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Fulfilment of current VTE prophylaxis guidelines and risk factors linked to complications of VTE prophylaxis in medical patients.

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3 **Title:** Fulfilment of current VTE prophylaxis guidelines and risk factors linked to
4 complications of VTE prophylaxis in medical patients.
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3 ABSTRACT:
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5 *Objectives:* the main objectives were to evaluate the grade of fulfillment of
6 current guidelines regarding venous thromboembolism (VTE) prophylaxis in medical
7 patients during admission and to identify risk factors linked to complications of this
8 prophylaxis.
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14 *Design:* we conducted a prospective cohort study.
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17 *Setting:* Internal Medicine Department of the University Hospital of Santiago de
18 Compostela (third level institution).
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22 *Participants:* we included 396 hospitalized non-surgical patients with no active
23 or previous oral anticoagulation or low molecular weight heparin (LMWH) treatment
24 (during the previous year) and who received VTE prophylaxis during admission.
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29 *Primary and secondary outcome measures:* the grade of fulfilment of current
30 guidelines was estimated by calculating PADOVA and IMPROVE index in all cases.
31 We analysed the development of the following complications: major and minor
32 bleeding, major and minor hematoma and decrease of platelet count.
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38 *Results:* we found that VTE prophylaxis was correctly indicated in 88.4% of
39 patients. We found 2 (0.5%) major bleeding, 17 (4.3%) minor bleeding, 30 (7.6%)
40 platelet count decrease, 29 (7.3%) major hematoma and 82 (20.7%) minor hematoma.
41 The presence of major hematomas was linked to obesity (OR=4.1; IC 95% 1.8–9.2; $P =$
42 0.001), concomitant antiplatelet treatment (OR=2.7; IC 95% 1.1–6.5; $P = 0.03$) and
43 enoxaparin use (OR=3.5; IC 95% 1.1–10.9; $P = 0.029$) and the presence of minor
44 hematomas was associated with PADOVA index < 4 points (OR=3.1; IC 95% 1.5–6.4;
45 $P = 0.003$) and Diabetes Mellitus (OR=2; IC 95% 1.1–3.7; $P = 0.031$).
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3 *Conclusions:* complications during VTE prophylaxis in elderly hospitalized
4 medical patients are frequent despite a correct application of current guidelines. The
5 main factors linked to hematomas were obesity and concomitant antiplatelet treatment
6 and its presence should advise physicians to extreme precautions. The use of tinzaparin
7 for VTE prophylaxis in these patients could have a better security profile.
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13 14 15 16 STRENGTHS AND LIMITATIONS OF THIS STUDY:

17 18 19 *Strengths:*

- 20 -Clinical study in elderly patients, usually excluded from large studies.
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- 22 -Analysis of the fulfilment of current guidelines in VTE prophylaxis in real-life
23 conditions.
- 24
- 25 -Detection of minor complications and risk factors usually undervalued in
26 previous studies.
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33 34 35 *Limitations:*

- 36 -Observational study, which did not allow a correct homogenization of
37 subgroups.
- 38
- 39
- 40
- 41 -The study was developed in only one department of a single hospital.
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48 funding agency in the public, commercial or not-for-profit sectors.
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54 COMPETING INTERESTS STATEMENT: all authors declare no competing
55 interests.
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INTRODUCTION:

Low molecular weight heparin (LMWH) use is extended in hospitalized patients since most of them met high-risk criteria for venous and pulmonary embolism [1]. These criteria have been re-defined by the American College of Chest Physicians and focused on calculate the risk of venous thromboembolism (VTE) development and the bleeding risk before starting VTE prophylaxis on both surgical and non-surgical inpatients [2,3]. In these sense, it is remarkable that the factors linked to a higher bleeding risk have been intensely analysed in patients who underwent to surgical procedures; but there are lack of data in the case of non-surgical patients [4]. Moreover, the apparition of some non-life-threatening secondary effects, like abdominal hematomas, has been poorly studied during VTE prophylaxis in non-surgical patients [5].

The adequacy of the real daily clinical practice to the current recommendations constitutes another interesting point of view. Previous studies showed an acceptable match between guidelines and clinical practice in surgical patients but, again, we can find only a few observational studies in non-surgical patients analysing this fact [1,6–8].

Thus, the aim of the present study was, in the one hand, to analyse the fulfilment of current VTE prophylaxis guidelines in non-surgical patients in an Internal Medicine Department and, in the other hand, to describe the incidence of major and minor secondary effects with LMWH prophylaxis and to detect potential risk factors linked to them.

PATIENTS AND METHODS:

The inclusion criteria were hospitalized non-surgical patients with no active or previous oral anticoagulation or LMWH treatment (during the previous year). There was no restriction regarding the cause of hospital admission. In all cases physicians indicated VTE prophylaxis with no intervention from the study staff. Written informed consent was request to all patients and the data collection was performed through a personal interview by trained staff and revision of their electronic medical history.

Age-adjusted Charlson's index (ACI) was used to assess the comorbidity degree of the included patients [9]. We also applied the Barthel's index (BI) to calculate the functional status [10], the CONUT Score (CS) to detect and establish nutritional deficiencies [11] and the Pfeiffer's test (PT) to conduct a mental status evaluation of all the included patients [12].

In light of current recommendations, the PADOVA index was calculated in all cases to check the adequacy of the clinical practice to guidelines [4]. VTE prophylaxis was considered as indicated with at least 4 points in PADOVA index [13]. In the other hand, the IMPROVE index was used to calculate the bleeding risk, considering as high-risk patients with at least 7 points [14].

Chronic Kidney Disease (CKD) was assessed in patients with decreased glomerular filtration rate (GFR) (<60 mL/min) for at least 3 months before the admission, following current guidelines [15]. Acute Kidney Injury (AKI) was considered in patients with GFR < 60 mL/min at admission without previous diagnosis of CKD. Patients with previous CKD and worsening of GFR at admission were coded as CKD exacerbation (CKDE). GFR was calculated using 2009 CKD-Epidemiology Collaboration (EPI) creatinine equation in all cases [16].

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3 Regarding obesity, it was considered in all patients with a Body Mass Index
4 (BMI) over 30 kg/m² and for the main alterations in blood count we applied World
5 Health Association (WHO) criteria for anemia and we coded as thrombocytopenia at
6 admission all patients with values under 120000/ μ L. Concerning coagulation tests
7 alterations we considered them in all cases with an International Normalized Ratio
8 (INR) over 1.2 or Activated Partial Thromboplastin Time (APTT) over 35 seconds.
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12 The available heparin types in our center during the study period were only
13 enoxaparin and tinzaparin, so they are the only included heparins in our analysis.
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16 In the case of the analysed complications, we defined them as follows:
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19 -Major bleeding: gastrointestinal or intracranial bleeding, haemoptysis, epistaxis
20 or haematuria with a decrease of at least 2 g/dL in haemoglobin level.
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23 -Minor bleeding: haemoptysis, epistaxis or haematuria without analytical impact
24 or with a decrease of less than 2 g/dL.
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27 -Platelet count decrease: loss of at least 50% compared to the baseline value.
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30 -Major hematoma: retroperitoneal or straight abdominal muscles locations were
31 considered as major hematoma in all cases. We also considered as major hematoma an
32 abdominal hematoma in other locations which implied a loss of at least 2 points in
33 hemoglobin levels.
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36 -Minor hematoma: abdominal wall hematoma (any location) with an extension
37 of more than 5 cm without hemoglobin loss or with a hemoglobin loss lower than 2
38 points. We also considered as minor hematoma all abdominal wall hematomas of any
39 extension which caused symptoms like pain or pruritus which required specific
40 treatment.
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3 -Pulmonary embolism (PE) we coded all cases diagnosed during hospital stay
4 which were undiagnosed an unsuspected at admission.
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7 -Deep venous thrombosis (DVT): we considered all cases diagnosed during
8 hospital stay which were undiagnosed an unsuspected at admission.
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11 A descriptive analysis was performed, by calculating qualitative-variable rates
12 plus mean and standard deviation. We used the Chi-square test or Fisher's exact test, as
13 appropriate (expected frequency value <5), to compare qualitative variables, and the
14 Student's t test for quantitative variables. A multivariate logistic regression analysis was
15 conducted to identify factors associated with complications. A *P*-value <0.05 was
16 regarded as significant. All analyses were performed using the SPSS v. 22.0 software
17 package (SPSS Inc., Chicago, IL, USA).
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30 RESULTS:

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33 We included 396 consecutive inpatients that were given VTE prophylaxis during
34 their hospital stay, of them, 51.8% were women and the mean age was 80.7 (Standard
35 Deviation [SD] = 11.5) years old. Only 32 patients (8.1%) lived in nursing homes and
36 the average scores of the different classification tools applied at admission were: ACI
37 5.5 (SD = 2.2) points, BI 55.5 (SD = 35.5) points, PT 3.3 (SD = 3) mistakes and CS 6.2
38 (SD = 2.6) points. CKD was present in 91 (23.2%) patients and Diabetes Mellitus in
39 111 (28.3%) of them, as well as obesity (111 patients). Other remarkable comorbidities
40 were active cancer (37 patients, 9.5%) and haematological diseases (9 patients, 2.5%)
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42 The complete baseline characteristics and frequencies of the main thrombosis risk
43 factors are detailed in Table 1.
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3 After the application of PADOVA index, we found that VTE prophylaxis was
4 correctly indicated in 88.4% of patients, following these criteria. In the case of
5 IMPROVE index, we found that 6.3% of patients had a high theoretical bleeding risk
6 which should advise against VTE prophylaxis prescription. It is also remarkable that 22
7 patients (5.7%) achieved both PADOVA and IMPROVE criteria, which means
8 concomitant high VTE and bleeding risk. We only found 2 patients (0.5%) with less
9 than 4 points in PADOVA index and high bleeding risk in IMPROVE index.
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18 Regarding general condition at admission, 316 (79.8%) patients presented an
19 infection, 155 (39.1%) had anemia, 137 (34.6%) had an acute heart failure, 95 (24%)
20 met AKI criteria and 79 (19.9) met CKDE criteria. If we focus on platelet count and
21 coagulation tests, 93 (23.5%) patients had an alteration on coagulation tests at
22 admission and 27 (6.8%) thrombocytopenia.
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30 Considering the VTE prophylaxis, the most used LMWH was enoxaparin
31 (69.7% of cases) followed by tinzaparin (30.3%) and the mean duration of it was 12
32 (Standard Deviation [SD] = 11.8) days. The most commonly used treatment regimens
33 were 4000 International Units (IU) daily for enoxaparin (219 patients) and 3500 IU
34 daily for tinzaparin (103 patients). We did not register any episode of VTE during the
35 study period.
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43 With regard to complications we found 2 patients (0.5%) who presented major
44 bleeding, 17 (4.3%) a minor bleeding episode, 30 (7.6%) developed a platelet count
45 decrease, 29 (7.3%) had a major hematoma and 82 (20.7%) a minor hematoma. All
46 patients who developed complications were managed through conservative treatment
47 and the evolution was favourable in all cases. After the univariate analysis, we found an
48 association between minor bleeding and the presence of anemia at admission and AKI.
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56 In the case of major hematomas, this analysis showed significant differences in patients
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3 with obesity, concomitant antiplatelet treatment, an infection or heart failure as main
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5 cause of admission and the use of enoxaparin. With regard to minor hematomas, we
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7 found an association with diabetes and a PADOVA index lower than 4 points. Finally, a
8
9 platelet count decrease was only linked to an infection as cause of admission.
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12 After performing a multivariable analysis none variable showed association with
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14 minor bleeding or platelet count decrease, the presence of major hematomas was linked
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16 to obesity (OR = 4.1; IC 95% 1.8 – 9.2; $P = 0.001$), concomitant antiplatelet treatment
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18 (OR = 2.7; IC 95% 1.1 – 6.5; $P = 0.03$) and enoxaparin use (OR = 3.5; IC 95% 1.1 –
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20 10.9; $P = 0.029$) and the presence of minor hematomas was associated with the absence
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22 of indication of VTE prophylaxis following recommendations (PADOVA index < 4
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24 points) (OR = 3.1; IC 95% 1.5 – 6.4; $P = 0.003$) and the presence of Diabetes Mellitus
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26 (OR = 2; IC 95% 1.1 – 3.7; $P = 0.031$).
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30 In view of these results, we performed a sub-analysis to compare the clinical
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32 profile of patients who received enoxaparin and tinzaparin, which showed significant
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34 differences only regarding renal function, as it is showed in Table 1.
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39 DISCUSSION:

