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

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ABSTRACT:

Objectives: the main objectives were to evaluate the grade of fulfillment of current guidelines regarding venous thromboembolism (VTE) prophylaxis in medical patients during admission and to identify risk factors linked to complications of this prophylaxis.

Design: we conducted a prospective cohort study.

Setting: Internal Medicine Department of the University Hospital of Santiago de Compostela (third level institution).

Participants: we included 396 hospitalized non-surgical patients with no active or previous oral anticoagulation or low molecular weight heparin (LMWH) treatment (during the previous year) and who received VTE prophylaxis during admission.

Primary and secondary outcome measures: the grade of fulfilment of current guidelines was estimated by calculating PADOVA and IMPROVE index in all cases. We analysed the development of the following complications: major and minor bleeding, major and minor hematoma and decrease of platelet count.

Results: we found that VTE prophylaxis was correctly indicated in 88.4% of patients. We found 2 (0.5%) major bleeding, 17 (4.3%) minor bleeding, 30 (7.6%) platelet count decrease, 29 (7.3%) major hematoma and 82 (20.7%) minor hematoma. The presence of major hematomas was linked to obesity (OR=4.1; IC 95% 1.8–9.2; P = 0.001), concomitant antiplatelet treatment (OR=2.7; IC 95% 1.1–6.5; P = 0.03) and enoxaparin use (OR=3.5; IC 95% 1.1–10.9; P = 0.029) and the presence of minor hematomas was associated with PADOVA index < 4 points (OR=3.1; IC 95% 1.5–6.4; P = 0.003) and Diabetes Mellitus (OR=2; IC 95% 1.1–3.7; P = 0.031).

Conclusions: complications during VTE prophylaxis in elderly hospitalized medical patients are frequent despite a correct application of current guidelines. The main factors linked to hematomas were obesity and concomitant antiplatelet treatment and its presence should advise physicians to extreme precautions. The use of tinzaparin for VTE prophylaxis in these patients could have a better security profile.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

Strengths:

-Clinical study in elderly patients, usually excluded from large studies.

-Analysis of the fulfilment of current guidelines in VTE prophylaxis in real-life conditions.

-Detection of minor complications and risk factors usually undervalued in previous studies.

Limitations:

-Observational study, which did not allow a correct homogenization of subgroups.

-The study was developed in only one department of a single hospital.

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COMPETING INTERESTS STATEMENT: all authors declare no competing interests.

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].

Regarding obesity, it was considered in all patients with a Body Mass Index (BMI) over 30 kg/m^2 and for the main alterations in blood count we applied World Health Association (WHO) criteria for anemia and we coded as thrombocytopenia at admission all patients with values under 120000/µL. Concerning coagulation tests alterations we considered them in all cases with an International Normalized Ratio (INR) over 1.2 or Activated Partial Thromboplastin Time (APTT) over 35 seconds.

The available heparin types in our center during the study period were only enoxaparin and tinzaparin, so they are the only included heparins in our analysis.

In the case of the analysed complications, we defined them as follows:

-Major bleeding: gastrointestinal or intracranial bleeding, haemoptysis, epistaxis or haematuria with a decrease of at least 2 g/dL in haemoglobin level.

-Minor bleeding: haemoptysis, epistaxis or haematuria without analytical impact or with a decrease of less than 2 g/dL.

-Platelet count decrease: loss of at least 50% compared to the baseline value.

-Major hematoma: retroperitoneal or straight abdominal muscles locations were considered as major hematoma in all cases. We also considered as major hematoma an abdominal hematoma in other locations which implied a loss of at least 2 points in hemoglobin levels.

-Minor hematoma: abdominal wall hematoma (any location) with an extension of more than 5 cm without hemoglobin loss or with a hemoglobin loss lower than 2 points. We also considered as minor hematoma all abdominal wall hematomas of any extension which caused symptoms like pain or pruritus which required specific treatment.

-Pulmonary embolism (PE) we coded all cases diagnosed during hospital stay which were undiagnosed an unsuspected at admission.

-Deep venous thrombosis (DVT): we considered all cases diagnosed during hospital stay which were undiagnosed an unsuspected at admission.

A descriptive analysis was performed, by calculating qualitative-variable rates plus mean and standard deviation. We used the Chi-square test or Fisher's exact test, as appropriate (expected frequency value <5), to compare qualitative variables, and the Student's t test for quantitative variables. A multivariate logistic regression analysis was conducted to identify factors associated with complications. A *P*-value <0.05 was regarded as significant. All analyses were performed using the SPSS v. 22.0 software package (SPSS Inc., Chicago, IL, USA).

RESULTS:

We included 396 consecutive inpatients that were given VTE prophylaxis during their hospital stay, of them, 51.8% were women and the mean age was 80.7 (Standard Deviation [SD] = 11.5) years old. Only 32 patients (8.1%) lived in nursing homes and the average 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.

After the application of PADOVA index, we found that VTE prophylaxis was correctly indicated in 88.4% of patients, following these criteria. In the case of IMPROVE index, we found that 6.3% of patients had a high theoretical bleeding risk which should advise against VTE prophylaxis prescription. It is also remarkable that 22 patients (5.7%) achieved both PADOVA and IMPROVE criteria, which means concomitant high VTE and bleeding risk. We only found 2 patients (0.5%) with less than 4 points in PADOVA index and high bleeding risk in IMPROVE index.

Regarding general condition at admission, 316 (79.8%) patients presented an infection, 155 (39.1%) had anemia, 137 (34.6%) had an acute heart failure, 95 (24%) met AKI criteria and 79 (19.9) met CKDE criteria. If we focus on platelet count and coagulation tests, 93 (23.5%) patients had an alteration on coagulation tests at admission and 27 (6.8%) thrombocytopenia.

Considering the VTE prophylaxis, the most used LMWH was enoxaparin (69.7% of cases) followed by tinzaparin (30.3%) and the mean duration of it was 12 (Standard Deviation [SD] = 11.8) days. The most commonly used treatment regimens were 4000 International Units (IU) daily for enoxaparin (219 patients) and 3500 IU daily for tinzaparin (103 patients). We did not register any episode of VTE during the study period.

With regard to complications we found 2 patients (0.5%) who presented major bleeding, 17 (4.3%) a minor bleeding episode, 30 (7.6%) developed a platelet count decrease, 29 (7.3%) had a major hematoma and 82 (20.7%) a minor hematoma. All patients who developed complications were managed through conservative treatment and the evolution was favourable in all cases. After the univariate analysis, we found an association between minor bleeding and the presence of anemia at admission and AKI. In the case of major hematomas, this analysis showed significant differences in patients

with obesity, concomitant antiplatelet treatment, an infection or heart failure as main cause of admission and the use of enoxaparin. With regard to minor hematomas, we found an association with diabetes and a PADOVA index lower than 4 points. Finally, a platelet count decrease was only linked to an infection as cause of admission.

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

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

DISCUSSION:

The present study shows, for the first time to our knowledge, an exhaustive analysis of clinically relevant complications during VTE prophylaxis and the main risk factors linked to them.

If we focus on the adaptation of the clinical practice to current guidelines, it is remarkable the high grade of adaptation observed, despite the existence of a narrow margin for improvement. Our study included only patients with VTE prophylaxis during hospital stay, which makes difficult the comparison with studies like ENDORSE

or AVAIL ME, which showed lower percentages of correct application of recommendations, even under 50% [17,18].

Another relevant difference of our study is the exclusive inclusion of medical patients and the extremely high age and grade of comorbidity of our cohort, compared with larger series, which included patients with a mean age more than 10 years lower and very low rates of multiple comorbidity [19,20].

The absence of VTE cases in our study reflects a high efficacy of VTE prophylaxis in medical patients, which has been largely studied and supported by high-quality evidence [21,22].

Regarding complications, it is remarkable that we have analyzed minor complications, like hematomas, that usually are undervalued by physicians, but have an important relevance for patients. Thus, we consider that our results could help physicians to improve their daily clinical practice and the patient´s experience during a hospital admission.

If we focus on bleeding episodes, they were infrequent, but the association between anemia and minor bleeding could reflect the existence of previous digestive bleeding, increased during admission by LMWH, and the association with AKI could be due to a heparin over effect in these patients, although we did not detect significant rates of unadjusted dosage in our cohort. In fact, an increased bleeding risk was one of the main risk factors considered on IMPROVE score, although anemia was not a useful marker of bleeding risk in that study [14]. Thus, our results could contribute to expand the available tools to identify patients with high bleeding risk before prescribing VTE prophylaxis.

In the case of major hematomas, we must highlight the relative high percentage of patients who developed these complications. Despite the clinical relevance of abdominal and retroperitoneal hematomas, large series did not analyze these complications and we only can compare our results with small series and case reports [14,18,23,24]. In this sense, previous reports suggested an estimated incidence of 5% for abdominal hematomas in patients receiving VTE prophylaxis, which could be comparable to ours [25]. With regard to risk factors, previous studies showed that elderly patients had a higher risk of abdominal hematomas [23,25,26]; we did not identify this association, probably due to the absence of patients with ages lower than 65 years old. Concomitant antiplatelet treatment has been identify as a risk factors linked to hematomas by other authors, due to the synergic action with LMWH [23,25,26]. Obesity has also been described as a risk factor in previous studies [25,27], and this relationship could be due to an adipose tissue dysfunction in obese patients, linked to an abnormal subcutaneous vascularization and extracellular matrix changes [28–30]. These alterations lead to a higher risk of local hematomas in obese patients under VTE prophylaxis, independently of the plasmatic levels of HBPM achieved [26].

