

Journal Pre-proof



Overuse and underuse of thromboprophylaxis in medical inpatients

Barbara Kocher, Pauline Darbellay Farhoumand, MD, Damiana Pulver, Basil Kopp, Damien Choffat, Tobias Tritschler, MD, MSc, Peter Vollenweider, MD, Jean-Luc Reny, MD, PhD, Nicolas Rodondi, MD, MAS, Drahomir Aujesky, MD, MSc, Marie Méan, MD, Christine Baumgartner, MD, MAS

PII: S2475-0379(23)00236-4

DOI: <https://doi.org/10.1016/j.rpth.2023.102184>

Reference: RPTH 102184

To appear in: *Research and Practice in Thrombosis and Haemostasis*

Received Date: 17 February 2023

Revised Date: 14 August 2023

Accepted Date: 15 August 2023

Please cite this article as: Kocher B, Farhoumand PD, Pulver D, Kopp B, Choffat D, Tritschler T, Vollenweider P, Reny J-L, Rodondi N, Aujesky D, Méan M, Baumgartner C, Overuse and underuse of thromboprophylaxis in medical inpatients, *Research and Practice in Thrombosis and Haemostasis* (2023), doi: <https://doi.org/10.1016/j.rpth.2023.102184>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2023 The Author(s). Published by Elsevier Inc. on behalf of International Society on Thrombosis and Haemostasis.

1 **Overuse and underuse of thromboprophylaxis in medical inpatients**

2 Barbara Kocher^{1,6}, Pauline Darbellay Farhoumand² MD, Damiana Pulver¹, Basil Kopp¹,
3 Damien Choffat³, Tobias Tritschler^{1,4} MD, MSc, Peter Vollenweider³ MD, Jean-Luc Reny²
4 MD, PhD, Nicolas Rodondi^{1,5} MD, MAS, Drahomir Aujesky¹ MD, MSc, Marie Méan^{3*} MD,
5 Christine Baumgartner^{1*} MD, MAS (* co-last authorship)

6 **Affiliations**

7 ¹ Department of General Internal Medicine, Inselspital, Bern University Hospital, University of
8 Bern, Bern, Switzerland

9 ² Division of General Internal Medicine, Department of Medicine, Geneva University Hospitals
10 (HUG), Geneva, Switzerland

11 ³ Division of Internal Medicine, Department of Medicine, Lausanne University Hospital (CHUV),
12 Lausanne, Switzerland

13 ⁴ Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada

14 ⁵ Institute of Primary Health Care (BIHAM), University of Bern, Switzerland

15

16 **Name of the institution where the work was carried out:** ⁶Department of General Internal
17 Medicine, Inselspital, Bern University Hospital, Bern, Switzerland

18

19 **Correspondence**

20 Christine Baumgartner, Department of General Internal Medicine, Inselspital, Bern University
21 Hospital, Freiburgstrasse 16p, CH-3010 Bern, Switzerland

22 Christine.Baumgartner@insel.ch; phone: +41 (0)31 632 21 11; fax: +41 31 664 43 60

23

24 **Total word count:** 7993, **Main text word count:** 4274, **Abstract word count:** 250, **Tables:**
25 **4, Supplemental Tables:** 3, **Figures:** 2, **Number of References:** 43.

Abstract

Background: Thromboprophylaxis (TPX) prescription is recommended in medical inpatients categorized as high risk of venous thromboembolism (VTE) by validated risk assessment models (RAMs), but how various RAMs differ in categorizing patients in risk groups, and whether the choice of RAM influences estimates of appropriate TPX use is unknown.

Objectives: To determine the proportion of medical inpatients categorized as high or low risk according to validated RAMs, and to investigate the appropriateness of TPX prescription.

Methods: This is a prospective cohort study of acutely ill medical inpatients from three Swiss university hospitals. Participants were categorized as high or low risk of VTE by validated RAMs (i.e., the Padua, IMPROVE, simplified, and original Geneva score). We assessed prescription of any TPX at baseline. We considered TPX prescription in high-risk and no TPX prescription in low-risk patients as appropriate.

Results: Among 1352 medical inpatients, the proportion categorized as high risk ranged from 29.8% with the IMPROVE to 66.1% with the original Geneva score. Overall, 24.6% were consistently categorized as high risk, and 26.3% as low risk by all four RAMs. Depending on the RAM used, TPX prescription was appropriate in 58.7-63.3% of high-risk (i.e., 36.7-41.3% underuse) and 52.4-62.8% of low-risk patients (i.e., 37.2-47.6% overuse).

Conclusion: The proportion of medical inpatients considered as high or low VTE risk varied widely according to different RAMs. Only half of patients were consistently categorized in the same risk group by all RAMs. While TPX remains underused in high-risk patients, overuse in low-risk patients is even more pronounced.

22

Keywords: Hospitalization, inpatients, prescriptions, risk assessment, thrombosis, venous thromboembolism

25

26

27

1 **Essentials**

- 2 1. Risk models aim to identify medical inpatients at risk of venous thromboembolism
3 (VTE).
4 2. We assessed thromboprophylaxis (TPX) prescribing using validated models to predict
5 VTE risk.
6 3. Depending on the risk model, the proportion categorized as high risk varied from 30
7 to 66%.
8 4. TPX is underused in 37-41% of high-risk patients and overused in 37-48% of low-risk
9 patients.

10

11 **Registration:** ClinicalTrials.gov NCT04439383

12

Journal Pre-proof

1 Introduction

2 Venous thromboembolism (VTE), defined as deep vein thrombosis (DVT) or
3 pulmonary embolism (PE), is a common complication of a hospitalization. About 50% of all
4 VTE events occur during or up to 3 months after hospitalization (i.e., hospital-acquired
5 VTE).¹⁻³ VTE risk is particularly high after surgery,⁴ but hospitalization for acute medical
6 illness is also a risk factor.¹ Up to 75% of all hospital-acquired VTE occur in non-surgical
7 patients.⁵ VTE is associated with high mortality and morbidity and the consequences of VTE,
8 especially in case of PE, can be fatal.^{1,6} Randomized controlled trials performed two decades
9 ago have shown that pharmacological thromboprophylaxis (TPX) in medical inpatients was
10 effective in reducing the VTE risk.⁷⁻⁹ Based on available evidence, clinical guidelines
11 recommend administering pharmacological TPX with low molecular weight heparin (LMWH)
12 or fondaparinux in a prophylactic dose to medical inpatients at increased VTE risk during
13 their inpatient stay, provided there is no active bleeding and no increased risk of major
14 bleeding.¹⁰ While in surgical inpatients the VTE risk is determined by the type and duration of
15 intervention,⁴ risk assessment in medical inpatients is more difficult and requires
16 consideration of multiple factors.^{11,12}

17 To target the use of pharmacological TPX and to simplify VTE risk stratification in
18 medical inpatients, guidelines suggest the use of validated risk assessment models
19 (RAMs),¹⁰ such as the Padua,¹³ the IMPROVE,^{14,15} the original^{16,17} or simplified¹⁸ Geneva
20 score. These RAMs provide a summary score based on differently weighted VTE risk factors.
21 Depending on the summary score, patients are categorized into a low or high VTE risk
22 group, with the aim to guide provision of TPX to those at high risk.¹³⁻¹⁸ Despite existing
23 guidelines, pharmacological TPX is often inappropriately used in this population. Previous
24 studies have reported that the proportion of high-risk patients with an appropriate prescription
25 of TPX is only 40%, whereas almost half of all low-risk patients are prescribed unnecessary
26 TPX,^{12,17} although the definition of appropriate and inappropriate prescription of TPX varies
27 widely depending on the criteria used.¹⁹ The comparative performance of various RAMs to
28 predict VTE has been studied,¹⁸ although it is unclear how they differ categorizing patients in

1 high and low VTE risk groups. In addition, how the choice of a particular RAM influences
2 estimates of overuse and underuse of TPX is currently unknown.

