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Prophylaxis of venous thromboembolism in elderly patients with multimorbidity

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Abstract Pharmacological thromboprophylaxis (TP) is known to reduce venous thromboembolism (VTE) in medical inpatients, but the criteria for risk-driven prescription, safety and impact on mortality are still debated. We analyze data on elderly patients with multimorbidities admitted in the year 2010 to the Italian internal medicine wards participating in the REPOSI registry to investigate the rate of TP during the hospital stay, and analyze the factors that are related to its prescription. Multivariate logistic regression, area under the ROC curve and CART analysis were performed to look for independent predictors of TP prescription. Association between TP and VTE, bleeding and death in hospital and during the 3-month post-discharge follow-up were explored by logistic regression and propensity score analysis. Among the 1,380 patients enrolled, 171 (15.2 %) were on TP during the hospital stay (162 on low molecular weight heparins, 9 on fondaparinux). The disability Barthel index was the main independent predictor of TP prescription. Rate of fatal and non-fatal VTE and bleeding during and after hospitalization did not differ between TP and non-TP patients. In-hospital and post-discharge mortality was significantly higher in patients on TP, that however was not an independent predictor of mortality. Among elderly medical patients there was a relatively low rate of TP, that was more frequently prescribed to patients with a higher degree of disability and who had an overall higher mortality.

Keywords Thromboprophylaxis · Venous thromboembolism · Medical patients

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Introduction

Large population-based cohort studies agree that the incidence of venous thromboembolism (VTE) is around 1 per 1,000 person-year in the overall population, but up to 6 times higher in the elderly [1, 2]. In the elderly VTE is frequently associated with recent hospitalization or immobilization and the presence of chronic cardio-pulmonary diseases [3]. Advancing age and age-related multimorbidity also represent a risk factor for more severe VTE, with a higher proportion of pulmonary embolism (PE) over isolated deep vein thrombosis (DVT, and a higher mortality rate [2, 4, 5]. Furthermore, elderly patients with VTE less likely complain of typical symptoms [3] and frequently have high D-dimer levels at baseline [6], thus

making the diagnostic process more difficult. Hence, acutely ill elderly medical patients represent a pivotal target for strategies of VTE prevention. Risk assessment models assign a low weight to advanced age when it is the only risk factor for VTE [7–10], but elderly patients often present clusters of high-risk conditions for VTE which make them strong candidates for pharmacological thromboprophylaxis (TP). By contrast, international registries on modalities and frequencies of TP use [11, 12] show a low rate of prescription even in hospitalized medical patients who meet the guideline recommendations [13]. Retrospective registries on patients with VTE show that only 30–40 % of the elderly have received TP [3], and as few as 20 % of those older than 90 years [5]. All the registries clearly show that advanced age is also a risk factor for bleeding during therapeutic or prophylactic anticoagulation [14, 15]. The need to balance the thrombotic and bleeding risks is reflected by the most recent scientific guidelines that, rather than making detailed indications for TP in nonsurgical settings, recommend a balanced evaluation of the risks of thrombosis and bleeding [16, 17]. Such guidelines framed on caution, together with the practical difficulty to assess a risk/benefit balance, may partly explain the widespread underuse of TP.

To improve practice in this field, more knowledge on the frequency and modalities of TP prescription in acutely ill elderly medical patients is needed, particularly in those with multimorbidity who are often excluded from randomized clinical trials. Pursuing this primary objective, this study evaluated the prescription rate of TP in elderly patients admitted to Italian internal medicine wards participating in the REPOSI registry, and which were the risk factors associated with physicians' decision. We also tried to investigate, within the limits of an observational design, the association between TP prescription and the occurrence of such events as bleeding and death during the hospital stay and at 3-month post-discharge follow-up.