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42 The present study shows, for the first time to our knowledge, an exhaustive
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44 analysis of clinically relevant complications during VTE prophylaxis and the main risk
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46 factors linked to them.
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50 If we focus on the adaptation of the clinical practice to current guidelines, it is
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52 remarkable the high grade of adaptation observed, despite the existence of a narrow
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54 margin for improvement. Our study included only patients with VTE prophylaxis
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56 during hospital stay, which makes difficult the comparison with studies like ENDORSE
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3 or AVAIL ME, which showed lower percentages of correct application of
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5 recommendations, even under 50% [17,18].
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8 Another relevant difference of our study is the exclusive inclusion of medical
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10 patients and the extremely high age and grade of comorbidity of our cohort, compared
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12 with larger series, which included patients with a mean age more than 10 years lower
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14 and very low rates of multiple comorbidity [19,20].
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17 The absence of VTE cases in our study reflects a high efficacy of VTE
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19 prophylaxis in medical patients, which has been largely studied and supported by high-
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21 quality evidence [21,22].
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24 Regarding complications, it is remarkable that we have analyzed minor
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26 complications, like hematomas, that usually are undervalued by physicians, but have an
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28 important relevance for patients. Thus, we consider that our results could help
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30 physicians to improve their daily clinical practice and the patient's experience during a
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32 hospital admission.
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35 If we focus on bleeding episodes, they were infrequent, but the association
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37 between anemia and minor bleeding could reflect the existence of previous digestive
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39 bleeding, increased during admission by LMWH, and the association with AKI could be
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41 due to a heparin over effect in these patients, although we did not detect significant rates
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43 of unadjusted dosage in our cohort. In fact, an increased bleeding risk was one of the
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45 main risk factors considered on IMPROVE score, although anemia was not a useful
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47 marker of bleeding risk in that study [14]. Thus, our results could contribute to expand
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49 the available tools to identify patients with high bleeding risk before prescribing VTE
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51 prophylaxis.
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3 In the case of major hematomas, we must highlight the relative high percentage
4 of patients who developed these complications. Despite the clinical relevance of
5 abdominal and retroperitoneal hematomas, large series did not analyze these
6 complications and we only can compare our results with small series and case reports
7 [14,18,23,24]. In this sense, previous reports suggested an estimated incidence of 5%
8 for abdominal hematomas in patients receiving VTE prophylaxis, which could be
9 comparable to ours [25]. With regard to risk factors, previous studies showed that
10 elderly patients had a higher risk of abdominal hematomas [23,25,26]; we did not
11 identify this association, probably due to the absence of patients with ages lower than 65
12 years old. Concomitant antiplatelet treatment has been identify as a risk factors linked to
13 hematomas by other authors, due to the synergic action with LMWH [23,25,26].
14 Obesity has also been described as a risk factor in previous studies [25,27], and this
15 relationship could be due to an adipose tissue dysfunction in obese patients, linked to an
16 abnormal subcutaneous vascularization and extracellular matrix changes [28–30]. These
17 alterations lead to a higher risk of local hematomas in obese patients under VTE
18 prophylaxis, independently of the plasmatic levels of HBPM achieved [26].
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38 If we focus on the different HBPM used in our study we found a lower risk of
39 major hematomas with tinzaparin as the only significant difference. It is remarkable that
40 the characteristics of patients treated with both of them were different regarding renal
41 function, so the use of tinzaparin in patients with poorer renal function could have alert
42 physicians to a better dose adjustment. Thus, it could be considered as a potential
43 selection bias which should be taken into account during the interpretation of our
44 results. Despite this, a potential superior security profile in elderly patients with high
45 comorbidity emerges and even differences in device, needles and mode of
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3 administration should be considered. Further studies will be necessary to properly
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5 establish this difference.
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8 If we focus on minor hematomas, it is remarkable that is a complication usually
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10 not considered as clinically relevant; despite this, we decided to include it due to the
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12 perception that it is completely relevant for our patients. In this sense, the association
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14 with a PADOVA index lower than 4 points cannot be considered as a risk factor itself
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16 but helps us to highlight the importance of a correct application of VTE prophylaxis
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18 guidelines. In the case of Diabetes Mellitus, it has not been previously described as a
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20 risk factor for abdominal hematomas development but microvascular diabetic
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22 complications might underlie this association [25].
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28 CONCLUSIONS:

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30 The development of complications during VTE prophylaxis in elderly
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32 hospitalized medical patients is higher than expected in other populations despite a
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34 correct application of current guidelines. The main factors linked to hematomas in our
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36 cohort were obesity and concomitant antiplatelet treatment and its presence should
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38 advise physicians to extreme precautions. The use of tinzaparin for VTE prophylaxis in
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40 these patients could have a better security profile.
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47 AUTHOR'S CONTRIBUTIONS:

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49 -Study concept and design: Drs. Antonio Pose-Reino, Ignacio Novo-Veleiro
50
51 and Lucía Alvela-Suárez.
52

53
54 -Acquisition of subjects and/or data: Drs. Ignacio Novo-Veleiro, Lucía
55
56 Alvela-Suárez and Alba Costa-Grille.
57

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2
3 -Analysis and interpretation of data: Drs. Ignacio Novo-Veleiro, Javier
4
5 Suárez-Dono, Fernando Ferrón-Vidán and Antonio Pose-Reino.

6
7 -Preparation of manuscript: Drs. Ignacio Novo-Veleiro, Lucía Alvela-Suárez
8
9 and Antonio Pose-Reino.

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14 DATA SHARING STATEMENT: Technical appendix, statistical code, and
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16 dataset will be available from the Dryad repository if required.
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Table 1. Global baseline characteristics and analysis of differences regarding the type of HBPM used for VTE prophylaxis.

Variable	Global (396)	Tinzaparin (120)	Enoxaparin (276)	P
Male	191 (48)	57 (47.5)	134 (48.5)	0.848
CKD	91 (23)	43 (36)	48 (17)	<0.001
Diabetes mellitus	112 (28)	38 (32)	74 (27)	0.324
Neoplasia	37 (9)	11 (9)	26 (9)	0.928
Obesity	113 (28.5)	30 (25)	83 (30)	0.342
Previous VTE	4 (1)	3 (2.5)	1 (0.4)	0.085
30-day surgery	5 (1)	1 (1)	4 (1.5)	0.521
Stroke	49 (12)	13 (11)	36 (13)	0.539
Autoimmune disease	17 (4)	2 (2)	15 (5.5)	0.089
Liver disease	24 (6)	8 (7)	16 (5.5)	0.739
Antiplatelet treatment	182 (46)	53 (44)	129 (47)	0.271
Infectious disease	316 (80)	92 (77)	224 (81)	0.306
Anemia	156 (39)	54 (45)	102 (37)	0.116
AKI	95 (24)	41 (34)	54 (19.5)	0.002
CKD exacerbation	79 (20)	39 (32.5)	40 (14.5)	<0.001
Heart failure	137 (34.5)	50 (42)	87 (31.5)	0.051
PADOVA > 4	342 (86)	112 (93)	230 (83)	0.001
IMPROVE > 7	24 (6)	9 (7.5)	15 (5.5)	0.387
BARTHEL < 20	56 (14)	21 (17.5)	35 (13)	0.218
PFEIFFER > 5	154 (39)	51 (42.5)	103 (37)	0.257

CKD: Chronic Kidney Disease. VTE: Venous Thromboembolism. AKI: Acute Kidney Injury.

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8 **December 20th 2017**
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12 Dear Editor:

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16 Enclosed please find our paper entitled "Fulfilment of current VTE prophylaxis
17 guidelines and risk factors linked to complications of VTE prophylaxis in medical
18 patients". Considering that our work is the first one to analyse the main risk factors of
19 VTE in medical elderly patients, we believe that our results are of great interest in this
20 field of research. Thus we hope you could accept our work as a candidate for
21 publication in your journal.
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26 The submitted manuscript has been read and approved by all authors. Besides, all
27 authors acknowledge that they have exercised due care in ensuring the integrity of the
28 work. The study protocol was revised and approved by the Ethics Committee of the
29 University Hospital of Santiago de Compostela and it conforms to the provision of the
30 Declaration of Helsinki. All participants gave informed consent and anonymity was
31 preserved in all the stages of the study. Finally, none of the original material contained
32 in the manuscript has been submitted for consideration nor will any of it be published
33 elsewhere except in abstract form in connection with scientific meetings.
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39 Sincerely,

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	5-7
Study size	10	Explain how the study size was arrived at	5-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6-7
		(b) Describe any methods used to examine subgroups and interactions	6-7
		(c) Explain how missing data were addressed	6-7
		(d) If applicable, explain how loss to follow-up was addressed	-
		(e) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	-
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-9
		(b) Indicate number of participants with missing data for each variable of interest	7-9
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-9
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(b) Report category boundaries when continuous variables were categorized	7-9
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	-

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Compliance with current VTE prophylaxis guidelines and risk factors linked to complications of VTE prophylaxis in medical patients: a prospective study in an Internal Medicine Department.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-021288.R1
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Keywords:	Thromboembolism < CARDIOLOGY, GERIATRIC MEDICINE, Bleeding disorders & coagulopathies < HAEMATOLOGY