If we focus on the different HBPM used in our study we found a lower risk of major hematomas with tinzaparin as the only significant difference. It is remarkable that the characteristics of patients treated with both of them were different regarding renal function, so the use of tinzaparin in patients with poorer renal function could have alert physicians to a better dose adjustment. Thus, it could be considered as a potential selection bias which should be taken into account during the interpretation of our results. Despite this, a potential superior security profile in elderly patients with high comorbidity emerges and even differences in device, needles and mode of

administration should be considered. Further studies will be necessary to properly establish this difference.

If we focus on minor hematomas, it is remarkable that is a complication usually not considered as clinically relevant; despite this, we decided to include it due to the perception that it is completely relevant for our patients. In this sense, the association with a PADOVA index lower than 4 points cannot be considered as a risk factor itself but helps us to highlight the importance of a correct application of VTE prophylaxis guidelines. In the case of Diabetes Mellitus, it has not been previously described as a risk factor for abdominal hematomas development but microvascular diabetic complications might underlie this association [25].

CONCLUSIONS:

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

AUTHOR´S CONTRIBUTIONS:

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

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

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

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

DATA SHARING STATEMENT: Technical appendix, statistical code, and dataset will be available from the Dryad repository if required.

REFERENCES

1 Nieto Rodríguez JA, ENDORSE. [Venous thromboembolism risk and antithrombotic prophylaxis among patients admitted to Spanish hospitals (ENDORSE study)]. *Med Clin (Barc)* 2009;**133**:1–7. doi:10.1016/j.medcli.2009.01.040

2 Gould MK, Garcia DA, Wren SM, *et al.* Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e227S–e277S. doi:10.1378/chest.11-2297

3 Falck-Ytter Y, Francis CW, Johanson NA, *et al.* Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e278S–e325S. doi:10.1378/chest.11-2404

4 Kahn SR, Lim W, Dunn AS, *et al.* Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e195S–e226S. doi:10.1378/chest.11-2296

5 Decousus H, Tapson VF, Bergmann J-F, *et al.* Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. *Chest* 2011;**139**:69–79. doi:10.1378/chest.09-3081

6 Ruiz-Artacho P, Pérez Peña C, Iriarte A, *et al.* [Adequation of thromboprophylaxis during former admission in patients attended in emergencies with thromboembolic disease]. *Med Clin (Barc)* 2013;**141**:130–1. doi:10.1016/j.medcli.2012.12.014

7 Gallardo Jiménez P, Guijarro Merino R, Vallejo Herrera V, *et al.* [Assessment of venous thromboembolism risk in hospitalized medical patients. Concordance between PRETEMED guide and the recommendations of the viii conference of the American College of Chest Physicians]. *Med Clin (Barc)* 2012;**139**:467–72. doi:10.1016/j.medcli.2011.07.022

8 Borobia AM, Fernández Capitán C, Iniesta Arandia N, *et al.* [Risk of thromboembolic events and evaluation of the use of venous thromboembolism prophylaxis in hospitalized medical patients and after discharge]. *Rev Clin Esp* 2009;**209**:15–20.

9 Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373–83.

10 Mahoney FI, Barthel DW. FUNCTIONAL EVALUATION: THE BARTHEL INDEX. *Md State Med J* 1965;**14**:61–5.

11 Ignacio de Ulíbarri J, González-Madroño A, de Villar NGP, *et al.* CONUT: a tool for controlling nutritional status. First validation in a hospital population. *Nutr Hosp* 2005;**20**:38–45.

12 Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc* 1975;**23**:433–41.

13 Barbar S, Noventa F, Rossetto V, *et al.* A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost JTH* 2010;**8**:2450–7. doi:10.1111/j.1538-7836.2010.04044.x

14 Hostler DC, Marx ES, Moores LK, *et al.* Validation of the International Medical Prevention Registry on Venous Thromboembolism Bleeding Risk Score. *Chest* 2016;**149**:372–9. doi:10.1378/chest.14-2842

15 National Guideline Clearinghouse (NGC). Guideline summary: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. In: National Guideline Clearinghouse (NGC) [Web site]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2013 Jan 01. [cited 2017 Jun 29]. Available: https://www.guideline.gov.

16 Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12.

17 Taher AT, Aoun J, Salameh P. The AVAIL ME study: a multinational survey of VTE risk and prophylaxis. *J Thromb Thrombolysis* 2011;**31**:47–56. doi:10.1007/s11239-010-0492-2

18 Cohen AT, Tapson VF, Bergmann J-F, *et al.* Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet Lond Engl* 2008;**371**:387–94. doi:10.1016/S0140-6736(08)60202-0

19 Nieto JA, Cámara T, Camacho I, *et al.* Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients. A retrospective multicenter study. *Eur J Intern Med* 2014;**25**:717–23. doi:10.1016/j.ejim.2014.07.005

20 Tapson VF, Decousus H, Pini M, *et al.* Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. *Chest* 2007;**132**:936–45. doi:10.1378/chest.06-2993

21 Francis CW. Clinical practice. Prophylaxis for thromboembolism in hospitalized medical patients. *N Engl J Med* 2007;**356**:1438–44. doi:10.1056/NEJMcp067264

22 Dentali F, Douketis JD, Gianni M, *et al.* Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. *Ann Intern Med* 2007;**146**:278–88.

23 Triscott J, Mercer S, Tian PGJ, *et al.* Retroperitoneal haematoma associated with enoxaparin use in an elderly woman with chronic kidney disease. *BMJ Case Rep* 2015. doi:10.1136/bcr-2015-211699

24 Madridano O, Martín Del Pozo M, Masso P, *et al.* [Hematoma of the rectus abdominis muscle in patients treated with low-molecular-weight heparin: four clinical cases]. *Rev Clin Esp* 2011;**211**:109–10. doi:10.1016/j.rce.2010.09.007

25 Nourbakhsh E, Anvari R, Nugent K. Abdominal wall hematomas associated with low-molecular-weight heparins: an important complication in older adults. *J Am Geriatr Soc* 2011;**59**:1543–5. doi:10.1111/j.1532-5415.2011.03529.x

26 Macías-Robles MD, Peliz MG, Gonzalez-Ordonez AJ. Prophylaxis with enoxaparin can produce a giant abdominal wall haematoma when associated with low doses of aspirin among elderly patients suffering cough attacks. *Blood Coagul Fibrinolysis Int J Haemost Thromb* 2005;**16**:217–9.

27 Goldstein JM, Sebire D. Abdominal wall haematoma in the obese: a dangerous phenomenon. *J Surg Case Rep* 2013;**2013**. doi:10.1093/jscr/rjt060

28 Blüher M. Adipose tissue dysfunction in obesity. *Exp Clin Endocrinol Diabetes Off J Ger Soc Endocrinol Ger Diabetes Assoc* 2009;**117**:241–50. doi:10.1055/s-0029-1192044

29 Baptista LS, da Silva KR, da Pedrosa CSG, *et al.* Adipose tissue of control and ex-obese patients exhibit differences in blood vessel content and resident mesenchymal stem cell population. *Obes Surg* 2009;**19**:1304–12. doi:10.1007/s11695-009-9899-2

30 Spencer M, Unal R, Zhu B, *et al.* Adipose tissue extracellular matrix and vascular abnormalities in obesity and insulin resistance. *J Clin Endocrinol Metab* 2011;**96**:E1990–1998. doi:10.1210/jc.2011-1567

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.

December 20th 2017

Dear Editor:

Enclosed please find our paper entitled "Fulfilment of current VTE prophylaxis guidelines and risk factors linked to complications of VTE prophylaxis in medical patients". Considering that our work is the first one to analyse the main risk factors of VTE in medical elderly patients, we believe that our results are of great interest in this field of research. Thus we hope you could accept our work as a candidate for publication in your journal.

The submitted manuscript has been read and approved by all authors. Besides, all authors acknowledge that they have exercised due care in ensuring the integrity of the work. The study protocol was revised and approved by the Ethics Committee of the University Hospital of Santiago de Compostela and it conforms to the provision of the Declaration of Helsinki. All participants gave informed consent and anonymity was preserved in all the stages of the study. Finally, none of the original material contained in the manuscript has been submitted for consideration nor will any of it be published elsewhere except in abstract form in connection with scientific meetings.

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.

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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.

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Title: 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.

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ABSTRACT:

Objectives: the main objectives were to evaluate the degree of compliance with current guidelines regarding venous thromboembolism (VTE) prophylaxis in medical patients during admission and to identify risk factors linked to complications of this prophylaxis.

Design: a prospective cohort study was conducted.