Methods

Data collection

We analyzed the data collected from January to December 2010 during the annual data collection for REPOSI (REgistro POliterapie Società Italiana di Medicina Interna) [18], a prospective registry stemming from the collaboration between the Italian Society of Internal Medicine and the Mario Negri Institute for Pharmacological Research. Patients were eligible for REPOSI if: (1) they were admitted to one of the participating wards during the 4 index weeks chosen for recruitment (one per season); (2) their age was ≥65 years; (3) gave informed consent. A web-based case report form (CRF) was filled with data on socio-demographic and clinical parameters, reasons for hospital admission, diagnoses at admission and discharge, clinical events and main laboratory data occurring in hospital and pharmacotherapy at admission, in hospital and at discharge. Diseases were coded according to the International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM], Sixth Edition, World Health Organization 1987, and summarized by indexes of multimorbidity burden and severity according to the Cumulative Illness Rating Scale [CIRS] [19]: impairment of major organ/systems is rated from 1 (no impairment) to 5 (life-threatening impairment); the index of comorbidity is equal to the number of impaired systems, with a scale of at least 3; the severity index corresponds to the mean degree of impairment. Drugs were encoded according to the Anatomical Therapeutic Chemical [ATC] classification system); for each drug physicians filling the CRF were asked to specify the dose prescribed. Additional functional data were collected on the patient cognitive status according to the Short Blessed test [20], presence of depression using the Geriatric Depression Scale [21], and performance in basic activities of daily living according to the Barthel Index [BI] [22]. Finally, information on post-discharge therapies and outcomes were collected by a follow-up phone call 3 months after hospital discharge.

Study population and TP definition

We defined patients prescribed with pharmacological TP those on treatment with subcutaneous low molecular weight heparin (LMWH), low-dose unfractionated heparin (UFH) or fondaparinux during the hospital stay, provided that VTE prophylaxis was reported as the reason for prescription regardless of the drug and dose administered. Patients on LMWH/UFH/fondaparinux during the hospital stay for reasons different from TP and patients on therapy with vitamin K antagonists (VKA) were excluded from the study population.

Statistical analyses

Factors associated to TP prescription. Whether and which possible risk factors for VTE [7–10, 23–25] were associated to TP prescription was investigated. The effect of some risk factors for bleeding possibly associated to lack of prescription was also explored; Table 1 shows the variables evaluated. Since the data collected in REPOSI did not include specific information on reduced mobility/constrained bed rest, as an alternative we tried to evaluate the relationship between TP prescription and such a measure of patient performance status as the Barthel Index (BI) calculated at admission. The BI is calculated upon ten items

Table 1 Characteristics of patients on thromboprophylaxis (TP) or not during hospital stay

	Patients on TP ($n = 171$)	Patients not on TP ($n = 950$)	p value
Male, *n* (%)	65 (38.0)	483 (50.8)	0.002
Mean age (SD), years	81.4 (7.5)	78.4 (7.3)	<0.001
Mean BMI (SD), kg/m^2	28.0 (32.9)	27.5 (17.8)	0.136
Mean duration of hospital stay (SD), days	16.5 (28.1)	10.5 (8.1)	<0.001
Mean Barthel index score (SD)	56.5 (36.2)	80.0 (28.7)	<0.001
Barthel index score <50, *n* (%)	75 (44.4)	147 (15.7)	
Barthel mobility items score ≤3, *n* (%)	84 (49.7)	167 (17.7)	
Clinical history			
Mean CIRS severity index score(SD)	1.7 (0.3)	1.6 (0.3)	0.049
Mean CIRS co-morbidity index score (SD)	3.0 (1.8)	2.8 (1.7)	0.218
Congestive heart failure, n (%)	31 (18.1)	120 (12.6)	0.053
Chronic pulmonary disease, *n* (%)	49 (28.6)	233 (24.5)	0.252
Malignancy, *n* (%)	38 (22.2)	182 (19.2)	0.353
Chronic renal insufficiency, *n* (%)	27 (15.8)	148 (15.6)	0.944
Previous VTE, *n* (%)	8 (4.7)	28 (2.9)	0.273
Hospitalization for VTE during 6 months before admission, *n* (%)	1 (0.6)	5 (0.5)	0.923
Chronic venous insufficiency, *n* (%)	8 (4.7)	21 (2.2)	0.061
Thrombophilia[a], *n* (%)	2 (1.2)	27 (2.8)	0.205
Reasons of hospital admission			
Decompensated/acute heart failure, *n* (%)	21 (12.3)	59 (6.2)	0.005
Decompensated COPD, *n* (%)	7 (4.1)	22 (2.3)	0.178
Acute respiratory failure (including pneumonia), *n* (%)	12 (7.0)	13 (1.4)	<0.001
Septicemia/sepsis, *n* (%)	3 (1.7)	11 (1.2)	0.518
Active cancer, *n* (%)	3 (1.7)	41 (4.3)	0.112
Ischemic stroke/TIA, *n* (%)	4 (2.3)	24 (2.5)	0.885
Treatments at admission			
Antitumoral chemotherapy, *n* (%)	4 (2.3)	17 (1.8)	0.625
Estro-progestogen therapy (tamoxifen included), *n* (%)	–	1 (0.1)	0.671
Factors possibly affecting TP prescription			
History of bleeding, *n* (%)	6 (3.5)	37 (3.9)	0.809
History of intracranial bleeding, *n* (%)	1 (0.6)	6 (0.6)	0.943
Hospitalization for bleeding during 6 months before admission, *n* (%)	2 (1.2)	14 (1.5)	0.758
Hospitalization for intracranial bleeding during 6 months before admission, *n* (%)	–	1 (0.1)	0.671
Actual hospitalization for bleeding, *n* (%)	2 (1.2)	31 (3.3)	0.136
Actual hospitalization for intracranial bleeding, *n* (%)	–	1 (0.1)	0.671
Mean platelet count (SD) at admission, 10^3/mm^3	252.1 (102.3)	227.7 (128.9)	<0.001
Platelet count <130 × 10^3/mm^3, *n* (%)	13 (7.6)	134 (14.1)	0.020
Antiplatelet therapy, *n* (%)	74 (43.3)	406 (42.7)	0.896
ACCP2004/2008 criteria[b] for TP prescription, *n* (%)	60 (35.1)	133 (14.0)	<0.001
Padua Score[b], median (range)	4 (0–9)	2 (0–11)	<0.001
Padua Score[b] ≥4, *n* (%)	104 (60.8)	332 (34.9)	<0.001