3 The aim of this study is to determine the proportion of medical inpatients categorized
4 as high or low risk of VTE according to validated RAMs, and to investigate the
5 appropriateness of TPX in high-risk and low-risk patients based on each RAM, using data
6 from a prospective cohort study of medical inpatients.

7

Journal Pre-proof

1 **Methods**

2 **Setting and Population**

3 We used data from the RISE study, a multicenter non-interventional prospective
4 cohort study of adult patients hospitalized for acute illness in general internal medicine wards
5 of three Swiss university hospitals between May 2020 and January 2022.
6 The trial protocol has been previously published.²⁰ On weekdays, study personnel screened
7 consecutive patients on general internal medicine wards that were newly admitted to the
8 hospital. Inclusion criteria were age ≥ 18 years and admission for hospitalization >24 hours to
9 general internal medicine due to an acute illness. Exclusion criteria were the need for
10 therapeutic anticoagulation (e.g., atrial fibrillation), life expectancy <30 days, insufficient
11 proficiency of the German or French language, unwillingness to provide informed consent,
12 and prior enrolment in the study. Patients who were unable to give informed consent (e.g.,
13 due to mental illness or cognitive impairment) were not excluded from participation, because
14 the risks of VTE, immobilization, and associated adverse outcomes are particularly high in
15 the elderly,^{21,22} where cognitive impairment is more prevalent. Written informed consent was
16 obtained from their legally authorized representative. Eligible study participants were enrolled
17 within 72 hours of admission. The study was approved by the Ethics committees of the
18 participating sites.

19 **Baseline data collection**

20 Trained study personnel collected baseline information about demographic
21 characteristics, all items of selected validated RAMs (Padua,¹³ IMPROVE,^{14,15} original^{16,17}
22 and simplified¹⁸ Geneva score; **Table 1**), other VTE risk factors, comorbidities, potential
23 contraindications to pharmacological TPX, and medications at admission with a potential
24 antithrombotic effect. At the discharge visit, information about treatments during the current
25 hospital stay was collected. Data were collected at the bedside and from electronic health
26 records using standardized forms. Previous VTE was defined as prior DVT or PE.
27 Hypercoagulable state / thrombophilia included diagnoses of antithrombin deficiency,
28 activated protein C resistance, protein C or protein S deficiency, factor V Leiden, G20210A

1 prothrombin-mutation, or antiphospholipid syndrome. Active cancer was defined as
2 metastatic cancer, cancer treated with radiotherapy, chemotherapy, immunotherapy, or
3 surgery within the past 6 months. Myeloproliferative syndrome referred to essential
4 thrombocytopenia, polycythemia vera, myelofibrosis, or chronic myeloid leukemia. Cardiac
5 failure was defined as diagnosis of acute or chronic heart failure with preserved or reduced
6 ejection fraction in medical records, or a documented left ventricular ejection fraction of
7 <40%. Respiratory failure was defined as an acute or chronic need for supplemental oxygen.
8 Reduced mobility / immobilization was defined as anticipated bed rest with or without
9 bathroom privileges for ≥ 3 days for the Padua score,¹³ as confinement to chair or bed with or
10 without bathroom privileges for ≥ 7 days immediately prior to and during hospital admission
11 for the IMPROVE score,^{14,15} and as complete bedrest or inability to walk for 30 minutes per
12 day during ≥ 3 days for the original^{16,17} and simplified¹⁸ Geneva score. Obesity referred to a
13 body mass index (BMI) of ≥ 30 kg/m². Hormonal treatment referred to hormonal
14 contraception, post-menopausal hormone therapy, or antitumor therapy containing estrogen,
15 ethinylestradiol, or estradiol. Contraindications to pharmacological TPX included liver
16 failure and any other active bleeding disorders, active bleeding, or hemorrhagic
17 transformation of acute ischemic stroke.¹² Liver failure was defined as diagnosis of liver
18 failure in medical records, or cirrhosis with spontaneous international normalized ratio (INR)
19 >2. Active bleeding disorder referred to the presence of any bleeding disorder except for liver
20 disease, e.g. hemophilia, von Willebrand disease, idiopathic thrombocytopenia. For each
21 participant, the Padua, the IMPROVE, and the original and simplified Geneva score were
22 calculated for the purpose of this study, as previously described (**Table 1**).¹³⁻¹⁸ The treating
23 physicians were not informed about the RAM scores, and none of the centers had a specific
24 RAM integrated in their order sets or in their electronic medical records. However, all three
25 hospitals had internal guidelines regarding the prescription of TPX. At the university hospitals
26 in Bern and Lausanne, the Padua score was recommended to assess the indication for TPX
27 prescription, while it was the simplified Geneva score at the university hospital of Geneva.
28 While these internal guidelines indicated that non-pharmacological TPX prophylaxis should

1 be used in patients with both an increased bleeding and VTE risk, none of the guidelines
2 explicitly listed bleeding risk factors or recommended the use of a formal bleeding risk score.

3 **Outcomes**

4 The primary outcome of the present analysis was the proportion of medical inpatients
5 categorized as high or low risk of VTE by each RAM. Patients were categorized as high or
6 low VTE risk according to each RAM at baseline; high VTE risk was defined as a score of ≥ 4
7 points on the Padua,¹³ ≥ 2 points on the IMPROVE,^{14,15} and ≥ 3 points on the original^{16,17} and
8 simplified¹⁸ Geneva score (**Table 1**).

9 Secondary outcomes were the prescription of any TPX, as well as underuse and
10 overuse of TPX. Prescription of any TPX was defined as pharmacological or mechanical TPX
11 for at least one day, at baseline (i.e., within 72 hours of admission) and anytime during the
12 entire hospital stay. LMWH, unfractionated heparin (UFH), fondaparinux, or direct oral
13 anticoagulants (DOACs, [Apixaban, Rivaroxaban]) in a prophylactic dose were considered as
14 pharmacological TPX. Mechanical TPX was defined as use of lower extremity compression
15 stockings or bandages, or intermittent pneumatic compression devices. Prescription of TPX
16 was collected from medical records. We defined underuse of TPX as failure to prescribe TPX
17 to patients categorized as high VTE risk, and overuse as prescription of TPX to patients
18 categorized as low VTE risk based on a particular RAM. In other words, we considered TPX
19 prescription in high-risk patients and no TPX prescription in low-risk patients as appropriate,
20 in line with the American College of Chest Physicians Evidence-Based Clinical Practice
21 Guidelines;²³ conversely no TPX prescription in high-risk patients and TPX prescription in
22 low-risk patients was considered as inappropriate. Given that classification of high and low
23 VTE risk is dependent on the particular RAM used, the results on overuse, underuse,
24 appropriate and inappropriate use varied based on which RAM was considered. Finally, we
25 assessed prescription of mechanical and pharmacological TPX among high-risk and low-risk
26 patients with a contraindication to pharmacological TPX.

27 Finally, we also assessed clinical outcome events, including symptomatic VTE during
28 90 days after study inclusion, in-hospital clinically relevant bleeding and major bleeding.