Setting: Internal Medicine Department of the University Hospital of Santiago de Compostela (tertiary referral hospital).

Participants: 396 hospitalized, non-surgical elderly patients with no active or previous oral anticoagulation or low molecular weight heparin (LMWH) treatment (during the previous year) and who received VTE prophylaxis during admission.

Primary and secondary outcome measures: the degree of compliance with the current guidelines was estimated by calculating PADOVA and IMPROVE indexes in all cases. We analysed the development of the following complications: major and minor bleeding, major and minor hematoma and decrease of platelet count.

Results: we found that VTE prophylaxis was correctly indicated in 88.4% of patients. We found 2 (0.5%) major bleeding, 17 (4.3%) minor bleeding, 30 (7.6%) platelet count decrease, 29 (7.3%) major hematoma and 82 (20.7%) minor hematoma. After a multivariate logistic regression analysis, the presence of major hematomas was linked to obesity (OR=4.1; IC 95% 1.8–9.2; P = 0.001), concomitant antiplatelet treatment (OR=2.7; IC 95% 1.1–6.5; P = 0.03) and enoxaparin use (OR=3.5; IC 95% 1.1–10.9; P = 0.029) and the presence of minor hematomas was associated with PADOVA index < 4 points (OR=3.1; IC 95% 1.5–6.4; P = 0.003) and Diabetes Mellitus (OR=2; IC 95% 1.1–3.7; P = 0.031).

Conclusions: complications during VTE prophylaxis in elderly hospitalized medical patients are frequent despite a correct application of current guidelines. The main factors linked to hematomas were obesity and concomitant antiplatelet treatment and their presence should lead physicians to exercise extreme caution. The use of tinzaparin for VTE prophylaxis in these patients could have a better safety profile.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

Strengths:

-Clinical study in elderly patients, who are usually excluded from large studies.

-Analysis of compliance with current guidelines in VTE prophylaxis in real-life conditions.

-Detection of minor complications and risk factors that have usually been underestimated in previous studies.

Limitations:

-Observational study conducted in only one department of a single hospital, which did not allow for a correct homogenization of subgroups.

-The inclusion of patients with VTE prophylaxis only could be a selection bias.

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COMPETING INTERESTS STATEMENT: all authors declare that they have no competing interests.

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].

As to obesity, it was considered in all patients with a Body Mass Index (BMI) over 30 kg/m^2 .For the main alterations in blood count we applied World Health Association (WHO) criteria for anemia and we coded as thrombocytopenia at admission all patients with values under 120000/μL. As to coagulation tests alterations, we considered them in all cases with an International Normalized Ratio (INR) over 1.2 or Activated Partial Thromboplastin Time (APTT) over 35 seconds.

The heparin types available in our center for the duration of the study were only enoxaparin and tinzaparin. They are therefore the only heparins included in our analysis.

With regard to the analysed complications, we defined them as follows:

-Major bleeding: gastrointestinal or intracranial bleeding, haemoptysis, epistaxis or haematuria with a decrease of at least 2 g/dL in haemoglobin level.

-Minor bleeding: haemoptysis, epistaxis or haematuria without analytical impact or with a decrease of less than 2 g/dL.

-Platelet count decrease: loss of at least 50% compared to the baseline value.

-Major hematoma: retroperitoneal or straight abdominal muscles locations were considered as major hematoma in all cases. We also considered as major hematoma an abdominal hematoma in other locations which implied a loss of at least 2 points in hemoglobin levels.

-Minor hematoma: abdominal wall hematoma (any location) with an extension of more than 5 cm without hemoglobin loss or with a hemoglobin loss lower than 2 points. We also considered as minor hematoma all abdominal wall hematomas of any extension, which caused symptoms like pain or pruritus requiring specific treatment.

-Pulmonary embolism (PE): we coded all cases diagnosed during hospital stay which were undiagnosed and unsuspected at admission.

-Deep venous thrombosis (DVT): we considered all cases diagnosed during hospital stay which were undiagnosed and unsuspected at admission.

A descriptive analysis was performed by calculating qualitative-variable rates plus mean and standard deviation. We used the Chi-square test or Fisher's exact test, as appropriate (expected frequency value <5), to compare qualitative variables, and the Student's t test for quantitative variables. A multivariate logistic regression analysis was conducted to identify factors associated with complications. A *P*-value <0.05 was regarded as significant. All analyses were performed using the SPSS v. 22.0 software package (SPSS Inc., Chicago, IL, USA).

The protocol of the present study was reviewed and approved by the Clinical Investigations Ethical Committee of Galicia.

Patient and Public Involvement

There were no patient or public involvement in the development of the study design, protocol, recruitment or dissemination of results.

RESULTS:

We included 396 consecutive inpatients that were given VTE prophylaxis during their hospital stay. Of them, 51.8% were women and the mean age was 80.7 years (Standard Deviation [SD] = 11.5, Range = 22 - 107). Only 32 patients (8.1%) lived in nursing homes and the average 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 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
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 index, we found that 6.3% of patients had a high theoretical bleeding risk, which should

advise against VTE prophylaxis prescription. 22 patients (5.7%) fulfilled both PADOVA and IMPROVE criteria, which means concomitant high VTE and bleeding risk. We only found 2 patients (0.5%) with less than 4 points in the PADOVA index and high bleeding risk in the IMPROVE index.

Regarding their general condition at admission, 316 (79.8%) patients presented with an infection, 155 (39.1%) had anaemia, 137 (34.6%) had an acute heart failure, 95 (24%) met AKI criteria and 79 (19.9) met CKDE criteria. As to platelet count and coagulation tests, 93 (23.5%) patients had an alteration on coagulation tests at admission and 27 (6.8%) thrombocytopenia.

Considering the VTE prophylaxis, the most used LMWH was enoxaparin (69.7% of cases) followed by tinzaparin (30.3%) and the mean duration was 12 (SD = 11.8) days. The most commonly used treatment regimens were 4000 International Units (IU) daily for enoxaparin (219 patients) and 3500 IU daily for tinzaparin (103 patients). The dose adjustment in patients with CKD, CKDE or AKI was correct in all cases. We did not register any episode of VTE during the study period.

With regard to complications, we found 2 patients (0.5%) who presented with major bleeding, 17 (4.3%) with a minor bleeding episode, 30 (7.6%) developed a platelet count decrease, 29 (7.3%) had a major hematoma (9 located in straight abdominal muscles and 20 in other abdominal locations) and 82 (20.7%) a minor hematoma. All patients who developed complications were managed through conservative treatment and the course was favourable in all cases. After the univariate analysis, we found an association between minor bleeding and the presence of anaemia at admission and AKI. In the case of major hematomas, this analysis showed significant differences in patients with obesity, concomitant antiplatelet treatment, an infection or heart failure as main cause of admission and the use of enoxaparin. With regard to

minor hematomas, we found an association with diabetes and a PADOVA index lower than 4 points. Finally, a platelet count decrease was only linked to an infection as the cause of admission and it was not associated with the other analysed complications.

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

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

DISCUSSION:

The present study shows, for the first time to our knowledge, an exhaustive analysis of clinically relevant complications during VTE prophylaxis in non-surgical patients and the main risk factors linked to them.

As to the adaptation of the clinical practice to current guidelines, the high degree of adaptation observed is remarkable. There is, however, a narrow margin for improvement, particularly in the case of over-prescription in low-risk patients. Our study included only patients with VTE prophylaxis during hospital stay, which makes the comparison with studies like ENDORSE or AVAIL ME difficult as they showed

lower percentages of correct application of recommendations, even as low as below 50% [17,18].

Another relevant difference of our study is that it is exclusively confined to medical patients as well as the extremely high age and degree of comorbidity of our cohort, compared with larger series where patients with a mean age more than 10 years lower and very low rates of multiple comorbidity [19,20] were included.

The absence of VTE cases in our study reflects a high efficacy of VTE prophylaxis in medical patients, which has been largely studied and supported by high-quality evidence [21,22].

With respect to complications, we analyzed minor complications, like hematomas, that are usually undervalued by physicians, but for patients are important. Indeed, we consider that our results could help physicians to improve their daily clinical practice and the patient´s experience during a hospital admission.

As far as bleeding episodes are concerned, they were infrequent. But the association between anemia and minor bleeding could reflect the existence of previous digestive bleeding, increased during admission by LMWH, and the association with AKI could be explained by a heparin over-effect in these patients, although we did not detect significant rates of unadjusted dosage in our cohort. In fact, an increased bleeding risk was one of the main risk factors considered on the IMPROVE score, although anemia was not a useful marker of bleeding risk in that study [14]. Thus, our results could contribute to expand the tools available to identify patients with high bleeding risk before prescribing VTE prophylaxis.

