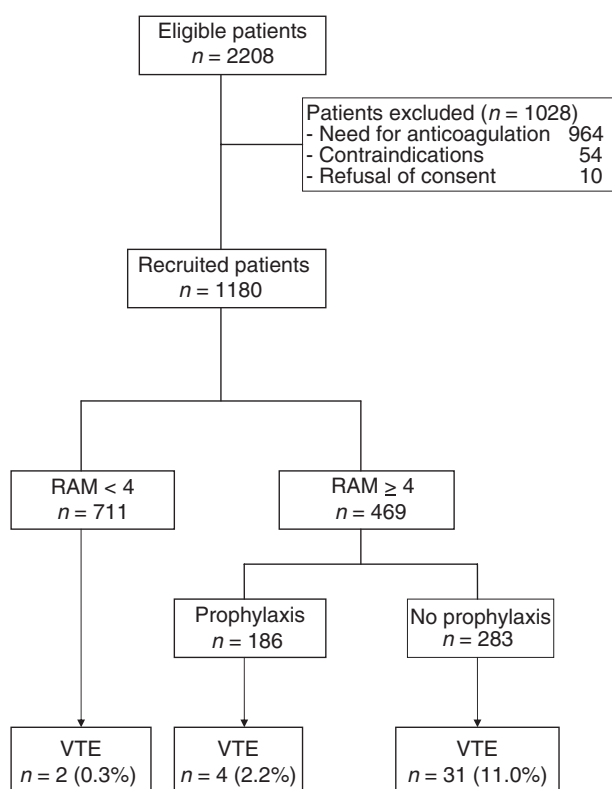


Fig. 1. Flow diagram of the study.

any form of prophylaxis (218) or received inadequate prophylaxis (65) (e.g. compression stockings alone or insufficient doses of heparin) (Fig. 1). Patients belonging to the former group were on average older, while gender and duration of hospitalization did not differ between the two high-risk groups (Table 2). Pharmacological thromboprophylaxis was administered also in 52 of the 711 patients (7.3%) who were classified as having a low risk of VTE.

Table 2 shows the distribution of RAM items in the low-risk group and in each of the two high-risk groups (those who received prophylaxis and those who did not). On average, the risk profile was higher in high-risk patients who received thromboprophylaxis than in those who did not (mean RAM 5.4 ± 1.3 vs. 4.5 ± 0.9 ; $P = 0.001$): 35 patients (18.8%) as compared with 10 (3.5%) scored at least 7; 41 (22.0%) as compared with 16 (5.7%) scored 6; 68 (36.6%) as compared with 79 (27.9%) scored 5; while 42 (22.6%) as compared with 178 (62.9%) scored 4.

The prolongation of prophylaxis beyond the hospitalization period was left to the discretion of attending physicians. Indeed, thromboprophylaxis was continued for variable periods (ranging from 1 to 3 weeks) in only 17 patients (9.1%) at high risk of VTE.

During the study period 113 patients died: 24 in the group of 186 high-risk patients (12.9%) who received prophylaxis, 32 in the group of 283 (11.3%) who did not receive it, and 57 in the group of 711 patients (8.0%) at low risk of VTE. Of these deaths, one occurring in the group of the 283 patients at high

risk who had not received thromboprophylaxis was attributed to PE. Sudden otherwise unexplained deaths occurred in 7, 15 and 12 patients, respectively.

Overall, six patients were unavailable for post-discharge observation, mostly on account of geographic inaccessibility: two in the group of 469 patients (0.4%) at high risk of VTE, and four in the group of 711 patients (0.6%) at low risk.

VTE complications

During the study period, VTE complications developed in 37 of the 1180 patients (3.1%): 35 in the 469 high-risk patients (7.5%), and two in the 711 low-risk patients (0.3%).

Out of the 469 patients at high risk, VTE complications developed in four of the 186 (2.2%; 95% CI, 0.8–5.4) patients who received prophylaxis, and in 31 of the 283 (11.8%; 95% CI, 7.8–15.1) who did not (crude RR, 0.20; 95% CI, 0.07–0.52). After adjusting for the unbalanced distribution of the risk factors for thrombosis in the two groups, the HR of VTE was 0.13 (95% CI, 0.04–0.40; $P < 0.001$). Of the four events that occurred in the former group, three were primary DVT, and one primary non-fatal PE; three of the four events occurred after hospital discharge in patients in whom thromboprophylaxis had been discontinued. Of the 31 events that occurred in the latter group, 19 were isolated DVT, 11 non-fatal PE with or without DVT, and one fatal PE; 28 occurred after hospital discharge; five occurred in the 65 (7.7%) who had received inadequate prophylaxis.