1 Symptomatic VTE included objectively confirmed pulmonary embolism, distal and proximal
2 deep vein thrombosis of the upper and lower extremity.²⁰ In hospital clinically relevant
3 bleeding was defined as combined major and clinically relevant non-major bleeding. The
4 definition of major bleeding was based on the criteria from the International Society of
5 Thrombosis and Haemostasis, which includes fatal bleeding and/or symptomatic bleeding in
6 a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal,
7 intraarticular, pericardial, or intramuscular with compartment syndrome) and/or bleeding with
8 a reduction of hemoglobin ≥ 20 g/l, or leading to the transfusion ≥ 2 units of packed red blood
9 cells.²⁴ Clinically relevant non-major bleeding referred to overt bleeding that does not meet
10 criteria for major bleeding but is associated with a medical intervention, bleeding important
11 enough to be documented in the medical chart for inpatients, or bleeding resulting in pain or
12 impairment of activities of daily living.²⁰ VTE and bleeding outcomes were adjudicated by
13 three independent clinical experts.

14 **Statistical analysis**

15 Patient characteristics were presented using descriptive statistics. We calculated the
16 proportion of patients at high and at low VTE risk according to each RAM. In addition, we
17 assessed the proportion of patients who would have been categorized as high risk and low
18 risk by all four RAMs, respectively. The proportion of overall TPX at baseline and anytime
19 during the entire hospitalization was calculated for high-risk and low-risk patients based on
20 each score, and for patients categorized as high or low risk by all four RAMs, respectively.
21 The proportion of VTE outcomes during 90 days, in-hospital clinically relevant bleeding, and
22 major bleeding was presented for categories of underuse, appropriate use, and overuse of
23 any TPX during hospitalization based on each RAM, and compared using the chi-squared
24 test. All analyses were performed using Stata statistical software, Release 16 (Stata
25 Corporation, College Station, TX, USA). Two-sided p-values < 0.05 were considered
26 statistically significant.

1 Results

2 Overall, 1352 medical inpatients were included in the study (**Figure 1**). Among all
3 participants, the median age was 67 years (interquartile range [IQR] 54-77 years), 590
4 (43.6%) were female (**Table 2**), and the median duration of hospital stay was 6 days (IQR 4-
5 10 days). The most common risk factors for VTE were older age, acute infection, reduced
6 mobility / immobilization for ≥ 3 days, obesity, and active cancer (**Table 2**). Given that we
7 enrolled only patients that were admitted for hospitalization to general internal medicine
8 wards, none of the participants had a stay in intensive or coronary care unit at baseline.

9 Risk of VTE according to validated RAMs

10 According to the Padua score, 646 (47.8%) patients were categorized as high risk.
11 The IMPROVE score categorized 403 (29.8%) patients as high risk. Based on the original
12 and simplified Geneva score, 893 (66.1%) and 854 (63.2%) patients were classified as high
13 risk, respectively. Overall, 333 (24.6%) of patients were consistently categorized as high risk,
14 and 356 (26.3%) as low risk by all four RAMs (**Figure 2**).

15 Overuse and underuse of TPX

16 At baseline, 698 (51.6%) patients had a prescription for any TPX (mechanical TPX
17 n=11, pharmacological TPX n=687). During the entire hospitalization, 866 (64.1%) patients
18 had a prescription for any TPX. Of these, 842 patients were prescribed a pharmacological
19 TPX (type and dose shown in **Supplemental Table 1**) and 74 a mechanical TPX (combined
20 mechanical and pharmacological TPX in 50 patients). The most common pharmacological
21 TPX prescribed was LMWH, followed by UFH (**Figure 1**). The median duration of
22 pharmacological TPX was 5 days (IQR 3-8 days); TPX was started on the day of admission
23 in 34.5% and until the first day after admission in 76.4% of patients receiving any TPX during
24 hospitalization (**Supplemental Table 2**). In most patients (n=71), compression stockings or
25 bandages were used for mechanical TPX (**Figure 1**).

26 Depending on the RAM used, 58.7% to 63.3% of high-risk patients had a prescription
27 of any TPX at baseline. Throughout the hospital stay the proportion increased to 71.3% to
28 75.7% (**Figure 2**). Thus, the proportion of patients categorized as high risk who were not

1 prescribed any TPX at baseline and during the entire hospitalization (i.e., TPX underuse)
2 were 36.7% to 41.3% and 24.3% to 28.7%, respectively. In contrast, 37.2% to 47.6% and
3 49.0% to 60.2% of patients categorized as low risk by any of the RAMs were prescribed any
4 TPX at baseline and during the entire hospitalization (i.e., TPX overuse), respectively
5 **(Figure 2)**. The results were similar in patients who were grouped in the same risk category
6 by all four RAMs. Among patients consistently categorized as high risk by all four RAMs,
7 62.2% had a prescription of TPX at baseline and 75.4% at any time during hospitalization,
8 while among patients consistently categorized as low risk it was 32.6% and 44.9%,
9 respectively **(Figure 2)**.

10 **Patients with a contraindication to pharmacological TPX**

11 Overall, 119 (8.8%) of patients had at least one or several contraindications to
12 pharmacological TPX, including liver failure, any other active bleeding disorder, or active
13 bleeding **(Table 2)**. Despite the presence of a contraindication, 26 patients were prescribed
14 pharmacological TPX at baseline. Among patients with a contraindication, 38 patients were
15 consistently categorized as high risk and 41 consistently as low risk by all four RAMs. TPX
16 was prescribed to 14 high-risk patients with a contraindication (pharmacological TPX only in
17 12 patients) and to 8 low-risk patients with a contraindication (all with pharmacological TPX
18 only; **Table 3**).

19 **Venous thromboembolism and bleeding outcomes according to underuse, appropriate** 20 **use, and overuse of TPX**

21 A total of 28 (2.1%) VTE events occurred during 90 days after study inclusion. There
22 were no significant differences in VTE outcomes between groups with underuse, appropriate
23 use, or overuse of TPX, irrespective of the RAM used **(Table 4)**. During their hospital stay,
24 64 (4.7%) patients suffered from a clinically relevant bleeding event, and 34 (2.5%) had
25 major bleeding. Overall, risk for both in-hospital clinically relevant bleeding as well as in-
26 hospital major bleeding tended to be increased in high VTE risk patients with underuse of
27 TPX, and lower in patients at low VTE risk patients with overuse of TPX compared to
28 patients with appropriate TPX prescription. However, the difference was only statistically

- 1 significant for in-hospital clinically relevant bleeding in groups of underuse, appropriate use,
- 2 or overuse of TPX based on the IMPROVE score (**Table 4**). Results for bleeding risk were
- 3 similar after exclusion of 40 participants who were started on therapeutic dose
- 4 anticoagulation during the index hospitalization (**Supplemental Table 3**).
- 5

Journal Pre-proof

1 Discussion

2 Our prospective multicenter cohort study showed that the proportion of medical
3 inpatients categorized as high risk of VTE varies widely according to different validated
4 RAMs. Only a quarter of patients were consistently categorized in the high risk group by all
5 four RAMs. Overall, TPX at baseline was underused in up to 41% of high-risk and overused
6 in up to 48% of low-risk patients. Overuse and underuse of TPX based on RAMs did not
7 seem to be associated with adverse VTE and bleeding outcomes in our cohort, with similar
8 VTE risk in patients with underuse, appropriate use or overuse of TPX.