[a] It includes rheumatological disorders (such as rheumatoid arthritis, diffuse collagen diseases and vasculitis), lupus anticoagulant (ICD-9 286.5) and other coagulation disorders (ICD-9 790.92), myeloproliferative syndromes

[b] Malignancy was considered as risk factor independently of its activity since informative data were not available

(stool and urinary incontinence, help needed with grooming, toilet use, bathing, feeding, transfers, walking, dressing and climbing stairs) and is expressed as a score of 0–100, a score lower than 50 being associated with total-severe impairment. We separately evaluated as predictors the global BI and the score for BI items more directly related

to patient global mobility (transfer and walking items), a reduced mobility being accounted for when the score for transfer or walking items was ≤3. Patients on TP or not during the hospital stay were compared for the distribution of the putative predictors and risk factors according to Pearson Chi squared (categorical variables) or Mann–Whitney (continuous variables) tests. Multivariate logistic regression (p value for retaining <0.05) with the evaluation of area under the ROC curve (c-statistics) was performed to identify independent predictors of TP prescription. The logistic results were confirmed and depicted by a Classification and Regression Tree (CART) analysis [26]. The latter is a non-parametric technique used to hierarchically select among a large number of variables those that better split the population between patients who experienced or not the outcome of interest (receiving or not TP, in this study), exploring also the reciprocal interactions between covariates. Those variables are represented as splitting knots from which one branch springs up for each value of the variable associated with a different probability of the outcome for each terminal branch (a branch not followed by any knot) a measure of the relative risk of outcome is provided. Finally, to allow a comparison with the results of previous registries [11, 12] the frequency of TP prescription was recalculated using as denominator the patients who would have met the prescription guidelines of the American College of Chest Physicians (ACCP), 7th edition, 2004 [13] (chosen because they were used as reference in previously published international registries on TP [11, 12]), and the criteria for high risk of VTE according to the Padua Prediction Score [9] suggested by the most recent ACCP guidelines [17]. Also for the ACCP 2004 criteria and for the Padua score, the "reduced mobility" definition was substituted by the BI mobility items as mentioned above. In addition, the discriminative power (c-statistics) of the ACCP 2004 criteria and the Padua Score was calculated in the population.

