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préparée sous la direction du Docteure Marie Méan

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Damien CHOFFAT

Médecin diplômé(e) de la Confédération Suisse
Originaire de Neuchâtel (NE) et Tramelan (BE)

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IMPRIMATUR

La Faculté de biologie et médecine de l'Université de Lausanne, sur proposition du jury, autorise l'impression de la thèse de doctorat rédigée par

Damien CHOFFAT

intitulée

Association of pharmacologic thromboprophylaxis with clinically relevant bleeding and hospital-acquired anemia in medical inpatients: the risk stratification for hospital-acquired venous thromboembolism in medical patients study

sans se prononcer sur les opinions exprimées dans cette thèse.

Directrice	Docteure Marie Méan
Expert interne	Professeur Lorenzo Alberio
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Lausanne, le 30.01.2024

pour Le Doyen
de la Faculté de Biologie et de Médecine

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Association entre la thromboprophylaxie pharmacologique, les saignements cliniquement significatif et l'anémie acquise à l'hôpital chez les patients hospitalisés en médecine : l'étude RISE

Résumé

Contexte : La thromboprophylaxie pharmacologique (pTPX) pourrait augmenter le risque de saignements cliniquement significatif (CRB) et d'anémie acquise à l'hôpital (HAA) chez les personnes âgées hospitalisées atteintes de multiples pathologies. Nous avons évalué l'association entre l'utilisation de pTPX et le CRB ainsi que l'HAA.

Méthode : Nous avons utilisé des données issues d'une étude de cohorte prospective menée dans trois hôpitaux universitaires suisses. Les adultes admis dans des services de médecine interne sans anticoagulation thérapeutique ont été inclus. L'utilisation de pTPX a été enregistrée pendant l'hospitalisation. Les mesures principales étaient les CRB et l'HAA durant l'hospitalisation. Nous avons calculé les taux d'incidence selon le statut de pTPX. Nous avons évalué l'association entre pTPX et CRB en utilisant une analyse de survie, ajusté pour le score de risque hémorragique du Registre international de prévention médicale des thromboembolies veineuses (IMPROVE-BRS). Nous avons également évalué l'association entre le pTPX et l'HAA en utilisant une régression logistique, ajustée pour l'infection, la durée du séjour et le score IMPROVE-BRS.

Résultats : Parmi 1305 participant·e·s (âge moyen, 63,7 ans ; 44% de femmes, 90% à faible risque de saignement), 809 (62%) ont reçu une pTPX. L'incidence du CRB était de 2,4 pour 1000 patient·e-jours et n'était pas significativement plus élevée chez les personnes ayant reçu pTPX que chez celles qui ne l'avaient pas reçu. Nous n'avons trouvé aucune association statistiquement significative entre pTPX et CRB. L'HAA était fréquente (20,2%) et plus élevée chez les personnes ayant reçu pTPX que chez celles qui ne l'avaient pas reçu (23,2% contre 15,3%). L'incidence de l'HAA était de 21,2 pour 1000 patient·e-jours et ne différait pas significativement entre les individus ayant reçu pTPX et ceux qui ne l'avaient pas reçu. Nous avons trouvé une association entre pTPX et HAA (rapport de cotes ajusté, 1,4 ; IC à 95 %, 1,0-2,1).

Conclusion : Notre étude confirme la sécurité de la pTPX concernant le CRB chez les personnes admises en médecine interne à faible risque de saignement. L'administration de pTPX était associée à l'HAA, et des études supplémentaires sont nécessaires pour explorer cette constatation. En attendant, il est recommandé d'appliquer les lignes directrices cliniques qui recommandent d'administrer une pTPX aux personnes présentant un risque accru de maladie thromboembolique veineuse, à condition qu'elles présentent un faible risque de saignement.

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ORIGINAL ARTICLE

Association of pharmacologic thromboprophylaxis with clinically relevant bleeding and hospital-acquired anemia in medical inpatients: the risk stratification for hospital-acquired venous thromboembolism in medical patients study

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Abstract

Background: Pharmacologic thromboprophylaxis (pTPX) might exacerbate the risk of clinically relevant bleeding (CRB) and hospital-acquired anemia (HAA) in older multimorbid inpatients.

Objectives: We aimed to evaluate the association of pTPX use with CRB and HAA.

Methods: We used data from a prospective cohort study conducted in 3 Swiss university hospitals. Adult patients admitted to internal medicine wards with no therapeutic anticoagulation were included. pTPX use was ascertained during hospitalization. Outcomes were in-hospital CRB and HAA. We calculated incidence rates by status of pTPX. We assessed the association of pTPX with CRB using survival analysis and with HAA using logistic regression, adjusted for infection, length of stay, and the International Medical Prevention Registry on Venous Thromboembolism bleeding risk score.