In the case of major hematomas, we must underscore the relatively high percentage of patients who developed these complications. Despite the clinical

relevance of abdominal and retroperitoneal hematomas, large series did not analyze these complications and we can only compare our results with small series and case reports [14,18,23,24]. In this sense, previous reports suggested an estimated incidence of 5% for abdominal hematomas in patients receiving VTE prophylaxis, which could be comparable to ours [25]. With regard to risk factors, previous studies showed that elderly patients had a higher risk of abdominal hematomas [23,25,26]; we did not identify this association, probably because of the little number of patients aged below 65 years. Concomitant antiplatelet treatment has been identified as a risk factor linked to hematomas by other authors, due to the synergic action with LMWH, and our findings reinforce the importance of assessing the need to maintain these drugs during hospital admission in elderly patients [23,25,26]. Obesity has also been described as a risk factor in previous studies [25,27], and this relationship could be due to an adipose tissue dysfunction in obese patients linked to an abnormal subcutaneous vascularization and extracellular matrix changes [28–30]. These alterations lead to a higher risk of local hematomas in obese patients under VTE prophylaxis, independently of the plasmatic levels of LMWH achieved [26].

As to the different LMWH used in our study, we found a lower risk of major hematomas with tinzaparin as the only significant difference. Interestingly, the characteristics of patients treated with both of them were different regarding renal function, so the use of tinzaparin in patients with poorer renal function could have alerted physicians to the need of better dose adjustment. Thus, it could be considered as a potential selection bias, which should be taken into account during the interpretation of our results. Despite this, a potential superior safety profile in elderly patients with high comorbidity emerges and even differences in device, needles and mode of

administration should be considered. Further studies will be necessary to properly establish this difference.

As to minor hematomas, it is remarkable that this complication is not usually considered as clinically relevant. However, we decided to include it as we considered that it is completely relevant for our patients. In this sense, the association with a PADOVA index lower than 4 points cannot be considered as a risk factor itself, but it helps us to highlight the importance of a correct application of VTE prophylaxis guidelines. In the case of Diabetes Mellitus, it has not been previously described as a risk factor for abdominal hematomas development but microvascular diabetic complications might underlie this association [25].

Despite the high percentage of patients with alterations in coagulation tests (23.5%), we found no association between these alterations and the related complications. This could be due to the little relevance of most of alterations in coagulation tests, consisting of small increments of INR or APTT.

CONCLUSIONS:

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

AUTHOR´S CONTRIBUTIONS:

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

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

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

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

DATA SHARING STATEMENT: Technical appendix, statistical code, and dataset will be available from the Dryad repository if required.

FUNDING STATEMENT: this research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS STATEMENT: all authors declare that they have no competing interests.

REFERENCES

1 Nieto Rodríguez JA, ENDORSE. [Venous thromboembolism risk and antithrombotic prophylaxis among patients admitted to Spanish hospitals (ENDORSE study)]. *Med Clin (Barc)* 2009;**133**:1–7. doi:10.1016/j.medcli.2009.01.040

2 Gould MK, Garcia DA, Wren SM, *et al.* Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e227S–e277S. doi:10.1378/chest.11-2297

3 Falck-Ytter Y, Francis CW, Johanson NA, *et al.* Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e278S–e325S. doi:10.1378/chest.11-2404

4 Kahn SR, Lim W, Dunn AS, *et al.* Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e195S–e226S. doi:10.1378/chest.11-2296

5 Decousus H, Tapson VF, Bergmann J-F, *et al.* Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. *Chest* 2011;**139**:69–79. doi:10.1378/chest.09-3081

6 Ruiz-Artacho P, Pérez Peña C, Iriarte A, *et al.* [Adequation of thromboprophylaxis during former admission in patients attended in emergencies with thromboembolic disease]. *Med Clin (Barc)* 2013;**141**:130–1. doi:10.1016/j.medcli.2012.12.014

7 Gallardo Jiménez P, Guijarro Merino R, Vallejo Herrera V, *et al.* [Assessment of venous thromboembolism risk in hospitalized medical patients. Concordance between PRETEMED guide and the recommendations of the viii conference of the American College of Chest Physicians]. *Med Clin (Barc)* 2012;**139**:467–72. doi:10.1016/j.medcli.2011.07.022

8 Borobia AM, Fernández Capitán C, Iniesta Arandia N, *et al.* [Risk of thromboembolic events and evaluation of the use of venous thromboembolism prophylaxis in hospitalized medical patients and after discharge]. *Rev Clin Esp* 2009;**209**:15–20.

9 Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373–83.

10 Mahoney FI, Barthel DW. FUNCTIONAL EVALUATION: THE BARTHEL INDEX. *Md State Med J* 1965;**14**:61–5.

11 Ignacio de Ulíbarri J, González-Madroño A, de Villar NGP, *et al.* CONUT: a tool for controlling nutritional status. First validation in a hospital population. *Nutr Hosp* 2005;**20**:38–45.

12 Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc* 1975;**23**:433–41.

13 Barbar S, Noventa F, Rossetto V, *et al.* A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost JTH* 2010;**8**:2450–7. doi:10.1111/j.1538-7836.2010.04044.x

14 Hostler DC, Marx ES, Moores LK, *et al.* Validation of the International Medical Prevention Registry on Venous Thromboembolism Bleeding Risk Score. *Chest* 2016;**149**:372–9. doi:10.1378/chest.14-2842

15 National Guideline Clearinghouse (NGC). Guideline summary: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. In: National Guideline Clearinghouse (NGC) [Web site]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2013 Jan 01. [cited 2017 Jun 29]. Available: https://www.guideline.gov.

16 Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12.

17 Taher AT, Aoun J, Salameh P. The AVAIL ME study: a multinational survey of VTE risk and prophylaxis. *J Thromb Thrombolysis* 2011;**31**:47–56. doi:10.1007/s11239-010-0492-2

18 Cohen AT, Tapson VF, Bergmann J-F, *et al.* Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet Lond Engl* 2008;**371**:387–94. doi:10.1016/S0140-6736(08)60202-0

19 Nieto JA, Cámara T, Camacho I, *et al.* Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients. A retrospective multicenter study. *Eur J Intern Med* 2014;**25**:717–23. doi:10.1016/j.ejim.2014.07.005

20 Tapson VF, Decousus H, Pini M, *et al.* Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. *Chest* 2007;**132**:936–45. doi:10.1378/chest.06-2993

21 Francis CW. Clinical practice. Prophylaxis for thromboembolism in hospitalized medical patients. *N Engl J Med* 2007;**356**:1438–44. doi:10.1056/NEJMcp067264

22 Dentali F, Douketis JD, Gianni M, *et al.* Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. *Ann Intern Med* 2007;**146**:278–88.

23 Triscott J, Mercer S, Tian PGJ, *et al.* Retroperitoneal haematoma associated with enoxaparin use in an elderly woman with chronic kidney disease. *BMJ Case Rep* 2015;**2015**. doi:10.1136/bcr-2015-211699

24 Madridano O, Martín Del Pozo M, Masso P, *et al.* [Hematoma of the rectus abdominis muscle in patients treated with low-molecular-weight heparin: four clinical cases]. *Rev Clin Esp* 2011;**211**:109–10. doi:10.1016/j.rce.2010.09.007

25 Nourbakhsh E, Anvari R, Nugent K. Abdominal wall hematomas associated with low-molecular-weight heparins: an important complication in older adults. *J Am Geriatr Soc* 2011;**59**:1543–5. doi:10.1111/j.1532-5415.2011.03529.x

26 Macías-Robles MD, Peliz MG, Gonzalez-Ordonez AJ. Prophylaxis with enoxaparin can produce a giant abdominal wall haematoma when associated with low doses of aspirin among elderly patients suffering cough attacks. *Blood Coagul Fibrinolysis Int J Haemost Thromb* 2005;**16**:217–9.

27 Goldstein JM, Sebire D. Abdominal wall haematoma in the obese: a dangerous phenomenon. *J Surg Case Rep* 2013;**2013**. doi:10.1093/jscr/rjt060

28 Blüher M. Adipose tissue dysfunction in obesity. *Exp Clin Endocrinol Diabetes Off J Ger Soc Endocrinol Ger Diabetes Assoc* 2009;**117**:241–50. doi:10.1055/s-0029-1192044

29 Baptista LS, da Silva KR, da Pedrosa CSG, *et al.* Adipose tissue of control and ex-obese patients exhibit differences in blood vessel content and resident mesenchymal stem cell population. *Obes Surg* 2009;**19**:1304–12. doi:10.1007/s11695-009-9899-2

30 Spencer M, Unal R, Zhu B, *et al.* Adipose tissue extracellular matrix and vascular abnormalities in obesity and insulin resistance. *J Clin Endocrinol Metab* 2011;**96**:E1990–1998. doi:10.1210/jc.2011-1567

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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Keywords:	Thromboembolism < CARDIOLOGY, GERIATRIC MEDICINE, Bleeding disorders & coagulopathies < HAEMATOLOGY

Title: 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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ABSTRACT:

Objectives: the main objectives were to evaluate the degree of compliance with current guidelines regarding venous thromboembolism (VTE) prophylaxis in medical patients during admission and to identify risk factors linked to complications of this prophylaxis.

Design: a prospective cohort study was conducted.

Setting: Internal Medicine Department of the University Hospital of Santiago de Compostela (tertiary referral hospital).

Participants: 396 hospitalized, non-surgical elderly patients with no active or previous oral anticoagulation or low molecular weight heparin (LMWH) treatment (during the previous year) and who received VTE prophylaxis during admission.