9 Only half of patients were consistently categorized in the same risk group by all four
10 RAMs. The proportion of patients classified as high risk varied widely from 30 to 66%
11 according to different validated scores. Such large differences have also been shown in other
12 studies,^{18,25-27} For example, a recently published meta-analysis compared the Padua, the
13 original Geneva, and the Caprini score and the American College of Chest Physicians
14 (ACCP) criteria for VTE risk stratification, and found that 30 to 63% of patients were
15 classified as high risk depending on the risk score used.²⁵ Although RAMs consist of some
16 similar items, the wide variation in their estimation of which individuals are at high risk is due
17 to variation in content and number of items, and possibly due to the fact that these items,
18 e.g., mobility, are defined and weighted differently. Current guidelines recommend to perform
19 VTE risk stratification in medical inpatients to support clinical-decision making for TPX
20 provision, but they acknowledge the uncertainty about optimal VTE risk stratification.¹⁰ In a
21 post-hoc analysis of a prospective cohort study¹⁸ and various systematic reviews,^{26,28,29}
22 different RAMs have been compared in terms of their validity, applicability, and predictive
23 accuracy. All RAMs have methodological and practical limitations, such as suboptimal
24 sensitivity to identify high-risk patients,^{18,26} non-uniform cut-off values to define low and high
25 risk groups,¹⁴ or excessive complexity,¹⁷ that could limit their use in clinical practice.²⁶

26 Our study showed that only about two thirds of patients classified as high risk had an
27 appropriate prescription of any TPX at baseline, while this increased up to 75% when
28 considering prescription of any TPX during the entire hospitalization, resulting in an estimate

1 of TPX underuse of 25-30% in high-risk patients. The issue of underuse of TPX in high-risk
2 patients is well known. In the multinational cross-sectional ENDORSE study including
3 ~38,000 medical inpatients from 32 countries, around 40% were categorized as high VTE
4 risk by the ACCP criteria. TPX underuse was observed in up to 60% of high-risk patients.¹² In
5 a recently published systematic review and meta-analysis of studies that included 135,000
6 medical inpatients from 20 countries, only about 55% of high-risk patients had a prescription
7 of pharmacological TPX.²⁵ A potential explanation for the higher estimates of TPX underuse
8 in these studies compared to ours is that appropriateness of TPX prescription may differ
9 according to geographic regions.²⁵ TPX is influenced by many factors, such as national
10 guidelines, physician and public VTE awareness, health system standards, or
11 reimbursement.^{25,30,31} In addition, a physician's estimation regarding an increased bleeding
12 risk could contribute to underuse of TPX in selected patients at high VTE risk. This potential
13 explanation for TPX underuse is supported by our results showing a trend towards an
14 increased risk of in-hospital bleeding events in patients with underuse of TPX. Considering
15 only the results for Switzerland in the ENDORSE study (61%) and for Europe in the meta-
16 analysis (67%), the percentage of high-risk patients with an appropriate TPX prescription is
17 similar to our findings. As a result of underuse, high-risk patients may be unnecessarily
18 exposed to VTE risk. However, we did not find an increased risk of VTE events in patients
19 with underuse of TPX in our study; in fact, VTE risk was similar in groups of underuse,
20 appropriate use, and overuse of TPX. Given that the incidence of hospital-acquired VTE in
21 medical patients can be decreased by more than 50% with appropriate TPX based on
22 historical randomized controlled trials,^{7,8} this observation suggests that current RAMs may be
23 suboptimal to predict VTE risk,²⁶ or the current real-life impact of TPX is overestimated.

24 Overuse of TPX seems to be even more pronounced than underuse. This results in a
25 substantial proportion of low-risk patients that are unnecessarily exposed to an increased risk
26 of bleeding (approximately 1.6-fold increased risk of major bleeding with any heparin, with a
27 lower risk in patients receiving LMWH compared to UFH),⁸ heparin-induced
28 thrombocytopenia, as well as potentially painful TPX injections. However, based on our

1 results, patients at low VTE risk in whom TPX is overused in our cohort seem to be those at
2 particular low risk of bleeding. Unlike with underuse, the percentage of overuse was more
3 dependent on the RAM used. The proportion of overuse was smallest with the use of both
4 Geneva scores, which is not surprising, as these two RAMs classify more patients as high
5 risk compared to other scores.¹⁸ In previous studies, estimates of overuse were somewhat
6 smaller or comparable to our study. In the ENDORSE study, 30% of low-risk patients were
7 prescribed any TPX.¹² In another study, the overuse of TPX in low-risk patients was around
8 48-57%.^{17,26} A potential explanation for overuse of TPX could be the concern about patient
9 safety, as the risks of unnecessary TPX may be outweighed by the risk of a VTE event that
10 could potentially be prevented.³² A previous study could not identify any clinical factors
11 predicting the overuse of TPX in low risk patients, and the authors hypothesized that non-
12 clinical factors such as local habits may play a role.³³

13 About 3% of all VTE high-risk patients had a contraindication to pharmacological
14 TPX. Nonetheless, approximately one third of these patients were prescribed
15 pharmacological TPX, which is consistent with findings of previous studies.³⁴ Despite
16 guidelines recommending to prescribe mechanical TPX among high-risk patient with a
17 contraindication to pharmacological TPX,^{3,10} mechanical TPX was only prescribed in a
18 minority of these patients in our study, suggesting that physicians seem to be insufficiently
19 aware of this option or participating hospitals do not follow this recommendation. Another
20 possible explanation could be the limited evidence for benefit of mechanical prophylaxis in
21 medical inpatients,¹⁰ with a concern for harm, such as skin damage on the legs due to
22 intermittent pneumatic compression.³⁵ Among low-risk patients with a contraindication, one
23 quarter was prescribed pharmacological TPX. Even though the absolute number of patients
24 was small, this result is alarming given that they were unnecessarily exposed to an increased
25 bleeding risk associated with TPX.

26 Evidence of underuse and overuse emphasizes the need for increased VTE
27 awareness to optimize VTE prevention.³⁰ VTE awareness campaigns such as the annual
28 World Thrombosis Day that has been launched in 2014 have a growing but still insufficient

1 impact.³⁶ The American Heart Association and the International Society of Thrombosis and
2 Haemostasis have drafted a scientific statement outlining their implementation in practice to
3 improve VTE prevention.³⁷ Besides the lack of awareness, another potential explanation for
4 inappropriate TPX use is the uncertainty about optimal VTE risk stratification of medical
5 inpatients by physicians, which may arise from the lack of an optimal and easy-to-use RAM
6 and the inconsistent classification of patients into VTE risk groups by various existing RAMs,
7 as shown in our study.³⁸ Consequently, RAMs do not seem to be consistently used in clinical
8 practice to guide TPX prescription. A prospective cohort study with dedicated collection of
9 RAM items allowing a head-to-head comparison of validated RAMs in hospitalized medical
10 inpatients is currently lacking and needed to provide clear guidance for physicians about
11 optimal VTE risk assessment. In addition, objectively measurable items could potentially help
12 to standardize risk stratification and ultimately classification into risk groups. However, even
13 an ideal and standardized risk assessment strategy will only improve appropriateness of TPX
14 if it is applied correctly in everyday clinical practice. The introduction of institutional guidelines
15 does not seem to sufficiently improve adequacy of TPX prescription, as shown previously.³⁹
16 Computer-alert programs with integration of a RAM to identify high-risk patients as well as
17 contraindications to pharmacological TPX may improve TPX prescription and decrease in the
18 rate of VTE compared to usual care.⁴⁰ However, evidence on the beneficial effect of
19 computer alert systems are inconsistent, as electronic alerts may be ignored by physicians.⁴¹