TP and outcomes. Patients on TP or not during the hospital stay were compared for the occurrence of the following outcomes: VTE events (overall and fatal), bleeding events (overall and fatal), and death for any cause occurring during hospital stay or during the 3-month post-discharge follow-up. The REPOSI database did not allow an accurate classification of non-fatal bleeding as major or minor, but any such event occurring during follow-up was defined as having or not caused hospitalization. Only those patients for whom data on 3-month follow-up were available were included in the analyses on post-discharge outcomes. In order to selectively evaluate the effect on post-discharge outcomes of TP administered during the hospital stay, these analyses were repeated excluding patients prescribed with TP at discharge. In consideration of the relative short duration of the observation time, the association between TP and outcomes was looked at by logistic regression models. Being the factors associated to TP prescription potentially associated to death for any cause, mortality analyses were adjusted for those factors behaving as confounders by performing multivariate logistic regressions, and also according to a propensity score analysis for TP [27] calculated including the risk factors found to be associated to TP prescription in the previous analyses. The average treatment effect on the treated (ATT) was calculated using the Kernel matching method with bootstrapped standard errors.

Additional analyses on TP at discharge. Patients prescribed with TP at discharge were compared to patients not prescribed (irrespective of whether they were on TP during the hospital stay) for the occurrence of non-fatal and fatal VTE and bleeding events during follow-up.

In order to take into account the multi-center origin of the REPOSI data, we adopted robust variance estimates, obtained in all regression models by the Huber/White/sandwich estimator that considers observations as independent across groups (the REPOSI centers in this case). STATA was used to perform all the analyses (version 9.2 and 11, Statacorp, College Station, Tx, US).

Results

During 2010, 1,380 patients were enrolled in REPOSI (mean age 79.0 ± 7.3 years; median 79.1 years, range 65.0–101.4 years). After excluding those on LMWH/UFH/fondaparinux during the hospital stay for reasons other than TP and those on therapy with VKA, 1121 REPOSI patients were included in these analyses (median age 82, range 65–101 years; 49 % males). The median number of morbidities diagnosed per patient at admission was 5 (range 1–21), with a median CIRS comorbidity index of 3/13 (range 0–8) a median CIRS severity index of 1.6 range (1–2.7). The median number of drugs taken per patient at admission was 5 (range 1–15). Among those 1,121 patients, 171 (15.2 %, or 12.4 % when considering all the REPOSI 2010 population) were on TP; 158 were on LMWH, 4 on UFH, 9 on fondaparinux. The flow chart in Fig. 1 summarizes the primary study population and sub-populations.

Predictors of TP prescription

Table 1 compares patients prescribed or not with TP with respect to general demographic and clinical characteristics, with particular emphasis on those that may have influenced prescription. In univariate logistic regressions, the following characteristics were associated with TP prescription/non prescription during the hospital stay (listed in decreasing order of AUC value): BI (AUC 0.709 for

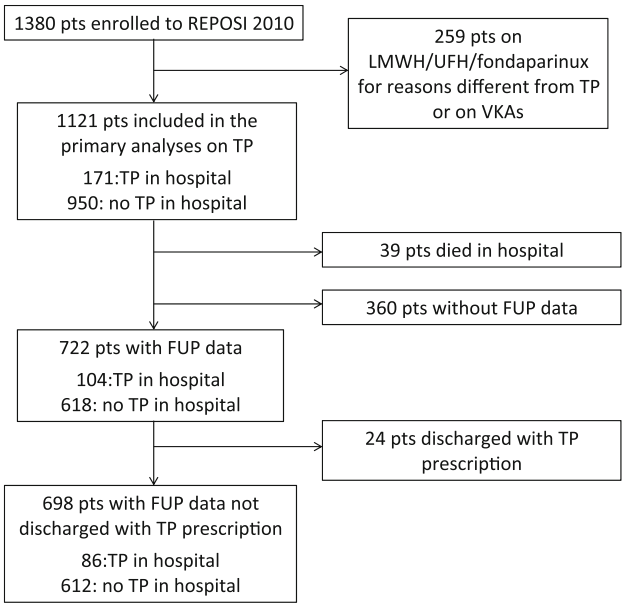

Fig. 1 Study population. *Pts* patients, *LWMH* low weight molecular heparin, *UFH* unfractionated heparin, *VKAs* vitamin K antagonists, *TP* thromboprophylaxis, *FUP* follow-up

continuous variable, 0.643 for dichotomized variable with 50 as cut-off, 0.660 for BI mobility items score ≥ or <3), length of hospital stay (AUC 0.625), age (AUC 0.616 for continuous variable, 0.606 for 80 years old dichotomized variable), platelet count (AUC 0.581 for continuous variable, 0.532 for dichotomized variable with $130 \times 10^3/mm^3$ as cut-off), gender (AUC 0.564), CIRS severity index (AUC 0.547), admission for acute heart failure (AUC 0.530) and for acute respiratory failure (AUC 0.528).