Primary and secondary outcome measures: the degree of compliance with the current guidelines was estimated by calculating PADOVA and IMPROVE indexes in all cases. We analysed the development of the following complications: major and minor bleeding, major and minor hematoma and decrease of platelet count.

Results: we found that VTE prophylaxis was correctly indicated in 88.4% of patients. We found 2 (0.5%) major bleeding, 17 (4.3%) minor bleeding, 30 (7.6%) platelet count decrease, 29 (7.3%) major hematoma and 82 (20.7%) minor hematoma. After a multivariate logistic regression analysis, the presence of major hematomas was linked to obesity (OR=4.1; IC 95% 1.8–9.2; P = 0.001), concomitant antiplatelet treatment (OR=2.7; IC 95% 1.1–6.5; P = 0.03) and enoxaparin use (OR=3.5; IC 95% 1.1–10.9; P = 0.029) and the presence of minor hematomas was associated with PADOVA index < 4 points (OR=3.1; IC 95% 1.5–6.4; P = 0.003) and Diabetes Mellitus (OR=2; IC 95% 1.1–3.7; P = 0.031).

Conclusions: complications during VTE prophylaxis in elderly hospitalized medical patients are frequent despite a correct application of current guidelines. The main factors linked to hematomas were obesity and concomitant antiplatelet treatment and their presence should lead physicians to exercise extreme caution. The use of tinzaparin for VTE prophylaxis in these patients could have a better safety profile.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

Strengths:

-Clinical study in elderly patients, who are usually excluded from large studies.

-Analysis of compliance with current guidelines in VTE prophylaxis in real-life conditions.

-Detection of minor complications and risk factors that have usually been underestimated in previous studies.

Limitations:

-Observational study conducted in only one department of a single hospital, which did not allow for a correct homogenization of subgroups.

-The inclusion of patients with VTE prophylaxis only could be a selection bias.

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COMPETING INTERESTS STATEMENT: all authors declare that they have no competing interests.

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.

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].

As to obesity, it was considered in all patients with a Body Mass Index (BMI) over 30 kg/m^2. For the main alterations in blood count we applied World Health Association (WHO) criteria for anemia and we coded as thrombocytopenia at admission all patients with values under 120000/μL. As to coagulation tests alterations, we considered them in all cases with an International Normalized Ratio (INR) over 1.2 or Activated Partial Thromboplastin Time (APTT) over 35 seconds.

The heparin types available in our center for the duration of the study were only enoxaparin and tinzaparin, which are therefore the only heparins included in our analysis.

With regard to the analysed complications, we defined them as follows:

-Major bleeding: gastrointestinal or intracranial bleeding, haemoptysis, epistaxis or haematuria with a decrease of at least 2 g/dL in haemoglobin level.

-Minor bleeding: haemoptysis, epistaxis or haematuria without changes in haemoglobin levels or with a decrease of less than 2 g/dL.

-Platelet count decrease: loss of at least 50% compared to the baseline value.

-Major hematoma: retroperitoneal or straight abdominal muscles locations were considered as major hematoma in all cases. We also considered as major hematoma an abdominal hematoma in other locations which implied a loss of at least 2 points in hemoglobin levels.

-Minor hematoma: abdominal wall hematoma (any location) with an extension of more than 5 cm without hemoglobin loss or with a hemoglobin loss lower than 2 points. We also considered as minor hematoma all abdominal wall hematomas of any extension, which caused symptoms like pain or pruritus requiring specific treatment.

-Pulmonary embolism (PE): we coded all cases diagnosed during hospital stay which were undiagnosed and unsuspected at admission.

-Deep venous thrombosis (DVT): we considered all cases diagnosed during hospital stay which were undiagnosed and unsuspected at admission.

A descriptive analysis was performed by calculating qualitative-variable rates plus mean and standard deviation. We used the Chi-square test or Fisher's exact test, as appropriate (expected frequency value <5), to compare qualitative variables, and the Student's t test for quantitative variables. A multivariate logistic regression analysis was conducted to identify factors associated with complications. A *P*-value <0.05 was regarded as significant. All analyses were performed using the SPSS v. 22.0 software package (SPSS Inc., Chicago, IL, USA).

The protocol of the present study was reviewed and approved by the Clinical Investigations Ethical Committee of Galicia.

Patient and Public Involvement

There were no patient or public involvement in the development of the study design, protocol, recruitment or dissemination of results.

RESULTS:

We included 396 consecutive inpatients that were given VTE prophylaxis during their hospital stay. Regarding gender, 51.8% were women and the global mean age was 80.7 years (Standard Deviation [SD] = 11.5, Range = 22 - 107), 91% of patients were over 65 years old. Only 32 patients (8.1%) lived in nursing homes and the average

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

index, we found that 6.3% of patients had a high theoretical bleeding risk, which should advise against VTE prophylaxis prescription. 22 patients (5.7%) fulfilled both PADOVA and IMPROVE criteria, which means concomitant high VTE and bleeding risk. We only found 2 patients (0.5%) with less than 4 points in the PADOVA index and high bleeding risk in the IMPROVE index.

Regarding their general condition at admission, 316 (79.8%) patients presented with an infection, 155 (39.1%) had anaemia, 137 (34.6%) had an acute heart failure, 95 (24%) met AKI criteria and 79 (19.9) met CKDE criteria. As to platelet count and coagulation tests, 93 (23.5%) patients had an alteration on coagulation tests at admission and 27 (6.8%) had thrombocytopenia.

Considering the VTE prophylaxis, the most used LMWH was enoxaparin (69.7% of cases) followed by tinzaparin (30.3%) and the mean duration was 12 (SD = 11.8) days. The most commonly used treatment regimens were 4000 International Units (IU) daily for enoxaparin (219 patients) and 3500 IU daily for tinzaparin (103 patients). The dose adjustment in patients with CKD, CKDE or AKI was correct in all cases. We did not register any episode of VTE during the study period.

With regard to complications, we found 2 patients (0.5%) who presented with major bleeding, 17 (4.3%) with a minor bleeding episode, 30 (7.6%) developed a platelet count decrease, 29 (7.3%) had a major hematoma (9 located in straight abdominal muscles and 20 in other abdominal locations) and 82 (20.7%) had a minor hematoma. All patients who developed complications were managed through conservative treatment and the course was favourable in all cases. After the univariate analysis, we found an association between minor bleeding and the presence of anaemia at admission and AKI. In the case of major hematomas, this analysis showed significant differences in patients with obesity, concomitant antiplatelet treatment, an infection or

heart failure as main cause of admission and the use of enoxaparin. With regard to minor hematomas, we found an association with diabetes and a PADOVA index lower than 4 points. Finally, a platelet count decrease was only linked to an infection as the cause of admission and it was not associated with the other analysed complications.

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

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

DISCUSSION:

The present study shows, for the first time to our knowledge, an exhaustive analysis of clinically relevant complications during VTE prophylaxis in non-surgical patients and the main risk factors linked to them.

As to the adaptation of the clinical practice to current guidelines, the high degree of compliance observed is remarkable. There is, however, a narrow margin for improvement, particularly in the case of over-prescription in low-risk patients. Our study included only patients with VTE prophylaxis during hospital stay, which makes

the comparison with studies like ENDORSE or AVAIL ME difficult as they showed lower percentages of correct application of recommendations, even as low as below 50% [17,18].

Another relevant difference of our study is that it is exclusively confined to medical patients, as well as the extremely high age and degree of comorbidity of our cohort, compared with larger series where patients with a mean age more than 10 years lower and very low rates of multiple comorbidity were included [19,20].

The absence of VTE cases in our study reflects a high efficacy of VTE prophylaxis in medical patients, which has been largely studied and supported by high-quality evidence [21,22].

With respect to complications, we analyzed minor complications, like hematomas, that are usually undervalued by physicians, but for patients are important. Indeed, we consider that our results could help physicians to improve their daily clinical practice and the patient´s experience during a hospital admission by adding tools to detect patients at risk of developing these complications.

As far as bleeding episodes are concerned, they were infrequent. Despite this, the association between anemia and minor bleeding could reflect the existence of previous digestive bleeding, increased during admission by LMWH, and the association with AKI could be explained by a heparin over-effect in these patients, although we did not detect significant rates of unadjusted dosage in our cohort. In fact, an increased bleeding risk was one of the main risk factors considered on the IMPROVE score, although anemia was not a useful marker of bleeding risk in that study [14]. Thus, our results could contribute to expand the tools available to identify patients with high bleeding risk before prescribing VTE prophylaxis.

