PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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.
AUTHORS	Novo-Veleiro, Ignacio; Alvela-Suárez, Lucía; Costa-Grille, Alba; Suárez-Dono, Javier; Ferrón-Vidan, Fernando; Reino, Antonio

VERSION 1 – REVIEW

REVIEWER	Alexander Gallus Flinders Medical Centre and University Adelaide, SA, AUSTRALIA
REVIEW RETURNED	18-Jan-2018

GENERAL COMMENTS	This report has strengths and limitations. Strengths: 1. the focus on bleeding complications of injected LMWHs for VTE prevention in elderly inpatients. Descriptions of categories are appropriate. As indicated by the authors, many studies of heparin prophylaxis have focused on efficacy over adverse effects. 2. Prospective observational study with predefined aims and methods. 3. Elderly population of inpatients consistent with age and comorbidities in many present-day medical inpatient units. Major limitation: The authors chose to study only patients who received a heparin. One objective was to 'evaluate the grade of fulfilment of current guidelines'. These 'recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis' 'for acutely ill hospitalized medical patients at low risk of thrombosis' (Kahn ACCP 2012). By studying only patients who received prophylaxis, the authors did not examine the equally important issue of overprescribing chemoprophylaxis for 'low risk' patients and their 'statement of aims' should reflect this (they mention the issue in their discussion). Other comments: 1. The author should provide a 'CONSORT' flow-sheet of all admissions during the study period, including admissions without prophylaxis (preferably with basic demographics) and any treated patients who escaped their study (did they record all consecutive patients?) 2. The high level of VTE risk (PADOVA score) in subjects who received chemoprophylaxis is reassuring. So is the low proportion (0.5%) with 'major' bleeding. Multivariate analysis suggests more major haematomas with enoxaparin then tinzaparin. Demographics indicate more patients given tinzaparin had kidney failure. Did this reflect local treatment guidelines or practice for kidney failure? 3. The authors define 'major haematoma' as retroperitoneal or rectus muscle locations, or other abdominal haematomas with at least 2 point (20 gm/L?) loss of Haemoglobin. Of 29 'major' haematomas, how many were retroperitoneal or rectus

	sheath (these can be life-threatening) and how many were more limited? A Table of major and minor bleeding events, including more information about 'major haematomas' would add perspective.

REVIEWER	Anneliese Schleyer MD Harborview Medical Center/ University of Washington, Seattle, WA, USA
REVIEW RETURNED	23-Jan-2018

GENERAL COMMENTS	This study has the potential to inform the literature about bleeding complications in medical patients receiving vte prophylaxis (and adherence to VTE prevention guidelines in this pt group). An important area of study. # While the results address the research question as stated, from a clinical perspective it would be helpful to distinguish "complications" that impact pts - is a platelet count decrease clinically significant? # The authors describe that data collection was performed by personal interview. Which information? Pt identification of bleeding events? Other? # Written informed consent was obtained. Was this study approved by a Human Subjects/Institutional Review Board? Additional comments: (May result from the fact that I only practice in the USA) # Fulfillment (needs two 'l's) of current guidelines is often referred to as adherence to guidelines # Complications might be more specifically identified as bleeding complications # What is a third level institution? # Abstract conclusions: Is the final sentence justified by the review? (tinzaparin could have a better security profile)? (In the US we call this safety profile) (# homogenization - might refer to bias) # Please further describe role of antiplatelets in this review # Were LMWH doses renally adjusted? How does this relate to AKI as described? # HBPM? Thank you for the opportunity to review this manuscript.

REVIEWER	Dr Corinne Frere Assistance Publique Hôpitaux de Paris, France
REVIEW RETURNED	27-Jan-2018

GENERAL COMMENTS	Novo-Veleiro et al. Conducted a prospective cohort study in 396 elderly hospitalized non-surgical elderly patients receiving VTE prophylaxis to evaluate the grade of fulfillment of current guidelines for VTE prophylaxis in medical patients and to identify risk factor for

	bleeding. They found that prophylaxis was correctly indicated in 88% of patients. Obesity, concomitant antiplatelet therapy and enoxaparin use were associated with a higher risk for major hematomas while diabetes mellitus and PADOVA index<4 were associated with a higher risk for minor hematomas. This is an interesting question and relevant paper for this particular patients. However, some points need minor revisions: Abstract P 2, line 22 : please mention that the study was conducted in elderly patients P 2, line 36 : please add a sentence on the statistical analysis Method section P7 line 1-10 : were PE ad DVT objectively confirmed? Result section P7 line 33-34 : “the mean age was 80.7” Please give the range P8 line 9 : suppress “it is also remarkable that” P8 line 54: “we found an association between minor..;” please add OR (95%CI) and p value for each variable Add a table to summarize multivariate analysis Table 1 : Add age in table & Are data n (%)? Discussion The authors found that 23.5% of patients had coagulation abnormalities, however coagulation abnormalities were not associated with bleeding. Please discuss this point

VERSION 1 – AUTHOR RESPONSE

Editorial Requests:

- Please revise your title so that it includes your study design and setting. This is the preferred format for the journal.