20 To our knowledge, this is the first multicenter prospective cohort study with dedicated
21 collection of RAM items and assessment of different validated RAMs and TPX use in newly
22 admitted medical inpatients. There are several previous studies which applied different
23 RAMs on the same population to assess their external validity.^{42,43} However, our study is the
24 first to examine how many of the patients were consistently classified as high risk or low risk
25 using all RAMs, thus, showing how the individual RAMs differ in classifying a particular
26 patient. However, several limitations should be noted. The generalizability of the study
27 results may be limited to a tertiary care hospital setting of high-income countries with
28 comprehensive health-care insurance and a mainly Caucasian population, given that it was

1 performed in Swiss university hospitals only, and detailed information on race and ethnicity
2 was not collected. In addition, we cannot rule out that physicians changed their TPX
3 prescription habit due to the conduct of this study. However, we communicated that the study
4 investigated mobility in hospitalized medical inpatients (a secondary goal of the RISE
5 cohort²⁰), but did not inform physicians explicitly about the aim to investigate VTE prevention
6 strategies and outcomes, which was also the reason why we were not able to compare the
7 performance RAMs to subjective clinical gestalt. Another potential limitation of the study is
8 that the appropriateness of TPX prescription is only based on VTE RAMs without including a
9 bleeding RAM. As suggested by our results showing no difference in VTE risk among those
10 with underuse of TPX but a trend towards a higher risk of bleeding compared to those with
11 appropriate TPX use, clinicians may be making tradeoffs between thrombosis and bleeding
12 risk when considering pharmacological TPX in medical inpatients, which may have
13 contributed in part to the underuse of pharmacological TPX.

14

15 **Conclusions**

16 Our study demonstrated that the risk stratification of VTE varies widely across
17 validated RAMs. Only half of patients were consistently classified into the same risk group by
18 all four RAMs. While TPX remains underused in high-risk patients, overuse in low-risk
19 patients is even more pronounced. However, we did not find a negative impact of
20 inappropriate TPX on VTE and bleeding outcomes, which may suggest suboptimal
21 performance of current RAMs. In addition, underuse of TPX in some patients classified as
22 high VTE risk may have been appropriate based on clinicians' concerns for bleeding risk.
23 Further studies are needed to identify optimal risk assessment strategies to improve VTE
24 prevention in hospitalized medical inpatients.

25

1 Funding

2 The RISE cohort was funded by the Swiss Society of General Internal Medicine (SSGIM)
3 Foundation, Novartis Biomedical Research Foundation, Swiss Heart Foundation, Chuard
4 Schmidt Foundation, and Gottfried und Julia Bangerter-Rhyner Foundation. The research
5 reported in this manuscript was presented at the SSGIM Congress, 1-3 June 2022,
6 Lausanne, Switzerland.

8 Relationship Disclosures

9 The authors have declared that no conflicts of interest exist. The sponsor had no role in in
10 the design and conduct of the study, in the collection, management, analysis, or
11 interpretation of the data, or the preparation, review, or approval of the manuscript.

13 Author Contributions

14 All authors participated in the research and preparation of the manuscript.

15 Study concept and design: C. Baumgartner, M. Méan, D. Aujesky

16 Data acquisition: D. Pulver, B. Kocher, B. Kopp, C. Baumgartner, M. Méan, D. Choffat

17 Statistical analysis: B. Kocher, C. Baumgartner

18 Interpretation of the data: B. Kocher, P. Darbellay Farhoumand, D. Pulver, B. Kopp, D.

19 Choffat, T. Tritschler, P. Vollenweider, J. L. Reny, N. Rodondi, D. Aujesky, M. Méan, C.

20 Baumgartner

21 Drafting the manuscript: B. Kocher, C. Baumgartner

22 Critical revision of the manuscript for important intellectual content: P. Darbellay

23 Farhoumand, D. Pulver, B. Kopp, D. Choffat, T. Tritschler, P. Vollenweider, J. L. Reny, N.

24 Rodondi, D. Aujesky, M. Méan, C. Baumgartner

25 Study supervision: C. Baumgartner, M. Méan

26

27

28

1 **Open Practices Statement**

2 After publication of the main study results,²⁰ de-identified and aggregated data may be
3 shared with researchers for scientific purposes upon request if the use has been approved
4 by an ethical committee. For data access, external researchers can contact the
5 corresponding author.

6

Journal Pre-proof

1 References

- 2 1. Heit JA, O'Fallon WM, Petterson TM, et al. Relative impact of risk factors for deep
3 vein thrombosis and pulmonary embolism: a population-based study. *Arch Intern Med*
4 2002;162(11):1245-8. DOI: 10.1001/archinte.162.11.1245.
- 5 2. Heit JA. Venous thromboembolism epidemiology: implications for prevention and
6 management. *Semin Thromb Hemost* 2002;28 Suppl 2:3-13. DOI: 10.1055/s-2002-
7 32312.
- 8 3. Guyatt GHA, E. A; Crowther, M.; Guttermann, D. D.; Schünemann, H. J.
9 Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of
10 Chest Physicians Evidence-Based Clinical Practice Guidelines. 2012.
- 11 4. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic
12 surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed:
13 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.
14 *Chest* 2012;141(2 Suppl):e278S-e325S. DOI: 10.1378/chest.11-2404.
- 15 5. Goldhaber SZ, Dunn K, MacDougall RC. New onset of venous thromboembolism
16 among hospitalized patients at Brigham and Women's Hospital is caused more often
17 by prophylaxis failure than by withholding treatment. *Chest* 2000;118(6):1680-4. DOI:
18 10.1378/chest.118.6.1680.
- 19 6. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd.
20 Predictors of survival after deep vein thrombosis and pulmonary embolism: a
21 population-based, cohort study. *Arch Intern Med* 1999;159(5):445-53. DOI:
22 10.1001/archinte.159.5.445.
- 23 7. Dentali F, Douketis JD, Gianni M, Lim W, Crowther MA. Meta-analysis: anticoagulant
24 prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical
25 patients. *Ann Intern Med* 2007;146(4):278-88. DOI: 10.7326/0003-4819-146-4-
26 200702200-00007.
- 27 8. Alikhan R, Bedenis R, Cohen AT. Heparin for the prevention of venous
28 thromboembolism in acutely ill medical patients (excluding stroke and myocardial