Table 2 shows the multivariate logistic model (AUC for the model 0.759). Similar results were obtained using the global BI or only the mobility BI items. The inclusion of the BI interaction term for each of the other variables allowed the demonstration that some risk factors were differently associated to TP in patients with or without performance or mobility impairment: gender was significant only in patients with a BI <50; age, length of hospital stay and admission for acute heart or respiratory failure were significant only in patients with a BI ≥50. These findings were generally confirmed by the CART analysis (Fig. 2). The tree shows that, taking a relative prescription ratio (RPR) of 1 as equipoise for TP prescription, patients with a low global BI (same results for a low BI mobility score) were more likely to receive TP (with a slight difference in probability between men and women); and that among patients with a higher BI (52–100), those staying in hospital for a long time or those admitted for acute respiratory failure (if not completely well performing, i.e., BI of 99–100) were still likely to receive TP. Age, both as continuous and dichotomized variables (using 80 or 70 years old as cut-off), was not retained as a discriminating variable in the CART analysis.

Table 2 Predictors of thromboprophylaxis prescription (multivariate logistic regression)

Covariate	OR (95 % CI)	*p* value
Barthel Index score <50[a]	3.74 (2.57–5.46)	<0.001
Sex (male vs. female)	0.69 (0.48–0.99)	0.049
Age >80 years old[a]	1.60 (1.10–2.32)	0.013
Length of hospital stay (days)	1.03 (1.02–1.05)	<0.001
Admission for acute heart failure	2.16 (1.22–3.83)	0.008
Admission for acute respiratory failure	5.81 (2.00–11.54)	<0.001
Platelet count $<130 \times 10^3/mm^3$[a]	0.51 (0.27–0.97)	0.040

BI Barthel Index, *OR* Odds Ratio, *CI* confidence interval

[a] For simplicity of interpretation the model with dichotomized variables is presented. When for age a dichotomized variable with 70 years as cut-off was included (for analogy to the Padua Prediction Score), age was no longer statistically significant

Prescription adherence to ACCP 2004 guidelines and the Padua prediction score

Only 14.9 % (17.2 % when a history for malignancy was considered a risk factor) of the 1,121 patients included in our study met the criteria for TP prescription according to the ACCP 2004 guidelines, 29.3 % (or 31.1 % when a history for malignancy was considered a risk factor) of those being actually prescribed with TP. The AUC for the ACCP 2004 criteria as predictor of TP prescription was 0.581, 95 % confidence interval (CI) 0.545–0.617 (or 0.605, 95 % CI 0.568–0.643, when a history for malignancy was considered a risk factor). 28.9 % of patients (39.9 % when a history for malignancy was considered a risk factor) met the criteria for high risk of VTE according to a Padua prediction score ≥4; 27.5 % (or 23.8 % when a history for malignancy was considered a risk factor) of those were prescribed with TP. The c-statistics for the Padua prediction score as predictor of TP prescription was higher: AUC 0.676 (95 % CI 0.634–0.717) or 0.686 (95 % CI 0.645–0.726) when used as continuous score, depending on the inclusion or not of all patients with a history of malignancy; 0. 629 (95 % CI 0.590–0.669) or 0.636 (0.597–0.676) when used as ≥ or <4 prescribing rule, depending the inclusion or not of all patients with a history of malignancy.