In the case of major hematomas, we must underscore the relatively high percentage of patients who developed these complications. Despite the clinical relevance of abdominal and retroperitoneal hematomas, large series did not analyze these complications and we can only compare our results with small series and case reports [14,18,23,24]. In this sense, previous reports suggested an estimated incidence of 5% for abdominal hematomas in patients receiving VTE prophylaxis, which could be comparable to ours [25]. With regard to risk factors, previous studies showed that elderly patients had a higher risk of abdominal hematomas [23,25,26]; we did not identify this association, probably because of the little number of patients aged below 65 years. Concomitant antiplatelet treatment has been identified as a risk factor linked to hematomas by other authors, due to the synergic action with LMWH, and our findings reinforce the importance of assessing the need to maintain these drugs during hospital admission in elderly patients [23,25,26]. Obesity has also been described as a risk factor in previous studies [25,27], and this relationship could be due to an adipose tissue dysfunction in obese patients, linked to an abnormal subcutaneous vascularization and extracellular matrix changes [28–30]. These alterations lead to a higher risk of local hematomas in obese patients under VTE prophylaxis, independently of the plasmatic levels of LMWH achieved [26].

As to the different LMWH used in our study, we found a lower risk of major hematomas with tinzaparin as the only significant difference. Interestingly, the characteristics of patients treated with both of them were different regarding renal function, so the use of tinzaparin in patients with poorer renal function could have alerted physicians to the need of better dose adjustment. Thus, it could be considered as a potential selection bias, which should be taken into account during the interpretation of our results. Despite this, a potential superior safety profile in elderly patients with

high comorbidity emerges and even differences in device, needles and mode of administration should be considered. Further studies will be necessary to properly establish this difference.

As to minor hematomas, it is remarkable that this complication is not usually considered as clinically relevant. However, we decided to include it as we considered that it is completely relevant for our patients. In this sense, the association with a PADOVA index lower than 4 points cannot be considered as a risk factor itself, but it helps us to highlight the importance of a correct application of VTE prophylaxis guidelines. In the case of Diabetes Mellitus, it has not been previously described as a risk factor for abdominal hematomas development but microvascular diabetic complications might underlie this association [25].

Despite the high percentage of patients with alterations in coagulation tests (23.5%), we found no association between these alterations and the related complications. This could be due to the little relevance of most of alterations in coagulation tests, consisting of small increments of INR or APTT.

In light of our results, we think that the presence of any risk factor for the development of major or minor complications linked to VTE prophylaxis should lead physicians to a meditation, before its prescription, about the indication, dosage and time of treatment, particularly in elderly patients.

CONCLUSIONS:

The development of complications during VTE prophylaxis in elderly hospitalized medical patients is higher than that expected in other populations even when the current guidelines are correctly applied. The main factors linked to hematomas

in our cohort were obesity and concomitant antiplatelet treatment and their presence should lead physicians to exercise extreme caution. The use of tinzaparin for VTE prophylaxis in these patients could have a better safety profile.

AUTHOR´S CONTRIBUTIONS:

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

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

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

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

DATA SHARING STATEMENT: Technical appendix, statistical code, and dataset will be available from the Dryad repository if required.

FUNDING STATEMENT: this research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS STATEMENT: all authors declare that they have no competing interests.

REFERENCES

1 Nieto Rodríguez JA, ENDORSE. [Venous thromboembolism risk and antithrombotic prophylaxis among patients admitted to Spanish hospitals (ENDORSE study)]. *Med Clin (Barc)* 2009;**133**:1–7. doi:10.1016/j.medcli.2009.01.040

2 Gould MK, Garcia DA, Wren SM, *et al.* Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e227S–e277S. doi:10.1378/chest.11-2297

3 Falck-Ytter Y, Francis CW, Johanson NA, *et al.* Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e278S–e325S. doi:10.1378/chest.11-2404

4 Kahn SR, Lim W, Dunn AS, *et al.* Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e195S–e226S. doi:10.1378/chest.11-2296

5 Decousus H, Tapson VF, Bergmann J-F, *et al.* Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. *Chest* 2011;**139**:69–79. doi:10.1378/chest.09-3081

6 Ruiz-Artacho P, Pérez Peña C, Iriarte A, *et al.* [Adequation of thromboprophylaxis during former admission in patients attended in emergencies with thromboembolic disease]. *Med Clin (Barc)* 2013;**141**:130–1. doi:10.1016/j.medcli.2012.12.014

7 Gallardo Jiménez P, Guijarro Merino R, Vallejo Herrera V, *et al.* [Assessment of venous thromboembolism risk in hospitalized medical patients. Concordance between PRETEMED guide and the recommendations of the viii conference of the American College of Chest Physicians]. *Med Clin (Barc)* 2012;**139**:467–72. doi:10.1016/j.medcli.2011.07.022

8 Borobia AM, Fernández Capitán C, Iniesta Arandia N, *et al.* [Risk of thromboembolic events and evaluation of the use of venous thromboembolism prophylaxis in hospitalized medical patients and after discharge]. *Rev Clin Esp* 2009;**209**:15–20.

9 Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373–83.

10 Mahoney FI, Barthel DW. FUNCTIONAL EVALUATION: THE BARTHEL INDEX. *Md State Med J* 1965;**14**:61–5.

11 Ignacio de Ulíbarri J, González-Madroño A, de Villar NGP, *et al.* CONUT: a tool for controlling nutritional status. First validation in a hospital population. *Nutr Hosp* 2005;**20**:38–45.

12 Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc* 1975;**23**:433–41.

13 Barbar S, Noventa F, Rossetto V, *et al.* A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost JTH* 2010;**8**:2450–7. doi:10.1111/j.1538-7836.2010.04044.x

14 Hostler DC, Marx ES, Moores LK, *et al.* Validation of the International Medical Prevention Registry on Venous Thromboembolism Bleeding Risk Score. *Chest* 2016;**149**:372–9. doi:10.1378/chest.14-2842

15 National Guideline Clearinghouse (NGC). Guideline summary: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. In: National Guideline Clearinghouse (NGC) [Web site]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2013 Jan 01. [cited 2017 Jun 29]. Available: https://www.guideline.gov.
16 Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12.
17 Taher AT, Aoun J, Salameh P. The AVAIL ME study: a multinational survey of VTE risk and prophylaxis. *J Thromb Thrombolysis* 2011;**31**:47–56. doi:10.1007/s11239-010-0492-2
18 Cohen AT, Tapson VF, Bergmann J-F, *et al.* Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet Lond Engl* 2008;**371**:387–94. doi:10.1016/S0140-6736(08)60202-0
19 Nieto JA, Cámara T, Camacho I, *et al.* Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients. A retrospective multicenter study. *Eur J Intern Med* 2014;**25**:717–23. doi:10.1016/j.ejim.2014.07.005
20 Tapson VF, Decousus H, Pini M, *et al.* Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. *Chest* 2007;**132**:936–45. doi:10.1378/chest.06-2993
21 Francis CW. Clinical practice. Prophylaxis for thromboembolism in hospitalized medical patients. *N Engl J Med* 2007;**356**:1438–44. doi:10.1056/NEJMcp067264
22 Dentali F, Douketis JD, Gianni M, *et al.* Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. *Ann Intern Med* 2007;**146**:278–88.
23 Triscott J, Mercer S, Tian PGJ, *et al.* Retroperitoneal haematoma associated with enoxaparin use in an elderly woman with chronic kidney disease. *BMJ Case Rep* 2015;**2015**. doi:10.1136/bcr-2015-211699
24 Madridano O, Martín Del Pozo M, Masso P, *et al.* [Hematoma of the rectus abdominis muscle in patients treated with low-molecular-weight heparin: four clinical cases]. *Rev Clin Esp* 2011;**211**:109–10. doi:10.1016/j.rce.2010.09.007
25 Nourbakhsh E, Anvari R, Nugent K. Abdominal wall hematomas associated with low-molecular-weight heparins: an important complication in older adults. *J Am Geriatr Soc* 2011;**59**:1543–5. doi:10.1111/j.1532-5415.2011.03529.x
26 Macías-Robles MD, Peliz MG, Gonzalez-Ordonez AJ. Prophylaxis with enoxaparin can produce a giant abdominal wall haematoma when associated with low doses of aspirin among elderly patients suffering cough attacks. *Blood Coagul Fibrinolysis Int J Haemost Thromb* 2005;**16**:217–9.
27 Goldstein JM, Sebire D. Abdominal wall haematoma in the obese: a dangerous phenomenon. *J Surg Case Rep* 2013;**2013**. doi:10.1093/jscr/rjt060
28 Blüher M. Adipose tissue dysfunction in obesity. *Exp Clin Endocrinol Diabetes Off J Ger Soc Endocrinol Ger Diabetes Assoc* 2009;**117**:241–50. doi:10.1055/s-0029-1192044
29 Baptista LS, da Silva KR, da Pedrosa CSG, *et al.* Adipose tissue of control and ex-obese patients exhibit differences in blood vessel content and resident mesenchymal stem cell population. *Obes Surg* 2009;**19**:1304–12. doi:10.1007/s11695-009-9899-2
30 Spencer M, Unal R, Zhu B, *et al.* Adipose tissue extracellular matrix and vascular abnormalities in obesity and insulin resistance. *J Clin Endocrinol Metab* 2011;**96**:E1990–1998. doi:10.1210/jc.2011-1567

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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Title: 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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ABSTRACT

Objectives: To evaluate the degree of compliance with current guidelines regarding venous thromboembolism (VTE) prophylaxis in medical patients during admission and to identify risk factors linked to complications of VTE prophylaxis.