SCHOLARONE™
Manuscripts

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3 **Title:** Compliance with current VTE prophylaxis guidelines and risk factors linked to
4 complications of VTE prophylaxis in medical patients: a prospective study in an
5 Internal Medicine Department.
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11 **Authors:** Ignacio Novo-Veleiro^{1*}, Lucía Alvela-Suárez², Alba Costa-Grille³, Javier
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3 ABSTRACT:
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5 *Objectives:* the main objectives were to evaluate the degree of compliance with
6 current guidelines regarding venous thromboembolism (VTE) prophylaxis in medical
7 patients during admission and to identify risk factors linked to complications of this
8 prophylaxis.
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14 *Design:* a prospective cohort study was conducted.
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17 *Setting:* Internal Medicine Department of the University Hospital of Santiago de
18 Compostela (tertiary referral hospital).
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22 *Participants:* 396 hospitalized, non-surgical elderly patients with no active or
23 previous oral anticoagulation or low molecular weight heparin (LMWH) treatment
24 (during the previous year) and who received VTE prophylaxis during admission.
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29 *Primary and secondary outcome measures:* the degree of compliance with the
30 current guidelines was estimated by calculating PADOVA and IMPROVE indexes in
31 all cases. We analysed the development of the following complications: major and
32 minor bleeding, major and minor hematoma and decrease of platelet count.
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38 *Results:* we found that VTE prophylaxis was correctly indicated in 88.4% of
39 patients. We found 2 (0.5%) major bleeding, 17 (4.3%) minor bleeding, 30 (7.6%)
40 platelet count decrease, 29 (7.3%) major hematoma and 82 (20.7%) minor hematoma.
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42 After a multivariate logistic regression analysis, the presence of major hematomas was
43 linked to obesity (OR=4.1; IC 95% 1.8–9.2; $P = 0.001$), concomitant antiplatelet
44 treatment (OR=2.7; IC 95% 1.1–6.5; $P = 0.03$) and enoxaparin use (OR=3.5; IC 95%
45 1.1–10.9; $P = 0.029$) and the presence of minor hematomas was associated with
46 PADOVA index < 4 points (OR=3.1; IC 95% 1.5–6.4; $P = 0.003$) and Diabetes Mellitus
47 (OR=2; IC 95% 1.1–3.7; $P = 0.031$).
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3 *Conclusions:* complications during VTE prophylaxis in elderly hospitalized
4 medical patients are frequent despite a correct application of current guidelines. The
5 main factors linked to hematomas were obesity and concomitant antiplatelet treatment
6 and their presence should lead physicians to exercise extreme caution. The use of
7 tinzaparin for VTE prophylaxis in these patients could have a better safety profile.
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13 14 15 16 STRENGTHS AND LIMITATIONS OF THIS STUDY:

17 18 *Strengths:*

- 19 - Clinical study in elderly patients, who are usually excluded from large studies.
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- 21 - Analysis of compliance with current guidelines in VTE prophylaxis in real-life
22 conditions.
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- 24 - Detection of minor complications and risk factors that have usually been
25 underestimated in previous studies.
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27 28 *Limitations:*

- 29 - Observational study conducted in only one department of a single hospital,
30 which did not allow for a correct homogenization of subgroups.
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- 32 - The inclusion of patients with VTE prophylaxis only could be a selection bias.
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36 FUNDING STATEMENT: this research received no specific grant from any
37 funding agency in the public, commercial or not-for-profit sectors.
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42 COMPETING INTERESTS STATEMENT: all authors declare that they have
43 no competing interests.
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INTRODUCTION:

Low molecular weight heparin (LMWH) use is extended in hospitalized patients, since most of them meet high-risk criteria for venous and pulmonary embolism [1]. These criteria have been re-defined by the American College of Chest Physicians and place an emphasis on calculating the risk of venous thromboembolism (VTE) development and the bleeding risk before starting VTE prophylaxis on both surgical and non-surgical inpatients [2,3]. In these sense, it is worth noting that the factors linked to a higher bleeding risk have been intensely analysed in patients who underwent surgical procedures; but there is lack of data in the case of non-surgical patients [4]. Moreover, the occurrence of some non-life-threatening secondary effects, like abdominal hematomas, has been poorly studied during VTE prophylaxis in non-surgical patients [5].

The alignment of real daily clinical practice with the current recommendations is another interesting point to which attention must be paid. Previous studies showed an acceptable match between guidelines and clinical practice in surgical patients but, again, only a few observational studies in non-surgical patients analyse this fact [1,6–8].

The aim of the present study was, therefore, on the one hand, to analyse compliance with current VTE prophylaxis guidelines in non-surgical patients in an Internal Medicine Department and, on the other hand, to describe the incidence of major and minor secondary effects with LMWH prophylaxis and to detect potential risk factors linked to them.

PATIENTS AND METHODS:

The inclusion criteria were: hospitalized non-surgical patients with no active or previous oral anticoagulation or LMWH treatment (during the previous year). There was no restriction regarding the cause of hospital admission. In all cases physicians indicated VTE prophylaxis with no intervention from the study staff. Written informed consent was obtained from all patients and data collection was performed through a personal interview by trained staff and a review of their electronic medical history.

Age-adjusted Charlson's index (ACI) was used to assess the comorbidity degree of the patients included [9]. We also applied the Barthel's index (BI) to calculate functional status [10], the CONUT Score (CS) to detect and establish nutritional deficiencies [11] and the Pfeiffer's test (PT) to conduct a mental status evaluation of all the patients included [12].

In light of current recommendations, the PADOVA index was calculated in all cases to check the adequacy of the clinical practice to guidelines [4]. VTE prophylaxis was considered as indicated with at least 4 points in PADOVA index [13]. On the other hand, the IMPROVE index was used to calculate bleeding risk, considering as high-risk patients those with at least 7 points [14].

Chronic Kidney Disease (CKD) was assessed in patients with decreased glomerular filtration rate (GFR) (<60 mL/min) for at least 3 months before admission, following current guidelines [15]. Acute Kidney Injury (AKI) was considered in patients with GFR < 60 mL/min at admission without previous diagnosis of CKD. Patients with previous CKD and worsening of GFR at admission were coded as CKD exacerbation (CKDE). GFR was calculated using 2009 CKD-Epidemiology Collaboration (EPI) creatinine equation in all cases [16].

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3 As to obesity, it was considered in all patients with a Body Mass Index (BMI)
4 over 30 kg/m². For the main alterations in blood count we applied World Health
5 Association (WHO) criteria for anemia and we coded as thrombocytopenia at admission
6 all patients with values under 120000/ μ L. As to coagulation tests alterations, we
7 considered them in all cases with an International Normalized Ratio (INR) over 1.2 or
8 Activated Partial Thromboplastin Time (APTT) over 35 seconds.
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16 The heparin types available in our center for the duration of the study were only
17 enoxaparin and tinzaparin. They are therefore the only heparins included in our
18 analysis.
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23 With regard to the analysed complications, we defined them as follows:

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25 -Major bleeding: gastrointestinal or intracranial bleeding, haemoptysis, epistaxis
26 or haematuria with a decrease of at least 2 g/dL in haemoglobin level.
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30 -Minor bleeding: haemoptysis, epistaxis or haematuria without analytical impact
31 or with a decrease of less than 2 g/dL.
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35 -Platelet count decrease: loss of at least 50% compared to the baseline value.
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38 -Major hematoma: retroperitoneal or straight abdominal muscles locations were
39 considered as major hematoma in all cases. We also considered as major hematoma an
40 abdominal hematoma in other locations which implied a loss of at least 2 points in
41 hemoglobin levels.
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46 -Minor hematoma: abdominal wall hematoma (any location) with an extension
47 of more than 5 cm without hemoglobin loss or with a hemoglobin loss lower than 2
48 points. We also considered as minor hematoma all abdominal wall hematomas of any
49 extension, which caused symptoms like pain or pruritus requiring specific treatment.
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3 -Pulmonary embolism (PE): we coded all cases diagnosed during hospital stay
4 which were undiagnosed and unsuspected at admission.
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7 -Deep venous thrombosis (DVT): we considered all cases diagnosed during
8 hospital stay which were undiagnosed and unsuspected at admission.
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11 A descriptive analysis was performed by calculating qualitative-variable rates
12 plus mean and standard deviation. We used the Chi-square test or Fisher's exact test, as
13 appropriate (expected frequency value <5), to compare qualitative variables, and the
14 Student's t test for quantitative variables. A multivariate logistic regression analysis was
15 conducted to identify factors associated with complications. A *P*-value <0.05 was
16 regarded as significant. All analyses were performed using the SPSS v. 22.0 software
17 package (SPSS Inc., Chicago, IL, USA).
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27 The protocol of the present study was reviewed and approved by the Clinical
28 Investigations Ethical Committee of Galicia.
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35 *Patient and Public Involvement*

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37 There were no patient or public involvement in the development of the study
38 design, protocol, recruitment or dissemination of results.
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45 RESULTS:

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47 We included 396 consecutive inpatients that were given VTE prophylaxis during
48 their hospital stay. Of them, 51.8% were women and the mean age was 80.7 years
49 (Standard Deviation [SD] = 11.5, Range = 22 - 107). Only 32 patients (8.1%) lived in
50 nursing homes and the average scores of the different classification tools applied at
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admission were: ACI 5.5 (SD = 2.2) points, BI 55.5 (SD = 35.5) points, PT 3.3 (SD = 3) mistakes and CS 6.2 (SD = 2.6) points. CKD was present in 91 (23.2%) patients and Diabetes Mellitus in 111 (28.3%) of them, as well as obesity (111 patients). Other remarkable comorbidities were active cancer (37 patients, 9.5%) and haematological diseases (9 patients, 2.5%) The complete baseline characteristics and frequencies of the main thrombosis risk factors are detailed in Table 1.

Table 1. Global baseline characteristics and analysis of differences regarding the type of HBPM used for VTE prophylaxis.

Variable	Global (396)	Tinzaparin (120)	Enoxaparin (276)	P
Male	191 (48)	57 (47.5)	134 (48.5)	0.848
Age	80.7 (11.6)	83 (9.6)	79.8 (12.2)	0.083
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PADOVA > 4	342 (86)	112 (93)	230 (83)	0.001
IMPROVE > 7	24 (6)	9 (7.5)	15 (5.5)	0.387
BARTHEL < 20	56 (14)	21 (17.5)	35 (13)	0.218
PFEIFFER > 5	154 (39)	51 (42.5)	103 (37)	0.257

Data are showed as n (%) or mean (SD). CKD: Chronic Kidney Disease. VTE: Venous Thromboembolism. AKI: Acute Kidney Injury.