TP and outcomes

During hospital stay, 6 patients among the 1,121 analyzed developed an isolated DVT (none a PE); 1 (0.6 % of them) was on TP and 5 (0.5 %) were not (p value = 0.923). Nineteen patients bled during the hospital stay; 3 (1.7 %)

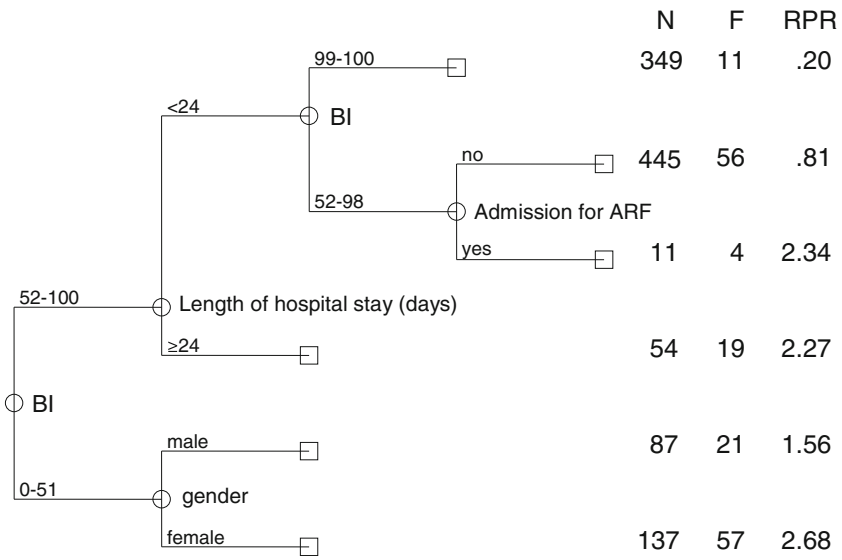

Fig. 2 Multivariate Classification and Regression Tree (CART) analysis. Only those variables found to be significantly related to VTE prophylaxis in univariate logistic regression were included in the analysis: gender, age (continuous), Barthel Index (continuous), length of hospital stay (continuous), CIRS severity, admission for acute heart failure or acute respiratory failure, platelet count at admission. The analysis retains only the best discriminating variables and models them hierarchically, by finding for continuous variable the best-splitting cut-point. *N* number, *F* Failures, *RPR* Relative Prescription Ratio, *BI* Barthel Index, *ARF* Acute Respiratory Failure

were on TP and 16 (1.7 %) were not (p value = 0.948). Among these one patient, not receiving TP, experienced both a non-fatal VTE and bleeding event. Four of the 722 patients followed up after discharge experienced a VTE event during the 3 months of follow-up; one (1.0 %) of them was on TP in hospital and 3 (0.5 %) were not (p value = 0.553). Two of them, 1 on TP in hospital (1.2 %) and 1 without (0.2 %), had fatal pulmonary embolisms (p value 0.207). Nine patients experienced bleeding (4 causing hospitalization) during the 3 months of follow-up; 3 (2.9 %) of them were on TP in hospital and 6 (1.0 %) were not (p value = 0.121). Two of them, 1 on TP in hospital (1.2 %) and 1 without (0.2 %), had fatal hemorrhages (p value 0.207). Similar results were obtained for outcomes at follow-up after excluding patients prescribed with TP at discharge.

Fifty of the 1,380 (3.6 %) patients and 39 of the 1,121 (3.5 %) included in our analyses died in hospital for any cause. In particular, 15/171 (18.1 %) of patients receiving TP and 24/950 (2.5 %) of those not on TP died in hospital (OR for univariate analysis 3.7, 95 % CI 1.9–7.2, $p < 0.001$). After adjusting with variables found to be associated both to TP prescription and hospital death for any cause (in univariate logistic analyses), TP prescription was no longer independently associated to death (Table 3a). Propensity score analysis confirmed these results, showing a non-significant difference for the occurrence of outcomes between patients receiving or not receiving TP during the hospital stay after adjustment for the probability to receive TP (Table 3a).

Eighty-two of the 899 patients (9.1 %) with available follow-up data and 68 of the 722 (9.4 %) included in our analyses died during the 3 months after discharge. In particular, 19/104 (18.3 %) of those receiving TP during the hospital stay and 49/618 (7.9 %) of those not receiving TP died in hospital (OR for univariate analysis 2.6, 95 % CI 1.5–4.6, $p = 0.001$). Because patients with available follow up data were a sample different from that of the primary analysis, we explored again in this group which factors were associated to in-hospital TP prescription. After adjusting for variables found to be associated to both in hospital TP prescription and death (in univariate logistic analyses), TP remained statistically significantly associated to death (Table 3b). Propensity score analysis failed to confirm these findings, even if the ATT was close to statistical significance (Table 3b).