Design: Prospective cohort study.

Setting: The Internal Medicine Department of the University Hospital of Santiago de Compostela (tertiary referral hospital).

Participants: A total of 396 hospitalized, elderly patients who did not undergo surgery and had no active or previous oral anticoagulation or low molecular weight heparin (LMWH) treatment (during the previous year) and who received VTE prophylaxis during admission.

Primary and secondary outcome measures: The degree of compliance with the current guidelines was estimated by calculating PADOVA and IMPROVE indexes in all cases. We analyzed the development of the following complications: major and minor bleeding, major and minor hematoma and decrease of platelet count.

Results: We found that VTE prophylaxis was correctly indicated in 88.4% of patients. We found 2 (0.5%) cases with major bleeding, 17 (4.3%) with minor bleeding, 30 (7.6%) with decreased platelet count, 29 (7.3%) with major hematoma and 82 (20.7%) with minor hematoma. After multivariate logistic regression analysis, the presence of major hematomas was linked to obesity (OR=4.1; IC95% 1.8–9.2; *P*=0.001), concomitant antiplatelet treatment (OR=2.7; IC95% 1.1–6.5; *P*=0.03) and enoxaparin use (OR=3.5; IC95% 1.1–10.9; *P*=0.029) and the presence of minor hematomas was associated with PADOVA index < 4 points (OR=3.1; IC95% 1.5–6.4; *P*=0.003) and diabetes mellitus (OR=2; IC95% 1.1–3.7; *P*=0.031).

Conclusions: complications during VTE prophylaxis in elderly hospitalized medical patients are frequent even with correct application of current guidelines. The main factors linked to hematomas were obesity and concomitant antiplatelet treatment, the presence of which should lead physicians to exercise extreme caution. The use of tinzaparin for VTE prophylaxis in these patients could have a better safety profile.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths:

-Clinical study in elderly patients, who are usually excluded from large studies.

-Analysis of compliance with current guidelines for VTE prophylaxis in real-world conditions.

-Detection of minor complications and risk factors that have usually been underestimated in previous studies.

Limitations:

-Observational study conducted in only one department of a single hospital, which did not allow for an accurate homogenization of subgroups.

-The inclusion of patients with VTE prophylaxis only could introduce selection bias.

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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].

All patients with a body mass index (BMI) over 30 kg/m^2 were considered obese. For the main alterations in blood count, we applied World Health Association (WHO) criteria for anemia and we classified all patients with values under 12,0000/μL at admission as having thrombocytopenia. We considered as elevated all cases of coagulation test with an international normalized ratio (INR) over 1.2 or activated partial thromboplastin time (APTT) over 35 seconds.

The heparin types available in our center for the duration of the study were only enoxaparin and tinzaparin, which are therefore the only heparins included in our analysis.

With regard to the analyzed complications, we defined them as follows:

-Major bleeding: gastrointestinal or intracranial bleeding, hemoptysis, epistaxis or hematuria with a decrease of at least 2 g/dL in hemoglobin level.

-Minor bleeding: hemoptysis, epistaxis or hematuria without changes in hemoglobin levels or with a decrease of less than 2 g/dL.

-Platelet count decrease: loss of at least 50% compared with the baseline value.

-Major hematoma: retroperitoneal or straight abdominal muscle locations were considered as major hematoma in all cases. We also considered as major hematoma an abdominal hematoma in other locations in which a loss of at least 2 points in hemoglobin levels was implied.

-Minor hematoma: abdominal wall hematoma (any location) with an extension of more than 5 cm without hemoglobin loss or with a hemoglobin loss lower than 2 points. We also considered as minor hematoma all abdominal wall hematomas of any extension, which caused symptoms like pain or pruritus requiring specific treatment.

-Pulmonary embolism (PE): we coded all cases diagnosed during the hospital stay that were undiagnosed and unsuspected at admission.

-Deep venous thrombosis (DVT): we considered all cases diagnosed during the hospital stay that were undiagnosed and unsuspected at admission.

A descriptive analysis was performed by calculating qualitative-variable rates plus mean and standard deviation. We used the Chi-square test or Fisher's exact test, as appropriate (expected frequency value <5), to compare qualitative variables, and the Student's t test for quantitative variables. A multivariate logistic regression analysis was conducted to identify factors associated with complications. A *P*-value <0.05 was regarded as significant. All analyses were performed using the SPSS v. 22.0 software package (SPSS Inc., Chicago, IL, USA).

The protocol of the present study was reviewed and approved by the Clinical Investigations Ethical Committee of Galicia.

Patient and Public Involvement

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

RESULTS

We included 396 consecutive inpatients who were given VTE prophylaxis during their hospital stay. Regarding gender, 51.8% were women and the global mean age was 80.7 years (Standard Deviation [SD] = 11.5, Range = 22–107), 91% of patients were over 65 years old. Only 32 patients (8.1%) lived in nursing homes and the average 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%), 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

index, we found that 6.3% of patients had a high theoretical bleeding risk, which should advise against VTE prophylaxis prescription. There were 22 patients (5.7%) who fulfilled both PADOVA and IMPROVE criteria, which means concomitant high risk of VTE and bleeding. We only found 2 patients (0.5%) with fewer than 4 points in the PADOVA index and high bleeding risk in the IMPROVE index.

Regarding their general condition at admission, 316 (79.8%) patients presented with an infection, 155 (39.1%) had anemia, 137 (34.6%) had an acute heart failure, 95 (24%) met AKI criteria and 79 (19.9) met CKDE criteria. In platelet count and coagulation tests, 93 (23.5%) patients had elevated coagulation tests at admission and 27 (6.8%) had thrombocytopenia.

With regard to VTE prophylaxis, the most used LMWH was enoxaparin (69.7% of cases) followed by tinzaparin (30.3%) and the mean duration was 12 (SD = 11.8) days. The most commonly used treatment regimens were 4000 International Units (IU) daily for enoxaparin (219 patients) and 3500 IU daily for tinzaparin (103 patients). The dose adjustment in patients with CKD, CKDE or AKI was correct in all cases. We did not register any episode of VTE during the study period.

With regard to complications, we found 2 patients (0.5%) who presented with major bleeding, 17 (4.3%) with a minor bleeding episode, 30 (7.6%) developed a platelet count decrease, 29 (7.3%) had a major hematoma (9 located in straight abdominal muscles and 20 in other abdominal locations) and 82 (20.7%) had a minor hematoma. All patients who developed complications were managed through conservative treatment and the course was favorable in all cases. After the univariate analysis, we found an association between minor bleeding and the presence of anemia at admission and AKI. In the case of major hematomas, this analysis showed significant differences in patients with obesity, concomitant antiplatelet treatment, an infection or

heart failure as main cause of admission and the use of enoxaparin. With regard to minor hematomas, we found an association with diabetes and a PADOVA index lower than 4 points. Finally, a platelet count decrease was only linked to an infection as the cause of admission and it was not associated with the other analyzed complications.

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

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

DISCUSSION

The present study shows, for the first time to our knowledge, an exhaustive analysis of clinically relevant complications and their main risk factors during VTE prophylaxis in non-surgical patients.

The high degree of observed compliance with current guidelines in clinical practice is remarkable. There is, however, a narrow margin for improvement, particularly in the case of over-prescription in low-risk patients. Our study included only patients given VTE prophylaxis during hospital stay, which makes comparison

with studies such as ENDORSE or AVAIL ME difficult because they showed lower percentages of correct application of recommendations, even as low as below 50% [17,18].

Another relevant difference of our study is that it is exclusively confined to medical patients, as well as the extremely high age and degree of comorbidity of our cohort, compared with larger series in which patients with a mean age more than 10 years younger and very low rates of multiple comorbidity were included [19,20].

The absence of VTE cases in our study reflects a high efficacy of VTE prophylaxis in medical patients, which has been studied extensively and supported by high-quality evidence [21,22].

With respect to complications, we analyzed minor complications such as hematomas that are usually undervalued by physicians, but are important for patients. Indeed, we consider that our results could help physicians to improve their daily clinical practice and the patient's experience during a hospital admission by adding tools to detect patients at risk of developing these complications.

Bleeding episodes were infrequent, but the association between anemia and minor bleeding could reflect the existence of previous digestive tract bleeding, increased during admission by LMWH. The association with AKI could be explained by a heparin over-effect in these patients, although we did not detect significant rates of unadjusted dosage in our cohort. In fact, an increased bleeding risk was one of the main risk factors considered on the IMPROVE score, although anemia was not a useful marker of bleeding risk in that study [14]. Thus, our results could contribute to expanding the tools available to identify patients with high bleeding risk before prescribing VTE prophylaxis.