Authors: We have changed the title following your recommendations.

- The manuscript contains some typographical/ grammatical errors. Please thoroughly proofread the paper before submitting your revision.

Authors: We have reviewed the manuscript and corrected all the errors. A native English-speaker also has reviewed the manuscript.

- Please add a statement to the methods section of the manuscript confirming that the study received approval from your local ethics committee. Please include the specific name of the ethics committee that approved the study along with the reference number if applicable.

Authors: We have added the requested information to the reviewed manuscript.

- Please also improve the clarity of the following sentence: "Written informed consent was request to all patients and the data collection.." Please amend to: "Written informed consent was obtained from all patients.."

Authors: We have amended the sentence following the Editor´s suggestion.

Response to reviewers:
Reviewer: 1
Reviewer Name: Alexander Gallus
Institution and Country: Flinders Medical Centre and University, Adelaide, SA, AUSTRALIA
Competing Interests: None declared

Reviewer:
This report has strengths and limitations.
Strengths: 1. the focus on bleeding complications of injected LMWHs for VTE prevention in elderly inpatients. Descriptions of categories are appropriate. As indicated by the authors, many studies of heparin prophylaxis have focused on efficacy over adverse effects. 2. Prospective observational study with predefined aims and methods. 3. Elderly population of inpatients consistent with age and comorbidities in many present-day medical inpatient units.
Major limitation: The authors chose to study only patients who received a heparin. One objective was to 'evaluate the grade of fulfilment of current guidelines'. These 'recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis' 'for acutely ill hospitalized medical patients at low risk of thrombosis' (Kahn ACCP 2012). By studying only patients who received prophylaxis, the authors did not examine the equally important issue of overprescribing chemoprophylaxis for 'low risk' patients and their 'statement of aims' should reflect this (they mention the issue in their discussion).

Authors:
We thank the reviewer for his comments and agree with him that this is a limitation and consequently we have described it as such in the discussion section. The percentage of patients without VTE prophylaxis in our department is very low and when designing the study, we considered that the inclusion of this small group of patients could be a confounding factor. Nevertheless, the over-prescription of VTE prophylaxis in low-risk patients was already analysed in our study since we calculated the individualized risk and detected 46 low-risk patients with VTE prophylaxis prescription. We have underscored this fact in the results and discussion sections for clarity's sake. Despite this, we still consider this fact as an important limitation and therefore, we have added a statement in this regard in the strengths and limitations section, following the reviewer´s suggestion.

Other comments:
Reviewer: 1. The author should provide a 'CONSORT' flow-sheet of all admissions during the study period, including admissions without prophylaxis (preferably with basic demographics) and any treated patients who escaped their study (did they record all consecutive patients?)

Authors: We agree with the reviewer that this information would be extremely interesting. Unfortunately, we are not able to provide this information. As noted in the previous commentary, we have not included or recorded the information regarding patients admitted without VTE prophylaxis. In the case of patients with VTE prophylaxis, we included all consecutive patients without losses.

Reviewer: 2. The high level of VTE risk (PADOVA score) in subjects who received chemoprophylaxis is reassuring. So is the low proportion (0.5%) with 'major' bleeding. Multivariate analysis suggests more major haematomas with enoxaparin then tinzaparin. Demographics indicate more patients given tinzaparin had kidney failure. Did this reflect local treatment guidelines or practice for kidney failure?

Authors: We appreciate the reviewer´s commentary and we also consider that these differences are interesting. The prescription of tinzaparin in patients with CKD in our department did not result from the implementation of local guidelines and we assume that physicians considered it safer in these patients for clinical reasons and the double mechanism of metabolism of Tinzaparin.

Reviewer: 3. The authors define 'major haematoma' as retroperitoneal or rectus muscle locations, or other abdominal haematomas with at least 2 point (20 gm/L?) loss of Haemoglobin. Of 29 'major' haematomas, how many were retroperitoneal or rectus sheath (these can be life-threatening) and how many were more limited? A Table of major and minor bleeding events, including more information about 'major haematomas' would add perspective.

Authors: We agree with the reviewer that this differentiation is important, and we have added information on the type of major hematomas. We consider that the information in the manuscript on this regard is clear enough and that an additional table could be redundant. However, we will add it if the Editor deems it necessary.