After the application of the PADOVA index, we found that VTE prophylaxis was correctly indicated in 88.4% of patients following these criteria, which means a prescription of VTE prophylaxis in 46 low-risk patients. In the case of the IMPROVE index, we found that 6.3% of patients had a high theoretical bleeding risk, which should

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3 advise against VTE prophylaxis prescription. 22 patients (5.7%) fulfilled both
4 PADOVA and IMPROVE criteria, which means concomitant high VTE and bleeding
5 risk. We only found 2 patients (0.5%) with less than 4 points in the PADOVA index and
6 high bleeding risk in the IMPROVE index.
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12 Regarding their general condition at admission, 316 (79.8%) patients presented
13 with an infection, 155 (39.1%) had anaemia, 137 (34.6%) had an acute heart failure, 95
14 (24%) met AKI criteria and 79 (19.9) met CKDE criteria. As to platelet count and
15 coagulation tests, 93 (23.5%) patients had an alteration on coagulation tests at
16 admission and 27 (6.8%) thrombocytopenia.
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23 Considering the VTE prophylaxis, the most used LMWH was enoxaparin
24 (69.7% of cases) followed by tinzaparin (30.3%) and the mean duration was 12 (SD =
25 11.8) days. The most commonly used treatment regimens were 4000 International Units
26 (IU) daily for enoxaparin (219 patients) and 3500 IU daily for tinzaparin (103 patients).
27 The dose adjustment in patients with CKD, CKDE or AKI was correct in all cases. We
28 did not register any episode of VTE during the study period.
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37 With regard to complications, we found 2 patients (0.5%) who presented with
38 major bleeding, 17 (4.3%) with a minor bleeding episode, 30 (7.6%) developed a
39 platelet count decrease, 29 (7.3%) had a major hematoma (9 located in straight
40 abdominal muscles and 20 in other abdominal locations) and 82 (20.7%) a minor
41 hematoma. All patients who developed complications were managed through
42 conservative treatment and the course was favourable in all cases. After the univariate
43 analysis, we found an association between minor bleeding and the presence of anaemia
44 at admission and AKI. In the case of major hematomas, this analysis showed significant
45 differences in patients with obesity, concomitant antiplatelet treatment, an infection or
46 heart failure as main cause of admission and the use of enoxaparin. With regard to
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3 minor hematomas, we found an association with diabetes and a PADOVA index lower
4 than 4 points. Finally, a platelet count decrease was only linked to an infection as the
5 cause of admission and it was not associated with the other analysed complications.
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10 After performing a multivariable analysis none of the variables showed an
11 association with minor bleeding or platelet count decrease. The presence of major
12 hematomas was linked to obesity (OR = 4.1; IC 95% 1.8 – 9.2; $P = 0.001$), concomitant
13 antiplatelet treatment (OR = 2.7; IC 95% 1.1 – 6.5; $P = 0.03$) and enoxaparin use (OR =
14 3.5; IC 95% 1.1 – 10.9; $P = 0.029$) and the presence of minor hematomas was
15 associated with the absence of indication of VTE prophylaxis following
16 recommendations (PADOVA index < 4 points) (OR = 3.1; IC 95% 1.5 – 6.4; $P = 0.003$)
17 and the presence of Diabetes Mellitus (OR = 2; IC 95% 1.1 – 3.7; $P = 0.031$).
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27 In view of these results, we performed a sub-analysis to compare the clinical
28 profile of patients who received enoxaparin and tinzaparin, which showed significant
29 differences regarding renal function only, as shown in Table 1.
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37 DISCUSSION:

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39 The present study shows, for the first time to our knowledge, an exhaustive
40 analysis of clinically relevant complications during VTE prophylaxis in non-surgical
41 patients and the main risk factors linked to them.
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46 As to the adaptation of the clinical practice to current guidelines, the high degree
47 of adaptation observed is remarkable. There is, however, a narrow margin for
48 improvement, particularly in the case of over-prescription in low-risk patients. Our
49 study included only patients with VTE prophylaxis during hospital stay, which makes
50 the comparison with studies like ENDORSE or AVAIL ME difficult as they showed
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3 lower percentages of correct application of recommendations, even as low as below
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5 50% [17,18].
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8 Another relevant difference of our study is that it is exclusively confined to
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10 medical patients as well as the extremely high age and degree of comorbidity of our
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12 cohort, compared with larger series where patients with a mean age more than 10 years
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14 lower and very low rates of multiple comorbidity [19,20] were included.
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17 The absence of VTE cases in our study reflects a high efficacy of VTE
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19 prophylaxis in medical patients, which has been largely studied and supported by high-
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21 quality evidence [21,22].
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24 With respect to complications, we analyzed minor complications, like
25
26 hematomas, that are usually undervalued by physicians, but for patients are important.
27
28 Indeed, we consider that our results could help physicians to improve their daily clinical
29
30 practice and the patient's experience during a hospital admission.
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33 As far as bleeding episodes are concerned, they were infrequent. But the
34
35 association between anemia and minor bleeding could reflect the existence of previous
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37 digestive bleeding, increased during admission by LMWH, and the association with
38
39 AKI could be explained by a heparin over-effect in these patients, although we did not
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41 detect significant rates of unadjusted dosage in our cohort. In fact, an increased bleeding
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43 risk was one of the main risk factors considered on the IMPROVE score, although
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45 anemia was not a useful marker of bleeding risk in that study [14]. Thus, our results
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47 could contribute to expand the tools available to identify patients with high bleeding
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49 risk before prescribing VTE prophylaxis.
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53 In the case of major hematomas, we must underscore the relatively high
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55 percentage of patients who developed these complications. Despite the clinical
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3 relevance of abdominal and retroperitoneal hematomas, large series did not analyze
4 these complications and we can only compare our results with small series and case
5 reports [14,18,23,24]. In this sense, previous reports suggested an estimated incidence
6 of 5% for abdominal hematomas in patients receiving VTE prophylaxis, which could be
7 comparable to ours [25]. With regard to risk factors, previous studies showed that
8 elderly patients had a higher risk of abdominal hematomas [23,25,26]; we did not
9 identify this association, probably because of the little number of patients aged below
10 65 years. Concomitant antiplatelet treatment has been identified as a risk factor linked
11 to hematomas by other authors, due to the synergic action with LMWH, and our
12 findings reinforce the importance of assessing the need to maintain these drugs during
13 hospital admission in elderly patients [23,25,26]. Obesity has also been described as a
14 risk factor in previous studies [25,27], and this relationship could be due to an adipose
15 tissue dysfunction in obese patients linked to an abnormal subcutaneous vascularization
16 and extracellular matrix changes [28–30]. These alterations lead to a higher risk of local
17 hematomas in obese patients under VTE prophylaxis, independently of the plasmatic
18 levels of LMWH achieved [26].

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38 As to the different LMWH used in our study, we found a lower risk of major
39 hematomas with tinzaparin as the only significant difference. Interestingly, the
40 characteristics of patients treated with both of them were different regarding renal
41 function, so the use of tinzaparin in patients with poorer renal function could have
42 alerted physicians to the need of better dose adjustment. Thus, it could be considered as
43 a potential selection bias, which should be taken into account during the interpretation
44 of our results. Despite this, a potential superior safety profile in elderly patients with
45 high comorbidity emerges and even differences in device, needles and mode of
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3 administration should be considered. Further studies will be necessary to properly
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5 establish this difference.
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8 As to minor hematomas, it is remarkable that this complication is not usually
9
10 considered as clinically relevant. However, we decided to include it as we considered
11
12 that it is completely relevant for our patients. In this sense, the association with a
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14 PADOVA index lower than 4 points cannot be considered as a risk factor itself, but it
15
16 helps us to highlight the importance of a correct application of VTE prophylaxis
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18 guidelines. In the case of Diabetes Mellitus, it has not been previously described as a
19
20 risk factor for abdominal hematomas development but microvascular diabetic
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22 complications might underlie this association [25].
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25 Despite the high percentage of patients with alterations in coagulation tests
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27 (23.5%), we found no association between these alterations and the related
28
29 complications. This could be due to the little relevance of most of alterations in
30
31 coagulation tests, consisting of small increments of INR or APTT.
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34 35 36 37 CONCLUSIONS:

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40 The development of complications during VTE prophylaxis in elderly
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42 hospitalized medical patients is higher than that expected in other populations even
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44 when the current guidelines are correctly applied. The main factors linked to hematomas
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46 in our cohort were obesity and concomitant antiplatelet treatment and their presence
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48 should lead physicians to exercise extreme caution. The use of tinzaparin for VTE
49
50 prophylaxis in these patients could have a better safety profile.
51
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53 54 55 56 AUTHOR'S CONTRIBUTIONS:

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2
3 -Study concept and design: Drs. Antonio Pose-Reino, Ignacio Novo-Veleiro
4 and Lucía Alvela-Suárez.
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6
7 -Acquisition of subjects and/or data: Drs. Ignacio Novo-Veleiro, Lucía
8 Alvela-Suárez and Alba Costa-Grille.
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11 -Analysis and interpretation of data: Drs. Ignacio Novo-Veleiro, Javier
12 Suárez-Dono, Fernando Ferrón-Vidán and Antonio Pose-Reino.
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14
15 -Preparation of manuscript: Drs. Ignacio Novo-Veleiro, Lucía Alvela-Suárez
16 and Antonio Pose-Reino.
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23 DATA SHARING STATEMENT: Technical appendix, statistical code, and
24 dataset will be available from the Dryad repository if required.
25

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29
30 FUNDING STATEMENT: this research received no specific grant from any
31 funding agency in the public, commercial or not-for-profit sectors.
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38 COMPETING INTERESTS STATEMENT: all authors declare that they have
39 no competing interests.
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	5-7
Study size	10	Explain how the study size was arrived at	5-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6-7
		(b) Describe any methods used to examine subgroups and interactions	6-7
		(c) Explain how missing data were addressed	6-7
		(d) If applicable, explain how loss to follow-up was addressed	-
		(e) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	-
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-9
		(b) Indicate number of participants with missing data for each variable of interest	7-9
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-9
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(b) Report category boundaries when continuous variables were categorized	7-9
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	-

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Compliance with current VTE prophylaxis guidelines and risk factors linked to complications of VTE prophylaxis in medical inpatients: a prospective cohort study in a Spanish Internal Medicine Department.