Results: Among 1305 patients (mean age, 63.7 years; 44% women, 90% at low risk of bleeding), 809 (62%) received pTPX. The incidence of CRB was 2.4 per 1000 patient-days and was not significantly higher in patients with pTPX than in those without. We found no significant association between pTPX and CRB. HAA was frequent (20.2%) and higher in patients with pTPX than in those without (23.2% vs 15.3%). The incidence of HAA was 21.2 per 1000 patient-days and did not significantly differ between patients with pTPX and those without. We found an association between pTPX and HAA (adjusted odds ratio, 1.4; 95% CI, 1.0-2.1).

Conclusion: Our study confirmed the safety of pTPX in medical inpatients at low risk of bleeding but identified an association between pTPX and HAA. Adherence to guidelines that recommend administering pTPX to medical inpatients at increased venous thromboembolism risk and low bleeding risk is necessary.

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Christine Baumgartner and Marie Méan are colast authors.

KEYWORDS
anemia, hemorrhage, heparin, inpatients, internal medicine, venous thromboembolism

1 | INTRODUCTION

Hospital-acquired venous thromboembolism (VTE) is one of the leading preventable causes of in-hospital mortality [1]. Several meta-analyses of randomized controlled trials (RCTs) have shown that pharmacologic thromboprophylaxis (pTPX) is effective in reducing its incidence in acutely ill medical inpatients at high risk of hospital-acquired VTE [2–6].

Clinically relevant bleeding (CRB) is a frequent complication in medical inpatients (2%-3%) [7–9] and is associated with increased all-cause mortality (hazard ratio [HR], 3.5-8.5) [10]. Data on safety of pTPX are conflicting. Indeed, meta-analyses of RCTs could not determine whether pTPX is associated with a significantly increased risk of major bleeding (MB). Several meta-analyses showed a nonsignificant trend of increased risk of MB with pTPX use [2,3]. However, only 1 meta-analysis showed a significant increase in MB risk [4]. Observational studies about the association of pTPX with MB are not in agreement either. European data from a registry study showed no significant increase in bleeding risk in patients receiving pTPX compared to those not receiving pTPX [7]. On the other hand, a retrospective American cohort study found a significant increase in CRB risk in patients treated with pTPX compared to that among patients who were not treated with pTPX [9].

Hospital-acquired anemia (HAA) is a common complication of hospitalization and increases all-cause mortality [11]. Furthermore, HAA might be an indicator of occult bleeding and greater severity of illness with more frequent blood draws. Two postcommercialization safety studies in surgical settings reported the risk of HAA while using pTPX (0.5%-6%) [12,13]. However, so far, no safety study has included anemia as an outcome in medical inpatients using pTPX.

Therefore, we aimed to determine the bleeding and anemia risk associated with pTPX use in a Swiss prospective cohort of medical inpatients.

2 | METHODS

2.1 | Study population

Risk stratification for hospital-acquired VTE in medical patients (RISE) study is a multicenter observational prospective cohort study designed to assess hospital-acquired VTE prevention. Consecutive patients newly hospitalized for acute illness in general internal medicine wards of 3 Swiss university hospitals between June 2020 and January 2022 were invited to participate in this study upon admission. Patients (aged ≥18 years) were eligible if admitted to a medical ward with a minimum stay of 24 hours. Patients who were unable to give informed consent due to cognitive impairment were not excluded from participation. The risks of VTE and immobilization are particularly high in the elderly, where cognitive impairment is more prevalent. Consent was obtained from a legally authorized representative. Exclusion criteria were indication for therapeutic anticoagulation, life expectancy of less than 30 days according to the evaluation of the study collaborator, and insufficient proficiency in German or French. We also excluded transfer from the intensive care unit and surgical wards because of their higher risk of VTE than most medical inpatients. For this analysis, we excluded patients with missing outcome and pTPX data and patients who withdrew their consent and refused the use of their data. Participants with therapeutic anticoagulation initiated during the hospital stay were excluded due to their higher risk of bleeding [14].

This study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 Good Clinical Practice guidelines, and all applicable legal and regulatory requirements. The ethics committees of the Canton of Vaud, Berne, and Geneva authorized the RISE study (reference number: 2020-0060). The detailed methods of the RISE study have been published previously [15].

2.2 | Data collection

At the time of hospital admission, we collected data on sociodemographics, potential VTE and bleeding risk factors, potential contraindications to pTPX, and laboratory examinations. We collected data on administration of aspirin (ASA) (dose of 100 mg daily) or dual antiplatelet therapy (DAPT), which was considered as the concomitant use of ASA and 1 P2Y inhibitor (clopidogrel [75 mg daily], ticagrelor [at least 60 mg twice a day], or prasugrel [at least 5 mg daily]). We calculated the Charlson Comorbidity Index at baseline [16].

Study investigators calculated both the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) bleeding risk score and the simplified Geneva score at the time of data collection. According to the IMPROVE bleeding risk score, patients with a score of ≥7 points were at high risk of bleeding within 14 days of admission [8,9] (Supplementary Table 1). According to the simplified Geneva score, which is a 9-item score to assess the risk of developing VTE in medical inpatients, patients with a score of ≥3 points were at high risk of VTE within 90 days of admission [17,18] (Supplementary Table 2).