No significant association was found between TP prescription and death due to VTE or death due to bleeding, in hospital and after discharge.

Additional analyses on TP at discharge. After excluding patients discharged on LWMH/UFH/fondaparinux for reasons different from TP and patients on VKAs, 704 were included in this additional analysis: 24/704 (3.4 %) were discharged from the hospital with a TP prescription, two of them in critical conditions; six of them were not prescribed TP in hospital. None of the patients discharged on TP experienced VTE during follow-up, whereas 4 (0.6 %) total events (p value for Pearson $\chi^2 = 0.142$), with 2 (0.3 %) fatal PE (p value for Pearson $\chi^2 = 0.071$) occurred in patients not prescribed TP. In 1 of 24 patients (4.2)

Table 3 Thromboprophylaxis and death for any cause: multivariate logistic regression and propensity score analysis

Covariate	OR (95 % CI)	*p* value
Multivariate logistic regression		
(a) Death during the hospital stay		
TP during the hospital stay	1.84 (0.88–3.85)	0.107
Age (continuous)	1.03 (0.98–1.08)	0.187
Barthel Index score (continuous)	0.98 (0.97–0.99)	<0.001
CIRS severity index score	4.10 (1.59–10.55)	0.003
Admission for acute respiratory failure	3.24 (0.98–10.70)	0.053
Propensity score analysis	ATT[a] (se)	*t*
All covariates	0.034 (0.026)	1.283
(b) Death during the post-discharge follow up$^{\Omega}$		
TP during the hospital stay	2.15 (1.11–4.17)	0.023
Age (continuous)	1.03 (0.99–1.07)	0.084
Sex (male vs. female)	2.98 (1.64–5.41)	<0.001
Barthel Index score (continuous)	0.98 (0.97–0.99)	<0.001
CIRS severity index score	1.93 (0.86–4.31)	0.109
Platelet count $<130 \times 10^3/mm^3$	2.10 (1.07–4.13)	0.031
Propensity score analysis	ATT[a] (se)	*t*
All covariates	0.044 (0.023)	1.886

[a] Average treatment effect on the treated using Kernel matching method with bootstrapped standard errors

discharged on TP a bleeding event was fatal, compared to 8/680 (1.2 %) total bleeding events and 1/680 (0.1 %) fatal event among patients discharged not on TP (p value = 0.231, for total events; p value = 0.018, for fatal events). TP prescription at discharge remained statistically significantly associated to death due to bleeding even after adjusting for risk factors for TP prescription.

Discussion

Using data stemming from a registry, this study has shown that less than one-fifth of the more than 65 years old patients with multimorbidity and polipharmacy admitted to 70 internal medicine wards in Italy were prescribed TP in hospital. Among the putative risk factors considered, impaired global performance as measured by the Barthel Index and, to a lesser degree, the duration of hospital stay and hospitalization due to clinical conditions leading to acute respiratory failure were the main independent predictors of TP prescription. No statistically significant association was found between TP prescription and outcome, but patients receiving compared to those not receiving TP had more frequent fatal and non-fatal bleeding events during the 3 months of post-discharge follow-up, as well as a higher mortality for any cause both in hospital and after discharge.

The hierarchy of factors associated to TP prescription found in this analysis is quite consistent with the Padua Risk Score, that assigns a higher weight to reduced mobility (3 points) compared to medical conditions such as heart or respiratory failure (1 point). Likewise, the most recent ACCP guidelines [17] that recommend to use the Padua Risk Score to stratify the risk of VTE in medical patients mark a shift towards the attribution of a higher importance to reduced mobility as risk factor, in comparison to previous ACCP guidelines [13, 24]. Notwithstanding, not only the ACCP 2004 criteria but also the Padua Risk Score had a poor to fair predictive ability for TP prescription among REPOSI patients. The REPOSI study collects data from an unselected setting aimed to be representative of the elderly patients with multimorbidity populating the internal medicine wards. Actually, our sample of patients typically represents the conditions of multimorbidity and polipharmacy [28, 29]. Hence our findings point out the difficult application of prediction schemes, even when validated, in such a really complex and increasing patient population.