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Primary Subject Heading:	Haematology (incl blood transfusion)
Secondary Subject Heading:	Geriatric medicine, Medical management, Patient-centred medicine
Keywords:	Thromboembolism < CARDIOLOGY, GERIATRIC MEDICINE, Bleeding disorders & coagulopathies < HAEMATOLOGY

SCHOLARONE™
Manuscripts

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3 **Title:** Compliance with current VTE prophylaxis guidelines and risk factors linked to
4 complications of VTE prophylaxis in medical inpatients: a prospective cohort study in a
5 Spanish Internal Medicine Department.
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3 ABSTRACT:
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5 *Objectives:* the main objectives were to evaluate the degree of compliance with
6 current guidelines regarding venous thromboembolism (VTE) prophylaxis in medical
7 patients during admission and to identify risk factors linked to complications of this
8 prophylaxis.
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14 *Design:* a prospective cohort study was conducted.
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17 *Setting:* Internal Medicine Department of the University Hospital of Santiago de
18 Compostela (tertiary referral hospital).
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22 *Participants:* 396 hospitalized, non-surgical elderly patients with no active or
23 previous oral anticoagulation or low molecular weight heparin (LMWH) treatment
24 (during the previous year) and who received VTE prophylaxis during admission.
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29 *Primary and secondary outcome measures:* the degree of compliance with the
30 current guidelines was estimated by calculating PADOVA and IMPROVE indexes in
31 all cases. We analysed the development of the following complications: major and
32 minor bleeding, major and minor hematoma and decrease of platelet count.
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38 *Results:* we found that VTE prophylaxis was correctly indicated in 88.4% of
39 patients. We found 2 (0.5%) major bleeding, 17 (4.3%) minor bleeding, 30 (7.6%)
40 platelet count decrease, 29 (7.3%) major hematoma and 82 (20.7%) minor hematoma.
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42 After a multivariate logistic regression analysis, the presence of major hematomas was
43 linked to obesity (OR=4.1; IC 95% 1.8–9.2; $P = 0.001$), concomitant antiplatelet
44 treatment (OR=2.7; IC 95% 1.1–6.5; $P = 0.03$) and enoxaparin use (OR=3.5; IC 95%
45 1.1–10.9; $P = 0.029$) and the presence of minor hematomas was associated with
46 PADOVA index < 4 points (OR=3.1; IC 95% 1.5–6.4; $P = 0.003$) and Diabetes Mellitus
47 (OR=2; IC 95% 1.1–3.7; $P = 0.031$).
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3 *Conclusions:* complications during VTE prophylaxis in elderly hospitalized
4 medical patients are frequent despite a correct application of current guidelines. The
5 main factors linked to hematomas were obesity and concomitant antiplatelet treatment
6 and their presence should lead physicians to exercise extreme caution. The use of
7 tinzaparin for VTE prophylaxis in these patients could have a better safety profile.
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13 14 15 16 STRENGTHS AND LIMITATIONS OF THIS STUDY:

17 18 19 *Strengths:*

- 20 -Clinical study in elderly patients, who are usually excluded from large studies.
- 21
- 22 -Analysis of compliance with current guidelines in VTE prophylaxis in real-life
23 conditions.
- 24
- 25 -Detection of minor complications and risk factors that have usually been
26 underestimated in previous studies.
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34 35 36 *Limitations:*

- 37 -Observational study conducted in only one department of a single hospital,
38 which did not allow for a correct homogenization of subgroups.
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- 41 -The inclusion of patients with VTE prophylaxis only could be a selection bias.
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47 FUNDING STATEMENT: this research received no specific grant from any
48 funding agency in the public, commercial or not-for-profit sectors.
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54 COMPETING INTERESTS STATEMENT: all authors declare that they have
55 no competing interests.
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INTRODUCTION:

Low molecular weight heparin (LMWH) use is extended in hospitalized patients, since most of them meet high-risk criteria for venous and pulmonary embolism [1]. These criteria have been re-defined by the American College of Chest Physicians and place an emphasis on calculating the risk of venous thromboembolism (VTE) development and the bleeding risk before starting VTE prophylaxis on both surgical and non-surgical inpatients [2,3]. In these sense, it is worth noting that the factors linked to a higher bleeding risk have been intensely analysed in patients who underwent surgical procedures; but there is lack of data in the case of non-surgical patients [4]. Moreover, the occurrence of some non-life-threatening secondary effects, like abdominal hematomas, has been poorly studied during VTE prophylaxis in non-surgical patients [5].

The alignment of real daily clinical practice with the current recommendations is another interesting point that deserves attention. Previous studies showed an acceptable match between guidelines and clinical practice in surgical patients but, again, only a few observational studies in non-surgical patients have analysed this fact [1,6–8].

The aim of the present study was, therefore, on the one hand, to analyse compliance with current VTE prophylaxis guidelines in non-surgical patients in an Internal Medicine Department and, on the other hand, to describe the incidence of major and minor secondary effects with LMWH prophylaxis and to detect potential risk factors linked to them.

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3 PATIENTS AND METHODS:
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5 The inclusion criteria were: hospitalized non-surgical patients with no active or
6 previous oral anticoagulation or LMWH treatment (during the previous year). There
7 was no restriction regarding the cause of hospital admission. In all cases physicians
8 indicated VTE prophylaxis with no intervention from the study staff. Written informed
9 consent was obtained from all patients and data collection was performed through a
10 personal interview by trained staff and a review of their electronic medical history.
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18 Age-adjusted Charlson's index (ACI) was used to assess the comorbidity degree
19 of the patients included [9]. We also applied the Barthel's index (BI) to calculate
20 functional status [10], the CONUT Score (CS) to detect and establish nutritional
21 deficiencies [11] and the Pfeiffer's test (PT) to conduct a mental status evaluation of all
22 the patients included [12].
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30 In light of current recommendations, the PADOVA index was calculated in all
31 cases to check the adequacy of the clinical practice to guidelines [4]. VTE prophylaxis
32 was considered as indicated with at least 4 points in PADOVA index [13]. On the other
33 hand, the IMPROVE index was used to calculate bleeding risk, considering as high-risk
34 patients those with at least 7 points [14].
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41 Chronic Kidney Disease (CKD) was assessed in patients with decreased
42 glomerular filtration rate (GFR) (<60 mL/min) for at least 3 months before admission,
43 following current guidelines [15]. Acute Kidney Injury (AKI) was considered in
44 patients with GFR < 60 mL/min at admission without previous diagnosis of CKD.
45 Patients with previous CKD and worsening of GFR at admission were coded as CKD
46 exacerbation (CKDE). GFR was calculated using 2009 CKD-Epidemiology
47 Collaboration (EPI) creatinine equation in all cases [16].
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3 As to obesity, it was considered in all patients with a Body Mass Index (BMI)
4 over 30 kg/m². For the main alterations in blood count we applied World Health
5 Association (WHO) criteria for anemia and we coded as thrombocytopenia at admission
6 all patients with values under 120000/ μ L. As to coagulation tests alterations, we
7 considered them in all cases with an International Normalized Ratio (INR) over 1.2 or
8 Activated Partial Thromboplastin Time (APTT) over 35 seconds.
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16 The heparin types available in our center for the duration of the study were only
17 enoxaparin and tinzaparin, which are therefore the only heparins included in our
18 analysis.
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23 With regard to the analysed complications, we defined them as follows:

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25 -Major bleeding: gastrointestinal or intracranial bleeding, haemoptysis, epistaxis
26 or haematuria with a decrease of at least 2 g/dL in haemoglobin level.
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30 -Minor bleeding: haemoptysis, epistaxis or haematuria without changes in
31 haemoglobin levels or with a decrease of less than 2 g/dL.
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35 -Platelet count decrease: loss of at least 50% compared to the baseline value.
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38 -Major hematoma: retroperitoneal or straight abdominal muscles locations were
39 considered as major hematoma in all cases. We also considered as major hematoma an
40 abdominal hematoma in other locations which implied a loss of at least 2 points in
41 hemoglobin levels.
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46 -Minor hematoma: abdominal wall hematoma (any location) with an extension
47 of more than 5 cm without hemoglobin loss or with a hemoglobin loss lower than 2
48 points. We also considered as minor hematoma all abdominal wall hematomas of any
49 extension, which caused symptoms like pain or pruritus requiring specific treatment.
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3 -Pulmonary embolism (PE): we coded all cases diagnosed during hospital stay
4 which were undiagnosed and unsuspected at admission.
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7 -Deep venous thrombosis (DVT): we considered all cases diagnosed during
8 hospital stay which were undiagnosed and unsuspected at admission.
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11 A descriptive analysis was performed by calculating qualitative-variable rates
12 plus mean and standard deviation. We used the Chi-square test or Fisher's exact test, as
13 appropriate (expected frequency value <5), to compare qualitative variables, and the
14 Student's t test for quantitative variables. A multivariate logistic regression analysis was
15 conducted to identify factors associated with complications. A *P*-value <0.05 was
16 regarded as significant. All analyses were performed using the SPSS v. 22.0 software
17 package (SPSS Inc., Chicago, IL, USA).
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27 The protocol of the present study was reviewed and approved by the Clinical
28 Investigations Ethical Committee of Galicia.
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32 33 34 35 *Patient and Public Involvement* 36

37 There were no patient or public involvement in the development of the study
38 design, protocol, recruitment or dissemination of results.
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45 RESULTS: 46

47 We included 396 consecutive inpatients that were given VTE prophylaxis during
48 their hospital stay. Regarding gender, 51.8% were women and the global mean age was
49 80.7 years (Standard Deviation [SD] = 11.5, Range = 22 - 107), 91% of patients were
50 over 65 years old. Only 32 patients (8.1%) lived in nursing homes and the average
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scores of the different classification tools applied at admission were: ACI 5.5 (SD = 2.2) points, BI 55.5 (SD = 35.5) points, PT 3.3 (SD = 3) mistakes and CS 6.2 (SD = 2.6) points. CKD was present in 91 (23.2%) patients and Diabetes Mellitus in 111 (28.3%) of them, as well as obesity (111 patients). Other remarkable comorbidities were active cancer (37 patients, 9.5%) and haematological diseases (9 patients, 2.5%) The complete baseline characteristics and frequencies of the main thrombosis risk factors are detailed in Table 1.

Table 1. Global baseline characteristics and analysis of differences regarding the type of LMWH used for VTE prophylaxis.

Variable	Global (396)	Tinzaparin (120)	Enoxaparin (276)	P
Male	191 (48)	57 (47.5)	134 (48.5)	0.848
Age	80.7 (11.6)	83 (9.6)	79.8 (12.2)	0.083
CKD	91 (23)	43 (36)	48 (17)	<0.001
Diabetes mellitus	112 (28)	38 (32)	74 (27)	0.324
Neoplasia	37 (9)	11 (9)	26 (9)	0.928
Obesity	113 (28.5)	30 (25)	83 (30)	0.342
Previous VTE	4 (1)	3 (2.5)	1 (0.4)	0.085
30-day surgery	5 (1)	1 (1)	4 (1.5)	0.521
Stroke	49 (12)	13 (11)	36 (13)	0.539
Autoimmune disease	17 (4)	2 (2)	15 (5.5)	0.089
Liver disease	24 (6)	8 (7)	16 (5.5)	0.739
Antiplatelet treatment	182 (46)	53 (44)	129 (47)	0.271
Infectious disease	316 (80)	92 (77)	224 (81)	0.306
Anemia	156 (39)	54 (45)	102 (37)	0.116
AKI	95 (24)	41 (34)	54 (19.5)	0.002
CKD exacerbation	79 (20)	39 (32.5)	40 (14.5)	<0.001
Heart failure	137 (34.5)	50 (42)	87 (31.5)	0.051
PADOVA > 4	342 (86)	112 (93)	230 (83)	0.001
IMPROVE > 7	24 (6)	9 (7.5)	15 (5.5)	0.387
BARTHEL < 20	56 (14)	21 (17.5)	35 (13)	0.218
PFEIFFER > 5	154 (39)	51 (42.5)	103 (37)	0.257

Data are showed as n (%) or mean (SD). CKD: Chronic Kidney Disease. VTE: Venous Thromboembolism. AKI: Acute Kidney Injury.