We defined the use of pTPX as administration of low-molecular-weight heparin (LMWH), unfractionated heparin, fondaparinux, or direct oral anticoagulants in a prophylactic dose (enoxaparin dose, up to 60 mg daily; fondaparinux dose, 2.5 mg daily; unfractionated

heparin dose, up to 15 000 IU daily; rivaroxaban dose, 10 mg daily; and apixaban dose, 2.5 mg twice a day) at least once during the hospital stay. Type and duration of pTPX use during hospitalization were ascertained. Mechanical thromboprophylaxis (mTPX) use was defined as use of either an intermittent pneumatic compression device or elastic stocking during the hospital stay.

The treating physicians were not informed about the risk assessment model scores, and none of the centers had a specific risk assessment model integrated into their order sets or electronic medical records. However, all 3 hospitals had internal guidelines regarding the prescription of thromboprophylaxis (TPX). At the university hospitals in Bern and Lausanne, the Padua score was recommended to assess the indication for TPX prescription, while the simplified Geneva score was recommended at the university hospital of Geneva. For the bleeding risk assessment, there was no risk assessment model recommended. pTPX was contraindicated if the patient presented an augmented bleeding risk based on the treating physician's clinical judgment, active bleeding, or thrombocytopenia ($<50 \times 10^9$ thrombocytes per liter). The treating physicians had no information about the aims of this study, and the prescriptions of TPX regimens were left at their discretion.

2.3 | Outcomes

The primary outcome was the occurrence of a first in-hospital CRB, which is a composite endpoint of MB and clinically relevant nonmajor bleeding. According to the International Society on Thrombosis and Haemostasis, MB is defined as fatal bleeding, bleeding in a critical localization (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intra-articular, or intramuscular), bleeding causing a decrease in hemoglobin level of at least 20 g/L or leading to transfusion of ≥2 units of packed red blood cells [19]. Clinically relevant nonmajor bleeding is defined as overt bleeding, which does not meet the criteria for MB but is associated with medical intervention, unscheduled physician contact (visit or telephone call), pain, or impairment of daily life activities [20]. We did not assess the occurrence of minor bleeding because a standardized definition is unavailable, and its clinical significance may be limited in the hospital setting. Information on bleeding outcomes was collected from the participants at hospital discharge or from chart review. A committee of 3 blinded clinical experts adjudicated all outcomes and classified the bleeding events; final decisions were made based on the full consensus of this committee.

Our secondary outcome was the occurrence of HAA. Hemoglobin measurements at admission and discharge were prespecified endpoints in the RISE protocol [15], were ordered as part of the usual care, and were extracted from laboratory records. Based on previous reports, we defined new anemia at discharge as a hemoglobin value of <120 g/L in women and <130 g/L in men at discharge [21] in participants with a normal hemoglobin value at admission. We then defined worsening of anemia as a fall in the hemoglobin value of ≥20 g/L between admission and discharge [22]. HAA is a composite outcome of new anemia at discharge and worsening of anemia at discharge.

2.4 | Statistical analysis

Baseline characteristics were expressed as *n* (%) for categorical variables and mean (SD) for continuous variables and compared between participants with and those without pTPX provision, in-hospital CRB, and HAA using chi-squared tests for categorical variables and Student's *t*-tests or Wilcoxon rank-sum tests for continuous variables, as appropriate.

We calculated in-hospital incidence rates of CRB and HAA by status of pTPX with corresponding 95% CIs. The *P* values for incidence rate comparisons were computed with mid-*P* adjustment. The *P* values for the number of events were based on chi-squared tests.

To evaluate the association between pTPX and CRB, we used time-to-event analysis. We used this analysis because we had the timing of the CRB. Unadjusted HRs and HRs adjusted for patient age and the IMPROVE bleeding risk score were calculated. As antiplatelet therapy alters the natural clotting capacity and increases the bleeding risk [23], we included a categorical variable showing whether pTPX was prescribed alone, with ASA, or with DAPT (none, TPX, ASA, DAPT, TPX + ASA, and TPX + DAPT).

To evaluate the association between pTPX and HAA, we used logistic regression. Odds ratios (ORs) were then calculated crudely and adjusted for variables already described in the literature as risk factors for anemia, ie, the length of hospital stay, the age of the patient, the occurrence of an active infection, and all the variables from the IMPROVE bleeding risk score (Supplementary Table 1). We additionally adjusted for the length of stay as an extrapolated marker for number of blood draws, as several studies showed that high number of blood draws was a predictor of HAA [11,24]. We additionally adjusted for the occurrence of an active infection, which was previously reported to be associated with HAA [11,24].

We included a categorical variable showing whether pTPX was prescribed alone, with ASA, or with DAPT. We investigated the association of pTPX and each component of the secondary outcome (ie, new anemia and worsening of anemia at discharge). To verify that HAA was not overestimated due to CRB, we also excluded patients with CRB in a sensitivity analysis and computed the incidence of HAA again.