Reviewer: 2
Reviewer Name: Anneliese Schleyer MD
Institution and Country: Harborview Medical Center/ University of Washington, Seattle, WA, USA
Competing Interests: None declared

Reviewer: This study has the potential to inform the literature about bleeding complications in medical patients receiving vte prophylaxis (and adherence to VTE prevention guidelines in this pt group). An important area of study.

While the results address the research question as stated, from a clinical perspective it would be helpful to distinguish "complications" that impact pts - is a platelet count decrease clinically significant?

Authors: We thank the reviewer for this remark and we would like to clarify that the platelet count decrease itself was not clinically relevant for the patients included in the study, but we nonetheless decided to include this information to evaluate whether this fact was linked to a higher risk of further complications. It was not. We have elaborated this fact in the reviewed version of the manuscript to make it clearer.

Reviewer: # The authors describe that data collection was performed by personal interview. Which information? Pt identification of bleeding events? Other?

Authors: All the information was collected by the study team, including the physical exam and the identification of all complications.

Reviewer: # Written informed consent was obtained. Was this study approved by a Human Subjects/Institutional Review Board?

Authors: The study protocol was evaluated an approved by the Clinical Investigations Ethical Committee of Galicia. This fact has been added to the reviewed manuscript.

Additional comments:
(May result from the fact that I only practice in the USA)

Reviewer: # Fulfillment (needs two 'l's) of current guidelines is often referred to as adherence to guidelines

Authors: As far as spelling is concerned, both are correct. It is matter of British vs. American English. As far as the choice of words is concerned, since we use the term "adherence" to refer to the correct accomplishment of a prescribed treatment by the patient, we decided to use another word in this case. Perhaps fulfilment/fulfilment could be replaced by “compliance”.

Reviewer: # Complications might be more specifically identified as bleeding complications

Authors: We have decided to maintain the term due to the inclusion of platelet count decrease as a non-bleeding complication.

Reviewer: # What is a third level institution?

Author: a third level institution means a Hospital with the highest level of health care services. For the sake of clarity, we have replaced this term in the manuscript for 'tertiary referral hospital'

Reviewer: # Abstract conclusions: Is the final sentence justified by the review? (tinzaparin could have a better security profile)? (In the US we call this safety profile)

Author: As we have explained in the discussion section, this finding will need further studies to be confirmed and could be influenced by a selection bias. We have changed the word security for safety as the reviewer suggest.

Reviewer: (# homogenization - might refer to bias)

Authors: We have added a sentence discussing a potential selection bias.

Reviewer: # Please further describe role of antiplatelets in this review

Authors: Antiplatelet treatment showed an association with major hematomas in our study. We have added a sentence in the discussion section to further clarify this fact.

Reviewer: # Were LMWH doses renally adjusted? How does this relate to AKI as described?

Authors: We thank the reviewer for this question and we have added a sentence to clarify that dose adjustment was correct in all cases with CKD, CKDE or AKI.

Reviewer: # HBPM?

Authors: we apologise for the mistake, which we have corrected.

Thank you for the opportunity to review this manuscript.

Reviewer: 3
Reviewer Name: Dr Corinne Frere
Institution and Country: Assistance Publique Hôpitaux de Paris, France
Competing Interests: None declared

Reviewer: Novo-Veleiro et al. Conducted a prospective cohort study in 396 elderly hospitalized non-surgical elderly patients receiving VTE prophylaxis to evaluate the grade of fulfillment of current guidelines for VTE prophylaxis in medical patients and to identify risk factor for bleeding.
They found that prophylaxis was correctly indicated in 88% of patients. Obesity, concomitant antiplatelet therapy and enoxaparin use were associated with a higher risk for major hematomas while diabetes mellitus and PADOVA index<4 were associated with a higher risk for minor hematomas.
This is an interesting question and relevant paper for this particular patients. However, some points need minor revisions:

Abstract
P 2, line 22 : please mention that the study was conducted in elderly patients

Authors: We thank the reviewer for this comment and we have added the information as suggested.

Reviewer: P 2, line 36 : please add a sentence on the statistical analysis

Authors: we have added the sentence as requested.

Reviewer: Method section
P7 line 1-10 : were PE ad DVT objectively confirmed?

Authors: As we mentioned in the results section, we have found no cases or PE or DVT.

Reviewer: Result section
P7 line 33-34 : “the mean age was 80.7” Please give the range

Authors: we have included the information as requested.

Reviewer: P8 line 9 : suppress “it is also remarkable that”

Authors: We have made the change.

Reviewer: P8 line 54: “we found an association between minor..;” please add OR (95%CI) and p value for each variable

Authors: we have provided OR and IC for all variables in multivariate analysis. As far as univariate analysis is concerned, a P value <0.05 was considered significant. We consider that including all P values in univariate analysis would not yield any valuable information.