After the application of the PADOVA index, we found that VTE prophylaxis was correctly indicated in 88.4% of patients following these criteria, which means a prescription of VTE prophylaxis in 46 low-risk patients. In the case of the IMPROVE

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3 index, we found that 6.3% of patients had a high theoretical bleeding risk, which should
4 advise against VTE prophylaxis prescription. 22 patients (5.7%) fulfilled both
5 PADOVA and IMPROVE criteria, which means concomitant high VTE and bleeding
6 risk. We only found 2 patients (0.5%) with less than 4 points in the PADOVA index and
7 high bleeding risk in the IMPROVE index.
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14 Regarding their general condition at admission, 316 (79.8%) patients presented
15 with an infection, 155 (39.1%) had anaemia, 137 (34.6%) had an acute heart failure, 95
16 (24%) met AKI criteria and 79 (19.9) met CKDE criteria. As to platelet count and
17 coagulation tests, 93 (23.5%) patients had an alteration on coagulation tests at
18 admission and 27 (6.8%) had thrombocytopenia.
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25 Considering the VTE prophylaxis, the most used LMWH was enoxaparin
26 (69.7% of cases) followed by tinzaparin (30.3%) and the mean duration was 12 (SD =
27 11.8) days. The most commonly used treatment regimens were 4000 International Units
28 (IU) daily for enoxaparin (219 patients) and 3500 IU daily for tinzaparin (103 patients).
29 The dose adjustment in patients with CKD, CKDE or AKI was correct in all cases. We
30 did not register any episode of VTE during the study period.
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39 With regard to complications, we found 2 patients (0.5%) who presented with
40 major bleeding, 17 (4.3%) with a minor bleeding episode, 30 (7.6%) developed a
41 platelet count decrease, 29 (7.3%) had a major hematoma (9 located in straight
42 abdominal muscles and 20 in other abdominal locations) and 82 (20.7%) had a minor
43 hematoma. All patients who developed complications were managed through
44 conservative treatment and the course was favourable in all cases. After the univariate
45 analysis, we found an association between minor bleeding and the presence of anaemia
46 at admission and AKI. In the case of major hematomas, this analysis showed significant
47 differences in patients with obesity, concomitant antiplatelet treatment, an infection or
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3 heart failure as main cause of admission and the use of enoxaparin. With regard to
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5 minor hematomas, we found an association with diabetes and a PADOVA index lower
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7 than 4 points. Finally, a platelet count decrease was only linked to an infection as the
8
9 cause of admission and it was not associated with the other analysed complications.
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12 After performing a multivariable analysis none of the variables showed an
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14 association with minor bleeding or platelet count decrease. The presence of major
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16 hematomas was linked to obesity (OR = 4.1; IC 95% 1.8 – 9.2; $P = 0.001$), concomitant
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18 antiplatelet treatment (OR = 2.7; IC 95% 1.1 – 6.5; $P = 0.03$) and enoxaparin use (OR =
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20 3.5; IC 95% 1.1 – 10.9; $P = 0.029$) and the presence of minor hematomas was
21
22 associated with the absence of indication of VTE prophylaxis following
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24 recommendations (PADOVA index < 4 points) (OR = 3.1; IC 95% 1.5 – 6.4; $P = 0.003$)
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26 and the presence of Diabetes Mellitus (OR = 2; IC 95% 1.1 – 3.7; $P = 0.031$).
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30 In view of these results, we performed a sub-analysis to compare the clinical
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32 profile of patients who received enoxaparin and tinzaparin, which showed significant
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34 differences regarding renal function only, as shown in Table 1.
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39 DISCUSSION:

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42 The present study shows, for the first time to our knowledge, an exhaustive
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44 analysis of clinically relevant complications during VTE prophylaxis in non-surgical
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46 patients and the main risk factors linked to them.
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50 As to the adaptation of the clinical practice to current guidelines, the high degree
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52 of compliance observed is remarkable. There is, however, a narrow margin for
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54 improvement, particularly in the case of over-prescription in low-risk patients. Our
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56 study included only patients with VTE prophylaxis during hospital stay, which makes
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3 the comparison with studies like ENDORSE or AVAIL ME difficult as they showed
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5 lower percentages of correct application of recommendations, even as low as below
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7 50% [17,18].
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10 Another relevant difference of our study is that it is exclusively confined to
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12 medical patients, as well as the extremely high age and degree of comorbidity of our
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14 cohort, compared with larger series where patients with a mean age more than 10 years
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16 lower and very low rates of multiple comorbidity were included [19,20].
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19 The absence of VTE cases in our study reflects a high efficacy of VTE
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21 prophylaxis in medical patients, which has been largely studied and supported by high-
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23 quality evidence [21,22].
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26 With respect to complications, we analyzed minor complications, like
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28 hematomas, that are usually undervalued by physicians, but for patients are important.
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30 Indeed, we consider that our results could help physicians to improve their daily clinical
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32 practice and the patient's experience during a hospital admission by adding tools to
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34 detect patients at risk of developing these complications.
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37 As far as bleeding episodes are concerned, they were infrequent. Despite this,
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39 the association between anemia and minor bleeding could reflect the existence of
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41 previous digestive bleeding, increased during admission by LMWH, and the association
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43 with AKI could be explained by a heparin over-effect in these patients, although we did
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45 not detect significant rates of unadjusted dosage in our cohort. In fact, an increased
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47 bleeding risk was one of the main risk factors considered on the IMPROVE score,
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49 although anemia was not a useful marker of bleeding risk in that study [14]. Thus, our
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51 results could contribute to expand the tools available to identify patients with high
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53 bleeding risk before prescribing VTE prophylaxis.
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3 In the case of major hematomas, we must underscore the relatively high
4 percentage of patients who developed these complications. Despite the clinical
5 relevance of abdominal and retroperitoneal hematomas, large series did not analyze
6 these complications and we can only compare our results with small series and case
7 reports [14,18,23,24]. In this sense, previous reports suggested an estimated incidence
8 of 5% for abdominal hematomas in patients receiving VTE prophylaxis, which could be
9 comparable to ours [25]. With regard to risk factors, previous studies showed that
10 elderly patients had a higher risk of abdominal hematomas [23,25,26]; we did not
11 identify this association, probably because of the little number of patients aged below
12 65 years. Concomitant antiplatelet treatment has been identified as a risk factor linked
13 to hematomas by other authors, due to the synergic action with LMWH, and our
14 findings reinforce the importance of assessing the need to maintain these drugs during
15 hospital admission in elderly patients [23,25,26]. Obesity has also been described as a
16 risk factor in previous studies [25,27], and this relationship could be due to an adipose
17 tissue dysfunction in obese patients, linked to an abnormal subcutaneous vascularization
18 and extracellular matrix changes [28–30]. These alterations lead to a higher risk of local
19 hematomas in obese patients under VTE prophylaxis, independently of the plasmatic
20 levels of LMWH achieved [26].
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42 As to the different LMWH used in our study, we found a lower risk of major
43 hematomas with tinzaparin as the only significant difference. Interestingly, the
44 characteristics of patients treated with both of them were different regarding renal
45 function, so the use of tinzaparin in patients with poorer renal function could have
46 alerted physicians to the need of better dose adjustment. Thus, it could be considered as
47 a potential selection bias, which should be taken into account during the interpretation
48 of our results. Despite this, a potential superior safety profile in elderly patients with
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3 high comorbidity emerges and even differences in device, needles and mode of
4 administration should be considered. Further studies will be necessary to properly
5 establish this difference.
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10 As to minor hematomas, it is remarkable that this complication is not usually
11 considered as clinically relevant. However, we decided to include it as we considered
12 that it is completely relevant for our patients. In this sense, the association with a
13 PADOVA index lower than 4 points cannot be considered as a risk factor itself, but it
14 helps us to highlight the importance of a correct application of VTE prophylaxis
15 guidelines. In the case of Diabetes Mellitus, it has not been previously described as a
16 risk factor for abdominal hematomas development but microvascular diabetic
17 complications might underlie this association [25].
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28 Despite the high percentage of patients with alterations in coagulation tests
29 (23.5%), we found no association between these alterations and the related
30 complications. This could be due to the little relevance of most of alterations in
31 coagulation tests, consisting of small increments of INR or APTT.
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37 In light of our results, we think that the presence of any risk factor for the
38 development of major or minor complications linked to VTE prophylaxis should lead
39 physicians to a meditation, before its prescription, about the indication, dosage and time
40 of treatment, particularly in elderly patients.
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48 CONCLUSIONS:

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51 The development of complications during VTE prophylaxis in elderly
52 hospitalized medical patients is higher than that expected in other populations even
53 when the current guidelines are correctly applied. The main factors linked to hematomas
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3 in our cohort were obesity and concomitant antiplatelet treatment and their presence
4 should lead physicians to exercise extreme caution. The use of tinzaparin for VTE
5 prophylaxis in these patients could have a better safety profile.
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12 AUTHOR'S CONTRIBUTIONS:

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15 -Study concept and design: Drs. Antonio Pose-Reino, Ignacio Novo-Veleiro
16 and Lucía Alvela-Suárez.
17

18
19 -Acquisition of subjects and/or data: Drs. Ignacio Novo-Veleiro, Lucía
20 Alvela-Suárez and Alba Costa-Grille.
21

22
23 -Analysis and interpretation of data: Drs. Ignacio Novo-Veleiro, Javier
24 Suárez-Dono, Fernando Ferrón-Vidán and Antonio Pose-Reino.
25

26
27 -Preparation of manuscript: Drs. Ignacio Novo-Veleiro, Lucía Alvela-Suárez
28 and Antonio Pose-Reino.
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35 DATA SHARING STATEMENT: Technical appendix, statistical code, and
36 dataset will be available from the Dryad repository if required.
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44 funding agency in the public, commercial or not-for-profit sectors.
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50 COMPETING INTERESTS STATEMENT: all authors declare that they have
51 no competing interests.
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	5-7
Study size	10	Explain how the study size was arrived at	5-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6-7
		(b) Describe any methods used to examine subgroups and interactions	6-7
		(c) Explain how missing data were addressed	6-7
		(d) If applicable, explain how loss to follow-up was addressed	-
		(e) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	-
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-9
		(b) Indicate number of participants with missing data for each variable of interest	7-9
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-9
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(b) Report category boundaries when continuous variables were categorized	7-9
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	-

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Compliance with current VTE prophylaxis guidelines and risk factors linked to complications of VTE prophylaxis in medical inpatients: a prospective cohort study in a Spanish Internal Medicine Department.