TPX provision in participants at low risk for hospital-acquired VTE (simplified Geneva score, <3 points) does not improve clinical outcomes and might increase the harmful effect of TPX [5,6]. Therefore, we performed a subgroup analysis in this group of participants. We calculated in-hospital incidence rates of CRB and HAA by status of pTPX with corresponding 95% CIs. The *P* values for incidence rate comparisons were computed with mid-*P* adjustment. The *P* values for the number of events were based on chi-squared tests.

3 | RESULTS

Between June 2020 and January 2022, 1353 patients were enrolled in the RISE cohort. For this analysis, 1305 patients were retained (Figure). The mean age was 63.7 years, 569 (43.6%) were women, and

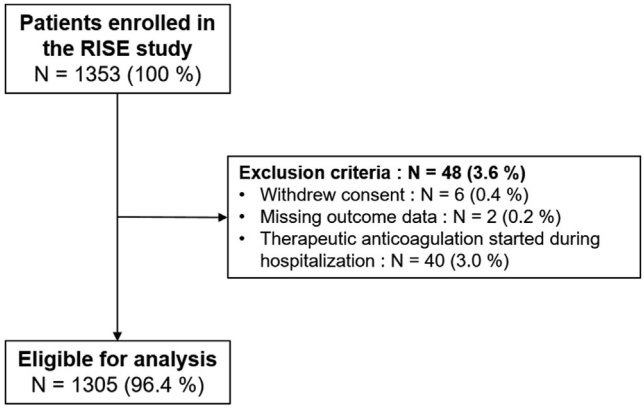

FIGURE Number of participants excluded and retained for analysis. RISE, risk stratification for hospital-acquired venous thromboembolism in medical patients.

the median length of stay was 7 days. Almost two-thirds (*n* = 809) of patients received pTPX during hospitalization for a mean time of 6.2 days. Among patients receiving pTPX, more than two-thirds were at high risk of hospital-acquired VTE (simplified Geneva score, ≥3 points), and 90% were at low risk of bleeding (IMPROVE bleeding risk score, <7 points). Among our participants, 70 tested positive for COVID-19, and 69 received pTPX (Table 1).

3.1 | pTPX and CRB

Twenty-nine in-hospital CRB cases (2.2%) were recorded, and none were fatal. Among patients with CRB, 16 had MB, 12 had clinically relevant nonmajor bleeding, and 1 patient had both MB and clinically relevant nonmajor bleeding. Participants who bled were older (mean age, 71.9 vs 63.5 years), more likely to be male (79.3% vs 55.9%), and more likely to have had surgery in the month prior to hospitalization (13.8% vs 3.6%). Compared to patients without CRB, bleeding patients more frequently received ASA therapy (44.8 vs 26.3%). Patients with CRB had a longer length of stay (24 vs 9.2 days) and longer time on pTPX (12.3 vs 6.5 days) (Supplementary Table 3).

Incidence rate of CRB was 2.4 per 1000 patient-days (95% CI, 1.7-3.5) and was not significantly higher in patients receiving pTPX than in those not receiving it. For MB and clinically relevant nonmajor bleeding, the incidence rates were 1.4 (95% CI, 0.9-2.3) and 1.1 (95% CI, 0.6-1.8), respectively, and similar in participants with and without TPX (Table 2).

There was no significant association between pTPX use and CRB (adjusted HR, 1.1; 95% CI, 0.4-3.0), whereas an association between ASA and CRB was found (adjusted HR, 2.8; 95% CI, 1.1-7.3), in comparison with patients who did not have TPX, ASA, or DAPT (Table 3).

3.2 | pTPX and HAA

Overall, 264 participants (20.2%) developed HAA during their hospitalization. Compared to participants who did not develop HAA, they were more likely to have an acute infection (50.8% vs 40.9%), a longer length of stay (11.6 vs 9.0 days), and a longer time on pTPX (8.1 vs 5.6 days) (Supplementary Table 4).

Patients on pTPX more frequently had HAA than those not on pTPX (23.2% vs 15.3%). Incidence rate of HAA was 21.2 per 1000 patient-days without a significant difference between patients with and without pTPX. New anemia at discharge occurred in 17% of participants and was more frequent in patients receiving pTPX than those who did not receive TPX (19.7% vs 12.1%). Worsening anemia developed in 3.4% and was similar in patients receiving pTPX and those not receiving it (Table 2). After excluding patients with CRB, the incidence of HAA was still approximately 20% (result not shown). The overall median fall of hemoglobin was of 5 g/L (IQR, 0-13 g/L), with a significant difference ($P < .001$) between patients receiving pTPX and those not receiving pTPX (7 g/L [IQR, 0-15 g/L] vs 2 g/L [IQR, 0-11 g/L]) (Table 2).