- 1 infarction). *Cochrane Database Syst Rev* 2014(5):CD003747. DOI:
2 10.1002/14651858.CD003747.pub4.
- 3 9. Lloyd NS, Douketis JD, Moinuddin I, Lim W, Crowther MA. Anticoagulant prophylaxis
4 to prevent asymptomatic deep vein thrombosis in hospitalized medical patients: a
5 systematic review and meta-analysis. *J Thromb Haemost* 2008;6(3):405-14. DOI:
6 10.1111/j.1538-7836.2007.02847.x.
- 7 10. Schunemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology
8 2018 guidelines for management of venous thromboembolism: prophylaxis for
9 hospitalized and nonhospitalized medical patients. *Blood Adv* 2018;2(22):3198-3225.
10 DOI: 10.1182/bloodadvances.2018022954.
- 11 11. Bergmann JF, Cohen AT, Tapson VF, et al. Venous thromboembolism risk and
12 prophylaxis in hospitalised medically ill patients. The ENDORSE Global Survey.
13 *Thromb Haemost* 2010;103(4):736-48. DOI: 10.1160/TH09-09-0667.
- 14 12. Cohen AT, Tapson VF, Bergmann J-F, et al. Venous thromboembolism risk and
15 prophylaxis in the acute hospital care setting (ENDORSE study): a multinational
16 cross-sectional study. *The Lancet* 2008;371(9610):387-394. DOI: 10.1016/s0140-
17 6736(08)60202-0.
- 18 13. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification
19 of hospitalized medical patients at risk for venous thromboembolism: the Padua
20 Prediction Score. *J Thromb Haemost* 2010;8(11):2450-7. DOI: 10.1111/j.1538-
21 7836.2010.04044.x.
- 22 14. Spyropoulos AC, Anderson FA, Jr., FitzGerald G, et al. Predictive and associative
23 models to identify hospitalized medical patients at risk for VTE. *Chest*
24 2011;140(3):706-714. DOI: 10.1378/chest.10-1944.
- 25 15. Rosenberg D, Eichorn A, Alarcon M, McCullagh L, McGinn T, Spyropoulos AC.
26 External validation of the risk assessment model of the International Medical
27 Prevention Registry on Venous Thromboembolism (IMPROVE) for medical patients in

- 1 a tertiary health system. *J Am Heart Assoc* 2014;3(6):e001152. DOI:
2 10.1161/JAHA.114.001152.
- 3 16. Chopard P, Spirk D, Bounameaux H. Identifying acutely ill medical patients requiring
4 thromboprophylaxis. *J Thromb Haemost* 2006;4(4):915-6. DOI: 10.1111/j.1538-
5 7836.2006.01818.x.
- 6 17. Nendaz M, Spirk D, Kucher N, et al. Multicentre validation of the Geneva Risk Score
7 for hospitalised medical patients at risk of venous thromboembolism. *Explicit*
8 *ASsessment of Thromboembolic Risk and Prophylaxis for Medical PATients in*
9 *SwitzErland (ESTIMATE)*. *Thromb Haemost* 2014;111(3):531-8. DOI: 10.1160/TH13-
10 05-0427.
- 11 18. Blondon M, Spirk D, Kucher N, et al. Comparative Performance of Clinical Risk
12 Assessment Models for Hospital-Acquired Venous Thromboembolism in Medical
13 Patients. *Thromb Haemost* 2018;118(1):82-89. DOI: 10.1160/TH17-06-0403.
- 14 19. Avila Ferreira B, de Bastos M, Rezende SM. Unmet definitions in thromboprophylaxis
15 for hospitalized medical patients: An appraisal for the need of recommendation. *Res*
16 *Pract Thromb Haemost* 2022;6(7):e12827. DOI: 10.1002/rth2.12827.
- 17 20. Choffat D, Farhoumand PD, Jaccard E, et al. Risk stratification for hospital-acquired
18 venous thromboembolism in medical patients (RISE): Protocol for a prospective
19 cohort study. *PLoS One* 2022;17(5):e0268833. DOI: 10.1371/journal.pone.0268833.
- 20 21. Alikhan R, Cohen AT, Combe S, et al. Risk factors for venous thromboembolism in
21 hospitalized patients with acute medical illness: analysis of the MEDENOX Study.
22 *Arch Intern Med* 2004;164(9):963-8. DOI: 10.1001/archinte.164.9.963.
- 23 22. Laporte S, Mismetti P, Decousus H, et al. Clinical predictors for fatal pulmonary
24 embolism in 15,520 patients with venous thromboembolism: findings from the
25 Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry.
26 *Circulation* 2008;117(13):1711-6. DOI: 10.1161/CIRCULATIONAHA.107.726232.
- 27 23. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients:
28 *Antithrombotic Therapy and Prevention of Thrombosis*, 9th ed: American College of

- 1 Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2
2 Suppl):e195S-e226S. DOI: 10.1378/chest.11-2296.
- 3 24. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S,
4 Standardization Committee of the International Society on T, Haemostasis. Definition
5 of major bleeding in clinical investigations of antihemostatic medicinal products in
6 non-surgical patients. *J Thromb Haemost* 2005;3(4):692-4. DOI: 10.1111/j.1538-
7 7836.2005.01204.x.
- 8 25. Forgo G, Micieli E, Ageno W, et al. An update on the global use of risk assessment
9 models and thromboprophylaxis in hospitalized patients with medical illnesses from
10 the World Thrombosis Day steering committee: Systematic review and meta-analysis.
11 *J Thromb Haemost* 2022;20(2):409-421. DOI: 10.1111/jth.15607.
- 12 26. Stuck AK, Spirk D, Schaudt J, Kucher N. Risk assessment models for venous
13 thromboembolism in acutely ill medical patients. A systematic review. *Thromb*
14 *Haemost* 2017;117(4):801-808. DOI: 10.1160/TH16-08-0631.
- 15 27. Blondon M, Limacher A, Righini M, Aujesky D, Mean M. Underuse of medical
16 thromboprophylaxis in mobile elderly inpatients: The SWITCO65+ cohort. *Res Pract*
17 *Thromb Haemost* 2021;5(1):142-147. DOI: 10.1002/rth2.12361.
- 18 28. Horner D GS, Davis S, Burton N, Hunt B J. Which is the best model to assess risk for
19 venous thromboembolism in hospitalised patients? *BMJ* 2021;373:n1106. DOI:
20 <https://doi.org/10.1136/bmj.n1106>.
- 21 29. Pandor A, Tonkins M, Goodacre S, et al. Risk assessment models for venous
22 thromboembolism in hospitalised adult patients: a systematic review. *BMJ Open*
23 2021;11(7):e045672. DOI: 10.1136/bmjopen-2020-045672.
- 24 30. Wendelboe AM, McCumber M, Hylek EM, et al. Global public awareness of venous
25 thromboembolism. *J Thromb Haemost* 2015;13(8):1365-71. DOI: 10.1111/jth.13031.
- 26 31. Mahan CE, Barco S, Spyropoulos AC. Cost-of-illness model for venous
27 thromboembolism. *Thromb Res* 2016;145:130-2. DOI:
28 10.1016/j.thromres.2016.06.022.

- 1 32. Nendaz MR, Chopard P, Lovis C, et al. Adequacy of venous thromboprophylaxis in
2 acutely ill medical patients (IMPART): multisite comparison of different clinical
3 decision support systems. *J Thromb Haemost* 2010;8(6):1230-4. DOI:
4 10.1111/j.1538-7836.2010.03817.x.
- 5 33. Spirk D, Nendaz M, Aujesky D, et al. Predictors of thromboprophylaxis in hospitalised
6 medical patients. *Explicit ASsessment of Thromboembolic Risk and Prophylaxis for*
7 *Medical PATients in SwitzErland (ESTIMATE)*. *Thromb Haemost* 2015;113(5):1127-
8 34. DOI: 10.1160/TH14-06-0525.
- 9 34. Panju M, Raso D, Patel A, Panju A, Ginsberg J. Evaluation of the use of venous
10 thromboembolism prophylaxis in hospitalised medical patients. *J R Coll Physicians*
11 *Edinb* 2011;41(4):304-8. DOI: 10.4997/JRCPE.2011.404.
- 12 35. CLOTS Trial Collaboration, Dennis M, Sandercock P, Reid J, Graham C, Forbes J,
13 Murray G. Effectiveness of intermittent pneumatic compression in reduction of risk of
14 deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre
15 randomised controlled trial. *Lancet* 2013;382(9891):516-24. DOI: 10.1016/S0140-
16 6736(13)61050-8.
- 17 36. Wendelboe AM, St Germain L, Krolak B, Reiser T, Raskob G, Day ISCoWT. Impact
18 of World Thrombosis Day campaign. *Res Pract Thromb Haemost* 2017;1(1):138-141.
19 DOI: 10.1002/rth2.12021.
- 20 37. Cushman M, Barnes GD, Creager MA, et al. Venous Thromboembolism Research
21 Priorities: A Scientific Statement From the American Heart Association and the
22 International Society on Thrombosis and Haemostasis. *Circulation* 2020;142(6):e85-
23 e94. DOI: 10.1161/CIR.0000000000000818.
- 24 38. Theriault T, Touchette M, Goupil V, Echenberg D, Lanthier L. Thromboprophylaxis
25 adherence to the ninth edition of American college of chest physicians antithrombotic
26 guidelines in a tertiary care centre: a cross-sectional study. *J Eval Clin Pract*
27 2016;22(6):952-957. DOI: 10.1111/jep.12569.