Out of the 711 patients at low risk, two patients developed PE (associated in one with DVT) after hospital discharge (0.3%; 95% CI, 0.0–1.0): 1 in the group of 52 patients (1.9%) who had prophylaxis, and one in the group of 659 (0.2%) who did not. The crude RR of VTE in high-risk patients without prophylaxis versus low-risk patients was 38.9 (95% CI, 10.4–146.5). After adjusting for the unbalanced distribution of the risk factors for thrombosis in the two groups, the HR was 32.0 (95% CI, 4.1–251.0; $P = 0.001$).

Table 3 reports the main characteristics of the patients who developed thromboembolic events. Figure 2 displays the results of the Cox's product limit multivariate analysis.

Bleeding complications

Out of the 469 patients at high risk of VTE, major or clinically relevant bleeding complications developed in three of the 186 (1.6%; 95% CI, 0.5–4.6) patients who had received prophylaxis (gastrointestinal, intramuscular and cerebral, respectively), two of them occurring after hospital discharge in the group of 17 patients (11.8%) in whom thromboprophylaxis had not been discontinued, and in one of the 283 (0.4%; 95% CI, 0.0–2.0) who had not received prophylaxis (macroscopic hematuria).

Out of the 711 patients at low risk of VTE, one (0.1%; 95% CI, 0.0–0.8) belonging to the subgroup of those who had received thromboprophylaxis developed a gastrointestinal bleeding while in hospital.

All bleeding complications were non-fatal.

Table 3 Main characteristics of the patients who developed thromboembolic events

Number	Age	Sex	RAM	Clinical features*	Hospital stay (days)	Adequate prophylaxis	Type of VTE	Timing of VTE (days)
1	68	M	8	1, 3, 7, 9	46	Yes	PE	42
2	75	F	5	1, 6, 7	7	Yes	DVT	63
3	78	F	5	3, 6, 7	14	Yes	DVT	36
4	72	M	4	1, 6	6	Yes	DVT	7
5	78	M	8	1, 3, 6, 9	11	No	DVT	18
6	70	F	8	1, 3, 6, 9	7	No	PE	29
7	77	F	7	1, 4, 6	24	No	PE	37
8	88	M	6	3, 6, 7, 9	5	No	DVT	5
9	88	M	6	3, 6, 7, 9	25	No	DVT	30
10	71	F	5	1, 6, 10	25	No	DVT	77
11	77	F	5	1, 6, 7	4	No	PE	90
12	73	F	5	1, 6, 9	6	No	DVT	49
13	70	M	5	1, 6, 9	26	No	DVT	53
14	83	M	5	1, 6, 7	9	No	PE	26
15	78	M	5	1, 6, 9	16	No	DVT	28
16	88	F	5	3, 6, 7	5	No	PE	15
17	83	M	5	1, 6, 7	8	No	DVT	21
18	91	F	5	3, 6, 7	16	No	DVT	49
19	77	F	5	1, 6, 8	7	No	DVT	30
20	87	F	5	1, 6, 8	8	No	PE	30
21	82	F	4	1, 6	6	No	DVT	37
22	74	F	4	1, 6	6	No	DVT	24
23	70	M	4	1, 6	7	No	DVT	59
24	64	M	4	1, 9	21	No	PE	29
25	41	F	4	1, 11	24	No	DVT	87
26	36	M	4	1, 9	22	No	DVT	14
27	89	F	4	2, 6	7	No	FATAL PE	49
28	79	F	4	2, 6	7	No	PE	68
29	70	M	4	1, 6	9	No	PE	30
30	69	M	4	1, 9	10	No	DVT	62
31	86	M	4	1, 6	6	No	PE	55
32	88	F	4	3, 6	1\8	No	DVT	67
33	79	F	4	2, 6	11	No	DVT	14
34	70	M	4	1, 6	9	No	PE	77
35	50	F	4	1, 6	5	No	DVT	22
36	72	F	3	5, 6	8	Yes	PE	55
37	69	F	3	1	5	No	PE	87

*In the order they are reported in Table 1.

Additional observations

Of the 942 patients in the study cohort who did not receive prophylaxis, VTE developed in one of the 659 (0.2%) patients who scored less than 4, in 15 of the 178 (8.4%) who scored 4, in 11 of the 79 (13.9%) who scored 5, and in five of the 26 patients (19.2%) who scored more than 5.