We found an association between pTPX use and HAA (adjusted OR, 1.4; 95% CI, 1.0-2.1), in comparison with patients who did not have TPX, ASA, or DAPT. Results were similar for new anemia at discharge (adjusted OR, 1.7; 95% CI, 1.2-2.5). The coadministration of DAPT and pTPX was associated with new anemia at discharge (adjusted OR, 2.9; 95% CI, 1.0-8.6). No significant association between pTPX use and worsening anemia was found (adjusted OR, 0.7; 95% CI, 0.4-1.6) (Table 4).

3.3 | Participants at low risk for hospital-acquired VTE

In the subgroup analysis of 486 patients at low risk of hospital-acquired VTE (simplified Geneva score, <3 points), incidence rate for CRB was 2.1 per 1000 patient-days, with no significant difference between patients receiving pTPX and those without it. Almost 20% of patients (*n* = 94) developed HAA, and it was more frequent in patients receiving pTPX than in those who did not receive TPX (24.2% vs 14.9%). The overall incidence rate of HAA was 23.5 per 1000 patient-days, without significant difference between the groups (Supplementary Table 5).

4 | DISCUSSION

In our multicenter Swiss prospective cohort study of acutely ill medical inpatients, we found an overall in-hospital CRB incidence of 2%. We did not observe an association between pTPX and CRB. However, pTPX was associated with HAA compared to those without pTPX.

The risk of in-hospital CRB in our study was lower than that in the IMPROVE bleeding risk score derivation study (2.0% vs 3.2%) [9] and slightly lower than that in validation studies (2.2%-2.6%) [8,25,26]. This might be explained by the fact that the proportion of patients at high risk of bleeding was lower in our study (9.3% with an IMPROVE bleeding risk score of ≥7) compared to other studies (10%-22% with an IMPROVE bleeding risk score of ≥7) [8,9,25,26]. Furthermore, our

TABLE 1 Characteristics of study participants with and without thromboprophylaxis.

Characteristics	All (*N* = 1305)	Pharmacologic thromboprophylaxis		*P* value
		No (*n* = 496)	Yes (*n* = 809)	
Age (y)	63.7 (17.7)	59.8 (19.4)	66.0 (16.1)	<.001
Woman	569 (43.6)	223 (45.0)	346 (42.8)	.44
Body mass index (kg/m^2)	25.7 (6.1)	24.8 (5.5)	26.3 (6.4)	<.001
Charlson Comorbidity Index	4.1 (3.0)	3.6 (3.0)	4.4 (3.1)	<.001
Median length of stay (d)	7 (5-11)	6 (4-9)	8 (6-12)	<.001
Active cancer	249 (19.1)	66 (13.3)	183 (22.6)	<.001
Cardiac failure	128 (9.8)	47 (9.5)	81 (10.0)	.75
Respiratory failure	223 (17.1)	47 (9.5)	176 (21.8)	<.001
Renal failure	324 (24.8)	104 (21.0)	220 (27.2)	.011
Hepatic failure	95 (7.3)	38 (7.7)	57 (7.0)	.68
Acute infection	560 (42.9)	160 (32.3)	400 (49.4)	<.001
COVID-19–positive	70 (5.4)	1 (0.2)	69 (8.5)	<.001
Gastroduodenal ulcer	37 (2.8)	19 (3.8)	18 (2.2)	.09
Recent ischemic/hemorrhagic stroke[a]	11 (0.8)	4 (0.8)	7 (0.9)	.91
Recent myocardial infarction[a]	26 (2.0)	7 (1.4)	19 (2.3)	.24
Recent trauma[a]	79 (6.1)	29 (5.8)	50 (6.2)	.81
Recent surgery[a]	50 (3.0)	19 (3.8)	31 (3.8)	1.00
Active bleeding[b]	86 (6.6)	64 (12.9)	22 (2.7)	<.001
Prior bleeding within the last 3 mo	110 (8.4)	69 (13.9)	41 (5.1)	<.001
Blood dyscrasia	36 (2.8)	24 (4.8)	12 (1.5)	<.001
Anemia[b]	562 (43.1)	201 (40.5)	361 (44.6)	.15
Central vein catheter[c]	89 (6.8)	21 (4.2)	68 (8.4)	.004
Thrombocytopenia[b]				
<150 × 10^9 thrombocytes per liter	228 (17.5)	95 (19.2)	133 (16.5)	.21
<50 × 10^9 thrombocytes per liter	36 (2.8)	26 (5.2)	10 (1.2)	<.001
INR >2[b]	4 (0.3)	3 (0.7)	1 (0.1)	.12
Antiplatelet therapy[b]				
Aspirin therapy	349 (26.7)	130 (26.2)	219 (27.1)	.73
Dual antiplatelet therapy	38 (2.9)	19 (3.8)	19 (2.3)	.12
TPX type and duration[c]				
Any pharmacologic TPX	809 (62.0)		809 (62.0)	
LMWH	715 (88.4)		715 (88.4)	
UFH	91 (11.2)		91 (11.2)	
Fondaparinux	23 (2.8)		23 (2.8)	
DOACs[d]	10 (0.7)		10 (0.7)	
Any mechanical TPX	71 (5.4)	23 (4.6)	48 (5.9)	.32
Median duration on TPX (d)[e]	4 (2-8)		4 (2-8)	
IMPROVE Bleeding Risk Score				
High risk (≥7 points)	122 (9.3)	64 (12.9)	58 (7.2)	<.001