Reviewer: Add a table to summarize multivariate analysis

Authors: we think that such table would be redundant, but we could change data from main text to a table if the Editor considers it necessary.

Reviewer:
Table 1:
Add age in table &
Are data n (%)?

Authors: We have added age and clarified the data format.

Reviewer:
Discussion
The authors found that 23.5% of patients had coagulation abnormalities, however coagulation abnormalities were not associated with bleeding. Please discuss this point

Authors: we appreciate the reviewer´s suggestion and we have changed the test to clarify this fact.

FORMATTING AMENDMENTS (if any)
Required amendments will be listed here; please include these changes in your revised version:

1.Table not Embedded

- Kindly embed your table (should be editable). Tables should be placed in the main text where the table is first cited. Tables must be cited in the main text in numerical order. Please note that tables embedded as Excel files within the manuscript are NOT accepted. Do not upload your table separately.

2.Funding and Competing Interest statement

- Please embed the following statements to your main document just before your reference list

Authors: we have made the changes as requested.

VERSION 2 – REVIEW

REVIEWER	Anneliese M. Schleyer MD MHA Harborview Medical Center/ University of Washington United States of America
REVIEW RETURNED	01-Mar-2018

GENERAL COMMENTS	Thank you for revising your manuscript. It is much improved. Is the predominance of elderly pts a reflection of your general pt population? Is there a way to elucidate further to help readers understand applicability for their patients? % over/under 65? Some minor comments In title consider change patients to 'inpatients' p 6 - "minor bleeding" - analytical impact? Table 1 - HBPM? In discussion - p 11 minor complications - for pts important [agree] How can results help physicians improve clinical practice? Please elaborate? Avoid prophylaxis (at least in low risk pts)? Discuss risks with pt?

REVIEWER	Dr Corinne Frere Assistance Publique Hôpitaux de Paris France
REVIEW RETURNED	02-Mar-2018

GENERAL COMMENTS	The authors have now dealt with the comments.

REVIEWER	Alexander Gallus Flinders University and Flinders Medical Centre Adelaide, Australia
REVIEW RETURNED	04-Mar-2018

GENERAL COMMENTS	No further comments, except the Editors may choose to adjust English phraseology in several places.

VERSION 2 – AUTHOR RESPONSE

Editorial Requests:

- Can you please revise the title and abstract to include the full study design and country that the study took place in? We suggest amending the title to: "Compliance with current VTE prophylaxis guidelines and risk factors linked to complications of VTE prophylaxis in medical patients: a prospective cohort study in a Spanish Internal Medicine Department."

Authors: we have changed the title as it was suggested.

- We would be grateful if you could proofread the paper one more time. The quality of English could still be improved in places (e.g. page 7: “Of them, 51.8% were women and the mean age was 80.7 years..”).

Authors: a native English speaker has reviewed the manuscript again.

Reviewers' Comments to Author:

Reviewer: 1
Reviewer Name: Alexander Gallus
Institution and Country: Flinders University and Flinders Medical Centre, Adelaide, Australia
Competing Interests: None

No further comments, except the Editors may choose to adjust English phraseology in several places.

Authors: a native English speaker has reviewed the manuscript again.

Reviewer: 2
Reviewer Name: Anneliese M. Schleyer MD MHA
Institution and Country: Harborview Medical Center/ University of Washington, United States of America
Competing Interests: None declared

Thank you for revising your manuscript. It is much improved.

Is the predominance of elderly pts a reflection of your general pt population?
Is there a way to elucidate further to help readers understand applicability for their patients? % over/under 65?

Authors: yes, the predominance of elderly patients among patients admitted to Internal Medicine Departments in our area is absolute. Thus, 91% of our patients were over 65 years old. Both concepts had been explained in the new version of the manuscript.

Some minor comments

Reviewer:
In title consider change patients to 'inpatients'

Authors: we changed the title following the reviewer´s suggestion.

Reviewer:
p 6 - "minor bleeding" - analytical impact?

Authors: we mean the repercussion on haemoglobin levels. We changed the expression in the new version of the manuscript.

Reviewer:
Table 1 - HBPM?

Authors: we have corrected the mistake.

Reviewer:
In discussion - p 11
minor complications - for pts important [agree]
How can results help physicians improve clinical practice?
Please elaborate?
Avoid prophylaxis (at least in low risk pts)? Discuss risks with pt?

Authors: we have added the following sentence in the discussion section to explain this fact:

"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."

Reviewer: 3
Reviewer Name: Dr Corinne Frere
Institution and Country: Assistance Publique Hôpitaux de Paris, France
Competing Interests: None declared

The authors have now dealt with the comments.