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3 **Title:** Compliance with current VTE prophylaxis guidelines and risk factors linked to
4 complications of VTE prophylaxis in medical inpatients: a prospective cohort study in a
5 Spanish Internal Medicine Department.
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3 ABSTRACT
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5 *Objectives:* To evaluate the degree of compliance with current guidelines regarding
6 venous thromboembolism (VTE) prophylaxis in medical patients during admission and
7 to identify risk factors linked to complications of VTE prophylaxis.
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12 *Design:* Prospective cohort study.
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15 *Setting:* The Internal Medicine Department of the University Hospital of Santiago de
16 Compostela (tertiary referral hospital).
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20 *Participants:* A total of 396 hospitalized, elderly patients who did not undergo surgery
21 and had no active or previous oral anticoagulation or low molecular weight heparin
22 (LMWH) treatment (during the previous year) and who received VTE prophylaxis
23 during admission.
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29 *Primary and secondary outcome measures:* The degree of compliance with the current
30 guidelines was estimated by calculating PADOVA and IMPROVE indexes in all cases.
31 We analyzed the development of the following complications: major and minor
32 bleeding, major and minor hematoma and decrease of platelet count.
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38 *Results:* We found that VTE prophylaxis was correctly indicated in 88.4% of patients.
39 We found 2 (0.5%) cases with major bleeding, 17 (4.3%) with minor bleeding, 30
40 (7.6%) with decreased platelet count, 29 (7.3%) with major hematoma and 82 (20.7%)
41 with minor hematoma. After multivariate logistic regression analysis, the presence of
42 major hematomas was linked to obesity (OR=4.1; IC95% 1.8–9.2; $P=0.001$),
43 concomitant antiplatelet treatment (OR=2.7; IC95% 1.1–6.5; $P=0.03$) and enoxaparin
44 use (OR=3.5; IC95% 1.1–10.9; $P=0.029$) and the presence of minor hematomas was
45 associated with PADOVA index < 4 points (OR=3.1; IC95% 1.5–6.4; $P=0.003$) and
46 diabetes mellitus (OR=2; IC95% 1.1–3.7; $P=0.031$).
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3 *Conclusions:* complications during VTE prophylaxis in elderly hospitalized medical
4 patients are frequent even with correct application of current guidelines. The main
5 factors linked to hematomas were obesity and concomitant antiplatelet treatment, the
6 presence of which should lead physicians to exercise extreme caution. The use of
7 tinzaparin for VTE prophylaxis in these patients could have a better safety profile.
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13 14 15 16 STRENGTHS AND LIMITATIONS OF THIS STUDY

17 18 19 *Strengths:*

- 20 -Clinical study in elderly patients, who are usually excluded from large studies.
- 21
- 22 -Analysis of compliance with current guidelines for VTE prophylaxis in real-world
- 23 conditions.
- 24
- 25 -Detection of minor complications and risk factors that have usually been
- 26 underestimated in previous studies.
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34 35 36 *Limitations:*

- 37 -Observational study conducted in only one department of a single hospital, which did
- 38 not allow for an accurate homogenization of subgroups.
- 39
- 40
- 41 -The inclusion of patients with VTE prophylaxis only could introduce selection bias.
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47 FUNDING STATEMENT: this research received no specific grant from any funding
48 agency in the public, commercial or not-for-profit sectors.
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54 COMPETING INTERESTS STATEMENT: all authors declare that they have no
55 competing interests.
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INTRODUCTION

Low molecular weight heparin (LMWH) is widely prescribed in hospitalized patients who meet high-risk criteria for venous and pulmonary embolism [1]. The criteria for prescribing LMWH have been redefined by the American College of Chest Physicians. They now place an emphasis on calculating the risk of venous thromboembolism (VTE) development and the bleeding risk before starting VTE prophylaxis on both surgical and non-surgical inpatients [2,3]. In this sense, it is worth noting that the factors linked to higher bleeding risk have been intensely analyzed in patients who have undergone surgical procedures, but there is a lack of data for non-surgery patients [4]. Moreover, the occurrence of some non-life-threatening secondary effects, such as abdominal hematomas, has been poorly studied during VTE prophylaxis in patients who have not undergone surgery [5].

The alignment of real daily clinical practice with the current recommendations is another interesting point that deserves attention. Previous studies showed an acceptable match between guidelines and clinical practice in surgical patients but, again, only a few observational studies in non-surgical patients have analyzed this fact [1,6–8].

The aims of the present study were, therefore, on the one hand, to analyze compliance with current VTE prophylaxis guidelines in non-surgical patients in an internal medicine department and, on the other hand, to describe the incidence of major and minor secondary effects with LMWH prophylaxis and to detect potential risk factors linked to them.

PATIENTS AND METHODS

The inclusion criteria were: hospitalized non-surgical patients with no active or previous oral anticoagulation or LMWH treatment (during the previous year). There was no restriction with regard to the cause of hospital admission. In all cases, physicians indicated VTE prophylaxis with no intervention from the study staff. Written informed consent was obtained from all patients and data collection was performed through a personal interview by trained staff and a review of their electronic medical history.

Age-adjusted Charlson's index (ACI) was used to assess the comorbidity degree of the patients included [9]. We also applied the Barthel's index (BI) to calculate functional status [10], the CONUT Score (CS) to detect and establish nutritional deficiencies [11] and the Pfeiffer's test (PT) to conduct a mental status evaluation of all the patients included [12].

In light of current recommendations, the PADOVA index was calculated in all cases to check the adherence of the clinical practice to guidelines [4]. VTE prophylaxis was considered as indicated with at least 4 points in PADOVA index [13]. The IMPROVE index was used to calculate bleeding risk, with patients with at least 7 points considered as high-risk patients [14].

Chronic kidney disease (CKD) was assessed in patients with decreased glomerular filtration rate (GFR) (<60 mL/min) for at least 3 months before admission, following current guidelines [15]. Acute kidney injury (AKI) was considered in patients with GFR < 60 mL/min at admission without previous diagnosis of CKD. Patients with previous CKD and worsening of GFR at admission were coded as CKD exacerbation (CKDE). GFR was calculated using the 2009 CKD-Epidemiology Collaboration (EPI) creatinine equation in all cases [16].

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3 All patients with a body mass index (BMI) over 30 kg/m² were considered
4 obese. For the main alterations in blood count, we applied World Health Association
5 (WHO) criteria for anemia and we classified all patients with values under 12,000/ μ L
6 at admission as having thrombocytopenia. We considered as elevated all cases of
7 coagulation test with an international normalized ratio (INR) over 1.2 or activated
8 partial thromboplastin time (APTT) over 35 seconds.
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16 The heparin types available in our center for the duration of the study were only
17 enoxaparin and tinzaparin, which are therefore the only heparins included in our
18 analysis.
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23 With regard to the analyzed complications, we defined them as follows:

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25 -Major bleeding: gastrointestinal or intracranial bleeding, hemoptysis, epistaxis or
26 hematuria with a decrease of at least 2 g/dL in hemoglobin level.
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30 -Minor bleeding: hemoptysis, epistaxis or hematuria without changes in hemoglobin
31 levels or with a decrease of less than 2 g/dL.
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35 -Platelet count decrease: loss of at least 50% compared with the baseline value.
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38 -Major hematoma: retroperitoneal or straight abdominal muscle locations were
39 considered as major hematoma in all cases. We also considered as major hematoma an
40 abdominal hematoma in other locations in which a loss of at least 2 points in
41 hemoglobin levels was implied.
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47 -Minor hematoma: abdominal wall hematoma (any location) with an extension of more
48 than 5 cm without hemoglobin loss or with a hemoglobin loss lower than 2 points. We
49 also considered as minor hematoma all abdominal wall hematomas of any extension,
50 which caused symptoms like pain or pruritus requiring specific treatment.
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3 -Pulmonary embolism (PE): we coded all cases diagnosed during the hospital stay that
4 were undiagnosed and unsuspected at admission.
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7 -Deep venous thrombosis (DVT): we considered all cases diagnosed during the hospital
8 stay that were undiagnosed and unsuspected at admission.
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12 A descriptive analysis was performed by calculating qualitative-variable rates
13 plus mean and standard deviation. We used the Chi-square test or Fisher's exact test, as
14 appropriate (expected frequency value <5), to compare qualitative variables, and the
15 Student's t test for quantitative variables. A multivariate logistic regression analysis was
16 conducted to identify factors associated with complications. A *P*-value <0.05 was
17 regarded as significant. All analyses were performed using the SPSS v. 22.0 software
18 package (SPSS Inc., Chicago, IL, USA).
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28 The protocol of the present study was reviewed and approved by the Clinical
29 Investigations Ethical Committee of Galicia.
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32 33 34 35 *Patient and Public Involvement*

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38 There was no patient or public involvement in the development of the study design,
39 protocol, recruitment or dissemination of results.
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45 RESULTS

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48 We included 396 consecutive inpatients who were given VTE prophylaxis during their
49 hospital stay. Regarding gender, 51.8% were women and the global mean age was 80.7
50 years (Standard Deviation [SD] = 11.5, Range = 22–107), 91% of patients were over 65
51 years old. Only 32 patients (8.1%) lived in nursing homes and the average scores of the
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different classification tools applied at admission were: ACI 5.5 (SD = 2.2) points, BI 55.5 (SD = 35.5) points, PT 3.3 (SD = 3) mistakes and CS 6.2 (SD = 2.6) points. CKD was present in 91 (23.2%) patients and diabetes mellitus in 111 (28.3%), as well as obesity in 111 patients (28.3%). Other remarkable comorbidities were active cancer (37 patients, 9.5%) and hematological diseases (9 patients, 2.5%) The complete baseline characteristics and frequencies of the main thrombosis risk factors are detailed in Table 1.

Table 1. Global baseline characteristics and analysis of differences regarding the type of LMWH used for VTE prophylaxis.