(Continues)

TABLE 1 (Continued)

Characteristics	All (*N* = 1305)	Pharmacologic thromboprophylaxis		*P* value
		No (*n* = 496)	Yes (*n* = 809)	
Low risk (<7 points)	1183 (90.7)	442 (87.1)	751 (92.8)	
Simplified Geneva score				
High risk (≥3 points)	819 (62.8)	241 (48.6)	578 (71.4)	<.001
Low risk (<3 points)	486 (37.2)	261 (51.4)	231 (28.6)	

Results are expressed as number of participants (percentage) for categorical data, mean ± SD for continuous variables, or median and IQR.

DOAC, direct oral anticoagulant; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; INR, international normalized ratio; LMWH, low-molecular-weight heparin; TPX, thromboprophylaxis; UFH, unfractionated heparin.

[a] Event happened in the past month.

[b] At admission.

[c] During hospitalization.

[d] Apixaban 2.5 mg twice a day or rivaroxaban 10 mg once a day.

[e] Only for pharmacologic thromboprophylaxis.

study excluded patients transferred from the intensive care unit and enrolled patients who had fewer comorbidities compared to the Chinese and American populations included in the previously published studies [8,9,25,26].

The incidence of CRB did not increase in patients receiving pTPX compared to those without TPX in our study, which is in accordance with a Chinese study validating the IMPROVE bleeding risk score [25]. However, the American IMPROVE derivation study showed a statistically significant increase in the incidence of CRB within 14 days of admission in patients receiving pTPX (2.6% vs 1.7%) [9]. This might be explained by the fact that in American studies, pTPX was provided to patients at a higher risk of bleeding [8,9,26]. Indeed, 50% to 75% of patients with an IMPROVE bleeding risk score of ≥7 on admission received pTPX [8,9,26]. On the other hand, in our study, as well as in the Chinese study [25], less than 10% of patients at high risk of bleeding (an IMPROVE bleeding risk score of ≥7 on admission) received pTPX. This means that providing TPX in patients at low risk of bleeding (baseline IMPROVE bleeding risk score, <7 points) does not increase the bleeding risk, but the risk is only further increased in those at high risk of bleeding.

In our study, patients who bled were older, had more frequently a recent surgery, and presented more frequently with active or recent bleeding, anemia, and coagulopathy (a spontaneous international normalized ratio of >2 or blood dyscrasia) on admission compared to patients who did not bleed. Their length of stay and time on pTPX was longer. They more frequently underwent central line access placement. In summary, patients who bled were sicker and more acutely ill than those who did not bleed. However, sicker patients are frequently at higher risk for hospital-acquired VTE, and therefore, VTE prevention is particularly important in this population [3]. Three-quarters of patients with CRB were classified as high risk for hospital-acquired VTE by the simplified Geneva score, which is in accordance with previous studies [3,18]. The American College of Chest Physicians recommends "prescribing mTPX rather than pTPX for patients with active bleeding or in whom the risk of bleeding exceeds VTE risk" [6]. Accordingly, in our cohort, mTPX was used twice as frequently in patients with CRB than those without bleeding, indicating that physicians correctly considered mTPX in this population. However, some patients received both pTPX and mTPX, which disagrees with the 2018 American Society of Hematology guideline "In acutely or critically ill medical patients, the ASH guideline panel *suggests* pTPX or mTPX alone over pTPX and mTPX combined" [5], leaving room for improvement.

We found no significant association between pTPX and CRB, which seems to confirm the results of previous meta-analyses of RCTs [2,3]. However, one historic meta-analysis of RCTs found a significant risk of MB during hospitalization (OR, 1.65-1.81) [4]. This meta-analysis used RCTs performed between 1981 and 2010. Then, the length of stay (approximately 10 days) as well as the duration of pTPX were longer (from 8 to 10 days). Nowadays, the median length of stay (7 days in our study) and the time on pTPX are shorter (4 days in our study). Furthermore, up to two-thirds of our patients would not meet the eligibility criteria for these RCTs [27].

Compared to the absence of ASA, we found that ASA therapy alone tripled the risk of bleeding, which has been previously reported [23]. However, when combining ASA and pTPX, we found no significant association with bleeding. Comparison with the literature is limited. Few studies reported on the bleeding risk of coadministration of TPX and ASA in medical inpatients. In women with recurrent miscarriage, the association of prophylactic LMWH and ASA showed a 2-fold increase in bleeding complications compared to women with ASA only [28]. More recently, in COVID inpatients admitted to the intensive care unit, no increase in bleeding with combined pTPX (LMWH and ASA) was observed [29].