In a conservative calculation including sudden otherwise unexplained deaths among the VTE complications, the adjusted HR of VTE events in high-risk patients who received prophylaxis in comparison with those who did not was 0.31 (95% CI, 0.15–0.66; $P = 0.002$), and that of VTE in high-risk patients without prophylaxis as compared with low-risk patients was 8.0 (95% CI, 4.1–15.4; $P < 0.001$).

The adoption of the Kucher score would have produced the following results. Of the 1180 recruited patients, 226 (19.2%) would have been classified as being at high risk of VTE and the remaining 954 at low risk. Of the 37 VTE events recorded throughout the study, 26 developed in the 226 high-risk

patients (11.5%); three of the 74 (4.1%) who received prophylaxis and 23 of the 152 (15.1%) who did not. VTE events also developed in 12 (1.3%) of the 954 low-risk patients. While patients classified as being at high risk for VTE according to the Kucher score were also classified as being at high risk with the adoption of the Padua Prediction Score, 243 patients regarded as high risk according to our model would have been regarded as being at low risk if the Kucher score had been applied. Of these patients, nine (3.7%; 95%, 1.7–6.9) developed symptomatic VTE events, including two episodes of PE. Major bleeding complications developed in three of the 74 high-risk patients who received prophylaxis (4.1%), in one of the 152 (0.7%) who did not and in one of the 954 (0.1%) low-risk patients.

Discussion

Appropriate selection of hospitalized medical patients for VTE prophylaxis is an important unresolved issue. The

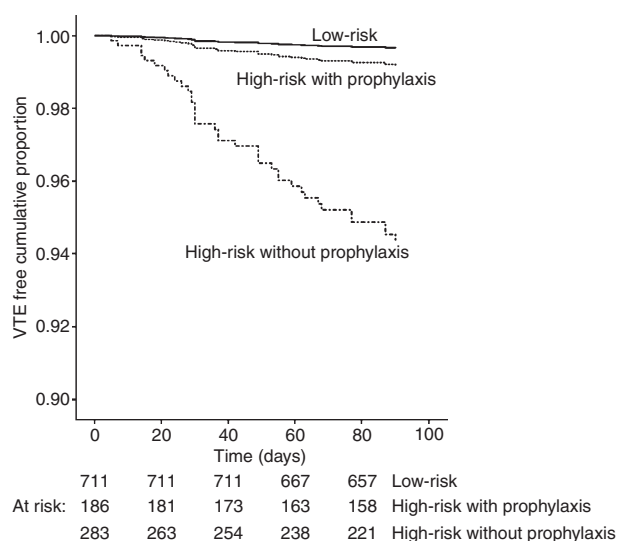


Fig. 2. Kaplan-Meier event-free probability in the three patient groups.

simple 20-point RAM adopted at our center clearly discriminated between hospitalized medical patients at high and low risk of VTE complications. Indeed, the rate of VTE complications occurring in patients who scored at least 4 and were left without thromboprophylaxis was found to be more than 30 times as high as in patients scoring less than 4. The implementation of in-hospital thromboprophylaxis in patients classified as being at high risk of thrombosis according to this RAM was highly effective, and was associated with an acceptably low risk of bleeding. Indeed, the frequency of VTE complications in patients who received adequate thromboprophylaxis was almost 90% lower than in those who did not (Fig. 2), and remained almost 70% lower even in a conservative calculation including sudden otherwise unexplained deaths. The strength of this conclusion is reinforced by the consideration that, in comparison with patients who were left without protection, patients who were administered thromboprophylaxis had on average a baseline profile compatible with a higher risk of VTE.

Our findings expand the results obtained by Kucher *et al.* [20] in selected populations, as they have the potential to identify virtually all those medical patients for whom the latest international guidelines strongly recommend thromboprophylaxis [4,5], even if they are free from cancer or previous thromboembolism (i.e. the two main determinants of the Kucher score). With the use of the Padua Prediction Score almost twice as many patients in our population were labelled as being at high risk of VTE as with the Kucher score. This approach resulted in a definitely higher degree of protection (without any apparent increase in the bleeding risk) against thromboembolic complications. Indeed, nine of the 37 (24.3%) events that were observed in the study period developed in the 243 high-risk patients who would have been misclassified as being at low risk according to the Kucher score.