- 1 39. Gharaibeh L, Albsoul-Younes A, Younes N. Evaluation of venous thromboembolism
2 prophylaxis after the introduction of an institutional guideline: Extent of application
3 and implementation of its recommendations. *J Vasc Nurs* 2015;33(2):72-8. DOI:
4 10.1016/j.jvn.2014.11.002.
- 5 40. Kucher N, Koo S, Quiroz R, et al. Electronic alerts to prevent venous
6 thromboembolism among hospitalized patients. *N Engl J Med* 2005;352(10):969-77.
7 DOI: 10.1056/NEJMoa041533.
- 8 41. Spirk D, Stuck AK, Hager A, Engelberger RP, Aujesky D, Kucher N. Electronic alert
9 system for improving appropriate thromboprophylaxis in hospitalized medical
10 patients: a randomized controlled trial. *J Thromb Haemost* 2017;15(11):2138-2146.
11 DOI: 10.1111/jth.13812.
- 12 42. Zhou C, Yi Q, Ge H, et al. Validation of Risk Assessment Models Predicting Venous
13 Thromboembolism in Inpatients with Acute Exacerbation Of Chronic Obstructive
14 Pulmonary Disease: A Multicenter Cohort Study in China. *Thromb Haemost*
15 2022;122(7):1177-1185. DOI: 10.1055/a-1693-0063.
- 16 43. Chen X, Huang J, Liu J, Deng H, Pan L. Venous thromboembolism risk factors and
17 prophylaxis of elderly intensive care unit patients in a Chinese general hospital. *Ann*
18 *Palliat Med* 2021;10(4):4453-4462. DOI: 10.21037/apm-21-464.
19

1 **Figure Legends**

2 **Figure 1.** Prescription and type of TPX in medical inpatients at baseline and at any time during
3 hospitalization for at least one day.

4 Abbreviations: DOAC, direct oral anticoagulant; TPX, thromboprophylaxis

5 * within 72 hours [median 24 hours] of admission

6 † defined as liver failure or any other active bleeding disorder, active bleeding, or

7 hemorrhagic transformation of acute ischemic stroke

8 § defined as low molecular weight heparin, unfractionated heparin, fondaparinux, or direct

9 oral anticoagulants in a prophylactic dose

10 ‡ defined as use of lower extremity compression stockings or bandages, or intermittent

11 pneumatic compression devices.

12

13 **Figure 2.** Proportion of medical inpatients at high and low VTE risk according to validated
14 RAMs and related prescription of TPX. Variables to calculate VTE risk according to each
15 RAM were collected at baseline (i.e. within 72 hours [median 24 hours] of admission).

16 Abbreviations: RAMs, risk assessment models; TPX, thromboprophylaxis; VTE, venous
17 thromboembolism

18 * refers to prescription of mechanical or pharmacological TPX at baseline

19 † refers to prescription of mechanical or pharmacological TPX anytime during the entire

20 hospitalization for at least one day

21

1 **Tables**2 **Table 1.** RAMs for risk stratification of VTE in medical inpatients.

Score items	Points			
	Padua score ¹³	IMPROVE score ^{14,15}	Original Geneva score ^{16,17}	Simplified Geneva score ¹⁸
Previous VTE *	3	3	2	3
Hypercoagulable state / thrombophilia †	3	2	2	2
Active cancer ‡	3	2	2	2
Myeloproliferative syndrome §	-	-	2	
Cardiac failure ¶	1	-	2	2
Respiratory failure **		-	2	
Acute infection	1	-	2	2
Acute rheumatologic disorder		-	2	
Reduced mobility / immobilization ††	3	1	1	2
Lower limb paralysis or paresis	-	2	-	-
Age >60 years	-	1	1	1
Age ≥70 years	1	-	-	-
Obesity / BMI ≥30 kg/m ²	1	-	1	1
Recent stroke (≤3 months)	1	-	2	1
Recent myocardial infarction (≤1 month)		-	2	
Nephrotic syndrome	-	-	2	-
Hormonal treatment †††	1	-	1	-
Recent travel >6 hours (≤7 days)	-	-	1	-
Chronic venous insufficiency	-	-	1	-
Pregnancy	-	-	1	-
Dehydration	-	-	1	-
Recent trauma or surgery (<1 month)	2	-	-	-
Stay in intensive or coronary care unit	-	1	-	-
Cut-offs ^{10,13,14,17,18}				
Low VTE risk	0-3	0-1	0-2	0-2
High VTE risk	≥4	≥2	≥3	≥3

3 Abbreviations: BMI, body mass index; RAMs, risk assessment models; VTE, venous

4 thromboembolism

5 * defined as prior deep vein thrombosis or pulmonary embolism

6 † defined as antithrombin deficiency, activated protein C resistance, protein C or protein S
7 deficiency, factor V Leiden, G20210A prothrombin-mutation, or antiphospholipid syndrome

8 ‡ defined as metastatic cancer, or cancer treated with radiotherapy, chemotherapy,

9 immunotherapy, or cancer surgery within last 6 months

10 § refers to essential thrombocytopenia, polycythemia vera, myelofibrosis, or chronic myeloid
11 leukemia

12 ¶ acute or chronic cardiac failure, defined as diagnosis of heart failure with preserved or

13 reduced ejection fraction in medical records, or known left ventricular ejection fraction <40%

- 1 ** acute or chronic respiratory failure, defined as need for supplemental oxygen
- 2 †† defined as reduced mobility with anticipated bed rest with or without bathroom privileges
- 3 for ≥ 3 days for the Padua score; defined as immobilization with confinement to chair or bed
- 4 with or without bathroom privileges for ≥ 7 days immediately prior to and during hospital
- 5 admission for the IMPROVE score; or defined as immobilization with complete bedrest or
- 6 inability to walk for 30 minutes per day or ≥ 3 days for the original and simplified Geneva
- 7 score
- 8 ‡‡ refers to hormonal contraception, post-menopausal hormone therapy, antitumor therapy
- 9 containing estrogen, ethinylestradiol, or estradiol

10

Journal Pre-proof

1 **Table 2.** Characteristics of all participants included in the RISE analysis (n=1352).