Approximately a fifth of our cohort developed HAA, which corroborates previously published data [11,30,31]. Half of the patients who developed HAA were hospitalized for acute infection, which can lead to anemia secondary to inflammation. Indeed, as the inflammatory cytokines increase the hepcidin levels and diminish iron serum levels, it results in anemia [24,32]. Bleeding or coagulation disorder (blood dyscrasia, thrombocytopenia, and spontaneous high international normalized ratio) seemed to play a minor role in HAA since these disorders were similar in patients with or without HAA. Moreover, HAA is often multifactorial and has many contributing factors, such as chronic inflammation; repetitive phlebotomy; repetitive

TABLE 2 Incidence rates of clinically relevant bleeding, major bleeding, clinically relevant nonmajor bleeding, hospital-acquired anemia, new anemia at discharge, and worsening anemia in all study participants.

	All	Provision of pharmacologic thromboprophylaxis		
Incidence rate	(*N* = 1305)	No (*n* = 496)	Yes (*n* = 809)	*P* value
Clinically relevant bleeding				
Incidence rate[a]	2.4 (1.7-3.5)	3.0 (1.6-5.3)	2.2 (1.4-3.55)	.43
Number of events (%)	29 (2.2)	11 (2.2)	18 (2.2)	.99
Patient-days	12 017	3732	8285	
Major bleeding				
Incidence rate[a]	1.4 (0.9-2.3)	1.6 (0.7-3.6)	1.3 (0.7-2.4)	.69
Number of events (%)	17 (1.3)	6 (1.2)	11 (1.1)	.82
Patient-days	12 145	3765	8380	
Clinically relevant nonmajor bleeding				
Incidence rate[a]	1.1 (0.6-1.8)	1.6 (0.7-3.5)	0.8 (0.4-1.7)	.26
Number of events (%)	13 (1.0)	6 (1.2)	7 (0.9)	.54
Patient-days	12 344	3812	8532	
Hospital-acquired anemia				
Incidence rate[a]	21.2 (18.8-23.9)	19.7 (15.8-24.7)	21.8 (18.9-25.1)	.46
Number of events (%)	264 (20.2)	76 (15.3)	188 (23.2)	.001
Patient-days	12 482	3855	8627	
Median drop in the hemoglobin value (g/L)[b]	5 (0-13)	2 (0-11)	7 (0-15)	<.001
New anemia at discharge				
Incidence rate[a]	17.6 (15.4-20.0)	15.6 (12.1-20.1)	18.4 (15.8-21.5)	.26
Number of events (%)	219 (16.8)	60 (12.1)	159 (19.7)	<.001
Patient-days	12 482	3855	8627	
Worsening of anemia				
Incidence rate[a]	3.6 (2.7-4.8)	4.1 (2.5-6.6)	3.4 (2.4-4.9)	.47
Number of events (%)	45 (3.4)	16 (3.2)	29 (3.6)	.73
Patient-days	12 483	3856	8627	

The *P* values for incidence rate comparisons are computed with mid-*P* adjustment. The *P* values for number of events are based on chi-squared tests, while the one for hemoglobin drop is based on Wilcoxon rank-sum test.

[a] Expressed as events per 1000 patient-days (95% CI).

[b] Variation of hemoglobin value between admission and discharge.

bleeding, including occult bleeding; blood loss related to invasive procedures; malnutrition; and vitamin deficiencies [24]. Almost 50% of our patients presented with anemia on admission, which is coherent with previously published studies [33,34]. However, anemia on admission was less frequent in patients who developed HAA. An explanation might be that common causes of anemia were screened, treatment was provided if needed (iron, B12 vitamin, folic acid, and control of bleeding source, among others), and preventive measures were implemented (limited and bundled blood draws) [24].

The risk of HAA rose with the provision of pTPX. To our knowledge, our study is the first to report an association between HAA and pTPX. Therefore, pTPX might not be as harmless as believed. Given the association of HAA with adverse health outcomes, including death, longer hospital stay, and higher risk of readmission [21,30,31,33–35]. Prevention of this complication is important to optimize care for medical inpatients and reduce the burden on the healthcare system. Thus, pTPX should be avoided in patients at low risk of hospital-acquired VTE to prevent unnecessary exposure to the risk of HAA.

4.1 | Strengths and limitations

This is, to our knowledge, the first prospective multicentric study to suggest the association between HAA and pTPX. The perfect study

TABLE 3 Association of pharmacologic thromboprophylaxis with clinically relevant bleeding based on survival analysis.