However surprising they may seem, our results suggest that the implementation of preventive measures during hospitaliza-

tion in patients labelled as having a high thrombotic risk confers longstanding protection against thromboembolic complications in comparison with untreated patients. Indeed, although prophylaxis was discontinued at the time of hospital discharge in the vast majority of patients who had it during hospitalization, the rate of late VTE complications in this subgroup of patients was acceptably low. Our results are in keeping with those observed in randomized clinical trials [7,9,20]. The correction of factors accounting for hospitalization even in chronically ill medical patients provides a plausible explanation for this otherwise surprising finding. Conversely, it is likely that those high-risk patients who are left without in-hospital prophylaxis develop subclinical thrombosis [7–9], which accounts for subsequent clinically symptomatic events, in analogy with what is commonly seen in surgical settings [4,5]. Of interest, two of the 17 patients (12%) in whom prophylaxis was continued developed clinically relevant bleeding complications. These findings are consistent with those obtained in a recently completed randomized clinical trial [25], and suggest that the decision to prolong prophylaxis beyond hospitalization in medical patients should be carefully weighed against the risk of bleeding complications.

It is worth mentioning the low proportion of high-risk patients who received adequate thromboprophylaxis during hospitalization (less than 40%, including a substantial proportion of patients with previous VTE!). Our findings are fully consistent with those obtained in important registries carried out virtually everywhere in the world [10–14], and confirm that, despite persuasive evidence suggesting the strong advantage of thromboprophylaxis in high-risk medical patients [4,5], this practise continues to be largely under-implemented [10–14]. As a result, the majority of both fatal and non-fatal PE episodes that are nowadays encountered in clinical practise arise in medical settings [26]. The adoption of electronic tools was found to be effective in encouraging physicians to use prophylaxis at least amongst subgroups of patients at high risk of thrombotic complications [20,21]. The electronic alerting systems, however, require sophisticated technology infrastructure and considerable financial resources, and are thus unlikely to find widespread acceptance across the many institutions that admit patients at risk of thrombosis. We believe that a self-explanatory, easy, suitable and effective RAM such as the one developed in our center has the potential to help physicians manage their patients without the need for supplementary electronic tools, and may result in an increasing implementation of antithrombotic prophylaxis in departments of internal medicine, in compliance with the recommendations of the main international guidelines [4,5] and with the auspices of several world health organizations [27].

The strength of our investigation lies in a number of factors. We adopted a scoring system that identifies all those medical conditions for which the latest international guidelines strongly recommend thromboprophylaxis [4,5]. We recruited a large cohort of consecutive patients admitted to a department of internal medicine during a 2-year period. We conducted a prospective 3-month follow-up of all

recruited patients, used objective methods for detection of symptomatic VTE complications, and had events adjudicated by an independent committee. Finally, the rate of patients lost to follow-up after hospital discharge was negligible.

A few study limitations deserve attention. Firstly and most importantly, for the generation of our RAM we did not use formal criteria for clinical prediction rule derivation (nor had they been used for the derivation of the Kucher score [20]). A more parsimonious rule could be developed in the future using more stringent criteria. Secondly, the lack of randomization of high-risk patients to receive thromboprophylaxis or not precludes a correct comparison between the two study groups. However, randomization would have been unethical [4,5]. In addition, it should be considered that patients who received prophylaxis exhibited a higher risk profile for subsequent VTE complications. Thirdly, testing for VTE was not routinely performed unless symptoms and/or signs were present. However, the adoption of surrogate endpoints is generally regarded as not necessary when a study is powered enough to obtain significant findings by simply including clinically relevant symptomatic endpoints. Finally, exclusion of patients with contraindications for antithrombotic drugs does not permit extending the implications of our study results to this patient category.

In conclusion, our results suggest that the Padua Prediction Score has the potential to improve stratification of the thromboembolic risk in hospitalized medical patients compared with usual practise. However, its validity requires proper confirmation and validation from other large prospective studies. In addition, whether the awareness of the potential value of this RAM can induce a higher rate of physicians to adopt proper thromboprophylaxis in their patients remains to be demonstrated. This issue is currently under investigation at our institution.

Addendum

Conception and design, S. Barbar, P. Prandoni, D. Tormene; acquisition of data, V. Rossetto, A. Ferrari, B. Brandolin, M. Perlati, E. De Bon; analysis and interpretation of data, F. Noventa; drafting of the manuscript, P. Prandoni, F. Noventa, S. Barbar; critical revision of the manuscript for important intellectual content, D. Tormene, V. Rossetto, A. Ferrari, B. Brandolin, M. Perlati, E. De Bon, A. Pagnan; administrative and logistic support, P. Prandoni, A. Pagnan; study supervision, P. Prandoni.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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