In the case of major hematomas, we must underscore the relatively high percentage of patients who developed these complications. Despite the clinical relevance of abdominal and retroperitoneal hematomas, these complications were not analyzed in any cohort study, and thus we can only compare our results with case reports [14,18,23,24]. In this sense, previous reports suggested an estimated incidence of 5% for abdominal hematomas in patients receiving VTE prophylaxis, which could be comparable to our results [25]. With regard to risk factors, previous studies showed that elderly patients had a higher risk of abdominal hematomas [23,25,26]; we did detect such an association, probably because of the small number of patients aged less than 65 years. Concomitant antiplatelet treatment has been identified as a risk factor linked to hematomas by other authors because of its synergic action with LMWH, and our findings reinforce the importance of assessing the need to maintain these drugs during hospital admission in elderly patients [23,25,26]. Obesity has also been described as a risk factor in previous studies [25,27], and this relationship could be due to an adipose tissue dysfunction in obese patients, linked to an abnormal subcutaneous vascularization and extracellular matrix changes [28–30]. These alterations lead to a higher risk of local hematomas in obese patients under VTE prophylaxis, independently of the plasmatic levels of LMWH achieved [26].

As to the different types of LMWH used in our study, we found a lower risk of major hematomas with tinzaparin as the only significant difference. Interestingly, the characteristics of patients treated with both LWMHs were different with regard to renal function, so the use of tinzaparin in patients with poorer renal function could have alerted physicians to the need for better dose adjustment. Thus, this could be considered as a potential selection bias that should be taken into account in the interpretation of our results. Despite this, a potential superior safety profile in elderly patients with high

comorbidity emerges and even differences in device, needles and mode of administration should be considered. Further studies will be necessary to properly establish this difference.

With regard to minor hematomas, it is remarkable that this complication is not usually considered clinically relevant. However, we decided to include it because we considered it to be highly relevant for our patients. The association with a PADOVA index lower than 4 points cannot be considered as a risk factor itself, but it helps us to highlight the importance of correct application of VTE prophylaxis guidelines. Diabetes mellitus has not been previously described as a risk factor for abdominal hematoma development but microvascular diabetic complications might underlie this association [25].

Despite the high percentage of patients with variations in coagulation tests (23.5%), we found no association between these variations and the related complications. This could be due to the little relevance of most variations in coagulation tests, consisting of small increments of INR or APTT.

In light of our results, we think that the presence of any risk factor for the development of major or minor complications linked to VTE prophylaxis should lead physicians to careful consideration of the indication, dosage and time of treatment before VTE prophylaxis is prescribed, particularly in elderly patients.

CONCLUSIONS

The incidence of complications developing during VTE prophylaxis in elderly hospitalized medical patients is higher than that expected in other populations even when the current guidelines are correctly applied. The main factors linked to hematomas

in our cohort were obesity and concomitant antiplatelet treatment, the presence of which should lead physicians to exercise extreme caution. The safety profile of tinzaparin for VTE prophylaxis in these patients could be improved.

AUTHOR'S CONTRIBUTIONS

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

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

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

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

DATA SHARING STATEMENT: Technical appendix, statistical code, and dataset will be available from the Dryad repository if required.

FUNDING STATEMENT: this research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS STATEMENT: all authors declare that they have no competing interests.

REFERENCES

1 Nieto Rodríguez JA, ENDORSE. [Venous thromboembolism risk and antithrombotic prophylaxis among patients admitted to Spanish hospitals (ENDORSE study)]. *Med Clin (Barc)* 2009;**133**:1–7. doi:10.1016/j.medcli.2009.01.040

2 Gould MK, Garcia DA, Wren SM, *et al.* Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e227S–e277S. doi:10.1378/chest.11-2297

3 Falck-Ytter Y, Francis CW, Johanson NA, *et al.* Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e278S–e325S. doi:10.1378/chest.11-2404

4 Kahn SR, Lim W, Dunn AS, *et al.* Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;**141**:e195S–e226S. doi:10.1378/chest.11-2296

5 Decousus H, Tapson VF, Bergmann J-F, *et al.* Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. *Chest* 2011;**139**:69–79. doi:10.1378/chest.09-3081

6 Ruiz-Artacho P, Pérez Peña C, Iriarte A, *et al.* [Adequation of thromboprophylaxis during former admission in patients attended in emergencies with thromboembolic disease]. *Med Clin (Barc)* 2013;**141**:130–1. doi:10.1016/j.medcli.2012.12.014

7 Gallardo Jiménez P, Guijarro Merino R, Vallejo Herrera V, *et al.* [Assessment of venous thromboembolism risk in hospitalized medical patients. Concordance between PRETEMED guide and the recommendations of the viii conference of the American College of Chest Physicians]. *Med Clin (Barc)* 2012;**139**:467–72. doi:10.1016/j.medcli.2011.07.022

8 Borobia AM, Fernández Capitán C, Iniesta Arandia N, *et al.* [Risk of thromboembolic events and evaluation of the use of venous thromboembolism prophylaxis in hospitalized medical patients and after discharge]. *Rev Clin Esp* 2009;**209**:15–20.

9 Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373–83.

10 Mahoney FI, Barthel DW. FUNCTIONAL EVALUATION: THE BARTHEL INDEX. *Md State Med J* 1965;**14**:61–5.

11 Ignacio de Ulíbarri J, González-Madroño A, de Villar NGP, *et al.* CONUT: a tool for controlling nutritional status. First validation in a hospital population. *Nutr Hosp* 2005;**20**:38–45.

12 Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc* 1975;**23**:433–41.

13 Barbar S, Noventa F, Rossetto V, *et al.* A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the

Padua Prediction Score. *J Thromb Haemost JTH* 2010;**8**:2450–7. doi:10.1111/j.1538-7836.2010.04044.x

14 Hostler DC, Marx ES, Moores LK, *et al.* Validation of the International Medical Prevention Registry on Venous Thromboembolism Bleeding Risk Score. *Chest* 2016;**149**:372–9. doi:10.1378/chest.14-2842

15 National Guideline Clearinghouse (NGC). Guideline summary: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. In: National Guideline Clearinghouse (NGC) [Web site]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2013 Jan 01. [cited 2017 Jun 29]. Available: https://www.guideline.gov.

16 Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12.

17 Taher AT, Aoun J, Salameh P. The AVAIL ME study: a multinational survey of VTE risk and prophylaxis. *J Thromb Thrombolysis* 2011;**31**:47–56. doi:10.1007/s11239-010-0492-2

18 Cohen AT, Tapson VF, Bergmann J-F, *et al.* Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet Lond Engl* 2008;**371**:387–94. doi:10.1016/S0140-6736(08)60202-0

19 Nieto JA, Cámara T, Camacho I, *et al.* Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients. A retrospective multicenter study. *Eur J Intern Med* 2014;**25**:717–23. doi:10.1016/j.ejim.2014.07.005

20 Tapson VF, Decousus H, Pini M, *et al.* Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. *Chest* 2007;**132**:936–45. doi:10.1378/chest.06-2993

21 Francis CW. Clinical practice. Prophylaxis for thromboembolism in hospitalized medical patients. *N Engl J Med* 2007;**356**:1438–44. doi:10.1056/NEJMcp067264

22 Dentali F, Douketis JD, Gianni M, *et al.* Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. *Ann Intern Med* 2007;**146**:278–88.

23 Triscott J, Mercer S, Tian PGJ, *et al.* Retroperitoneal haematoma associated with enoxaparin use in an elderly woman with chronic kidney disease. *BMJ Case Rep* 2015;**2015**. doi:10.1136/bcr-2015-211699

24 Madridano O, Martín Del Pozo M, Masso P, *et al.* [Hematoma of the rectus abdominis muscle in patients treated with low-molecular-weight heparin: four clinical cases]. *Rev Clin Esp* 2011;**211**:109–10. doi:10.1016/j.rce.2010.09.007

25 Nourbakhsh E, Anvari R, Nugent K. Abdominal wall hematomas associated with low-molecular-weight heparins: an important complication in older adults. *J Am Geriatr Soc* 2011;**59**:1543–5. doi:10.1111/j.1532-5415.2011.03529.x

26 Macías-Robles MD, Peliz MG, Gonzalez-Ordonez AJ. Prophylaxis with enoxaparin can produce a giant abdominal wall haematoma when associated with low doses of aspirin among elderly patients suffering cough attacks. *Blood Coagul Fibrinolysis Int J Haemost Thromb* 2005;**16**:217–9.

27 Goldstein JM, Sebire D. Abdominal wall haematoma in the obese: a dangerous phenomenon. *J Surg Case Rep* 2013;**2013**. doi:10.1093/jscr/rjt060

28 Blüher M. Adipose tissue dysfunction in obesity. *Exp Clin Endocrinol Diabetes Off J Ger Soc Endocrinol Ger Diabetes Assoc* 2009;**117**:241–50. doi:10.1055/s-0029-1192044

29 Baptista LS, da Silva KR, da Pedrosa CSG, *et al.* Adipose tissue of control and ex-obese patients exhibit differences in blood vessel content and resident mesenchymal stem cell population. *Obes Surg* 2009;**19**:1304–12. doi:10.1007/s11695-009-9899-2

30 Spencer M, Unal R, Zhu B, *et al.* Adipose tissue extracellular matrix and vascular abnormalities in obesity and insulin resistance. *J Clin Endocrinol Metab* 2011;**96**:E1990–1998. doi:10.1210/jc.2011-1567

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.