Clinically relevant bleeding	Crude HR (95% CI)	*P* value	Adjusted[a] HR (95% CI)	*P* value
No TPX, no ASA, no DAPT	1 (reference)		1 (reference)	
TPX only	1.0 (0.4-3.0)	.85	1.1 (0.4-3.0; 0.840)	.84
ASA only	3.8 (1.6-9.1)	.003	2.8 (1.1-7.3; 0.031)	.031
DAPT only	0.0 (–)		0.0 (–)	
TPX and ASA	1.5 (0.4-5.5)	.56	1.2 (0.3-4.9; 0.770)	.77
TPX and DAPT	0.0 (–)		0.0 (–)	

ASA, aspirin; DAPT, dual antiplatelet therapy; HR, hazard ratio; TPX, thromboprophylaxis.
[a] Adjusted for age and the International Medical Prevention Registry on Venous Thromboembolism.bleeding risk score.

design would have been an RCT as we could have established a causal association between pTPX and HAA. However, our study design is more pragmatic and generalizable to the medical population since we had less restrictive exclusion criteria than in RCTs. Furthermore, our study enrolled patients with cognitive impairment.

Our study also has limitations. First, we acknowledge that the exclusion criteria "life expectancy less than 30 days" was based on a subjective and pragmatic approach, as in previous studies [36–38]. However, no validated score is currently available to objectively predict life expectancy at 30 days after hospitalization. Since study

TABLE 4 Association of pharmacologic thromboprophylaxis with hospital-acquired anemia, new anemia at discharge, and worsening anemia, based on logistic regression.

Hospital-acquired anemia and component outcomes	Crude OR (95% CI)	*P* value	Adjusted[a] OR (95% CI)	*P* value
Hospital-acquired anemia				
No TPX, no ASA, no DAPT	1 (reference)		1 (reference)	
TPX only	1.6 (1.2-2.3)	.005	1.4 (1.0-2.1)	.039
ASA only	0.5 (0.2-1.0)	.05	0.5 (0.2-1.0)	.06
DAPT only	1.8 (0.6-5.1)	.28	1.8 (0.6-5.3)	.28
TPX and ASA	1.2 (0.8-1.9)	.40	1.1 (0.7-1.8)	.73
TPX and DAPT	1.8 (0.6-5.1)	.28	1.7 (0.6-5.0)	.35
New anemia at discharge				
No TPX, no ASA, no DAPT	1 (reference)		1 (reference)	
TPX only	1.9 (1.3-2.7)	.001	1.7 (1.2-2.5)	.005
ASA only	0.7 (0.3-1.4)	.31	0.8 (0.4-1.7)	.52
DAPT only	1.9 (0.6-5.8)	.29	2.0 (0.6-6.4)	.24
TPX and ASA	1.2 (0.8-2.0)	.42	1.2 (0.7-2.1)	.44
TPX and DAPT	2.5 (0.9-7.2)	.10	2.9 (1.0-8.6)	.06
Worsening of anemia				
No TPX, no ASA, no DAPT	1 (reference)		1 (reference)	
TPX only	0.8 (0.4-1.6)	.57	0.7 (0.4-1.6)	.46
ASA only	01.0 (–)		1.0 (–)	
DAPT only	1.3 (0.2-10.4)	.81	1.1 (0.1-10.0)	.91
TPX and ASA	1.1 (0.5-2.6)	.82	0.8 (0.3-2.0)	.58
TPX and DAPT	01.0 (–)		1.0 (–)	

ASA, aspirin; DAPT, dual antiplatelet therapy; OR, odds ratio; TPX, thromboprophylaxis.
[a] Adjusted for age, International Medical Prevention Registry on Venous Thromboembolism bleeding risk score, occurrence of acute infection, and length of stay.

collaborators could select either patients with shorter or longer life expectancy alternatively based on their own subjective assessment, we doubt that a systematic selection bias was introduced in our study. Second, both CRB and HAA shared a definition criterion (ie, a decrease of at least 20 g/L in the hemoglobin value). However, after excluding patients with CRB in a sensitivity analysis, the incidence of HAA remained similar; thus, the overlap was minimal. Third, as HAA is multifactorial, we adjusted the logistic regression for the length of stay, the presence of an active infection at baseline, and the IMPROVE bleeding risk score (central vein catheter, age, male sex, renal disease, liver disease, and cancer) [9]. We, therefore, tried to adjust for the more frequent risk factors of HAA. However, given the observational nature of this study, we could not exclude the presence of residual confounding factors [39]. Finally, one of the most frequently cited risk factors for HAA is the number and quantity of blood draws during the hospitalization. These data were not available for analysis in the RISE dataset; therefore, we used length of stay as a surrogate marker of blood draws, as in previous studies [31,40,41].

5 | CONCLUSION

Our study confirms the safety of pTPX regarding CRB in medical inpatients at low risk of bleeding. The provision of pTPX was associated with HAA, and further studies are needed to explore this finding. Meanwhile, adherence to clinical guidelines that recommend administering pTPX to medical inpatients at increased VTE risk, provided they are at low bleeding risk, is warranted.

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AUTHOR CONTRIBUTIONS

Study concept and design: M.M., C.B., and D.C.. Drafting of the manuscript: D.C., M.M., and C.B.. Critical revision of the manuscript for important intellectual content: J.-B.R., P.V., and D.A.. Statistical analysis plan: J.-B.R.. Obtained funding: M.M. and C.B.. Supervision: M.M. and C.B..

DECLARATION OF COMPETING INTERESTS

There are no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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