	n (%)
Baseline characteristics	
Age in years, median (IQR)	67 (54-77)
Female sex	590 (43.6)
Body mass index in kg/m ² , mean (SD)	25.8 (6.1)
VTE risk factors	
Previous VTE *	88 (6.5)
Hypercoagulable state / thrombophilia †	12 (0.9)
Active cancer ‡	263 (19.5)
Myeloproliferative syndrome §	12 (0.9)
Cardiac failure ¶	134 (9.9)
Respiratory failure **	237 (17.5)
Acute infection	581 (43.0)
Acute rheumatologic disorder	54 (4.0)
Reduced mobility for ≥3 days ††	485 (35.9)
Immobilization for ≥3 days ‡‡	382 (28.3)
Immobilization for ≥7 days §§	110 (8.1)
Paresis or paralysis of lower extremities	28 (2.1)
Age >60 years	846 (62.6)
Age ≥70 years	588 (43.5)
Obesity / BMI ≥30 kg/m ²	269 (19.9)
Stroke (≤3 months)	12 (0.9)
Stroke (≤ 1month)	9 (0.7)
Myocardial infarction (≤1 month)	26 (1.9)
Nephrotic syndrome	7 (0.5)
Hormonal treatment ¶¶	58 (4.3)
Travel >6 hours (≤7 days)	36 (2.7)
Chronic venous insufficiency	254 (18.8)
Pregnancy	4 (0.3)
Dehydration	158 (11.7)
Surgery (≤1 month)	49 (3.6)
Trauma (≤1 month)	84 (6.2)
Stay in intensive or coronary care unit	0 (0)
Contraindications to pharmacological TPX	
Any contraindication for pharmacological TPX ***	119 (8.8)
Liver failure †††	10 (0.7)
Any active bleeding	89 (6.6)
Hemorrhagic transformation or acute ischemic stroke	0 (0)
Any active bleeding disorder ‡‡‡	36 (2.7)

2 Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation; TPX,

3 thromboprophylaxis; VTE, venous thromboembolism

4 * defined as prior deep vein thrombosis or pulmonary embolism

5 † defined as antithrombin deficiency, activated protein C resistance, protein C or protein S
6 deficiency, factor V Leiden, G20210A prothrombin-mutation, or antiphospholipid syndrome

7 ‡ defined as metastatic cancer, or cancer treated with radiotherapy, chemotherapy,

8 immunotherapy, or cancer surgery within last 6 months

- 1 § refers to essential thrombocytopenia, polycythemia vera, myelofibrosis, or chronic myeloid
2 leukemia
- 3 ¶ acute or chronic cardiac failure, defined as diagnosis of heart failure preserved or reduced
4 or ejection fraction in medical records, or known left ventricular ejection fraction of <40%
- 5 ** acute or chronic respiratory failure, defined as need for supplemental oxygen
- 6 †† defined as anticipated bed rest with or without bathroom privileges for ≥3 days
- 7 ‡‡ defined as (anticipated) complete bedrest or inability to walk for >30 minutes per day for
8 ≥3 days
- 9 §§ defined as confinement to chair or bed with or without bathroom privileges for ≥7 days
10 immediately prior to and (anticipated) during hospital admission
- 11 ¶¶ refers to hormonal contraception, post-menopausal hormone therapy, antitumor therapy
12 containing estrogen, ethinylestradiol, or estradiol
- 13 *** defined as liver failure, any other active bleeding disorder, active bleeding, or
14 hemorrhagic transformation of acute ischemic stroke
- 15 ††† defined as diagnosis of liver failure in medical records, or cirrhosis with spontaneous
16 international normalized ratio (INR) >2
- 17 ‡‡‡ defined as the presence of any bleeding disorder except for liver disease, e.g.
18 hemophilia, von Willebrand disease, idiopathic thrombocytopenia
19

1 **Table 3.** Prescription of TPX in medical inpatients with a contraindication to pharmacological
 2 TPX at baseline.

Patients with a contraindication to pharmacological TPX	Overall *	Any TPX †	Pharmacological TPX ‡	Mechanical TPX §
	n (%)	n		
Overall	119 (8.8)	29	26	3
High VTE risk according to all 4 RAMs	38 (2.8)	14	12	2
Low VTE risk according to all 4 RAMs	41 (3.0)	8	8	0

3 Abbreviations: RAM, risk assessment model; TPX, thromboprophylaxis; VTE, venous
 4 thromboembolism

5 Variables to calculate VTE risk according to each RAM and information on TPX were
 6 collected at baseline (i.e. within 72 hours [median 24 hours] of admission). Contraindications
 7 to pharmacological TPX include liver failure, or any other active bleeding disorder, active
 8 bleeding, or hemorrhagic transformation of acute ischemic stroke.

9 * the proportion refers to the overall RISE study population (N=1352)

10 † relates to prescription of any mechanical or pharmacological TPX

11 ‡ defined as low molecular weight heparin, unfractionated heparin, fondaparinux, or direct
 12 oral anticoagulants in a prophylactic dose

13 § defined as prescription of lower extremity compression stockings or bandages, or
 14 intermittent pneumatic compression devices

15

1 **Table 4.** VTE within 90 days and in-hospital bleeding events according to appropriateness of
 2 TPX use based on each RAM.

RAM	Underuse of TPX *	Appropriate use of TPX †	Overuse of TPX ‡	p-value
	VTE events within 90 days / n participants (%)			
Padua score	4/157 (2.6)	16/818 (2.0)	8/377 (2.1)	0.89
IMPROVE score	2/108 (1.9)	13/673 (1.9)	13/571 (2.3)	0.90
Simplified Geneva score	3/232 (1.3)	22/876 (2.5)	3/244 (1.2)	0.30
Original Geneva score	3/256 (1.2)	23/867 (2.7)	2/229 (0.9)	0.13
High risk with all four RAMs	2/82 (2.4)	7/251 (2.8)	-	0.87
Low risk with all four RAMs	-	1/196 (0.5)	1/160 (0.6)	0.89
	in-hospital clinically relevant bleeding events / n participants (%)			
Padua score	12/157 (7.6)	38/818 (4.7)	14/377 (3.7)	0.15
IMPROVE score	10/108 (9.3)	37/673 (5.5)	17/571 (3.0)	0.008
Simplified Geneva score	15/232 (6.5)	44/876 (5.0)	5/244 (2.1)	0.061
Original Geneva score	14/256 (5.5)	44/867 (5.1)	6/229 (2.6)	0.25
High risk with all four RAMs	9/82 (11.0)	18/251 (7.2)	-	0.27
Low risk with all four RAMs	-	9/196 (4.6)	4/160 (2.5)	0.30
	in-hospital major bleeding events / n participants (%)			
Padua score	5/157 (3.2)	21/818 (2.6)	8/377 (2.1)	0.77
IMPROVE score	5/108 (4.6)	19/673 (2.8)	10/571 (1.8)	0.17
Simplified Geneva score	7/232 (3.0)	26/876 (3.0)	1/244 (0.4)	0.07
Original Geneva score	7/256 (2.7)	24/867 (2.8)	3/229 (1.3)	0.44
High risk with all four RAMs	4/82 (4.9)	10/251 (4.0)	-	0.73
Low risk with all four RAMs	-	5/196 (2.6)	1/160 (0.6)	0.16

3 Abbreviations: RAM, risk assessment model; TPX, thromboprophylaxis; VTE, venous
 4 thromboembolism

5 * refers to failure to prescribe any TPX during hospitalization to patients categorized as high
 6 VTE risk

7 † refers to prescription of any TPX during hospitalization in high-risk patients and no TPX
 8 prescription in low-risk patients

9 ‡ refers to prescription of any TPX during hospitalization to patients categorized as low VTE
 10 risk