Variable	Global (396)	Tinzaparin (120)	Enoxaparin (276)	P
Male	191 (48)	57 (47.5)	134 (48.5)	0.848
Age	80.7 (11.6)	83 (9.6)	79.8 (12.2)	0.083
CKD	91 (23)	43 (36)	48 (17)	<0.001
Diabetes mellitus	112 (28)	38 (32)	74 (27)	0.324
Neoplasia	37 (9)	11 (9)	26 (9)	0.928
Obesity	113 (28.5)	30 (25)	83 (30)	0.342
Previous VTE	4 (1)	3 (2.5)	1 (0.4)	0.085
30-day surgery	5 (1)	1 (1)	4 (1.5)	0.521
Stroke	49 (12)	13 (11)	36 (13)	0.539
Autoimmune disease	17 (4)	2 (2)	15 (5.5)	0.089
Liver disease	24 (6)	8 (7)	16 (5.5)	0.739
Antiplatelet treatment	182 (46)	53 (44)	129 (47)	0.271
Infectious disease	316 (80)	92 (77)	224 (81)	0.306
Anemia	156 (39)	54 (45)	102 (37)	0.116
AKI	95 (24)	41 (34)	54 (19.5)	0.002
CKD exacerbation	79 (20)	39 (32.5)	40 (14.5)	<0.001
Heart failure	137 (34.5)	50 (42)	87 (31.5)	0.051
PADOVA > 4	342 (86)	112 (93)	230 (83)	0.001
IMPROVE > 7	24 (6)	9 (7.5)	15 (5.5)	0.387
BARTHEL < 20	56 (14)	21 (17.5)	35 (13)	0.218
PFEIFFER > 5	154 (39)	51 (42.5)	103 (37)	0.257

Data are showed as n (%) or mean (SD). CKD: chronic kidney disease. VTE: venous thromboembolism. AKI: acute kidney injury.

After the application of the PADOVA index, we found that VTE prophylaxis was correctly indicated in 88.4% of patients following these criteria, which means that VTE prophylaxis was prescribed in 46 low-risk patients. In the case of the IMPROVE

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3 index, we found that 6.3% of patients had a high theoretical bleeding risk, which should
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5 advise against VTE prophylaxis prescription. There were 22 patients (5.7%) who
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7 fulfilled both PADOVA and IMPROVE criteria, which means concomitant high risk of
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9 VTE and bleeding. We only found 2 patients (0.5%) with fewer than 4 points in the
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11 PADOVA index and high bleeding risk in the IMPROVE index.
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14 Regarding their general condition at admission, 316 (79.8%) patients presented
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16 with an infection, 155 (39.1%) had anemia, 137 (34.6%) had an acute heart failure, 95
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18 (24%) met AKI criteria and 79 (19.9) met CKDE criteria. In platelet count and
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20 coagulation tests, 93 (23.5%) patients had elevated coagulation tests at admission and
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22 27 (6.8%) had thrombocytopenia.
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25 With regard to VTE prophylaxis, the most used LMWH was enoxaparin (69.7%
26
27 of cases) followed by tinzaparin (30.3%) and the mean duration was 12 (SD = 11.8)
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29 days. The most commonly used treatment regimens were 4000 International Units (IU)
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31 daily for enoxaparin (219 patients) and 3500 IU daily for tinzaparin (103 patients). The
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33 dose adjustment in patients with CKD, CKDE or AKI was correct in all cases. We did
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35 not register any episode of VTE during the study period.
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39 With regard to complications, we found 2 patients (0.5%) who presented with
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41 major bleeding, 17 (4.3%) with a minor bleeding episode, 30 (7.6%) developed a
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43 platelet count decrease, 29 (7.3%) had a major hematoma (9 located in straight
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45 abdominal muscles and 20 in other abdominal locations) and 82 (20.7%) had a minor
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47 hematoma. All patients who developed complications were managed through
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49 conservative treatment and the course was favorable in all cases. After the univariate
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51 analysis, we found an association between minor bleeding and the presence of anemia at
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53 admission and AKI. In the case of major hematomas, this analysis showed significant
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55 differences in patients with obesity, concomitant antiplatelet treatment, an infection or
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3 heart failure as main cause of admission and the use of enoxaparin. With regard to
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5 minor hematomas, we found an association with diabetes and a PADOVA index lower
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7 than 4 points. Finally, a platelet count decrease was only linked to an infection as the
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9 cause of admission and it was not associated with the other analyzed complications.

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12 After multivariable analysis, none of the variables showed an association with
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14 minor bleeding or platelet count decrease. The presence of major hematomas was linked
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16 to obesity (OR = 4.1; IC 95% 1.8 – 9.2; $P = 0.001$), concomitant antiplatelet treatment
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18 (OR = 2.7; IC 95% 1.1 – 6.5; $P = 0.03$) and enoxaparin use (OR = 3.5; IC 95% 1.1 –
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20 10.9; $P = 0.029$) and the presence of minor hematomas was associated with the absence
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22 of indication of VTE prophylaxis following recommendations (PADOVA index < 4
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24 points) (OR = 3.1; IC 95% 1.5 – 6.4; $P = 0.003$) and the presence of Diabetes Mellitus
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26 (OR = 2; IC 95% 1.1 – 3.7; $P = 0.031$).

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29 In view of these results, we performed a sub-analysis to compare the clinical
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31 profile of patients who received enoxaparin and tinzaparin, which showed significant
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33 differences regarding renal function only, as shown in Table 1.
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39 DISCUSSION

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42 The present study shows, for the first time to our knowledge, an exhaustive analysis of
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44 clinically relevant complications and their main risk factors during VTE prophylaxis in
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46 non-surgical patients.
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49 The high degree of observed compliance with current guidelines in clinical
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51 practice is remarkable. There is, however, a narrow margin for improvement,
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53 particularly in the case of over-prescription in low-risk patients. Our study included
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55 only patients given VTE prophylaxis during hospital stay, which makes comparison
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3 with studies such as ENDORSE or AVAIL ME difficult because they showed lower
4 percentages of correct application of recommendations, even as low as below 50%
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6 [17,18].
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10 Another relevant difference of our study is that it is exclusively confined to
11 medical patients, as well as the extremely high age and degree of comorbidity of our
12 cohort, compared with larger series in which patients with a mean age more than 10
13 years younger and very low rates of multiple comorbidity were included [19,20].
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18 The absence of VTE cases in our study reflects a high efficacy of VTE
19 prophylaxis in medical patients, which has been studied extensively and supported by
20 high-quality evidence [21,22].
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25 With respect to complications, we analyzed minor complications such as
26 hematomas that are usually undervalued by physicians, but are important for patients.
27 Indeed, we consider that our results could help physicians to improve their daily clinical
28 practice and the patient's experience during a hospital admission by adding tools to
29 detect patients at risk of developing these complications.
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34 Bleeding episodes were infrequent, but the association between anemia and
35 minor bleeding could reflect the existence of previous digestive tract bleeding,
36 increased during admission by LMWH. The association with AKI could be explained
37 by a heparin over-effect in these patients, although we did not detect significant rates of
38 unadjusted dosage in our cohort. In fact, an increased bleeding risk was one of the main
39 risk factors considered on the IMPROVE score, although anemia was not a useful
40 marker of bleeding risk in that study [14]. Thus, our results could contribute to
41 expanding the tools available to identify patients with high bleeding risk before
42 prescribing VTE prophylaxis.
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3 In the case of major hematomas, we must underscore the relatively high
4 percentage of patients who developed these complications. Despite the clinical
5 relevance of abdominal and retroperitoneal hematomas, these complications were not
6 analyzed in any cohort study, and thus we can only compare our results with case
7 reports [14,18,23,24]. In this sense, previous reports suggested an estimated incidence
8 of 5% for abdominal hematomas in patients receiving VTE prophylaxis, which could be
9 comparable to our results [25]. With regard to risk factors, previous studies showed that
10 elderly patients had a higher risk of abdominal hematomas [23,25,26]; we did detect
11 such an association, probably because of the small number of patients aged less than 65
12 years. Concomitant antiplatelet treatment has been identified as a risk factor linked to
13 hematomas by other authors because of its synergic action with LMWH, and our
14 findings reinforce the importance of assessing the need to maintain these drugs during
15 hospital admission in elderly patients [23,25,26]. Obesity has also been described as a
16 risk factor in previous studies [25,27], and this relationship could be due to an adipose
17 tissue dysfunction in obese patients, linked to an abnormal subcutaneous vascularization
18 and extracellular matrix changes [28–30]. These alterations lead to a higher risk of local
19 hematomas in obese patients under VTE prophylaxis, independently of the plasmatic
20 levels of LMWH achieved [26].
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42 As to the different types of LMWH used in our study, we found a lower risk of
43 major hematomas with tinzaparin as the only significant difference. Interestingly, the
44 characteristics of patients treated with both LWMHs were different with regard to renal
45 function, so the use of tinzaparin in patients with poorer renal function could have
46 alerted physicians to the need for better dose adjustment. Thus, this could be considered
47 as a potential selection bias that should be taken into account in the interpretation of our
48 results. Despite this, a potential superior safety profile in elderly patients with high
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3 comorbidity emerges and even differences in device, needles and mode of
4 administration should be considered. Further studies will be necessary to properly
5 establish this difference.
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10 With regard to minor hematomas, it is remarkable that this complication is not
11 usually considered clinically relevant. However, we decided to include it because we
12 considered it to be highly relevant for our patients. The association with a PADOVA
13 index lower than 4 points cannot be considered as a risk factor itself, but it helps us to
14 highlight the importance of correct application of VTE prophylaxis guidelines. Diabetes
15 mellitus has not been previously described as a risk factor for abdominal hematoma
16 development but microvascular diabetic complications might underlie this association
17 [25].
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28 Despite the high percentage of patients with variations in coagulation tests
29 (23.5%), we found no association between these variations and the related
30 complications. This could be due to the little relevance of most variations in coagulation
31 tests, consisting of small increments of INR or APTT.
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37 In light of our results, we think that the presence of any risk factor for the
38 development of major or minor complications linked to VTE prophylaxis should lead
39 physicians to careful consideration of the indication, dosage and time of treatment
40 before VTE prophylaxis is prescribed, particularly in elderly patients.
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48 CONCLUSIONS

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51 The incidence of complications developing during VTE prophylaxis in elderly
52 hospitalized medical patients is higher than that expected in other populations even
53 when the current guidelines are correctly applied. The main factors linked to hematomas
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3 in our cohort were obesity and concomitant antiplatelet treatment, the presence of which
4 should lead physicians to exercise extreme caution. The safety profile of tinzaparin for
5 VTE prophylaxis in these patients could be improved.
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14 -Study concept and design: Drs. Antonio Pose-Reino, Ignacio Novo-Veleiro and Lucía
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17 -Acquisition of subjects and/or data: Drs. Ignacio Novo-Veleiro, Lucía Alvela-Suárez
18 and Alba Costa-Grille.
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20 -Analysis and interpretation of data: Drs. Ignacio Novo-Veleiro, Javier Suárez-Dono,
21 Fernando Ferrón-Vidán and Antonio Pose-Reino.
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23 -Preparation of manuscript: Drs. Ignacio Novo-Veleiro, Lucía Alvela-Suárez and
24 Antonio Pose-Reino.
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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-7
		(b) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	5-7
Study size	10	Explain how the study size was arrived at	5-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6-7
		(b) Describe any methods used to examine subgroups and interactions	6-7
		(c) Explain how missing data were addressed	6-7
		(d) If applicable, explain how loss to follow-up was addressed	-
		(e) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	-
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-9
		(b) Indicate number of participants with missing data for each variable of interest	7-9
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-9
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(b) Report category boundaries when continuous variables were categorized	7-9
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	-

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.