The complex clinical setting of multimorbidity may also explain the low rate of TP prescription in REPOSI patients. The different clinical setting for our study (an elderly population, with probably a higher representation of frail patients) compared to those of the IMPROVE study [11] and the ENDORSE registry [12], may explain the lower rate of TP, considering as denominator the overall study population (15 % in our study and about 60 % in the IMPROVE) or only the patients who met the criteria for TP prescription according to the ACCP 2004 guidelines [13] (30 % in our study, 40 % in ENDORSE, 33 % among IMPROVE patients from United States, 47 % among those from other countries). A higher degree of frailty and clinical complexity might increase physician's concerns about

anticoagulant safety. Was concern about safety the reason for under-prescription of TP in REPOSI patients? Recent bleeding or potential risk factors for bleeding were less frequent in patients on TP. On the other hand, REPOSI physicians sometimes continued TP after discharge, in spite of the fact that published data not only fail to show a benefit of extended pharmacological TP, but also find it to increase the risk of bleeding [30]. Our additional analysis on TP prescribed after discharge confirmed the association between prolonged TP and risk of bleeding. However, it also confirmed that in hospitalized patients the risk of VTE persisted after hospital discharge, with lower rates of VTE occurrence in patients prescribed with TP after discharge. Perhaps the physician's concern to discharge patients who did not regain acceptable performance has become more compelling than available guidelines. Notwithstanding, the kind of analyses performed in REPOSI is unable to capture the physician's perception of a high risk of VTE or bleeding and can allow only to speculate on the actual physician's risk aversion. Moreover, we could not systematically include in the analysis many aspects that the physician may have taken into account in the choice: practical issues, patient preferences, hospital changes in clinical conditions, risk/benefit balances in patients with a poor prognosis.

We recognize that our study has relevant limitations. First, since the registry was not specifically designed to answer the question of TP and is based on chart records, a certain degree of underreporting is plausible. Underreporting might have involved the risk factors for VTE; this limitation, together with the inability of Barthel Index to capture the cases of reduced mobility prescribed by the physician, might have led to underestimate the percentages of patients classifiable at high risk for VTE according to the ACCP 2004 or Padua criteria. Also some data on TP prescription might be missing, so that a 15 % rate of prescription in the whole REPOSI population may represent an underestimation; conversely, since there is no reason for a non-random underreporting of risk factors and TP prescription, this limitation might have affected less the estimate of the proportion of TP among high risk patients (about 30 %). Because of the forementioned limitations in design, the rate of VTE and bleeding events was definitely lower than expected for such a high-risk population. The rate of VTE was similar to that of symptomatic events according to published trials [31]. As to the rate of bleeding, in the IMPROVE study the rate of bleeding was slightly higher than in our study, both in patients on TP and in those not [15]. Another important limitation is represented by the observational setting. Confounding by indication is a common problem for observational studies on treatment, because treatments are most often indicated in patients at high risk of poor outcomes, so that these studies may fail to demonstrate the efficacy of a drug or even find a relative harm [32, 33]. Therefore, we recognize the inability of this study to reliably conclude about any causal association between TP and outcome [34]. Nevertheless, we recognize the observational and clinical value of our findings concerning the tendency in patients prescribed with TP for a higher frequency of bleeding and, even more evidently, for a higher mortality, in hospital and after discharge, compared to those not prescribed.

In conclusion, it appears that TP prescription in elderly patients with multimorbidity cannot be confined to a problem of mere adherence to guidelines. Even if the overall rate of prescription was low and the predictive ability of guiding criteria not satisfying, a higher thrombotic risk profile was observed in patients prescribed versus those not prescribed with TP. Thus, the overall low rate of TP use cannot be unequivocally explained, but we hypothesize that in these patients the difficulty to prioritize among the several therapeutic needs, and not simply the fear of provoking bleeding, may explain the poor adherence to guidelines. In this context [35], an individualized patient management, where the physician joins scientific knowledge to the accurate evaluation of the patient, may be still the most recommendable in this setting, rather than a generalized "MUST" strategy [36].

Conflict of interest None.

Appendix

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